MAY 2011 www.TheOncologyNurse.com VOL 4, NO 3

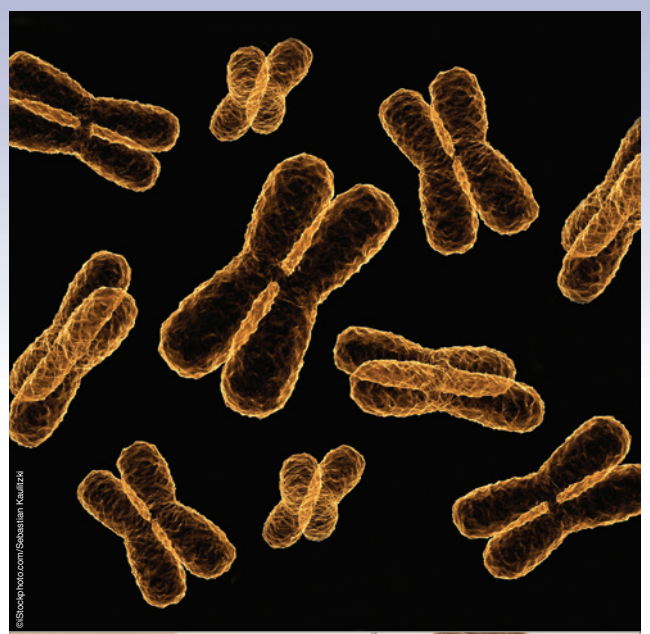
The Leader in News and Meeting Coverage

The Oncology Nurse®-APN/PA

The Official Publication for the Hem/Onc Nurse & Advanced Practitioner

3RD ANNUAL REVIEW ISSUE

A Look at Recent Advances in Cancer Care



Breast Cancer

Eribulin: A New Option for Metastatic Breast Cancer
Georgia Litsas, RN, NP

Prostate Cancer

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer
Guru Sonpavde, MD; Toni K. Choueiri, MD, MS; Philip W. Kantoff, MD

Ovarian Cancer

Developments in the Management of Ovarian Cancer
Maurie Markman, MD

Gastrointestinal Cancer

Advances in Treating Pancreatic Neuroendocrine Cancer
Dori L. Klemanski, MS, RN, CNP

Follicular Lymphoma

Emerging Agents & Regimens for Follicular Lymphomas
Elizabeth Reist, PharmD; Angie Elefante, PharmD, BCOP; Francisco Hernandez-Ilizaliturri, MD

Supportive Care

Early Intervention Palliative Care: Implications for Nurses
Constance M. Dahlin, MSN, ANP, FAAN; Emily R. Gallagher, RN; Jennifer S. Temel, MD

The first and only monoclonal antibody indicated for use in HER2+ metastatic gastric and gastroesophageal junction (GEJ) cancer

Indication

Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.

proven

to drive outcomes in HER2+ metastatic gastric/GEJ cancer

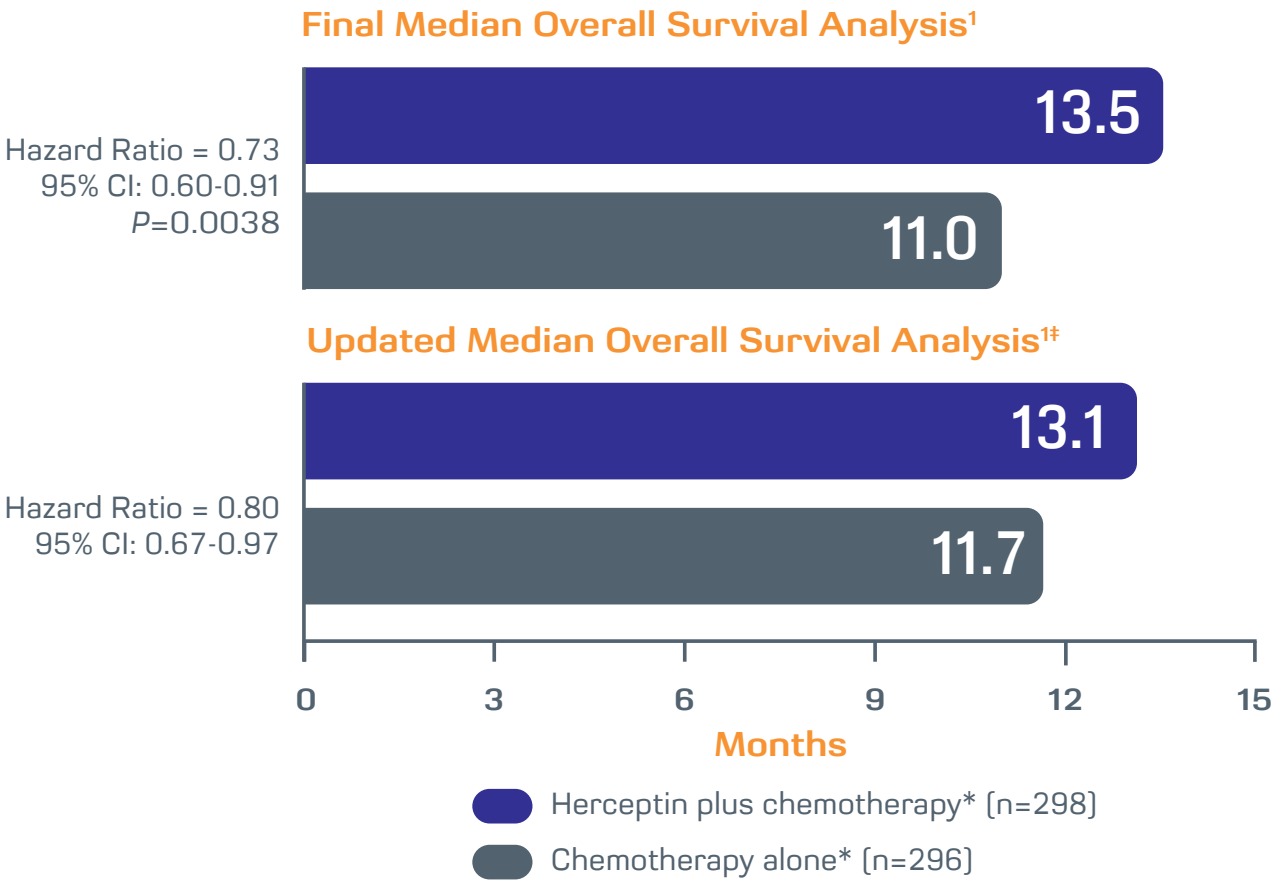
Boxed WARNINGS

- Herceptin administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving Herceptin with anthracycline-containing chemotherapy regimens. In a pivotal adjuvant breast cancer trial, one patient who developed CHF died of cardiomyopathy
- Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy
- Herceptin can result in serious and fatal infusion reactions and pulmonary toxicity. Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome
- Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death

Herceptin plus chemotherapy* extended median overall survival (OS) in HER2+ metastatic gastric and GEJ cancer[1]

- In the ToGA[†] trial:
  - The final overall survival analysis demonstrated a 13.5-month median OS with Herceptin + chemotherapy (cisplatin and either capecitabine or 5-fluorouracil) vs an 11.0-month median OS with chemotherapy alone[1]
  - The updated overall survival analysis demonstrated a 13.1-month median OS with Herceptin + chemotherapy (cisplatin and either capecitabine or 5-fluorouracil) vs an 11.7-month median OS with chemotherapy alone[1]
  - Herceptin should be administered until disease progression or unacceptable toxicity in HER2+ metastatic gastric and GEJ cancer[1]

[†]Trastuzumab for gastric cancer.



*Chemotherapy was cisplatin and either capecitabine or 5-FU.
[‡]The updated analysis was conducted one year after the final analysis. No *P* value was associated with the updated analysis in the Herceptin Prescribing Information because there was no preplanned statistical testing for OS after the final analysis.

Additional Important Safety Information

- Exacerbation of chemotherapy-induced neutropenia has also occurred
- Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy
- The most common adverse reactions associated with Herceptin were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia

Please see brief summary of full Prescribing Information, including **Boxed WARNINGS** and additional important safety information, on the following pages.

Reference: 1. Herceptin Prescribing Information. Genentech, Inc. October 29, 2010.

Genentech
A Member of the Roche Group

 HER0000330201 3/11

Herceptin® trastuzumab

HERCEPTIN® (trastuzumab)
Brief Summary For full Prescribing Information, see package insert.

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

Cardiomyopathy

Herceptin administration can result in sub clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving Herceptin with anthracycline containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and withhold Herceptin in patients with metastatic disease for clinically significant decrease in left ventricular function. [*see Warnings and Precautions and Dosage and Administration*]

Infusion Reactions; Pulmonary Toxicity

Herceptin administration can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of Herceptin administration. Interrupt Herceptin infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. [*see Warnings and Precautions*]

Embryo-Fetal Toxicity

Exposure to Herceptin during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. [*see Warnings and Precautions, Use in Specific Populations*]

INDICATIONS AND USAGE **Adjuvant Breast Cancer** Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature [*see Clinical Studies*] breast cancer • as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel • with docetaxel and carboplatin • as a single agent following multi-modality anthracycline based therapy. **Metastatic Breast Cancer** Herceptin is indicated: • In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer • As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. **Metastatic Gastric Cancer** Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease. **CONTRAINDICATIONS** None. **WARNINGS AND PRECAUTIONS** **Cardiomyopathy** Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death [*see Boxed Warning: Cardiomyopathy*]. Herceptin can also cause asymptomatic decline in left ventricular ejection fraction (LVEF). There is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving Herceptin as a single agent or in combination therapy compared with those not receiving Herceptin. The highest absolute incidence occurs when Herceptin is administered with an anthracycline. Withhold Herceptin for ≥16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥10% absolute decrease in LVEF from pretreatment values [*see Dosage and Administration*]. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied. *Cardiac Monitoring* Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended: • Baseline LVEF measurement immediately prior to initiation of Herceptin • LVEF measurements every 3 months during and upon completion of Herceptin • Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction [*see Dosage and Administration*] • LVEF measurements every 6 months for at least 2 years following completion of Herceptin as a component of adjuvant therapy. In Study 1, 16% (136/844) of patients discontinued Herceptin due to clinical evidence of myocardial dysfunction or significant decline in LVEF. In Study 3, the number of patients who discontinued Herceptin due to cardiac toxicity was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) patients in the TCH arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase) discontinued Herceptin due to cardiac toxicity. Among 32 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive heart failure, one patient died of cardiomyopathy and all other patients were receiving cardiac medication at last follow-up. Approximately half of the surviving patients had recovery to a normal LVEF (defined as ≥ 50%) on continuing medical management at the time of last follow-up. Incidence of congestive heart failure is presented in Table 1. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

Table 1 Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

Study	Regimen	Incidence of CHF	
		Herceptin	Control
1 & 2[a]	AC[b]→Paclitaxel+ Herceptin	2% (32/1677)	0.4% (7/1600)
3	Chemo→Herceptin	2% (30/1678)	0.3% (5/1708)
4	AC[b]→Docetaxel+ Herceptin	2% (20/1068)	0.3% (3/1050)
4	Docetaxel+Carbo+ Herceptin	0.4% (4/1056)	0.3% (3/1050)

[a] Includes 1 patient with fatal cardiomyopathy.
[b] Anthracycline (doxorubicin) and cyclophosphamide

Table 2 Incidence of Cardiac Dysfunction[a] in Metastatic Breast Cancer Studies

Study	Event	Incidence			
		NYHA I–IV		NYHA III–IV	
		Herceptin	Control	Herceptin	Control
5 (AC)[b]	Cardiac Dysfunction	28%	7%	19%	3%
5 (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
6	Cardiac Dysfunction[c]	7%	N/A	5%	N/A

[a] Congestive heart failure or significant asymptomatic decrease in LVEF.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[c] Includes 1 patient with fatal cardiomyopathy.

In Study 4, the incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the Herceptin containing regimens: (AC-TH: 0.3% (3/1068) and TCH 0.2% (2/1056)) as compared to none in AC-T. **Infusion Reactions** Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. [*see Adverse Reactions*] In postmarketing reports, serious and fatal infusion reactions have been reported. Severe reactions which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction. Interrupt Herceptin infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered, which may include: epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions. There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Herceptin after experiencing a severe infusion reaction. Prior to resumption of Herceptin infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated Herceptin infusions, others had recurrent severe infusion reactions despite pre-medications. **Embryo-Fetal Toxicity** Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise women of the potential hazard to the fetus resulting from Herceptin exposure during pregnancy and provide contraception counseling to women of childbearing potential. [*see Use in Specific Populations, Patient Counseling Information*]. **Pulmonary Toxicity** Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions [*see Warnings and Precautions*]. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity. **Exacerbation of Chemotherapy-Induced Neutropenia** In randomized, controlled clinical trials the per-patient incidences of NCI CTC Grade 3–4 neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received Herceptin and those who did not. [*see Adverse Reactions*] **HER2 Testing** Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied and for whom benefit has been shown. Due to differences in tumor histopathology, use FDA-approved tests for the specific tumor type (breast or gastric/gastroesophageal adenocarcinoma) to assess HER2 protein overexpression and HER2 gene amplification. Tests should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Several FDA-approved commercial assays are available to aid in the selection of breast cancer and metastatic gastric cancer patients for Herceptin therapy. Users should refer to the package inserts of specific assay kits for information on the Intended Use, and the validation and performance of each assay. Limitations in assay precision make it inadvisable to rely on a single method to rule out potential Herceptin benefit. Treatment outcomes for adjuvant breast cancer (Studies 2 and 3) and for metastatic breast cancer (Study 5) as a function of IHC and FISH testing are provided in Tables 8 and 10. Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers. Study 7 demonstrated that gene amplification and protein overexpression were not as well correlated as with breast cancer. Treatment outcomes for metastatic gastric cancer (Study 7), based on HER2 gene amplification (FISH) and HER2 protein overexpression (IHC) test results are provided in Table 12. **ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of the label: • Cardiomyopathy [*see Warnings and Precautions*] • Infusion reactions [*see Warnings and Precautions*] • Embryo-fetal Toxicity [*see Warnings and Precautions*] • Pulmonary toxicity [*see Warnings and Precautions*] • Exacerbation of chemotherapy-induced neutropenia [*see Warnings and Precautions*] The most common adverse reactions in patients receiving Herceptin in the adjuvant and metastatic breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of Herceptin treatment include CHF, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity [*see Dosage and Administration*]. In the metastatic gastric cancer setting, the most common adverse reactions (≥10%) that were increased (≥5% difference) in the Herceptin arm as compared to the chemotherapy alone arm were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. The most common adverse reactions which resulted in discontinuation of treatment on the Herceptin-containing arm in the absence of disease progression were infection, diarrhea, and febrile neutropenia. **Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. *Adjuvant Breast Cancer Studies* The data below reflect exposure to Herceptin across three randomized, open-label studies, Studies 1, 2, and 3, with (n= 3355) or without (n= 3308) trastuzumab in the adjuvant treatment of breast cancer. The data summarized in Table 3 below, from Study 3, reflect exposure to Herceptin in 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18. Among the 3386 patients enrolled in Study 3, the median age was 49 years (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.

Table 3 Adverse Reactions for Study 3, All Grades[a]:

Adverse Reaction	1 Year Herceptin (n= 1678)	Observation (n=1708)
Cardiac		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias[b]	40 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	4 (0.2%)	0 (0%)
Respiratory Thoracic Mediastinal Disorders		
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Pneumonitis	4 (0.2%)	0 (0%)
Gastrointestinal Disorders		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
Musculoskeletal & Connective Tissue Disorders		
Arthralgia	137 (8%)	98 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
Nervous System Disorders		
Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
Skin & Subcutaneous Tissue Disorders		
Rash	70 (4%)	10 (0.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritis	40 (2%)	10 (0.6%)
General Disorders		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Aesthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (0.06%)	0 (0%)
Infections		
Nasopharyngitis	135 (8%)	43 (3%)
UTI	39 (3%)	13 (0.8%)
Immune System Disorders		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

[a] The incidence of Grade 3/4 adverse reactions was <1% in both arms for each listed term.
[b] Higher level grouping term.

The data from Studies 1 and 2 were obtained from 3206 patients, of whom 1635 received Herceptin; the median treatment duration was 50 weeks. The median age was 49 years (range: 24–80); 84% of patients were White, 7% Black, 4% Hispanic, and 4% Asian. In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (31% vs. 28%), fatigue (28% vs. 22%), infection (22% vs. 14%), hot flashes (17% vs. 15%), anemia (13% vs. 7%), dyspnea (12% vs. 4%), rash/desquamation (11% vs. 7%), neutropenia (7% vs. 5%), headache (6% vs. 4%), and insomnia (3.7% vs. 1.5%). The majority of these events were Grade 2 in severity. In Study 2, data collection was limited to the following investigator-attributed treatment-related adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes, motor neuropathy, sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (11% vs. 8.4%), myalgia (10% vs. 8%), nail changes (9% vs. 7%), and dyspnea (2.5% vs. 0.1%). The majority of these events were Grade 2 in severity. Safety data from Study 4 reflect exposure to Herceptin as part of an adjuvant treatment regimen from 2124 patients receiving at least one dose of study treatment [AC-TH: n = 1068; TCH: n = 1056]. The overall median treatment duration was 54 weeks in both the AC-TH and TCH arms. The median number of infusions was 26 in the AC-TH arm and 30 in the TCH arm, including weekly infusions during the chemotherapy phase and every three week dosing in the monotherapy period. Among these patients, the median age was 49 years (range 22 to 74 years). In Study 4, the toxicity profile was similar to that reported in Studies 1, 2, and 3 with the exception of a low incidence of CHF in the TCH arm. *Metastatic Breast Cancer Studies* The data below reflect exposure to Herceptin in one randomized, open-label study, Study 5, of chemotherapy with (n=235) or without (n=234) trastuzumab in patients with metastatic breast cancer, and one single-arm study (Study 6; n=222) in patients with metastatic breast cancer. Data in Table 4 are based on Studies 5 and 6. Among the 464 patients treated in Study 5, the median age was 52 years (range: 25–77 years). Eighty-nine percent were White, 5% Black, 1% Asian and 5% other racial/ethnic groups. All patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months and ≥ 12 months were 58% and 9%, respectively. Among the 352 patients treated in single agent studies (213 patients from Study 6), the median age was 50 years (range 28–86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months and ≥ 12 months were 31% and 16%, respectively.

Table 4 Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6)

	Single Agent[a] n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC[b] n = 143	AC[b] Alone n = 135
Body as a Whole					
Pain	47%	61%	62%	57%	42%
Asthenia	42%	62%	57%	54%	55%
Fever	36%	49%	23%	56%	34%
Chills	32%	41%	4%	35%	11%
Headache	26%	36%	28%	44%	31%
Abdominal pain	22%	34%	22%	23%	18%
Back pain	22%	34%	30%	27%	15%
Infection	20%	47%	27%	47%	31%
Flu syndrome	10%	12%	5%	12%	6%
Accidental injury	6%	13%	3%	9%	4%
Allergic reaction	3%	8%	2%	4%	2%
Cardiovascular					
Tachycardia	5%	12%	4%	10%	5%
Congestive heart failure	7%	11%	1%	28%	7%
Digestive					
Nausea	33%	51%	9%	76%	77%
Diarrhea	25%	45%	29%	45%	26%
Vomiting	23%	37%	28%	53%	49%
Nausea and vomiting	8%	14%	11%	18%	9%
Anorexia	14%	24%	16%	31%	26%
Heme & Lymphatic					
Anemia	4%	14%	9%	36%	26%
Leukopenia	3%	24%	17%	52%	34%
Metabolic					
Peripheral edema	10%	22%	20%	20%	17%
Edema	8%	10%	8%	11%	5%
Musculoskeletal					
Bone pain	7%	24%	18%	7%	7%
Arthralgia	6%	37%	21%	8%	9%
Nervous					
Insomnia	14%	25%	13%	29%	15%
Dizziness	13%	22%	24%	24%	18%
Paresthesia	9%	48%	39%	17%	11%
Depression	6%	12%	13%	20%	12%
Peripheral neuritis	2%	23%	16%	2%	2%
Neuropathy	1%	13%	5%	4%	4%
Respiratory					
Cough increased	26%	41%	22%	43%	29%
Dyspnea	22%	27%	26%	42%	25%
Rhinitis	14%	22%	5%	22%	16%
Pharyngitis	12%	22%	14%	30%	18%
Sinusitis	9%	21%	7%	13%	6%
Skin					
Rash	18%	38%	18%	27%	17%
Herpes simplex	2%	12%	3%	7%	9%
Acne	2%	11%	3%	3%	< 1%
Urogenital					
Urinary tract infection	5%	18%	14%	13%	7%

[a] Data for Herceptin single agent were from 4 studies, including 213 patients from Study 6.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

Metastatic Gastric Cancer The data below are based on the exposure of 294 patients to Herceptin in combination with a fluoropyrimidine (capecitabine or 5-FU) and cisplatin (Study 7). In the Herceptin plus chemotherapy arm, the initial dose of Herceptin 8 mg/kg was administered on Day 1 (prior to chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was administered at 80 mg/m^2 on Day 1 and the fluoropyrimidine was administered as either capecitabine 1000 mg/m^2 orally twice a day on Days 1-14 or 5-fluorouracil 800 mg/m^2/day as a continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin infusions administered was eight.

Table 5 Study 7: Per Patient Incidence of Adverse Reactions of All Grades (Incidence ≥ 5% between Arms) or Grade 3 /4 (Incidence >1% between Arms) and Higher Incidence in Herceptin Arm

	Herceptin +FC (N = 294) N (%)		FC (N = 290) N (%)	
Body System/ Adverse Event	All Grades	Grades 3 / 4	All Grades	Grades 3/ 4
Investigations				
Neutropenia	230 (78)	101 (34)	212 (73)	83 (29)
Hypokalemia	83 (28)	28 (10)	69 (24)	16 (6)
Anemia	81 (28)	36 (12)	61 (21)	30 (10)
Thrombocytopenia	47 (16)	14 (5)	33 (11)	8 (3)
Blood And Lymphatic System Disorders				
Febrile Neutropenia	_	15 (5)	_	8 (3)
Gastrointestinal Disorders				
Diarrhea	109 (37)	27 (9)	80 (28)	11 (4)
Stomatitis	72 (24)	2 (1)	43 (15)	6 (2)
Dysphagia	19 (6)	7 (2)	10 (3)	1 (≤1)
Body as a Whole				
Fatigue	102 (35)	12 (4)	82 (28)	7 (2)
Fever	54 (18)	3 (1)	36 (12)	0 (0)
Mucosal Inflammation	37 (13)	6 (2)	18 (6)	2 (1)
Chills	23 (8)	1 (≤1)	0 (0)	0 (0)
Metabolism And Nutrition Disorders				
Weight Decrease	69 (23)	6 (2)	40 (14)	7 (2)
Infections And Infestations				
Upper Respiratory Tract Infections	56 (19)	0 (0)	29 (10)	0 (0)
Nasopharyngitis	37 (13)	0 (0)	17 (6)	0 (0)
Renal And Urinary Disorders				
Renal Failure and Impairment	53 (18)	8 (3)	42 (15)	5 (2)
Nervous System Disorders				
Dysgeusia	28 (10)	0 (0)	14 (5)	0 (0)

The following subsections provide additional detail regarding adverse reactions observed in clinical trials of adjuvant breast, metastatic breast cancer, metastatic gastric cancer, or post-marketing experience. *Cardiomyopathy* Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and 2, 23 months in the AC-T arm, 24 months in the AC-TH arm. In Studies 1 and 2, 6% of patients were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF < 50% or ≥ 15 point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients receiving Herceptin monotherapy compared to observation in Study 3 (see Table 6, Figures 1 and 2).

Table 6[a] Per-patient Incidence of New Onset Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4

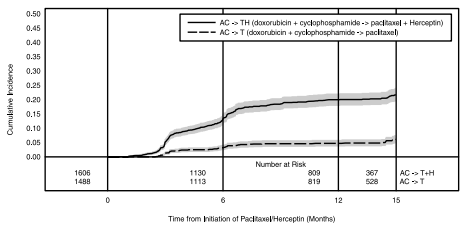
	LVEF <50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF <50%	≥10% decrease	≥16% decrease	<20% and ≥10%	≥20%
Studies 1 & 2[b]					
AC→TH (n=1606)	22.8% (366)	18.3% (294)	11.7% (188)	33.4% (536)	9.2% (148)
AC→T (n=1488)	9.1% (136)	5.4% (81)	2.2% (33)	18.3% (272)	2.4% (36)
Study 3					
Herceptin (n=1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n=1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
Study 4[c]					
TCH (n=1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n=1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n=1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

[a] For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization.

[b] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

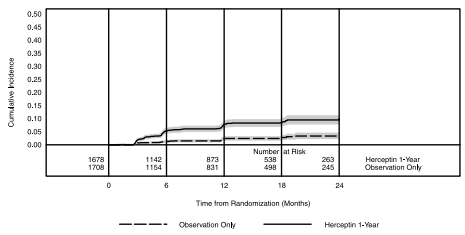
[c] Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

Figure 1 Studies 1 and 2: Cumulative Incidence of Time to First LVEF Decline of ≥10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



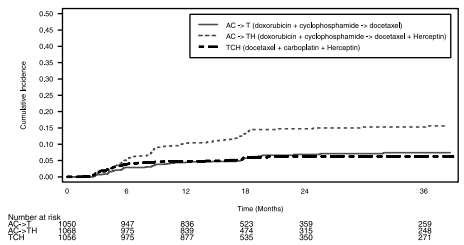
Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

Figure 2 Study 3: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization.

Figure 3 Study 4: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization.

The incidence of treatment emergent congestive heart failure among patients in the metastatic breast cancer trials was classified for severity using the New York Heart Association classification system (I–IV, where IV is the most severe level of cardiac failure) (see Table 2). In the metastatic breast cancer trials the probability of cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracyclines. In Study 7, 5.0% of patients in the Herceptin plus chemotherapy arm compared to 1.1% of patients in the chemotherapy alone arm had LVEF value below 50% with a ≥ 10% absolute decrease in LVEF from pretreatment values. *Infusion Reactions* During the first infusion with Herceptin, the symptoms most commonly reported were chills and fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of Herceptin infusion); permanent discontinuation of Herceptin for infusional toxicity was required in <1% of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. Infusional toxicity occurred in 21% and 35% of patients, and was severe in 1.4% and 9% of patients, on second or subsequent Herceptin infusions administered as monotherapy or in combination with chemotherapy, respectively. In the post-marketing setting, severe infusion reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported. *Anemia* In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]), of selected NCI-CTC Grade 2-5 anemia (12.5% vs. 6.6% [Study 1]), and of anemia requiring transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. Following the administration of Herceptin as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was < 1%. In Study 7 (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone arm the overall incidence of anemia was 28% compared 21% and of NCI CTC Grade 3/4 anemia was 12.2% compared to 10.3%. *Neutropenia* In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI-CTC Grade 4–5 neutropenia (2% vs. 0.7% [Study 2]) and of selected Grade 2–5 neutropenia (7.1% vs. 4.5% [Study 1]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7 (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone arm, the incidence of NCI CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile neutropenia 5.1% compared to 2.8%. *Infection* The overall incidences of infection (46% vs. 30% [Study 5]), of selected NCI-CTC Grade 2–5 infection/febrile neutropenia (22% vs. 14% [Study 1]) and of selected Grade 3–5 infection/febrile neutropenia (3.3% vs. 1.4%) [Study 2]), were higher in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. The most common site of infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract. In Study 4, the overall incidence of infection was higher with the addition of Herceptin to AC-T but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC Grade 3–4 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms. In a randomized, controlled trial in treatment of metastatic breast cancer, the reported incidence of febrile neutropenia was higher (23% vs. 17%) in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. *Pulmonary Toxicity* Adjuvant Breast Cancer Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC Grade 2–5 pulmonary toxicity (14% vs. 5% [Study 1]) and of selected NCI-CTC Grade 3–5 pulmonary toxicity and spontaneous reported Grade 2 dyspnea (3.4% vs. 1% [Study 2]) was higher in patients receiving Herceptin and chemotherapy compared with chemotherapy alone. The most common pulmonary toxicity was dyspnea (NCI-CTC Grade 2–5: 12% vs. 4% [Study 1]; NCI-CTC Grade 2–5: 2.5% vs. 0.1% [Study 2]). Pneumonitis/pulmonary infiltrates occurred in 0.7% of patients receiving Herceptin compared with 0.3% of those receiving chemotherapy alone. Fatal respiratory failure occurred in 3 patients receiving Herceptin, one as a component of multi-organ system failure, as compared to 1 patient receiving chemotherapy alone. In Study 3, there were 4 cases of interstitial pneumonitis in Herceptin-treated patients compared to none in the control arm. Metastatic Breast Cancer Among women receiving Herceptin for treatment of metastatic breast cancer, the incidence of pulmonary toxicity was also increased. Pulmonary adverse events have been reported in the post-marketing experience as part of the symptom complex of infusion reactions. Pulmonary events include bronchospasm, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see Warnings and Precautions. *Thrombosis/Embolism* In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies (3.0% vs. 1.3% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]). *Diarrhea* Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC Grade 2–5 diarrhea (6.2% vs. 4.8% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (1.6% vs. 0% [Study 2]), and of Grade 1–4 diarrhea (7% vs. 1% [Study 3]) were higher in patients receiving Herceptin as compared to controls. In Study 4, the incidence of Grade 3–4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving Herceptin. Of patients receiving Herceptin as a single agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was observed in patients receiving Herceptin in combination with chemotherapy for treatment of metastatic breast cancer. *Renal Toxicity* In Study 7 (metastatic gastric cancer) on the Herceptin-containing arm as compared to the chemotherapy alone arm the incidence of renal impairment was 18% compared to 14.5%. Severe (Grade 3/4) renal failure was 2.7% on the Herceptin-containing arm compared to 1.7% on the chemotherapy only arm. Treatment discontinuation for renal insufficiency/failure was 2% on the Herceptin-containing arm and 0.3% on the chemotherapy only arm. In the postmarketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18 months from initiation of Herceptin therapy. Pathologic findings included membranous glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure. **Immunogenicity** As with all therapeutic proteins, there is a potential for immunogenicity. Among 903 women with metastatic breast cancer, human anti-human antibody (HAHA) to Herceptin was detected in one patient using an enzyme-linked immunosorbent assay (ELISA). This patient did not experience an allergic reaction. Samples for assessment of HAHA were not collected in studies of adjuvant breast cancer. The incidence of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Herceptin with the incidence of antibodies to other products may be misleading. **Post-Marketing Experience** The following adverse reactions have been identified during post approval use of Herceptin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. • Infusion reaction [*see Warnings and Precautions*] • Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal abnormalities, and neonatal death [*see Warnings and Precautions*] • Glomerulopathy [*see Adverse Reactions*] **DRUG INTERACTIONS** In Study 5, the mean serum trough concentration of trastuzumab was consistently elevated approximately 1.5-fold, when administered in combination with paclitaxel as compared to trough concentrations of trastuzumab when administered in combination with an anthracycline and cyclophosphamide. In other pharmacokinetic studies, where Herceptin was administered in combination with paclitaxel, docetaxel or doxorubicin, Herceptin did not alter the plasma concentrations of these chemotherapeutic agents, or the metabolites that were analyzed. In a drug interaction substudy conducted in patients in Study 7, the pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered in combination with Herceptin. **USE IN SPECIFIC POPULATIONS Pregnancy: Category D [*see Warnings and Precautions, Nonclinical Toxicology*]** Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. These case reports described oligohydramnios in pregnant women who received Herceptin either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin therapy resumed after the amniotic fluid index improved, and oligohydramnios recurred. Monitor women exposed to Herceptin during pregnancy for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care. The efficacy of IV hydration in management of oligohydramnios due to Herceptin exposure is not known. Advise women of the potential hazard to the fetus resulting from Herceptin exposure during pregnancy. Encourage pregnant women with breast cancer who are using Herceptin to enroll in MotHER-the Herceptin Pregnancy Registry: phone 1-800-690-6720. [*see Patient Counseling Information*]. No teratogenic effects were observed in offspring from reproduction studies in cynomolgus monkeys at doses up to 25 times the recommended weekly human dose of 2 mg/kg trastuzumab. In mutant mice lacking HER2, embryos died in early gestation. Trastuzumab exposure was reported at delivery in offspring of cynomolgus monkeys treated during the early (Days 20-50 of gestation) or late (Days 120-150 of gestation) fetal development periods, at levels of 15 to 28% of the maternal blood levels. **Nursing Mothers** It is not known whether Herceptin is excreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Trastuzumab was present in the breast milk of lactating cynomolgus monkeys given 12.5 times the recommended weekly human dose of 2 mg/kg of Herceptin. Infant monkeys with detectable serum levels of trastuzumab did not have any adverse effects on growth or development from birth to 3 months of age; however, trastuzumab levels in animal breast milk may not accurately reflect human breast milk levels. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from Herceptin, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of trastuzumab and the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of Herceptin in pediatric patients has not been established. **Geriatric Use** Herceptin has been administered to 386 patients who were 65 years of age or over (253 in the adjuvant treatment and 133 in metastatic breast cancer treatment settings). The risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients in both those receiving treatment for metastatic disease in Studies 5 and 6, or adjuvant therapy in Studies 1 and 2. Limitations in data collection and differences in study design of the 4 studies of Herceptin in adjuvant treatment of breast cancer preclude a determination of whether the toxicity profile of Herceptin in older patients is different from younger patients. The reported clinical experience is not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of Herceptin treatment in older patients is different from that observed in patients <65 years of age for metastatic disease and adjuvant treatment. In Study 7 (metastatic gastric cancer), of the 294 patients treated with Herceptin 108 (37%) were 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or effectiveness were observed. **OVERDOSAGE** There is no experience with overdosage in human clinical trials. Single doses higher than 8 mg/kg have not been tested. **PATIENT COUNSELING INFORMATION** • Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [*see Boxed Warning Cardiomyopathy*]. • Advise pregnant women and women of childbearing potential that Herceptin exposure can result in fetal harm [*see Warnings and Precautions and Use in Specific Populations*]. • Advise women of childbearing potential to use effective contraceptive methods during treatment and for a minimum of six months following Herceptin [*see Warnings and Precautions*]. • Advise nursing mothers treated with Herceptin to discontinue nursing or discontinue Herceptin, taking into account the importance of the drug to the mother [*see Use in Specific Populations*]. • Encourage women who are exposed to Herceptin during pregnancy to enroll in MotHER- the Herceptin Pregnancy Registry (1-800-690-6720) [*see Warnings and Precautions and Use in Specific Populations*].

HERCEPTIN® [trastuzumab]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

Initial US Approval: September 1998
Revision Date: October 29, 2010
Herceptin® is a registered trademark of Genentech, Inc.
HER0000111000

Editorial Board

In multiple myeloma

RETHINK RELAPSED & REFRACTORY

The challenges of multiple myeloma need new approaches

In multiple myeloma, median survival from the time of diagnosis has been significantly longer in the current decade than in previous years—3.7 years vs 2.5 years.[1] However, patients still face significant challenges.

- Almost all patients eventually relapse[2]
- Patients may become refractory to multiple treatment options

Pursuing new treatment advances

Onyx Pharmaceuticals is pursuing potential new options for the treatment of relapsed and refractory multiple myeloma, with the ultimate goal of extending patients' lives.

References: 1. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111:2516-2520. **2.** Schwartz RN, Vozniak M. Current and emerging treatments for multiple myeloma. *J Manag Care Pharm*. 2008;14(suppl S):S12-S18.

ONYX PHARMACEUTICALS

The Oncology Nurse®-APN/PA
The Official Newspaper for the Hem/Onc Nurse & Advanced Practitioner

PUBLISHING STAFF

Senior Vice President, Sales & Marketing
Philip Pawelko
phil@greenhillhc.com

Publisher
John W. Hennessy
john@greenhillhc.com

Editorial Director
Christin Melton
christin@greenhillhc.com

Associate Editor
Dawn Lagrosa
dawn@greenhillhc.com

Quality Control Director
Barbara Marino

Production Manager
Stephanie Laudien

Business Manager
Blanche Marchitto
blanche@greenhillhc.com

Executive Administrator
Andrea Boylston

Circulation Department
circulation@greenhillhc.com

Editorial Contact:
Telephone: 732-992-1891
Fax: 732-656-7938

241 Forsgate Drive, Suite 205C
Monroe Twp, NJ 08831

Green Hill Healthcare Communications LLC
Your Innovative Partners in Medical Media

The Oncology Nurse®-APN/PA, ISSN 1944-9798 (print); ISSN 1944-9801 (online) is published 8 times a year by Green Hill Healthcare Communications, LLC, 241 Forsgate Drive, Suite 205C, Monroe Twp, NJ 08831. Telephone: 732.656.7935. Fax: 732.656.7938.

EDITORIAL CORRESPONDENCE should be addressed to **EDITORIAL DIRECTOR**, *The Oncology Nurse®-APN/PA*, 241 Forsgate Drive, Suite 205C, Monroe Twp, NJ 08831. E-mail: christin@greenhillhc.com. **YEARLY SUBSCRIPTION RATES:** United States and possessions: individuals, $105.00; institutions, $135.00; single issues, $17.00. Orders will be billed at individual rate until proof of status is confirmed. Prices are subject to change without notice. Correspondence regarding permission to reprint all or part of any article published in this journal should be addressed to **REPRINT PERMISSIONS DEPARTMENT**, Green Hill Healthcare Communications, LLC, 241 Forsgate Drive, Suite 205C, Monroe Twp, NJ 08831. The ideas and opinions expressed in *The Oncology Nurse®-APN/PA* do not necessarily reflect those of the Editorial Board, the Editorial Director, or the Publisher. Publication of an advertisement or other product mention in *The Oncology Nurse®-APN/PA* should not be construed as an endorsement of the product or the manufacturer's claims. Readers are encouraged to contact the manufacturer with questions about the features or limitations of the products mentioned. Neither the Editorial Board nor the Publisher assumes any responsibility for any injury and/or damage to persons or property arising out of or related to any use of the material contained in this periodical. The reader is advised to check the appropriate medical literature and the product information currently provided by the manufacturer of each drug to be administered to verify the dosage, the method and duration of administration, or contraindications. It is the responsibility of the treating physician or other healthcare professional, relying on independent experience and knowledge of the patient, to determine drug dosages and the best treatment for the patient. Every effort has been made to check generic and trade names, and to verify dosages. The ultimate responsibility, however, lies with the prescribing physician. Please convey any errors to the Editorial Director.

BPA Worldwide membership applied for April 2011.

In This Issue

A Look Back to See What Lies Ahead

By Editor-in-Chief Beth Faiman, RN, MSN, APRN, BC, AOCN

This month's Third Annual Review Issue of *The Oncology Nurse-APN/PA* highlights some of the top advances in cancer care over the past year. Although a few systemic cytotoxic therapies emerged as some of last year's winners—eribulin, sipuleucel-T, bevacizumab in ovarian cancer—most of the practice-changing studies reflect the continued shift in oncology toward greater personalization of care.

With a combined 10,000-plus abstracts submitted for just the American Society of Clinical Oncology and the American Society of Hematology annual meetings, the review issue of *The Oncology Nurse-APN/PA* would have to be larger than the Los Angeles phone book to address every important discovery from the past 12 months. While we managed to include several of the most noteworthy developments,

many of those not included have been discussed in previous issues and are likely to feature in upcoming issues as investigators release updated data from ongoing studies.

In putting together this issue, it became apparent how rapidly practices are changing and how important it is for nurses to be aware of those advances in care already affecting our patients or likely to affect them in the future. Some newer therapies improve overall survival minimally or not at all, yet they come with serious side effects and large price tags. Patients weighing their options after an existing drug regimen fails need to have realistic expectations about newer treatments, and informed nurses can help them make an educated choice.

We would like to thank all the authors who contributed to this important issue. Many were directly involved in the studies presented and others are experts in the therapeutic area discussed. All share a deep understanding of the subject and a passion for improving care for patients with cancer.

In addition to looking at what happened in oncology during the past year, we also took an opportunity to look ahead at what might happen in the coming year. Please take a moment to read the article at the end of the issue reviewing investigational therapies that appear to be just over the horizon. ●

Questions or comments about this issue?

E-mail us at editorial@greenhillhc.com.

Table 1. Adverse Reactions Occurring in ≥10% of Patients who Received VOTRIENT

	VOTRIENT (N = 290)			Placebo (N = 145)		
Adverse Reactions	All Grades[a] %	Grade 3 %	Grade 4 %	All Grades[a] %	Grade 3 %	Grade 4 %
Diarrhea	52	3	<1	9	<1	0
Hypertension	40	4	0	10	<1	0
Hair color changes	38	<1	0	3	0	0
Nausea	26	<1	0	9	0	0
Anorexia	22	2	0	10	<1	0
Vomiting	21	2	<1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Other adverse reactions observed more commonly in patients treated with VOTRIENT than placebo and that occurred in <10% (any grade) were alopecia (8% versus <1%), chest pain (5% versus 1%), dysgeusia (altered taste) (8% versus <1%), dyspepsia (5% versus <1%), facial edema (1% versus 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) (6% versus <1%), proteinuria (9% versus 0%), rash (8% versus 3%), skin depigmentation (3% versus 0%), and weight decreased (9% versus 3%).

Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients who Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus Placebo

	VOTRIENT (N = 290)			Placebo (N = 145)		
Parameters	All Grades[a] %	Grade 3 %	Grade 4 %	All Grades[a] %	Grade 3 %	Grade 4 %
Hematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Hepatic Toxicity: In a controlled clinical study with VOTRIENT for the treatment of RCC, ALT >3 X ULN was reported in 18% and 3% of the VOTRIENT and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received VOTRIENT and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of patients on VOTRIENT and 2/145 (1%) on placebo. *[See Dosage and Administration (2.2) and Warnings and Precautions (5.1).]* Hypertension: In a controlled clinical study with VOTRIENT for the treatment of RCC, 115/290 patients (40%) receiving VOTRIENT compared with 15/145 patients (10%) on placebo experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving VOTRIENT compared with 1/145 patients (<1%) on placebo. The majority of cases of hypertension were manageable with anti-hypertensive agents or dose reductions with 2/290 patients (<1%) permanently discontinuing treatment with VOTRIENT because of hypertension. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on VOTRIENT. [*See Warnings and Precautions (5.2).*] QT Prolongation and Torsades de Pointes: In a controlled clinical study with VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 3/290 (1%) of patients treated with VOTRIENT compared with no patients on placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with VOTRIENT in the RCC studies. *[See Warnings and Precautions (5.3).]* Arterial Thrombotic Events: In a controlled clinical study with VOTRIENT, the incidences of arterial thrombotic events such as myocardial infarction/ischemia [5/290 (2%)], cerebral vascular accident [1/290 (<1%)], and transient ischemic attack [4/290 (1%)] were higher in patients treated with VOTRIENT compared to the placebo arm (0/145 for each event). *[See Warnings and Precautions (5.4).]* Hemorrhagic Events: In a controlled clinical study with VOTRIENT, 37/290 patients (13%) treated with VOTRIENT and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four (4/290) (1%) patients treated with VOTRIENT died from hemorrhage compared with no (0/145) (0%) patients on placebo. *[See Warnings and Precautions (5.5).]* In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients treated with VOTRIENT. Hypothyroidism: In a controlled clinical study with VOTRIENT, more patients had a shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the normal range at any post-baseline visit in VOTRIENT compared with the placebo arm (27% compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with VOTRIENT and no patients (0%) in the placebo arm. *[See Warnings and Precautions (5.7).]* Diarrhea: Diarrhea occurred frequently and was predominantly mild to moderate in severity. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact. Proteinuria: In the controlled clinical study with VOTRIENT, proteinuria has been reported as an adverse reaction in 27 patients (9%) treated with VOTRIENT. In 2 patients, proteinuria led to discontinuation of treatment with VOTRIENT. Lipase Elevations: In a single-arm clinical study, increases in lipase values were observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (<1%). Cardiac Dysfunction: Pazopanib has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%).

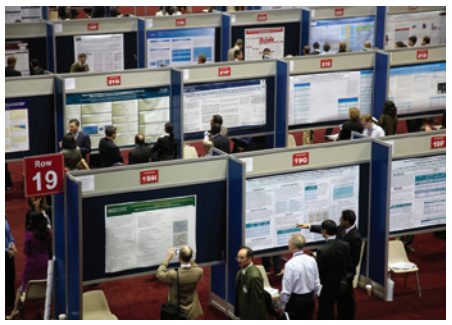
7 DRUG INTERACTIONS

7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes: In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib. CYP3A4 Inhibitors: Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations. A dose reduction for VOTRIENT should be considered when it must be coadministered with strong CYP3A4 inhibitors *[see Dosage and Administration (2.2)]*. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. CYP3A4 Inducers: CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. VOTRIENT should not be used if chronic use of strong CYP3A4 inducers can not be avoided *[see Dosage and Administration (2.2)]*. **7.2 Effects of Pazopanib on CYP Substrates:** Results from drug-drug interaction studies conducted in cancer patients suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19 *[see Clinical Pharmacology (12.3) of full prescribing information]*. Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events. *[See Clinical Pharmacology (12.3) of full prescribing information.]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Pregnancy Category D *[see Warnings and Precautions (5.10)]*. VOTRIENT can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of VOTRIENT in pregnant women. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis at a dose level of ≥3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or absent ossification. In addition, there was

46th Annual Meeting of the American Society of Clinical Oncology



ZETA: Vandetanib in Locally Advanced or Metastatic Medullary Thyroid Cancer

In this initial phase 3 trial of vandetanib, the agent significantly prolonged progression-free survival compared with placebo in patients with unresectable measurable, locally advanced, or metastatic medullary thyroid cancer (hereditary or sporadic). The ZETA researchers also found significant increases in the objective response rate, the disease control rate, and biochemical response. This once-daily oral inhibitor of RET, vascular endothelial growth factor receptor, and epidermal growth factor receptor signaling is the first therapy to demonstrate efficacy in this population. *Wells SA, et al. Abstract 5503.*

Effect of Early Palliative Care on Quality of Life, Aggressive Care at the End of Life, and Survival in Stage IV NSCLC Patients

For patients with newly diagnosed metastatic non–small cell lung cancer, researchers found that receiving palliative care soon after diagnosis was associated with improved mood and quality of life. Of significance is the prolongation of survival for these patients compared with those receiving standard oncology care. In addition, the palliative care patients received less aggressive end-of-life care. Patient-reported outcomes included the Functional Assessment of Cancer Therapy (FACT)-Lung, the Hospital Anxiety and Depression Scale (HADS), and the Patient Health Questionnaire (PHQ)-9. Data on end-of-life care also were collected. *Temel JS, et al. Abstract 7509.*

Effect of YOCAS Yoga on Sleep, Fatigue, and Quality of Life in Cancer Survivors

A yoga program developed for cancer survivors was shown to improve sleep quality, decrease fatigue, and enhance quality of life. In this study, survivors with nonmetastatic disease and moderate or greater sleep deprivation participated in the yoga program twice a week for 4 weeks. The program combined breathing exercises, gentle yoga postures, and meditation. On comparing these survivors with those receiving standard care monitoring, researchers found that yoga participants not only experienced improved sleep and quality of life but also reduced their use of sleep medication. The researchers concluded that their program should be considered for cancer survivors who report impaired sleep or fatigue. *Mustian KM, et al. Abstract 9013.*

Denosumab vs Zoledronic Acid in Patients with Bone Metastases from Castration-Resistant Prostate Cancer

Denosumab delayed the time to first on-study skeletal-related event (SRE) compared with zoledronic acid in patients with bone metastases from castration-resistant prostate cancer. Time to first and subsequent on-study SRE also was prolonged. In addition, researchers found that denosumab produced greater suppression of the bone turnover markers uNTx and BSAP than zoledronic acid. Adverse events were similar in both groups. Patients in this study were instructed to take supplemental calcium and vitamin D. SRE was defined as pathologic fracture, radiation or surgery to bone, or spinal cord compression. *Fizazi K, et al. Late Breaking Abstract 4507.* ●

New Horizons in CML Therapy

By A. Megan Cornelison, MSPA
Department of Leukemia, The University of Texas, M. D. Anderson Cancer Center, Houston

Elias Jabbour, MD
Department of Leukemia, The University of Texas, M. D. Anderson Cancer Center, Houston

Imatinib (Gleevec) revolutionized the treatment of Philadelphia chromosome–positive chronic myeloid leukemia (CML) and established targeting and inhibiting *BCR-ABL* as the standard of care.[1] In 2009, 8-year follow-up data from the landmark phase 3 IRIS (International Randomized Study of Interferon Versus STI571) trial were presented for the 553 patients with newly diagnosed chronic-phase (CP) CML randomized to imatinib. Findings showed a cumulative best complete cytogenetic response (CCyR) rate of 83% and an estimated rate of overall survival (OS) of 93% (CML-related deaths only).[2] Despite these positive results, 17% of patients treated with imatinib never achieve a CCyR, and 10% of those who do subsequently relapse. An additional 8% of patients are imatinib-intolerant.[2]

Second-generation tyrosine kinase inhibitors (TKIs) are more potent inhibitors of *BCR-ABL* and have demonstrated efficacy in patients resistant to or intolerant of imatinib (**Table 1**).[3-7] The US Food and Drug Administration has approved dasatinib (Sprycel) and nilotinib (Tasigna) as first- and second-line options in CP-CML. Both drugs are active against all *BCR-ABL* mutations except *T315I* and have well-established safety profiles.[8,9] Their increased potency makes them attractive candidates for use in the first-line setting.

Nilotinib

Three recent studies evaluated response to nilotinib in patients with newly diagnosed CP-CML (**Table 2**).[10-13] All point to nilotinib as being an effective and safe frontline option in this patient population.

A single-institution study at M. D. Anderson Cancer Center reported that 50 (98%) of the 51 evaluable patients treated with 400 mg of nilotinib twice daily for at least 3 months attained a CCyR and 39 (76%) attained a major molecular response (MMR).[10] The 3-month rate of CCyR was 96%, increasing to 98% at 6 months. The projected event-free survival (EFS) rate at 24 months was 90%. Grade 3/4 hematologic toxicities included neutropenia (12%) and thrombocytopenia (11%). Nonhematologic toxicities were grade 1/2 and manageable. Some patients required treatment interruptions and/or dose reductions; the median dose at 12 months was 800 mg.

The phase 2 GIMEMA (Italian Group for Hematological Malignancies of the Adult) trial treated 73 patients with a 400-mg dose of nilotinib twice daily; median follow-up was 30 months.[11] Rates of CCyR, MMR, and complete molecular response (CMR) at 24 months were 92%, 82%, and 12%, respectively. One patient progressed to advanced disease and was found to have developed a *T315I* mutation. The discontinuation rate due to adverse events was 5%.

ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients), a phase 3, randomized, open-label, multicenter study, compared the efficacy and safety profiles of nilotinib and imatinib.[12] Patients were assigned 1:1:1 to receive nilotinib 300 mg twice daily (n = 282), nilotinib 400 mg twice daily (n = 281), or imatinib 400 mg once daily (n = 283). The MMR rate at 12 months—the study's primary end point—was significantly higher in the nilotinib 300-mg arm and in the nilotinib 400-mg arm than in the imatinib arm (44% vs 43% vs 22%, respectively; P <.0001 for nilotinib vs imatinib comparisons). At 12 months, the best cumulative rates of MMR were also significantly higher for the nilotinib 300-mg and 400-mg arms than for the imatinib group (51% vs 50% vs 27%, respectively; P <.0001 for nilotinib vs imatinib comparisons), as were the cumulative CCyR rates (80% vs 78% vs 65%, respectively; P <.0001 for nilotinib vs imatinib comparisons).

Nilotinib was associated with faster responses, with a 6-month MMR rate of 33% in the nilotinib 400-mg arm and 30% in the nilotinib 300-mg group compared with 12% in the imatinib arm. At 9 months, the MMR rate was 43% in the nilotinib 300-mg arm, 38% in the nilotinib 400-mg group, and 18% in the imatinib arm. A greater proportion of patients achieved undetectable levels of disease (defined as a CMR ≤0.0032% *BCR-ABL* on the International Scale) with nilotinib 300-mg and 400-mg doses than with imatinib (13% vs 12% vs 4%, respectively), resulting in significantly fewer cases of progression in the nilotinib arms than in the imatinib group.

Grade 3/4 nonhematologic adverse events were uncommon in the ENESTnd trial; the only grade 3/4 nonhematologic adverse event to affect >1% of patients was rash, which occurred in 3% of patients treated with nilotinib 400 mg twice daily. None of the patients in the trial experienced QTcF prolongation >500 msec. Grade 3/4 laboratory abnormalities were uncommon among patients taking nilotinib, although the nilotinib arms had higher rates of grade 3/4 thrombocytopenia than the imatinib group. Patients treated with imatinib were more likely to experience grade 3/4 anemia and neutropenia than those given nilotinib, however.

At a minimum of 24 months of follow-up, nilotinib proved superior to imatinib across all efficacy end points assessed,[13] with significantly higher rates of MMR in the nilotinib 300-mg and 400-mg arms than in the imatinib group (71% vs 67% vs 44%, respectively; P <.0001 for nilotinib vs imatinib comparisons). The nilotinib 400-mg and

Table 1 Effectiveness of Second-Generation TKIs in Imatinib-Resistant or -Intolerant Patients with CML by Phase

	Dasatinib				Nilotinib				Bosutinib		
	CP (N = 387)	AP (n = 174)	MyBP (n = 109)	LyBP (n = 48)	CP (n = 321)	AP (N = 137)	MyBP (N = 105)	LyBP (N = 31)	CP (N = 146)	AP (N = 51)	BC (N = 38)
Median follow-up, mo	15	14	12+	12+	24	9	3	3	7	6	3
Imatinib resistant, %	74	93	91	88	70	80	82	82	69	NR	NR
Hematologic response, %	—	79	40	94	56	80	80	80	80	5.5	80
CHR	91	45	27	29	76	31	11	13	81	54	36
NEL	—	19	7	6	—	12	1	0	—	0	0
CyR, %	NR	44	36	52	NR	NR	NR	NR	—	NR	NR
CCyR	49	32	26	46	46	20	29	32	34	27	35
Partial	79	79	79	79	79	79	79	79	79	79	79
1-year OS, % (no.)	96 (15)	82 (12)	50 (12)	50 (5)	87 (24)	67 (24)	42 (12)	42 (12)	98 (12)	60 (12)	50 (10)

AP indicates accelerated phase; BC, blast crisis; CCyR, complete cytogenetic response; CHR, complete hematologic response; CML, chronic myeloid leukemia; CP, chronic phase; CyR, cytogenetic response; LyBP, lymphoid blast phase; MyBP, myeloid blast phase; NEL, no evidence of leukemia; NR, none reported; OS, overall survival; TKI, tyrosine kinase inhibitors. *Sources:* References 3-7.

300-mg arms continued to demonstrate significantly higher rates of CMR (26% vs 21% vs 10%, respectively) than the imatinib group (26% vs 21% vs 10%, respectively; nilotinib 400 mg vs imatinib, P <.0001; nilotinib 300 mg vs imatinib, P = .004). The safety and tolerability profiles of nilotinib and imatinib remained unchanged with longer follow-up.

Dasatinib

Response to dasatinib also was evaluated in 3 studies (**Table 3**).[14-16] Investigators for these studies concluded that dasatinib was an effective approach to managing CP-CML in the first-line setting, yielding high rates of CCyR and MMR. Adverse events were considered manageable.

A phase 2 study randomized patients with newly diagnosed CP-CML to 100 mg of dasatinib once daily or 50 mg of dasatinib twice daily in the first-line setting.[14] Median follow-up was 24 months, with 50 patients observed for at least 3 months. Of these 50 patients, 49 (98%) attained a CCyR and 41 (82%) attained an MMR. At 6 months, 94% of evaluable patients had attained CCyR. The treatment arms had similar rates of response. Investigators projected the EFS rate at 24 months would reach 88%. No significant differences were observed between the study arms in toxicity rates. Grade 3/4 hematologic toxicities included neutropenia (21%) and thrombocytopenia (10%). Nonhematologic toxicities were generally grade 1/2. Some patients required treatment interruptions and/or dose reductions, and the actual median dose at 12 months was 100 mg (range, 20 mg-100 mg).

The randomized, phase 3, multicenter DASISION (Dasatinib versus Imatinib Study in Treatment-Naïve CML-CP Patients) trial compared the efficacy and safety of dasatinib with imatinib, and its primary end point was the rate of confirmed CCyR at 12 months.[15] Patients with newly diagnosed CP-CML were assigned 1:1 to 100 mg of dasatinib once daily (n = 259) or 400 mg of imatinib daily (n = 260). At 12 months, the best cumulative MMR rate was significantly higher in the dasatinib arm than in the imatinib group (46% vs 28%, respectively; P <.0001) as was the best cumulative rate of CCyR (83% vs 72%, respectively; P <.001). Fewer patients on dasatinib progressed to accelerated phase or blast crisis compared with imatinib (1.9% vs 3.5%, respectively).

Grade 3/4 nonhematologic adverse events were uncommon in both treatment arms. Approximately 10% of patients treated with dasatinib experienced pleural effusions, but these were mostly grade 1/2. Rates of grade 3/4 anemia and thrombocytopenia were higher with dasatinib than with imatinib. In the dasatinib arm, 5% of patients discontinued because of drug-related adverse events compared with 4% of patients in the imatinib arm.

Table 2 Response Rates with First-Line Nilotinib

Phase	Patients, No.	Dose	CCyR, %	MMR, %
2	67	400 mg twice daily	93	81
2	73	400 mg twice daily	93	85
3	846[a]	300 mg (n = 282) 400 mg (n = 281)	80 78	44 43

CCyR indicates complete cytogenetic response; MMR, major molecular response.
[a]The remaining 283 patients received imatinib.
Sources: References 10-13.

Table 3 Response Rates with First-Line Dasatinib

Study	Patients, No.	CCyR, %	MMR, %	PFS, %	OS, %
MDACC	62	98	71	—	—
DASISION	259	78[a]	57	94.9 (at 18 mo)	96 (at 18 mo)
S0325	123	82	59	99 (at 12 mo)	100 (at 12 mo)

CCyR indicates complete cytogenetic response; MMR, major molecular response; OS, overall survival; PFS, progression-free survival.
[a]Confirmed CCyR.
Sources: References 14-16.

Similar results were reported at a median of 18 months of follow-up,[16] with a cumulative rate of CCyR of 85% in the dasatinib arm compared with 80% in the imatinib group. Cumulative rates of MMR were also significantly higher in the dasatinib group compared with the imatinib group (57% vs 41%, respectively; P = .0002). A greater proportion of patients in the dasatinib arm had CMR ≤0.0032% *BCR-ABL* on the International Scale compared with the imatinib arm (13% vs 7%, respectively) at any time. Longer follow-up demonstrated similar safety and tolerability profiles for dasatinib and imatinib.

The Southwest Oncology Group, the Eastern Cooperative Oncology Group, the Cancer and Leukemia Group B, the National Cancer Institute of Canada Clinical Trials Group collaborated on a phase 2 study comparing 100 mg of dasatinib daily (n = 123) with 400 mg of imatinib daily (n = 123) in patients with newly diagnosed CP-CML. Dasatinib was associated with deeper molecular responses than imatinib.[17] At 12-months' follow-up, patients in the dasatinib arm had achieved a median 3.3 log reduction in *BCR-ABL* transcript levels, which was significantly higher than the 2.8 log reduction seen with imatinib (P = .048). Rates of hematologic and cytogenetic responses and OS did not differ significantly between the treatment groups.

Bosutinib

The BELA (Bosutinib Efficacy and Safety in CML Trial), an international, multicenter, randomized, open-label phase 3 study, compared the novel TKI bosutinib (n = 250) with imatinib (n = 252) in the first-line setting.[18] A superior rate of CCyR at 12 months was the primary end point, with a superior MMR rate at 12 months as a secondary end point. For analysis purposes, nonevaluable patients at 12 months were categorized as nonresponders, and the study failed to meet its primary end point, demonstrating similar rates of CCyR in the bosutinib arm and the imatinib arm (70% vs 68%, respectively; P = .601). Limiting the analysis to evaluable patients indicated a significantly higher rate of CCyR with bosutinib compared with imatinib (78% vs 68%, respectively; P =.026). Bosutinib was also associated with a significantly higher MMR rate than imatinib in the intent-to-treat (39% vs 26%, respectively; P = .002) and the evaluable populations (43% vs 27%, respectively; P <.001). More follow-up is needed to determine whether patients' responses are durable and whether bosutinib is superior to imatinib.

Conclusion

Results of trials investigating second-generation TKIs in the first-line setting show that these agents provide faster response rates and deeper responses compared with imatinib. The newer TKIs are also associated with lower rates of progression to accelerated phase/blast crisis. Nilotinib and dasatinib (and possibly bosutinib, if approved) should join imatinib as acceptable first-line options for patients with newly diagnosed CP-CML. ●

References

1. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006;355:2408-2417.
2. Deininger M, O'Brien SG, Guilhot F, et al. International randomized study of interferon vs STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. *Blood (ASH Annual Meeting Abstracts)*. 2009;114:Abstract 1126.
3. Hochhaus A, Kantarjian HM, Baccarani M, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood*. 2007;109:2303-2309.
4. Hochhaus A, Baccarani M, Deininger M, et al. Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib. *Leukemia*. 2008;22:1200-1206.
5. Shah NP, Kantarjian HM, Kim DW, et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. *J Clin Oncol*. 2008;26:3204-3212.
6. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood*. 2007;110:3540-3546.
7. Bruemmendorf TH, Cervantes F, Kim D, et al. Bosutinib is safe and active in patients (pts) with chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to imatinib and other tyrosine kinase inhibitors. *J Clin Oncol*. 2008;26S:Abstract 7001.
8. Sprycel (dasatinib) [package insert]. Princeton, NJ: Bristol-Meyers Squibb Company; 2010.
9. Tasigna (nilotinib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2010.
10. Cortes JE, Jones D, O'Brien S, et al. Nilotinib as front-line therapy for patients with chronic myeloid leukemia in early chronic phase. *J Clin Oncol*. 2010;28:392-397.
11. Rosti G, Castagnetti F, Gugliotta G, et al. Excellent outcomes at 3 years with nilotinib 800 mg daily in early chronic phase, Ph+ chronic myeloid leukemia (CML): results of a phase 2 GIMEMA CML WP clinical trial. *Blood (ASH Annual Meeting Abstracts)*. 2010;116: Abstract 359.
12. Saglio G, Kim DW, Issaragrisil S, et al; for the ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362:2251-2259.
13. Hughes TP, Hochhaus A, Saglio G, et al. ENESTnd update: continued superiority of nilotinib versus imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP). Presented at: American Society of Hematology Annual Meeting and Exposition; December 4-7, 2010; Orlando, FL.
14. Cortes JE, Jones D, O'Brien S, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. *J Clin Oncol*. 2010;28:398-404.
15. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;362:2260-2270.
16. Shah N, Kantarjian H, Hochhaus A, et al. Dasatinib versus imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) in the DASISION trial: 18-month follow-up. *Blood (ASH Annual Meeting Abstracts)*. 2010; 21:Abstract 206.
17. Radich JP, Kopecky KJ, Kamel-Reid S, et al. A randomized phase II trial of dasatinib 100 mg vs imatinib 400 mg in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): the S0325 intergroup trial. *Blood (ASH Annual Meeting Abstracts)*. 2010;116: Abstract LBA-6.
18. Gambacorti-Passerini C, Kim DW, Kantarjian HM, et al. An ongoing phase 3 study of bosutinib (SKI-606) versus imatinib in patients with newly diagnosed chronic phase chronic myeloid leukemia. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:Abstract 208.

Getting You From A to V

VELCADE®
(bortezomib) FOR INJECTION

VELCADE Reimbursement Assistance Program

- Insurance Verification
- Coding and Billing Support
- Alternate Funding Searches
- Research Payer Policies
- Claim Appeals Support*
- Transportation Resources

VELCADE Reimbursement Assistance Program (VRAP) 1-866-VELCADE (835-2233), OPTION 2

Dedicated Case Managers are available 8:00 a.m. to 8:00 p.m. EST Monday through Friday

*The VELCADE Reimbursement Assistance Program does not file claims or appeal claims for callers, nor can it guarantee that you will be successful in obtaining reimbursement

Millennium Pharmaceuticals, Inc., Cambridge, MA 02139

Printed in USA V-10-0196 11/10

Emerging Agents and Regimens in the Management of Follicular Lymphomas

By Elizabeth Reist, PharmD
Department of Pharmacy, Roswell Park Cancer Institute, Buffalo, New York

Angie Elefante, PharmD, BCOP
Department of Pharmacy, Roswell Park Cancer Institute, Buffalo, New York

Francisco Hernandez-Ilizaliturri, MD
Assistant Professor of Medicine, Department of Medical Oncology; Assistant Professor of Immunology, Department of Immunology, Roswell Park Cancer Institute, Buffalo, New York

Follicular lymphoma (FL) is one of the most common subtypes of indolent non-Hodgkin lymphoma (NHL). Although FL is considered incurable with currently available therapy, the introduction of monoclonal antibodies has improved clinical outcomes for this group of patients. Ongoing research focuses on assisting practicing oncologists with selecting the proper therapeutic options for specific clinical scenarios. This article presents some of the most recent and novel approaches for treatment of FL, with regimens involving rituximab (Rituxan), bendamustine (Treanda), lenalidomide (Revlimid), and bortezomib (Velcade).

Rituximab Maintenance

This past January, the US Food and Drug Administration approved rituximab for maintenance therapy in patients with previously untreated FL who achieved a response to rituximab in combination with chemotherapy.[1] Updated results from the PRIMA (Primary Rituximab and Maintenance) trial (**Table 1**) showed sustained benefits from rituximab maintenance therapy in patients with FL who had high tumor burden (n = 1193). In the observational arm, 60.3% of patients achieved 3-year progression-free survival (PFS) compared with 78.6% of patients in the maintenance arm (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.44-0.68).[2,3] Similar to what was observed in rituximab maintenance clinical trials in the relapsed/refractory setting, improvements in PFS did not translate into improvement in overall survival (OS).[2,3]

For asymptomatic patients with nonbulky FL, many clinicians believe watchful waiting is superior to chemotherapy. As research on less toxic and effective therapies such as rituximab continues to emerge, clinicians are questioning the watchful waiting approach. For example, Ardeshna and colleagues reported results of a clinical trial comparing rituximab induction therapy followed by rituximab maintenance versus observation for nonbulky FL grades 1-3a (Table 1). Preliminary results are encouraging, with patients in the rituximab arm achieving a significant delay in the need to initiate new therapy compared with those in the watchful waiting arm (P <.001; 95% CI, 0.13-0.29).[4] Improvements in more clinically relevant end points, such as PFS and OS, have not yet been observed.

The benefit of rituximab maintenance in FL patients was further evaluated by Vidal and associates in a meta-analysis of clinical trials comparing rituximab maintenance with observation in previously untreated or relapsed/refractory FL. Results showed increased OS in the rituximab maintenance arm for relapsed/refractory FL (HR, 0.75; 95% CI, 0.57-0.91) but no significant change in OS for previously untreated patients (HR, 0.83; 95% CI, 0.56-1.23).[5] In the absence of a clear benefit in OS, clinicians must carefully weigh the benefits and risk for individual patients of starting rituximab maintenance in the first-line or relapsed/refractory setting.

As research on less toxic and effective therapies such as rituximab continues to emerge, clinicians are questioning the watchful waiting approach.

Rituximab in Combination with Lenalidomide

Several trials have evaluated the combination of rituximab and lenalidomide in FL patients. Ahmadi and colleagues treated rituximab-resistant relapsed/refractory indolent or mantle cell lymphoma patients with rituximab, lenalidomide, and dexamethasone (**Table 2**). Preliminary results showed an overall response rate (ORR) of 60% for the subset of 18 patients with FL, and 78% of all patients were progression-free at 12 months.[6] Another study evaluated the ability of lenalidomide to overcome the negative impact of low affinity *FCGR3* genotype on rituximab activity. Early analysis suggests that patients with the higher affinity *FCGR3* genotype (158V/V) appear to have significantly increased ORR and PFS compared with patients with the low-affinity *FCGR3* allele (158F) when treated with rituximab monotherapy.[7] Dutia and colleagues formally evaluated whether lenalidomide could improve rituximab activity in FL patients with *FCGR3-158V/F* or *FCGR3-158F/F* genotypes.

Patients with relapsed/refractory indolent lymphoma were treated with a combination of rituximab and lenalidomide. *FcγRIIIA* genotype was determined in DNA isolated from peripheral blood cells by polymerase chain reaction amplification followed by allele-specific restriction enzyme digestion. Preliminary results suggest an impressive ORR of 100% and median PFS of 14.85 months for patients with the *FCGR3-158V/F* polymorphism and 8.31 months for patients with the *FCGR3-158F/F* polymorphism. The subsets of patients with other polymorphisms of the *FCGR3* genotype were too small for researchers to draw any preliminary conclusions. Enrollment into the study continues, and final results might support using lenalidomide in combination with rituximab to treat relapsed/refractory lymphomas.[8]

Rituximab and lenalidomide were also tested in the first-line setting by Fowler and colleagues in a single-arm study that enrolled 30 patients with previously untreated NHL, including 17 patients with FL (Table 2).[9] The ORR was 86%; 79% of all patients and 94% of FL patients achieved a complete response (CR). Grade 3/4 adverse events consisted primarily of rash (6 patients), neutropenia (7 patients), and myalgia (4 patients). Other grade 3/4 adverse events included neuropathy, infection, fatigue, and thrombosis, each of which affected 1 patient. After a median follow-up period of 14.1 months, only 1 patient progressed. Based on these results, planned accrual was increased to 110 patients.

Rituximab in Combination with Bortezomib

Bortezomib plus rituximab has shown activity in FL patients. Preclinical data suggest rituximab and bortezomib interact biologically. Coiffier and asso-

Table 1 Rituximab Maintenance Studies

End Points by Study	Maintenance	Observation
PRIMA[2]	n = 505	n = 513
3-Year PFS, %	74.9	57.6
2-Year CR or uCR, No. (%)	361 (71.5)	268 (52.2)
Grade 3/4 AEs, No. (%)	121 (24)	84 (17)
Infections ≥grade 2, No. (%)	197 (39)	123 (24)
Ardeshna et al[4]	n = 192	n = 186
3-Year PFS, %	81	30
PR, %	36	6
PD, %	3	17
No change, %	74	11
3-Year OS, %	96	96
No new treatment at 3 years, %	91	48
Time to new treatment, mo	NR at 48	33
Serious AEs, No.	10	25

AE indicates adverse event; CR, complete response; NR, none reported; OS, overall survival;PD, progressive disease; PFS, progression-free survival; PR, partial response; uCR, unconfirmed complete response.

THANK YOU

Readers of *The Oncology Nurse*

Thank you for being a part of the Third Annual National Safe Handling Awareness Month and for encouraging best practices in preventing hazardous drug exposure.

If you did not have the opportunity to participate in the free Safe Handling Awareness Day CE webinar presented April 20, a recorded version is now available online.

To take advantage of this free webinar – and additional nursing CE programs offered compliments of Carmel Pharma, the maker of PhaSeal® – visit **www.carmelpharmausa.com/CE** or call 877-487-9250.

NATIONAL SAFE HANDLING awareness month

official sponsor Carmel Pharma

SW4 926

Protection is Prevention.

carmel.
Carmel Pharma

Table 2 Lenalidomide and Rituximab Trials

End Points by Study	Rituximab/Lenalidomide, %
Ahmadi et al (part II)[6]	N = 23; FL, n = 15
Overall ORR, %	60
FL-only ORR, %	57
1-Year PFS, %	78
Fowler et al[9]	N = 30; FL, n = 17
ORR	86
Overall CR/uCR, No. (%)	79
FL-only CR, No. (%)	94
PR, %	7
SD, %	14

CR indicates complete response; FL, follicular lymphoma; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease; uCR, unconfirmed complete response.

ciates presented the results of a phase 3 clinical trial evaluating the efficacy of bortezomib in combination with rituximab.[10] Relapsed rituximab-naïve or -sensitive FL patients were randomized to single-agent rituximab or the combination regimen. Preliminary results indicated that the doublet of rituximab and bortezomib resulted in a higher ORR than rituximab alone (63% vs 49%, respectively; *P* = .039). Patients receiving the combination were also more likely to experience CR than patients in the monotherapy arm (25% vs 18%, respectively; *P* = .035) and also demonstrated prolonged PFS (398 days vs 334 days, respectively; *P* <.001). At the time the data were presented, median OS had not been reached in either group. These findings suggest that bortezomib is potentially an active agent for patients with FL. Ongoing studies are seeking to better define the role of bortezomib in treating FL and to find ways to minimize the treatment-related toxicities observed when using this agent.

Rituximab in Combination with Bendamustine

The treatment of previously untreated FL continues to change. The incorporation of various chemotherapy agents focuses on improving clinical outcome and minimizing drug-related toxicities. A recent phase 3 clinical trial compared rituximab combined with a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) versus rituximab plus bendamustine for patients with grade 1/2 FL who required systemic chemotherapy (n = 549). Although the ORR was similar between the 2 treatment arms, the CR rate was higher in the group of patients receiving rituximab plus bendamustine than in the group of patients treated with rituximab-CHOP (40% vs 30%, respectively; *P* = .0323). In addition, median PFS was longer for patients treated with rituximab plus bendamustine than for those patients receiving rituximab-CHOP (54.8 vs 34.8 mo, respectively; *P* = .0002). Although these preliminary results are interesting, it is important to stress that only patients with grade 1/2 FL were included in this study. Symptomatic patients with grade 3a FL should be treated with rituximab-CHOP therapy.[11]

Conclusion

Results of recently completed and ongoing clinical studies are encouraging and suggest that several novel agents are someday likely to have a place in the management of untreated relapsed/refractory FL patients. The largest "obstacle" facing clinicians and researchers today is determining the best way to streamline evaluations of the large number of effective therapies and establishing the optimal use and sequencing of these agents. Overcoming these hurdles promises to improve the quantity and quality of life for FL patients today and in future generations. ●

References

1. US Food and Drug Administration. Rituximab 2011. February 2011. www.fda.gov/AboutFDA/CentersOffices/CDER/ucm241928.htm. Accessed March 6, 2011.

2. Salles GA, Seymour JF, Offner F. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet*. 2010;377:42-51.

3. Salles GA, Catalano J, Feugier P, et al. Updated results of the PRIMA study confirms the benefit of 2-years rituximab maintenance in follicular lymphoma patients responding to immunochemotherapy. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:Abstract 1788.

4. Ardeshna KR, Smith P, Qian W, et al. An intergroup randomised trial of rituximab versus a watch and wait strategy in patients with stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (grades 1, 2 and 3a). A preliminary analysis. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:Abstract 6.

5. Vidal L, Gafter-Gvili A, Salles G, et al. Rituximab maintenance for the treatment of patients with follicular lymphoma: systematic review and meta-analysis of randomized trials—2010 update. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:Abstract 1798.

6. Ahmadi T, Chong EA, Gordon A, et al. Phase II trial of lenalidomide-dexamethasone-rituximab in relapsed or refractory indolent B-cell or mantle cell lymphomas resistant to rituximab. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:Abstract 3962.

7. Taverna CJ, Bassi S, Hits F, et al. Rituximab maintenance treatment for a maximum of 5 years in follicular lymphoma: safety analysis of the randomized phase III trial SAKK 35/03. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:Abstract 1802.

8. Dutia M, DeRoock IB, Reed-Pease C, Tuscano J. Lenalidomide overcomes *FcgRIIIa*-mediated resistance to rituximab in patients with relapsed/refractory indolent non-Hodgkin's lymphoma (NHL): a correlative analysis of a phase 2 study. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:Abstract 3967.

9. Fowler NH, McLaughlin P, Hagemeister FB, et al. Complete response rates with lenalidomide plus rituximab for untreated indolent B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2010;28(15S):Abstract 8036.

10. Coiffier B, Osmanov E, Hong X, et al. A phase 3 trial comparing bortezomib plus rituximab with rituximab alone in patients with relapsed, rituximab-naive or -sensitive follicular lymphoma. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:Abstract 857.

11. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany). *Blood (ASH Annual Meeting Abstracts)*. 2009;114:Abstract 405.

Abstracts of Interest

52nd American Society of Hematology Annual Meeting & Exposition

Impaired Hydroxylation of 5-Methylcytosine in *TET2*-Mutated Myeloid Malignancies

Through the use of 2 assays (1 developed specifically for this study), researchers demonstrated for the first time that *TET2* mutations in predicted catalytic residues and other positions compromise *TET2* function in patients with various myeloid malignancies. Following in vitro study, researchers used methylation arrays in 62 of the study's 102 patients to analyze methylation patterns in patients with and without *TET2* mutations, finding that an associated methylation signature was skewed strongly toward hypomethylation compared with hypermethylation. The researchers concluded that their results suggest that *TET2* is involved in conversion of 5-methylcytosine to 5-hydroxymethylcytosine in DNA. *Jankowska A, et al. Abstract 1.*

Prophylactic Rituximab After ASCT Prevents Steroid-Requiring Chronic Graft-vs-Host Disease

In a phase 2 trial, rituximab at 3, 6, 9, and 12 months after allogeneic hematopoietic stem cell transplantation reduced the rate of steroid-requiring chronic graft-versus-host disease (GVHD) in patients in remission without active GVHD. At 1 year, researchers found that the cumulative incidence of chronic GVHD requiring corticosteroids was just more than half of historical levels at their institution. They also identified very low numbers of CD19+ B-cells during the first year after transplant, and that patients without chronic GVHD trended toward enhanced B-cell recovery. *BRAF* levels also trended higher in those without chronic GVHD as well as in those with chronic GVHD who did not require corticosteroid treatment. The researchers concluded that these findings predict that this therapy could free patients from or reduce the severity of chronic GVHD, but cautioned a randomized trial should confirm their findings. *Cutler C, et al. Abstract 214.*

Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Hodgkin Lymphoma

Brentuximab vedotin was observed to produce tumor shrinkage in 94% of 102 patients with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplant. In a phase 2, single-arm study, this novel antibody–drug conjugate targeted to CD30 also produced an objective response rate of 75%, and a B symptom resolution rate of 83%. The agent was found to have a manageable adverse event profile. Because of the poor prognosis of these patients, the researchers concluded that their results encourage further study of brentuximab vedotin. *Chen R, et al. Abstract 283.*

Crizotinib in Advanced, Chemoresistant *ALK*-Positive Lymphoma Patients

This report on 2 chemoresistant patients with *ALK*-positive anaplastic large cell lymphoma suggests that this disease is sensitive to ALK inhibition, in these cases through treatment with crizotinib. This agent, a competitive small-molecule inhibitor of the ALK and c-Met/HGF receptor tyrosine kinases with cellular IC50 values in *NPM-ALK* expressing cells comprised between 24 and 60 nM, achieved regression of superficial adenopathies in both patients with 8 days of treatment. Patient 1 achieved complete response, which is ongoing at 6 months. Patient 2 continues complete response at 5 months of treatment. *Gambacorti-Passerini CB, et al. Abstract 2877.*●

GET READY...
IT'S COMING SOON

ABIRATERONE ACETATE

Centocor Ortho Biotech Products, L.P.

Pancreatic Neuroendocrine Cancer

By Dori L. Klemanski, MS, MS, RN, CNP
The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, Ohio

Pancreatic neuroendocrine tumor (PNET) refers to several tumor types located in the pancreas. These tumors are classified as functional or nonfunctional depending on production and secretion of bioactive hormones. Functional PNETs cause clinical symptoms associated with their tumor classification. Some examples include gastrinomas, which are associated with gastrointestinal ulcers and diarrhea; glucagonomas, which are associated with diabetes, skin rash, and diarrhea; and vasoactive intestinal polypeptide tumors, which may produce extreme watery diarrhea, abdominal pain, and flushing.[1,2] Because nonfunctional PNETs do not produce bioactive hormones and do not cause clinical symptoms, these tumor types (eg, pancreatic polypeptidoma) are diagnosed at a more advanced stage, often presenting with symptoms related to mass effect or metastasis (eg, abdominal pain, obstructive jaundice, or weight loss).[3,4] PNET is relatively rare, with an incidence of <1 in 100,000.[5] Most diagnoses occur in patients aged >40 years, with equal gender distribution.[5] Causation of PNET is sporadic but associated less commonly with genetic syndromes (eg, multiple endocrine neoplasia type 1 or von Hippel-Lindau).[1]

The malignant potential for PNET is determined by clinical symptoms and presence of metastatic disease rather than a specific immunohistochemistry profile. In addition, neuroendocrine tumors (NETs) are classified according to their degree of pathologic differentiation. Well-differentiated NETs typically include low and intermediate grades, whereas poorly differentiated NETs are considered biologically aggressive.[6] Historically, staging of PNETs used the classification system of the World Health Organization, in which PNETs were considered (1) well-differentiated of benign or uncertain behavior, (2) well-differentiated with low malignant potential, or (3) poorly differentiated with high-grade malignant potential based on the proliferation index of the Ki67 marker.[6,7] The European Neuroendocrine Tumor Society (ENETS) developed a system of grading that uses both the Ki67 proliferation index and the number of mitoses per high-power field.[1,6] More recently, ENETS and the American Joint Committee on Cancer each proposed a TNM staging system.[2,3,7]

Treatment of PNET

Treatment of PNET is dependent on functional status as well as the absence or presence of metastatic disease. Optimal therapy for PNET includes medications (eg, somatostatin analogs, proton pump inhibitors) to control clinical symptoms followed by surgical resection, such as pancreaticoduodenectomy (also known as the Whipple procedure) or distal pancreatectomy, of the primary tumor.[2,3,8,9] Surgical resection of hepatic metastases from PNET has a low morbidity and mortality rate[10,11] and is recognized as the recommended treatment modality if >90% of a patient's tumor burden is resectable.[2,3]

Metastatic disease is not always amenable to surgical resection and requires alternative treatments, such as regional hepatic therapy (eg, radiofrequency ablation, arterial embolization, chemoembolization, and radioembolization) or peptide receptor radionucleotide therapy, which is currently only used outside the United States.[2,3] These treatments are not curative but may be used for symptom palliation or disease control.[12-16] Orthotopic liver transplantation has been attempted in a small subset of patients, but it has not received empirical support.[2,3,17-21]

> Studies have shown that everolimus, sunitinib, and bevacizumab effectively prolong PFS, generating optimism that these and other new therapies might alter the disease trajectory for patients with PNET.

Effectiveness of Chemotherapy Limited

An additional treatment modality is the use of systemic chemotherapeutics. Traditionally effective chemotherapy combinations for well-differentiated PNET have included streptozocin combined with doxorubicin, fluorouracil, or both.[1,3,22-25] Cisplatin and etoposide have been effective for short durations in poorly differentiated PNET.[26-28] Recent clinical trials have indicated the potential use of temozolomide (Temodar), an alkylating agent that causes apoptosis through damage to the tumor's DNA, alone or in combination with capecitabine (Xeloda) or thalidomide (Thalomid).[29-31] Patients with high expression levels of the DNA repair enzyme O6-methylguanine DNA-methyltransferase demonstrate virtually no response to temozolomide.[32]

Biotherapies Show Promise

Newer biologic agents are being used to treat PNET. Somatostatin analogs (eg, octreotide and lanreotide), which have long been used to mitigate the effects of functional PNETs, have recently been found to increase the effectiveness of octreotide acetate injection long-acting release (Sandostatin LAR) in patients with minimal hepatic tumor burden and delay disease progression. Preliminary data from the PROMID study revealed a median progression-free survival (PFS) of 14 months in patients who received octreotide LAR compared with 6 months for patients in the placebo group. Final results from the phase 3 trial, which aims to determine the effect of lanreotide autogel on nonfunctional PNETs, have not been published [clinicaltrials.gov identifier: NCT0035496].

Molecular genetic investigation into PNET suggests that the deactivation of tumor suppressor genes such as *TSC2* and *PTEN* activates the mammalian target of rapamycin (mTOR) pathway.[33] This pathway promotes angiogenesis and cell growth and proliferation in PNETs.[1,9,33] Two trials, RADIANT (RAD001 in Advanced Neuroendocrine Tumors)-1 and RADIANT-3, demonstrated that 10 mg daily of the mTOR inhibitor everolimus (Afinitor) might be an effective treatment option for patients with advanced PNET.[34,35] In the phase 2 RADIANT-1 trial, patients who received everolimus plus octreotide LAR demonstrated PFS of 16.7 months compared with 9.7 months for those given only everolimus. Clinical benefit, defined as stable disease and partial remission, was observed in both arms of the study.[34] The phase 3 RADIANT-3 trial reported longer PFS with everolimus than with placebo (11 vs 4.6 months, respectively) and minimal treatment-related adverse effects.[35]

Another promising therapy is sunitinib malate, a tyrosine kinase inhibitor that inhibits vascular endothelial growth factor (VEGF) and platelet-derived growth factor. One phase 3 trial demonstrated a median PFS of 11.4 months in patients with well-differentiated PNET who received a 37.5-mg daily dose of sunitinib compared with a median PFS of 5.5 months for patients who took placebo.[36] Additional trials investigating sunitinib in poorly differentiated NETs are planned.[37]

Bevacizumab (Avastin), a monoclonal antibody targeting VEGF receptors, has also been used to treat neuroendocrine cancers in clinical trials. Patients on stable doses of octreotide LAR were given bevacizumab or pegylated interferon-α-2b separately for 18 weeks, with treatment discontinued earlier if disease progression was observed.[38] After the initial trial phase, patients were started on a combination of bevacizumab and pegylated interferon-α-2b. At 18 weeks, the bevacizumab monotherapy arm demonstrated a higher rate of PFS than the pegylated interferon-α-2b group (95% vs 68%, respectively). As a result of these findings, an ongoing phase 2 trial is actively recruiting patients with locally advanced or metastatic PNET to study the effects of using a combination of everolimus and octreotide with or without bevacizumab [clinicaltrials.gov identifier: NCT01229943]. Several other phase 2 clinical trials in progress are evaluating the effects of bevacizumab combined with many of the therapies previously discussed.[39]

Conclusion

PNET is a rare tumor type for which surgical resection combined with cytotoxic chemotherapy has been the mainstay of treatment. Traditionally, the purpose of using medical therapies was to control clinical symptoms associated with functional PNETs. Chemotherapeutic agents such as streptozocin, cisplatin, and etoposide have been found to have minimal impact on disease survival, and recent clinical trials have investigated the efficacy and safety of biotherapies. Studies have shown that everolimus, sunitinib, and bevacizumab effectively prolong PFS, generating optimism that these and other new therapies might alter the disease trajectory for patients with PNET. ●

References

1. Öberg K. Pancreatic endocrine tumors. *Semin Oncol*. 2010;37:594-561.
2. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors*. V.2.2010. www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed April 7, 2011.
3. Kulke MH, Anthony LB, Bushnell DL, et al; for the North American Neuroendocrine Tumor Society. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas*. 2010;39:735-752.
4. Elaraj D, Sturgeon C. Neuroendocrine tumors of the pancreas. In: *ACS Surgery: Principles and Practice*. Philadelphia, PA: BC Decker, Inc; 2010. http://

129.49.170.167/Volumes/ACSCD+March+2010/ACSCD/pdf/ACS0540.pdf. Accessed April 7, 2011.
5. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol*. 2008;19:1727-1733.
6. International Agency for Research on Cancer. *WHO Classification of Tumours of the Digestive System*. 2000. www.iarc.fr/en/publications/pdfs-online/pat-gen/bb2/BB2.pdf. Accessed April 7, 2011.
7. Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas*. 2010;39:707-712.
8. Franko J, Feng W, Yip L, et al. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. *J Gastrointes Surg*. 2010;14:541-548.
9. Fazio N, Cinieri S, Lorizzo K, et al. Biological targeted therapies in patients with advanced enteropancreatic neuroendocrine carcinomas. *Cancer Treat Rev*. 2010;36(suppl 3):S87-S94.
10. Hemming AW, Magliocca JF, Fujita S, et al. Combined resection of liver and pancreas for malignancy. *J Am Coll Surg*. 2010;210:808-816.
11. Glazer ES, Tseng JF, Al-Refaie W, et al. Long-term survival after surgical management of neuroendocrine hepatic metastases. *HPB (Oxford)*. 2010;12:427-433.
12. Gamblin TC, Christians K, Pappas SG. Radiofrequency ablation of neuroendocrine hepatic metastasis. *Surg Oncol Clin N Am*. 2011;20:273-279.
13. Akyildiz HY, Mitchell J, Milas M, et al. Laparoscopic radiofrequency thermal ablation of neuroendocrine hepatic metastases: a long-term follow-up. *Surgery*. 2010;148:1288-1293.
14. King J, Quinn R, Glenn DM, et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. *Cancer*. 2008;113:921-929.
15. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin ^{90}Y-microspheres: early results in 148 patients. *Am J Clin Oncol*. 2008;31:271-279.
16. Varker K, Martin EW, Klemanski D, et al. Repeat transarterial chemoembolization (TACE) for progressive hepatic carcinoid metastases provides results similar to first TACE. *J Gastrointest Surg*. 2007;11:1680-1685.
17. Pascher A, Klupp J, Neuhaus P. Endocrine tumours of the gastrointestinal tract. Transplantation in the management of metastatic endocrine tumours. *Best Pract Res Clin Gastroenterol*. 2005;19:637-648.
18. Le Treut YP, Grégoire E, Belghiti J, et al. Predictors of long-term survival after liver transplantation for metastatic endocrine tumors: an 85-case French multicentric report. *Am J Transplant*. 2008;8:1205-1213.
19. Olausson M, Friman S, Herlenius G, et al. Orthotopic liver or multivisceral transplantation as treatment of metastatic neuroendocrine tumors. *Liver Transpl*. 2007;13:327-333.
20. Grégoire E, Le Treut YP. Liver transplantation for primary or secondary endocrine tumors. *Transplant Int*. 2010;23:704-711.
21. Stauffer JA, Steers JL, Bonatti H, etal. Liver transplantation and pancreatic resection: a single-center experience and a review of the literature. *Liver Transpl*. 2009;15:1728-1737.
22. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1980;303:1189-1194.
23. Moertel CG, Lefkopoulo M, Lipsitz S, et al. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1992;326:519-523.
24. Kouvaraki MA, Ajani JA, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol*. 2004;22:4762-4771.
25. Turner NC, Strauss SJ, Sarker D, et al. Chemotherapy with 5-fluorouracil, cisplatin and streptozocin for neuroendocrine tumours. *Br J Cancer*. 2010;102:1106-1112.
26. Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer*. 1991;68:227-232.
27. Mitry E, Baudin E, Ducreux M, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer*. 1999;81:1351-1355.
28. Fjallskog ML, Granberg DP, Welin SL, et al. Treatment with cisplatin and etoposide in patients with cisplatin and etoposide in patients with neuroendocrine tumors. *Cancer*. 2001;92:1101-1107.
29. Ekeblad S, Sundin A, Janson ET, et al. Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. *Clin Cancer Res*. 2007;13:2986-2991.
30. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer*. 2011;117:268-275.
31. Kulke MH, Stuart K, Enzinger PC, et al. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. *J Clin Oncol*. 2006;24:401-406.
32. Kulke MH, Hornick JL, Frauenhoffer C, et al. O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. *Clin Cancer Res*. 2009;15:338-345.
33. Missiaglia E, Dalai I, Barbi S, et al. Pancreatic endocrine tumors: expression profiling evidences a role for AKT-mTOR pathway. *J Clin Oncol*. 2010;28:245-255.
34. Yao JC, Phan AT, Chang DZ, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol*. 2008;26:4311-4318.
35. Yao JC, Shah MH, Ito T, et al; for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:514-523.
36. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:501-513.
37. Faivre S, Sablin MP, Dreyer C, Raymond E. Novel anticancer agents in clinical trials for well-differentiated neuroendocrine tumors. *Endocrinol Metab Clin North Am*. 2010;39:811-826.
38. Yao JC, Phan A, Hoff PM, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol*. 2008;26:1316-1323.
39. Raymond E, Hobday T, Castellano D, et al. Therapy innovations: tyrosine kinase inhibitors for the treatment of pancreatic neuroendocrine tumors. *Cancer Metastasis Rev*. 2011;30(suppl 1):19-26.

Recent Advances in the Management of Advanced Kidney Cancer

By Guru Sonpavde, MD
Texas Oncology Cancer Center, Houston; Michael E. DeBakey Veterans Affairs Medical Center; Baylor College of Medicine, Houston, Texas

C. Lance Cowey, MD
Michael E. DeBakey Veterans Affairs Medical Center; Baylor College of Medicine, Houston, Texas

Thomas E. Hutson, DO, PharmD
Baylor Sammons Cancer Center, Dallas, Texas

Guru Sonpavde, MD

C. Lance Cowey, MD

Thomas E. Hutson, DO, PharmD

Clear cell (CC)-renal cell carcinoma (RCC), the predominant histologic type of RCC, is highly dependent on angiogenesis, via the vascular endothelial growth factor (VEGF) pathway.[1] The mammalian target of rapamycin (mTOR) pathway also appears to play a role in VEGF production, as well as directly promote tumor cell growth.

First-Line Management

Sunitinib (Sutent), a multitargeted oral tyrosine kinase inhibitor (TKI) targeting VEGF receptors and multiple other molecular targets, yielded a greater median overall survival (OS) than interferon (IFN)-α in a landmark phase 3 trial (26.4 vs 21.8 mo, respectively; $P = .051$).[2] After censoring patients' crossing over from IFN-α to sunitinib, the difference was statistically significant. Median progression-free survival (PFS) was 11 months for sunitinib compared with 5 months for IFN-α ($P < .001$); objective response rate (ORR) was 47% for sunitinib compared with 12% for IFN-α ($P < .001$). The most common sunitinib-related grade 3 adverse events included hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%). All 3 Memorial Sloan-Kettering Cancer Center clinical risk groups (good, intermediate, and poor) appeared to benefit, although ~93% of patients had good- or intermediate-risk disease. In a presentation at the Genitourinary Cancers Symposium this past February, the renal EFFECT trial demonstrated that the conventional regimen of 50-mg daily 4 weeks on treatment/2 weeks off treatment was statistically superior to 37.5 mg daily given continuously on the composite end point of death, progression, and patient-reported outcomes.[3]

A phase 3 placebo-controlled study of pazopanib (Votrient), a VEGF receptor TKI, enrolled 435 patients with CC-RCC who were treatment-naïve or had received previous cytokine-based therapy.[4] Median PFS was 9.2 months in the pazopanib group compared with 4.2 months in the placebo group ($P < .0001$). When analyzed according to prior therapy, median PFS for treatment-naïve patients was 11.1 months compared with 2.8 months for placebo ($P < .0001$); and for cytokine-treated patients, median PFS was 7.4 months versus 4.3 months for placebo ($P < .001$). The ORR was 30% for the pazopanib arm and 3% for the placebo group. Common pazopanib-related adverse events included diarrhea, hypertension, hair depigmentation, nausea, anorexia, and vomiting. Elevated levels of alanine aminotransferase and aspartate aminotransferase were noteworthy laboratory abnormalities, and these were occasionally severe. Results from the completed phase 3 COMPARZ trial comparing pazopanib with sunitinib are eagerly awaited.

The AVOREN (Avastin and Roferon in Renal Cell Carcinoma) trial randomized 649 patients with CC-RCC to first-line IFN-α-2a plus placebo or IFN-α-2a plus bevacizumab (Avastin), a monoclonal antibody against VEGF, which was administered intravenously every 2 weeks.[5] Adding bevacizumab to IFN-α-2a significantly prolonged median PFS (10.2 vs 5.4 mo, respectively; $P < .0001$) and ORR (30.6% vs 12.4%, respectively; $P < .0001$). A trend toward improved OS was also observed with the addition of bevacizumab ($P = .3360$), but the availability of other active agents confounded the survival analysis. The contribution of IFN-α-2a to the efficacy of the combination is unclear, and the poor-risk subgroup might not benefit from the doublet. A similar Cancer and Leukemia Group B trial demonstrated a comparable extension in median PFS with the combination of bevacizumab and IFN.[6]

Management Algorithm for Advanced Clear Cell-Renal Cell Carcinoma

Treatment Setting	Therapy
Treatment-naïve, good-risk, intermediate-risk	Clinical trial Bevacizumab plus IFN-α-2a[5] HD IL-2[8,9] Pazopanib[4] Sunitinib[2]
Treatment-naïve, poor-risk	Clinical trial Temsirolimus[7]
Cytokine refractory	Clinical trial Pazopanib[4] Sorafenib[10]
Prior VEGF inhibitor	Clinical trial Axitinib (evidence emerging) Everolimus[13]
Prior mTOR inhibitor	Clinical trial

HD IL-2 indicates high-dose interleukin-2; IFN-α-2a, interferon-α-2a; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

Temsirolimus, an mTOR inhibitor administered via weekly intravenous infusion, prolonged median OS compared with IFN-α (10.9 vs 7.3 mo, respectively; $P = .008$) in patients with poor-risk RCC, defined as ≥3 poor risk factors by Memorial Sloan-Kettering risk classification.[7] Thus, the standard of care has changed relatively rapidly with the advent of these targeted biologic agents, which have generally supplanted cytokines as conventional therapy. High-dose (HD) interleukin (IL)-2 may retain a role in selected patients (good-risk CC-RCC, alveolar features and the absence of papillary or granular features, high *CAIX* expression, genomic signatures) with good performance status as a result of an ~7% durable complete remission and apparent cures.[8,9] The severe cardiovascular, pulmonary, and renal toxicities of HD IL-2 render it as an option only for relatively young patients without significant comorbidities. Unfortunately, the recent prospective SELECT (Selenium and Vitamin E Cancer Prevention Trial) was unable to validate tumor *CAIX* expression as a predictive factor for response.

To summarize, sunitinib, pazopanib, or bevacizumab-IFN are preferred first-line agents for good- and intermediate-risk CC-RCC, whereas temsirolimus is preferred for patients with poor-risk disease. HD IL-2 retains its role in a well-selected, good-risk subset. Phase 3 trials under way include tivozanib versus sorafenib (Nexavar) and axitinib versus sorafenib. Other ongoing studies are evaluating adjuvant therapy with VEGF and mTOR inhibitors.

Salvage Therapy

For salvage therapy after relapsed/refractory cytokine-based regimens, the evidence supports using pazopanib or sorafenib, although the other approved agents also demonstrate activity in this setting.[10,11] The TARGET (Treatment Approaches in Renal Cancer Global

Your goal is to give him a cancer treatment that's right for him.

When you choose a Lilly Oncology product, our goal is to make sure he has access to it.

PatientOne
1-866-4PatOne

Medication Access Support.

A cancer diagnosis presents many challenges for your patients—and for those who love and care for them. That's why ***PatientOne*** offers reimbursement support and financial assistance for eligible patients who are prescribed Lilly Oncology products. It's the kind of support that can make access to medication easier—and make a difference in the lives of your patients.

To learn more, visit **www.LillyPatientOne.com** or call **1-866-4PatOne (1-866-472-8663)**.

Patient Assistance | **Insurance Expertise** | **Claims Appeals**

Oncology Making science personal.

Lilly

Evaluation Trial) trial was limited to good- and intermediate-risk patients and demonstrated superior median PFS for sorafenib compared with placebo (5.5 vs 2.8 mo, respectively; $P < .000001$).[10] The 13.5% improvement in median OS seen with sorafenib over pazopanib was not significant (17.8 vs 15.2 mo, respectively; hazard ratio [HR], 0.88; $P = .146$). Secondary analysis censoring crossover data showed a significant OS benefit with sorafenib (HR, 0.78; $P = .0287$). Diarrhea, rash, fatigue, and hand-foot skin reactions were the most common adverse events associated with sorafenib; hypertension and cardiac ischemia were rare. A smaller randomized phase 2 trial in the first-line setting failed to demonstrate improved outcomes with sorafenib versus IFN-α.[12] Given the lack of robust frontline data, sorafenib increasingly is being reserved for salvage therapy following other agents.

Everolimus (Afinitor), an orally administered mTOR inhibitor, was recently approved in RCC based on findings from the RECORD (Renal Cell Cancer Treatment with Oral RAD001 Given Daily)-1 trial, which showed improved outcomes in patients previously treated with sunitinib and/or sorafenib.[13] Everolimus was associated with significant improvement in median PFS compared with placebo (4.0-1.9 mo; HR, 0.30; $P <.001$). The probability of 6-month PFS was 26% with everolimus versus 2% with placebo, though the RECIST response rate with everolimus was only 1%. Stomatitis, rash, and fatigue were the most common adverse events, but were mostly mild or moderate in severity. Observed class-specific toxicities consisted of interstitial pneumonitis, hyperlipidemia, and hyperglycemia.

For therapy following previous treatment with mTOR inhibitors, no definitive data exist demonstrating improved outcomes with currently available agents. There is evidence of incomplete cross-resistance between the newly approved agents discussed, with modest activity when switching agents.[14,15] Lack of complete cross-resistance occurs when sequentially administering the different antiangiogenic agents; for example, sorafenib → sunitinib, sunitinib → sorafenib, bevacizumab → sunitinib and sorafenib → axitinib.[14-17] A phase 3 trial comparing second-line sorafenib with axitinib in patients treated previously with sunitinib reported prolonged PFS with axitinib, but the data have not yet been presented formally. An ongoing phase 3 trial is comparing sorafenib with temsirolimus following previous treatment with sunitinib.

Prognostic and Predictive Factors

Known prognostic factors associated with outcomes in advanced RCC treated with IFN-α include performance status, disease-free interval, number of metastatic sites, hemoglobin, calcium, and lactate dehydrogenase (LDH).[18] Recent analysis from trials with anti-VEGF agents shows these factors continue to be of major importance, although notably neutrophilia and thrombocytosis replaced LDH in the newly created (2009) model.[19] Future prognostic models will attempt to incorporate molecular markers with clinical variables to refine prognosis prediction in patients with metastatic CC-RCC treated with novel antiangiogenic agents.

Conclusion

Despite providing important incremental improvements in outcomes, the novel antiangiogenic agents have not yielded complete responses or cures and are associated with significant toxicities, implying there is ample room for improvement and the need for continued commitment to clinical trials. Biomarkers potentially predictive of response are emerging and need to be incorporated into the clinical development of agents. Furthermore, the evaluation of adjuvant therapy using VEGF and mTOR inhibitors is ongoing after surgery. ●

Disclosures

Guru Sonpavde receives research support from Pfizer, Bristol-Myers Squibb, Cephalon, Celgene, and Bellicum and is on the speakers' bureau for GlaxoSmithKline, Novartis, and sanofi-aventis. Thomas E. Hutson receives research support from Bayer/Onyx, Pfizer, GlaxoSmithKline; is an advisory board/consultant for Bayer/Onyx, Pfizer, Dendreon, and sanofi-aventis; and is on the speakers' bureau for Bayer/Onyx, Pfizer, Amgen, sanofi-aventis, Novartis, and Genentech. Lance Cowey has nothing to disclose.

References

1. Erber R, Thurnher A, Katsen AD, et al. Combined inhibition of VEGF and PDGF signaling enforces tumor vessel regression by interfering with pericyte-mediated endothelial cell survival mechanisms. *FASEB J.* 2004;18:338-340.
2. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2009;27:3584-3590.
3. Motzer RJ, Hutson TE, Olsen MR, et al. Randomised phase II multicenter study of the efficacy and safety of sunitinib on the 4/2 versus continuous dosing schedule as first-line therapy of metastatic renal cell carcinoma (Renal EFFECT Trial). *J Clin Oncol.* 2011;29(suppl 7):LBA308.
4. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol.* 2010;28:1061-1068.
5. Escudier B, Bellmunt J, Négrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol.* 2010;28:2144-2150.
6. Rini BI, Halabi S, Rosenberg JE et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol.* 2008;26:5422-5428.
7. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007;356:2271-2281.
8. Fyfe G, Fisher RI, Rosenberg SA, et al. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol.* 1995;13:688-696.
9. McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2005;23:133-141.
10. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III Treatment Approaches in Renal Cancer Global Evaluation Trial. *J Clin Oncol.* 2009;27:3312-3318.
11. Hutson TE, Davis ID, Machiels JP, et al. Pazopanib (GW786034) is active in metastatic renal cell carcinoma (RCC): interim results of a phase II randomized discontinuation trial (RDT). *J Clin Oncol.* 2007; 25(18S):Abstract 5031.
12. Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon alfa-2a in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2009;27:1280-1289.
13. Motzer RJ, Escudier B, Oudard S, et al; for the RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet.* 2008;372:449-456.
14. Tamaskar I, Garcia JA, Elson P, et al. Antitumor effects of sunitinib or sorafenib in patients with metastatic renal cell carcinoma who received prior antiangiogenic therapy. *J Urol.* 2008;179:81-86.
15. Sablin MP, Negrier S, Ravaud A, et al. Sequential sorafenib and sunitinib for renal cell carcinoma. *J Urol.* 2009;182:29-34.
16. Rini BI, Michaelson MD, Rosenberg JE, et al. Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma. *J Clin Oncol.* 2008;26:3743-3748.
17. Rini BI, Wilding G, Hudes G, et al. Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. *J Clin Oncol.* 2009;27:4462-4468.
18. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol.* 2002;20:289-296.
19. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol.* 2009;27:5794-5799.

Developments in the Management of Ovarian Cancer

By Maurie Markman, MD
Cancer Treatment Centers of America, Eastern Regional Medical Center, Philadelphia, Pennsylvania

Over the past year, data regarding 2 specific ovarian cancer management strategies have generated considerable interest within the clinical gynecologic cancer community among patients, clinicians, and researchers. One strategy involves the use of bevacizumab (Avastin), and the other approach centers on poly(ADP-ribose) polymerase (PARP) inhibitors.

Bevacizumab

Preliminary results from 2 eagerly awaited phase 3 randomized studies examining a potential role for the antiangiogenic agent bevacizumab in the primary management of advanced ovarian cancer were presented at separate international cancer meetings (**Table**).[1,2] The first study was presented at the 2010 annual meeting of the American Society of Clinical Oncology. Investigators with the Gynecologic Oncology Group (GOG) sought to assess the utility of this drug combined with standard cytotoxic agents as an initial therapeutic strategy or as part of an initial strategy and then continued as maintenance therapy. Patients were randomized to 1 of 3 arms: standard chemotherapy with carboplatin and paclitaxel (the control arm); initial therapy with bevacizumab, carboplatin, and paclitaxel but no maintenance therapy; and initial therapy with bevacizumab plus the same 2 chemotherapy agents followed by 16 cycles of bevacizumab alone as a maintenance strategy.[1] The administration of bevacizumab with carboplatin/paclitaxel followed by bevacizumab monotherapy for 12 months of maintenance therapy following chemotherapy discontinuation resulted in statistically significant improvement in

One strategy involves the use of bevacizumab, and the other approach centers on poly(ADP-ribose) polymerase (PARP) inhibitors.

WISH NO. 537

"To never have to face cancer again."

Kathy Gram
Millennium Employee
& Cancer Survivor

THE PROMISE OF 1000 ORIGAMI CRANES

The ancient Japanese tradition of senbazuru promises that anyone who folds 1000 origami cranes will be granted a wish, such as long life or recovery from illness — at Millennium, our wish is to cure cancer.

We're committed to patients and strive to make a difference in their lives. 1000 Cranes of Hope is an online monument that contains the collective wishes of patients, caregivers, healthcare providers and our employees who all stand together in the fight against cancer.

Add your wish to create a new crane — and make a difference. For each crane created, Millennium will make a donation to benefit professional and charitable cancer organizations.

1000 CRANES™ OF HOPE

Visit **1000cranesofhope.com**
to add your wish to the flock.

Sponsored by Millennium: The Takeda Oncology Company

Table Phase 3 Trials Examining Bevacizumab in Advanced Ovarian Cancer

	PFS, mo (median)	OS, % (1 year)	OS, mo (median)
Gynecologic Oncology Group Trial[1]			
Upfront carboplatin/paclitaxel (control arm)	10.3	90.6	39.3
Upfront carboplatin/paclitaxel + bevacizumab (no maintenance)	11.2 HR, 0.098	90.4	38.7
Upfront carboplatin/paclitaxel + bevacizumab followed by maintenance with single-agent bevacizumab	14.1 HR, 0.717; *P* <.0001	91.3	39.7
ICON 7 Trial[2]			
Upfront carboplatin/paclitaxel (control arm)	17.3	93	NR
Upfront carboplatin/paclitaxel + bevacizumab followed by maintenance with single-agent bevacizumab	19.0 HR, 0.81; *P* = .0041	95	NR

HR, hazard ratio; NR, not reported; OS, overall survival; PFS, progression-free survival.

progression-free survival (PFS) compared with chemotherapy alone.

Considering this provocative outcome, it was somewhat surprising to find that patients in this trial randomized to treatment with chemotherapy plus bevacizumab who discontinued the antiangiogenic drug after completing chemotherapy experienced no improvement in PFS compared with patients in the control arm. At the time these data were presented, final information on overall survival (OS) was not available, but preliminary analyses of the median OS and the 1-year OS rate suggested no differences among the 3 study arms.

Data from ICON 7, the second frontline bevacizumab ovarian cancer study, were reported by an international team of investigators from the European Organisation for Research and Treatment of Cancer (EORTC) at the 35th European Society of Medical Oncology Congress in 2010. Patients were randomized to a control arm of carboplatin plus paclitaxel or an investigational regimen of the 2 cytotoxic agents plus bevacizumab.[2] In this study, bevacizumab was administered concurrently with chemotherapy and as a single-agent maintenance strategy following discontinuation of chemotherapy. Unlike the study discussed previously, ICON 7 did not include an arm of patients who received only the initial treatment regimen of bevacizumab, carboplatin, and paclitaxel, without any maintenance therapy.

Similar to the data reported from GOG, this study revealed a statistically significant improvement in PFS associated with adding bevacizumab to the cytotoxic regimen. At the time of this preliminary report, no statistically significant difference in OS was observed between the study arms.

It is important to note several major distinctions between the protocols for these 2 studies. The GOG trial was placebo-controlled, whereas the EORTC study made no attempt to conceal from participants or investigators which patients were receiving the antiangiogenic drug. It is reasonable to question, however, whether blinding in the GOG study was effective considering the frequency with which bevacizumab's well-recognized adverse effect of significant hypertension was observed.

The GOG trial used a 15-mg/kg dose of bevacizumab in the initial chemotherapy regimen and in the maintenance phase, whereas the EORTC trial used a 7.5-mg/kg dose of bevacizumab throughout the study. It remains to be determined whether this difference in drug dose, associated with differences in treatment cost, will affect the ultimate outcome of therapy.

> [Icon 7] revealed a statistically significant improvement in PFS associated with adding bevacizumab to the cytotoxic regimen.

On the question of OS, it is conceivable that the studies will ultimately reach different conclusions, potentially because of the general—but by no means universal—availability of bevacizumab in the United States as a single-agent treatment for platinum-resistant ovarian cancer. Third parties have provided financial coverage for bevacizumab use in this country based on data reported from several well-designed and well-conducted phase 2 trials. These studies have demonstrated that the overall clinical activity of single-agent bevacizumab is comparable to the activity seen with a number of other drugs routinely employed as monotherapy in this difficult clinical setting (eg, pegylated liposomal doxorubicin, topotecan, and altretamine).[3,4]

As a result of far more restrictive payment policies in European countries, it is less likely that a patient from the control arm of the EORTC study, treated with a carboplatin/paclitaxel regimen, will have access to bevacizumab at the time of disease progression compared with a patient in the control arm of the GOG study. How this factor might influence the ability to assess the level of benefit in OS seen with bevacizumab in the 2 studies is not clear.

PARP Inhibitors

The second category of agents of particular interest in ovarian cancer is PARP inhibitors. Recently reported data reveal as many as one-third of ovarian cancer patients with either a *BRCA1* or a *BRCA2* mutation achieve an objective response when treated with a single agent from this novel class of drugs in the second-line setting.[5,6] The hypothesis supporting this strategy is that women with *BRCA* abnormalities have an underlying defect in DNA repair, so using an inhibitor to interfere with PARP—a second relevant DNA repair mechanism—should seriously impair the survival of malignant cells.

As exciting as these data appear to be, germline *BRCA* mutations are only found in approximately 5% to 10% of all women with ovarian cancer, limiting the potential applicability of this novel approach. Recent data suggest, however, that up to an additional 10% to 20% of patients might possess somatic (nongermline) molecular abnormalities in their tumors that closely resemble the genetic defects observed in women with hereditary cancers.[7] If appropriately designed and conducted clinical studies ultimately demonstrate that cancers with this so-called "*BRCA*ness" profile are as sensitive to PARP inhibition as patients with germline mutations appear to be, it could substantially increase the proportion of women who stand to derive clinical benefit from this management strategy. The results of trials exploring the utility of this class of drugs in this specific patient population are keenly anticipated.

> Germline *BRCA* mutations are only found in approximately 5% to 10% of all women with ovarian cancer, limiting the potential applicability of [PARP inhibition].

Conclusion

Preliminary data from single-arm or randomized phase 2 trials regarding the potential efficacy of quite a number of novel traditional cytotoxic agents and more targeted antineoplastic agents in ovarian cancer were reported at several international meetings during the past year. Additional follow-up data and publication of these results in the peer-reviewed literature are needed before we can make a meaningful assessment of the possible role these strategies might play in the future management of ovarian cancer. It is not unreasonable to anticipate, however, that at least 1 of these approaches will someday find a place in the standard treatment of this hard-to-treat neoplasm. ●

References

1. Burger RA, Brady MF, Bookman MA, et al. Phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tumor cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2010;28(185): AbstractLBA1.

2. Perren T, Swart AM, Pfisterer J, et al. ICON 7: a phase III Gynecologic Cancer Intergroup (GCIG) trial of adding bevacizumab to standard chemotherapy in women with newly diagnosed epithelial ovarian, primary peritoneal or fallopian tube cancer. Presentation at: 35th ESMO Congress; October 8-12, 2010; Milan, Italy.

3. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JL. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2007;25:5165-5171.

4. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol.* 2007;25:5180-5186.

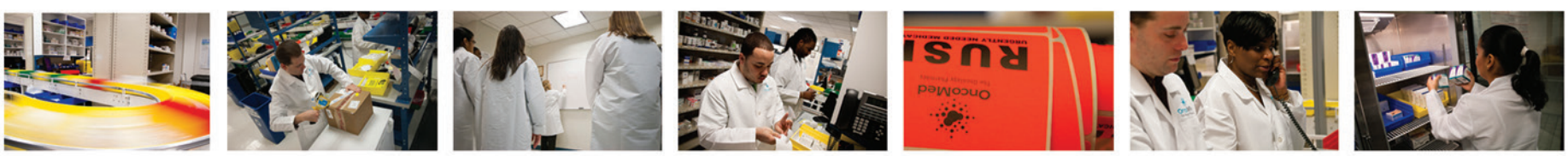
5. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol.* 2010;28:2512-2519.

6. Audeh MW, Carmichael J, Person RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet.* 2010;376:245-251.

7. Hennessy BT, Timms KM, Carey MS, et al. Somatic mutations in *BRCA1* and *BRCA2* could expand the number of patients that benefit from poly(ADP-ribose) polymerase inhibitors in ovarian cancer. *J Clin Oncol.* 2010;28:3570-3576.

CANCER MANAGEMENT IS COMPLEX.

THE DRUG SOLUTION IS SIMPLE.



For additional information, contact:

info@OncoMed.net

1.877.662.6633 x1298

OncoMed.net

OncoMed
The Oncology Pharmacy

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

By Guru Sonpavde, MD
Texas Oncology Cancer Center, Houston; Michael E. DeBakey Veterans Affairs Medical Center; the Baylor College of Medicine, Houston, Texas

Toni K. Choueiri, MD, MS
Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts

Philip W. Kantoff, MD
Dana-Farber Cancer Institute; Harvard Medical School, Boston, Massachusetts


Guru Sonpavde, MD


Toni K. Choueiri, MD, MS


Philip W. Kantoff, MD

When initial androgen-deprivation therapy (ADT) fails to control progression of metastatic prostate cancer, the disease is redefined as castration-resistant prostate cancer (CRPC). Studies have shown that using docetaxel and prednisone to treat men with CRPC only modestly extends median overall survival (OS) to ~19 months. In addition, only 18.6% of patients who receive this combination survive 3 years.[1,2] Recently, cabazitaxel (Jevtana), a novel taxane, was found to extend median OS in progressive metastatic CRPC following previous docetaxel, but only modestly compared with mitoxantrone (15.1 vs 12.7 months, P <.0001).[3] Novel and more tolerable options are needed to manage prostate cancer in this population of mostly elderly men, who often have multiple comorbidities. Sipuleucel- T (Provenge), an autologous dendritic cell–based vaccine approved by the US Food and Drug Administration (FDA) in 2010, is one such option. Studies show that it prolongs OS in men with metastatic CRPC and is well tolerated.[4]

Rationale for Immunotherapy in Metastatic CRPC

Humoral (antibody) and cellular (T cells, natural killer cells, macrophages) immune responses are involved in combating malignancies, with cellular immunity thought to play a more prominent role. Antigen-presenting cells (APCs), which include dendritic cells, are able to activate T lymphocytes by efficiently presenting them to T-cell receptors. Activation of T cells subsequently enhances B-lymphocyte response. Prostate cancer provides an excellent opportunity for applying immunotherapy, because it is relatively indolent and expresses several essentially organ-specific tumor-associated antigens, such as prostatic acid phosphatase (PAP) and prostate-specific antigen (PSA).

A Novel Vaccine

The sipuleucel-T vaccine, which consists of autologous APCs manufactured by processing the leukapheresis product and manipulating it to enhance the presentation of tumor antigens, has been evaluated extensively, culminating in FDA approval.[5-7] The vaccine contains APCs pulsed with PA2024, a fusion protein of PAP-granulocyte macrophage colony-stimulating factor.[8] In an initial small randomized trial enrolling 127 previously untreated men with asymptomatic, metastatic CRPC, sipuleucel-T prolonged median OS compared with placebo (25.9 vs 21.4 months, P = .01).[9]

Subsequently, the larger IMPACT (Immunotherapy Prostate Adenocarcinoma Treatment) trial randomized 512 men with asymptomatic metastatic CRPC at a 2:1 ratio to sipuleucel-T or placebo; the study's primary end point of OS.[4] Men with visceral metastasis were excluded. About 85% of patients were chemotherapy-naïve, and the 15% of men who received chemotherapy previously were required to have completed the treatment at least 3 months prior to enrollment. ADT was continued in all patients.

Treatment included 3 leukapheresis procedures (at weeks 0, 2, and 4). Approximately 3 days after each procedure, patients received a 60-minute infusion of sipuleucel-T or placebo following premedication with acetaminophen and an antihistamine. Even though the trial allowed patients assigned to placebo to crossover, median OS was still significantly improved in the sipuleucel-T arm compared with the placebo arm (25.8 vs 21.7 months, respectively; P = .02). The probability of 3-year survival was also better with sipuleucel-T than placebo (31.7% vs 23.0%, respectively). Approximately 55% of men in both groups received subsequent docetaxel at a median of 12 to 13 months after on-study therapy, but analyses did not suggest that the differences in the frequency of or time elapsed to docetaxel treatment could account for the differences in outcomes.

Notably, the time to disease progression was similar in the 2 groups and no clear early evidence of activity was observed. Confirmed PSA declines ≥50% were observed in only 8 of 311 (2.6%) patients in the sipuleucel-T group and in 2 of 153 (1.3%) patients in the placebo group. Sipuleucel-T was associated with mild and manageable grade 1 and 2 infusion-related adverse events, including fever (22.5%) and chills (51.2%). Antibody response against PAP or PA2024 (antibody titer exceeding 400) was observed in 66.2% of patients in the sipuleucel-T group and correlated with survival benefit. T-cell responses to the immunizing antigen also were observed but were not associated with survival.

Conclusion

Sipuleucel-T provides a modest extension of survival coupled with an excellent toxicity profile in generally chemotherapy-naïve and relatively asymptomatic patients without visceral metastases. Sipuleucel-T was highly tolerable, and no long-term and delayed adverse immune phenomena have been observed. Given the cost and a modest survival benefit, it is important to select patients appropriately based on the eligibility criteria used in the IMPACT trial.

Several other novel immunotherapeutic agents are being evaluated in clinical trials. Poxvirus-based vaccines and immune-checkpoint inhibitors of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death-1 (PD-1) appear promising. In addition, multiple emerging novel androgen-pathway inhibitors (abiraterone acetate, TAK700, MDV3100) are likely to expand the therapeutic armamentarium in the near future.[10] Therefore, the proper sequence of therapeutic agents and appropriate selection of patients likely to benefit from specific agents will assume great importance. ●

Disclosures

Guru Sonpavde is a speaker for Dendreon Corp, and his institution receives research funding from Bellicum Pharmaceuticals. Toni K. Choueiri has nothing to disclose. Philip W. Kantoff is a consultant for Dendreon Corp, Bellicum Pharmaceuticals, and BN ImmunoTherapeutics Inc.

References

1. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol.* 2008;26:242-245.
2. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004;351:1513-1520.
3. de Bono JS, Oudard S, Ozguroglu M, et al; for the TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet.* 2010;376:1147-1154.
4. Kantoff PW, Higano CS, Shore ND, et al; for the IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;363:411-422.
5. Sonpavde G, Slawin KM, Spencer DM, Levitt JM. Emerging vaccine therapy approaches for prostate cancer. *Rev Urol.* 2010;12:25-34.
6. Figdor CG, de Vries IJ, Lesterhuis WJ, Melief CJ. Dendritic cell immunotherapy: mapping the way. *Nat Med.* 2004;10:475-480.
7. Drake CG. Prostate cancer as a model for tumour immunotherapy. *Nat Rev Immunol.* 2010;10:580-593.
8. Small EJ, Fratesi P, Reese DM, et al. Immunotherapy of hormone-refractory prostate cancer with antigen-loaded dendritic cells. *J Clin Oncol.* 2000;18:3894-3903.
9. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J Clin Oncol.* 2006;24:3089-3094.
10. De Bono J LC, Logothetis CJ, Fizazi K, et al; for the COU-AA-301 investigators. Abiraterone acetate plus low dose prednisone improves overall survival in patients with metastatic castration resistant prostate cancer who have progressed after docetaxel-based chemotherapy: results of COU-AA-301, a randomized double-blind placebo-controlled phase III study. *Ann Oncol.* 2010;21(suppl 8):LBA5.

The osmotic effect of MiraLAX®

provides gentle, predictable relief of occasional constipation

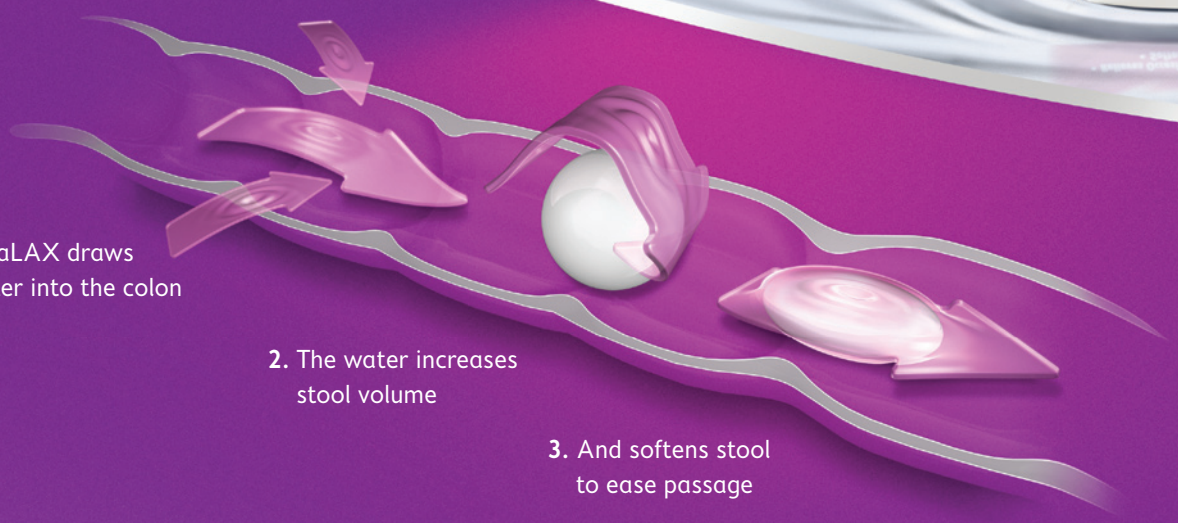
When MiraLAX® laxative draws water into the colon, the body responds **naturally for a normal bowel movement:**

- Complete, comfortable, and predictable[1-3]
- No harsh side effects[1-3]
  — No loss of control, no gas, no bloating, no cramping

MiraLAX is:

- Clinically proven safe and effective[1-3]
- Well tolerated[3]
- #1 doctor recommended laxative
- Preferred by patients over other types of laxatives[3*]

MiraLAX and the unique mechanism of action of polyethylene glycol 3350



*In an open-label, single product study, 68% of the 74 subjects who compared PEG3350 to their usual laxative preferred PEG3350 overall. Stoltz R, Weiss LM, Merkin DH, Cleveland MvB, Pelham RW. An efficacy and consumer preference study of polyethylene glycol 3350 for the treatment of constipation in regular laxative users. *Home Health Care Consultant*. 2001;8:21-26.

References: 1. DiPalma JA, et al. *Am J Gastroenterol*. 2007;102:1436-1441. **2.** DiPalma JA, et al. *Am J Gastroenterol*. 2007;102:1964-1971. **3.** Stoltz R, et al. *Home Health Care Consultant*. 2001;8:21-26.

www.MiraLAXMD.com

Restore your patients' natural rhythm™

Early Intervention Palliative Care: Implications for Nurses

By Constance M. Dahlin, MSN, ANP, FAAN
Clinical Director of the Palliative Care Service; Adjunct Clinical Associate Professor, Institute of Health Professions, Massachusetts General Hospital; Faculty, Harvard Medical School Center for Palliative Care, Boston, Massachusetts

Emily R. Gallagher, RN
Research Nurse, Thoracic Oncology, Massachusetts General Hospital, Boston, Massachusetts

Jennifer S. Temel, MD
Assistant Professor of Medicine, Harvard Medical School; Clinical Director, Thoracic Oncology, Massachusetts General Hospital, Boston, Massachusetts

Even though palliative care has been an important aspect of medical care in the United States for more than 25 years, it has yet to gain full public acceptance. Attempts to offer advanced care planning that allows patients to focus on care consistent with their values and preferences have been met with resistance. On January 1, 2011, Medicare proposed clinician reimbursement for advanced care planning. Within several weeks, however, this recommendation was reversed because some politicians worried the public would equate advanced care planning with healthcare rationing. Our recent publication in *The New England Journal of Medicine* directly addresses the impact of timely palliative care on quality of life and end-of-life care in patients with metastatic non–small cell lung cancer.[1] The article promoted conversation within the healthcare community about the benefits of palliative care as part of comprehensive oncology care.

Patients assigned to early palliative care had better quality of life compared with those receiving standard oncology care, as measured by the Trial Outcome Index.

Background

Studies demonstrate that patients with cancer are often offered palliative care too late in the course of their illness. One reason for delayed referrals is the lack of clinician understanding and experience with palliative care. Even Atul Gawande, MD, MPH, noted writer with *The New Yorker*, publicly acknowledged his confusion regarding the role of palliative care in patients who are not receiving hospice care. Until recently, he thought of the difference between standard medical care and palliative care as "the difference between treating and doing nothing."[2]

Our randomized controlled trial demonstrated the benefit of offering palliative care closer to diagnosis, confirming that standard medical care and palliative care are not mutually exclusive. As such, its publication spawned coverage in national print media, including *The New York Times*, *The Boston Globe*, and *USA Today*; and received nationwide television coverage on *NBC Nightly News* and *National Public Radio*. Endorsed by all major hospice and palliative care organizations—the Hospice and Palliative Nurses Association, the American Academy of Hospice and Palliative Medicine, the Center to Advance Palliative Care, and the National Hospice and Palliative Care Organization—the study cultivated discussion from other prominent healthcare institutions, with statements issued in response to the findings from the John Hartford Center, the National Cancer Institute, and the American Society of Clinical Oncology (ASCO).

A Randomized Controlled Trial of Early Palliative Care

Our study investigated the impact of early palliative care on quality of life and survival in patients with metastatic cancer. We randomized 151 patients with newly diagnosed metastatic non–small cell lung cancer to receive early palliative care integrated with standard oncology care (n = 77) or standard oncology care (n = 74). Patients assigned to early palliative care received at least 1 visit per month from the palliative care team in the ambulatory care setting throughout the course of their disease. Patients were also assured of 24/7 coverage by the palliative care team in response to any change in cancer status, worsening of symptoms, or difficulties in coping. The mean number of visits at 12 weeks postdiagnosis for patients receiving early palliative care was 4 (range, 0-8).

The palliative care team at Massachusetts General Hospital has provided inpatient care for 15 years and outpatient care for 10 years. During this study, the outpatient team consisted primarily of 6 palliative care physicians and 1 palliative care advanced practice nurse. Patient appointments were scheduled concomitantly with appointments with the oncology team or with chemotherapy or radiation treatment. To assure continuity of care, after randomization to a specific palliative care clinician, each patient received treatment primarily from that provider.

Standard oncology care was not dictated by the study protocol and incorporated any treatment recommended by the oncologist, including chemotherapy, radiation, and surgery. Patients assigned to the standard care group were not prohibited from receiving palliative care. The treatment team, the patient, or the patient's family could subsequently request a consult for palliative care. Only 10/74 (14%) patients receiving standard care had a palliative care visit in the first 12 weeks after diagnosis.

The study confirmed the hypothesis held within the palliative care community: Early palliative care provides significant benefits, even while patients are receiving cancer-directed therapies.[3] Patients assigned to early palliative care had better quality of life compared with those receiving standard oncology care, as measured by the Trial Outcome Index (59.0 ± 11.6 vs 53.0 ± 11.5, respectively; P = .009). They also had lower rates of depression than patients in the standard care group, as measured by the Hospital Anxiety and Depression Scale (16% vs 38%, respectively; P = .01). Patients receiving early palliative care were less likely than patients in the standard care group to receive aggressive end-of-life care, defined by ASCO as chemotherapy within 14 days of death, no hospice care, or admission to hospice ≤3 days prior to death (33% vs 54%, respectively; P = .05). We hypothesize that early intervention with palliative care promoted candid discussions regarding end-of-life care options and prognosis, thereby influencing decisions favoring better quality of life over aggressive, likely ineffective therapies.

Our study also found that patients receiving early palliative care lived longer than patients receiving standard oncology care. Despite receiving less aggressive end-of-life care, patients assigned to early palliative care survived 30% longer than those assigned to standard oncology care (median, 11.6 vs 8.9 months, respectively; P = .02). This finding contradicts the common assumption that less aggressive end-of-life care decreases longevity.

Discussion

Using a randomized trial design, our study found that early palliative care improves quality of life and reduces depression. There are several possible explanations for these effects. First, aggressive end-of-life care may produce sufficiently high levels of psychological distress when treatment produces more harm than good. Second, palliative care offers a high degree of psychosocial support and thus may directly reduce psychologic distress at the end of life.

Although these results are exciting and strongly support the notion that palliative care has beneficial effects, our study had a number of limitations. The study enrolled only patients with metastatic non–small cell lung cancer, and the findings may not be generalizable to other cancer populations. In addition, the study was conducted at a single tertiary care hospital with a mature, well-established, palliative care team that already had a collaborative relationship with the oncology division. Further studies should be conducted in other academic settings and use palliative care teams in varying stages of development to confirm our findings. Our study population was fairly homogeneous, with a predominance of white patients, and this limits the ability to generalize these findings to patient populations with more diverse cultural backgrounds.[3]

Nursing Implications

Oncology nurses in all settings are frequently present at the bedside, affording them abundant opportunities to initiate conversations that allow patients to reflect on their physical condition; their views on good quality of life; and their values, preferences, and beliefs about life-prolonging therapies. Many oncology nurses are present and provide oncology and pallia-

tive care at the time of diagnosis, during treatment, at recurrence, and at the news of disease progression. Nurses offer support and comfort at these transitions, particularly after difficult conversations with physicians and oncology nurse practitioners.[4] Careful timing and the skillful delivery of palliative care are essential to nurture and strengthen the nurse–patient relationship.

Oncology nurses can also promote early initiation of palliative care and its positive role to patients and the treating team. This can be done in conjunction with discussions on other aspects of comprehensive cancer care. For example, nurses might offer patients and their family access to a team that focuses on pain and symptom management and psychosocial support to improve quality of life. They can dispel concerns and fears that palliative care shortens life. Nurses are in a position to encourage acceptance and trust of palliative care and can introduce team members directly to patients and their families. They may also be able to recognize patients struggling with cancer treatment who need palliative care to help them complete therapy. For patients who are told no more treatment options are available, oncology nurses should discuss the benefits of and options for palliative care.

Nurses are in a position to encourage acceptance and trust of palliative care and can introduce team members directly to patients and their families.

To help nurses provide comprehensive care for patients, they must strive to understand the importance of integrating palliative care into oncology care and pursue education in palliative care. The Oncology Nursing Society (ONS) partnered with the End-of-Life Nursing Education Consortium to create a curriculum for oncology nurses, which is available at many ONS Annual Congresses. This curriculum offers nurses structured education through 9 modules: Overview of Palliative Nursing, Achieving Quality Care, Communication, Pain Management, Symptom Management, Loss and Grief, Culture, Final Hours, and Ethics.[5] In addition, oncology nurses should familiarize themselves with the National Consensus Project for Quality Palliative Care's Clinical Practice Guidelines. These guidelines cover 8 domains: Structure and Processes of Care; Physical Aspects of Care; Psychological and Psychiatric Aspects of Care; Social Aspects of Care; Spiritual, Religious and Existential Aspects of Care, Cultural Aspects of Care; Care of the Imminently Dying Patient; and Ethical and Legal Aspects of Care.[6]

Conclusion

Our study demonstrates the benefits of early palliative care: better quality of life, lower rates of depression, less aggressive end-of-life care, and increased survival, even in the absence of aggressive end-of-life treatment. With this new evidence, oncology nurses should feel more confident about promoting palliative care to their patients. ●

References

1. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363:733-742.
2. Gawande A. Letting go. *The New Yorker*. August 2, 2010:36-49.
3. Goldstein N, Anderson W. State of the science: update in hospice and palliative care. Presented at: Annual Assembly of the American Academy of Hospice and Palliative Medicine and Hospice and Palliative Nurses Association; February 19, 2011; Vancouver, BC.
4. Malloy P, Virani R, Kelly K, Munevar C. Beyond bad news—communication skills of nurses in palliative care. *J of Hospice Palliative Nurs*. 2010;12:166-174.
5. Coyne P, Paice JA, Ferrell BR, et al. Oncology End-of-Life Nursing Education Consortium training program: improving palliative care in cancer. *Oncol Nurs Forum*. 2007;34:801-807.
6. National Consensus Project for Quality Palliative Care. *Clinical Practice Guidelines for Quality Palliative Care*. 2nd ed. 2009. www.nationalconsensusproject.org/guideline.pdf. Accessed September 10, 2010.

Vitamin and Supplement Use in Oncology Patients

By Megan Hagerty, PharmD, BCOP
Department of Pharmacy Practice, Purdue University College of Pharmacy, Indianapolis, Indiana

After a diagnosis of cancer, patients often initiate or increase their use of vitamins and dietary supplements, and their use is prevalent among the 11.7 million adults in the United States living with cancer. Whereas 50% of healthy adults take 1 or more dietary supplements, between 64% and 81% of cancer survivors report that they use vitamin or dietary supplements.[1] Reasons offered for using these alternative therapies include strengthening the immune system, increasing the chance to be cured, and gaining a sense of control over their disease.

Although the American Cancer Society says, "A daily, multivitamin supplement in amounts equivalent to 100% of the [US Department of Agriculture Recommended] Daily Value is a good choice for anyone… who cannot eat a healthful diet,"[2] supplements do not come without risks. Because of limited US Food and Drug Administration regulations and published experience, little is known about how supplements interact with cancers and their treatments. For example, antioxidants might reduce the efficacy of radiation and chemotherapy by blocking reactive oxygen species[3] and some vitamins could stimulate cancer cell growth.[4]

More than half of cancer patients taking supplements do not inform their physician.[1] It is therefore important for all healthcare practitioners to be familiar with the current literature addressing vitamin and dietary supplement use in this patient population so they can assist physicians and help mitigate risks. In 2010, research literature included studies on multivitamins, selenium, and vitamin D. Caution should be taken when evaluating and applying literature to clinical practice. In addition to inconsistencies among these trials, some published reports rely on early-phase data.

> Emerging literature suggests a role for vitamin D in the prevention and treatment of cancer, but studies have failed to show any benefit with multivitamin and selenium use.

Multivitamin Use

To evaluate the effects of multivitamin use on survival in patients with stage III colon cancer, a prospective, observational study was conducted as a companion study to CALGB 89803.[5] Patients were asked to complete a diet and lifestyle questionnaire midway through therapy and again 6 months after treatment ended. During treatment, 49.9% (518/1038) of patients said they used multivitamins. Use remained consistent after treatment, with 51.4% (416/810) of patients reporting that they took multivitamins. The hazard ratio (HR) for disease-free survival for multivitamin users compared with nonusers was 0.94 (95% confidence interval [CI], 0.77-1.15). Multivitamin use during or following chemotherapy was not associated with a significant increase in recurrence-free survival (multivariate HR, 0.93; 95% CI, 0.75-1.15) or overall survival (multivariate HR, 0.92; 95% CI, 0.74-1.16). Women, patients with higher household incomes, and physically active patients were more likely to report multivitamin use.

Selenium

The proposed anticancer effects of selenium include supporting antioxidant status, increasing activity of proteins involved in apoptosis, and inhibiting transcription factors associated with carcinogenesis, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein-1.[6,7] Common adverse effects of selenium supplementation include brittle nails and hair, liver and kidney function test abnormalities, and cataracts. Previous trials have shown conflicting results regarding the ability of selenium to reduce the risk of developing cancer.[8,9]

Stratton and colleagues conducted a phase 2 trial to assess whether selenium supplementation reduces prostate cancer progression as measured by prostate-specific antigen (PSA) velocity.[10] A total of 140 patients with localized non–high-grade prostate cancer were randomized to receive daily placebo (n = 46), selenium 200 µg (n = 46), or selenium 800 µg (n = 47). After adjusting for confounders, PSA velocity did not differ significantly between the 3 groups. A subgroup analysis for the quartile of men with the highest baseline selenium levels who were randomized to the selenium 800-µg arm showed that they had significantly higher PSA velocity than men taking placebo (P = .018). The authors concluded that selenium did not demonstrate a protective effect on PSA velocity and that high-dose selenium supplementation might negatively affect PSA velocity.

Vitamin D

Vitamin D is a unique supplement, because daily intake is derived from diet and sun exposure. This nutrient regulates calcium and skeletal homeostasis and behaves like a hormone, regulating transcription of more than 200 genes. It is theorized that vitamin D might help prevent cancer by inducing cellular differentiation, inhibiting angiogenesis, and causing apoptosis. Observational studies have demonstrated a link between low levels of vitamin D and increased cancer incidence or poorer cancer prognosis.[11-13]

In November 2010, the Institute of Medicine (IOM) released a report proposing increases in the dietary reference intake values for calcium and vitamin D.[14] IOM tripled the recommended daily allowance of vitamin D for adults aged 31 to 50 years and increased it by 50% for adults aged 51 to 70 years, advising that all healthy, noninfant children and adults aged ≤70 years get 600 IU daily of vitamin D. The IOM said evidence of improved bone health was the only health condition that informed the suggested increases and cited mixed and inconclusive research about the use of vitamin D in the prevention and treatment of cancer.

A single-arm, phase 2 trial evaluated the palliative benefit of high-dose vitamin D3 (cholecalciferol) on pain scores and bone resorption markers in 38 patients with breast cancer and evidence of bone metastases.[15] Every day for 4 months, patients took 10,000 IU of oral vitamin D[3] and 1000 mg of calcium. Pain response was measured using 2 validated questionnaires, which were administered at baseline and repeated monthly. All patients continued on previously prescribed bisphosphonate therapy. No significant changes from baseline in pain score or daily morphine-equivalent analgesia use were observed, although there was a significant reduction in number of pain sites. In addition, daily use of high-dose vitamin D[3] and calcium did not significantly reduce levels of urinary bone resorption markers. The authors concluded that although the combination of daily high-dose vitamin D[3] and calcium appeared safe, it did not offer significant palliation or reduce bone resorption.

Your Role

Vitamin and mineral supplementation are often used to treat oncology patients. Emerging literature suggests a role for vitamin D in the prevention and treatment of cancer, but studies have failed to show any benefit with multivitamin and selenium use. Vitamin supplementation remains a promising area for research, but because of the risks and the inconsistent and conflicting data, it is important for healthcare professionals to evaluate the information carefully. This, in turn, allows medical professionals to assist cancer survivors in making appropriate treatment decisions. ●

References

1. Velicer CM, Ulrich CM. Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. *J Clin Oncol.* 2008;26:665-673.
2. Doyle C, Kushi LH, Byers T, et al; for the 2006 Nutrition, Physical Activity and Cancer Survivorship Advisory Committee; American Cancer Society. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin.* 2006;56:323-353.
3. Lawenda BD, Kelly KM, Ladas EJ, et al. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? *J Natl Cancer Ins*. 2008;100:773-783.
4. Giovannucci E, Chan AT. Role of vitamin and mineral supplementation and aspirin use in cancer survivors. *J Clin Oncol.* 2010;28:4081-4085.
5. Ng K, Meyerhardt JA, Chan JA, et al. Multivitamin use is not associated with cancer recurrence or survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol.* 2010;28:4354-4363.
6. Stratton MS, Reid ME, Schwartzberg G, et al. Selenium and inhibition of disease progression in men diagnosed with prostate carcinoma: study design and baseline characteristics of the "Watchful Waiting" Study. *Anticancer Drugs*. 2003;14:595-600.
7. Thompson IM. Chemoprevention of prostate cancer: agents and study designs. *J Urol.* 2007;178(3 pt 2):S9-S13.
8. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2009;301:39-51.
9. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutrition Prevention of Cancer Study Group [published correction appears in *JAMA*. 1997;277:1520]. *JAMA*. 1996;276:1957-1963.
10. Stratton MS, Algotar AM, Ranger-Moore J, et al. Oral selenium supplementation has no effect on prostate-specific antigen velocity in men undergoing active surveillance for localized prostate cancer. *Cancer Prev Res (Phila)*. 2010;3:1035-1043.
11. Chung M, Balk EM, Brendel M, et al. *Vitamin D and Calcium: A Systematic Review of Health Outcomes. Evidence Report no. 183*. Rockville, MD: Agency for Healthcare Research and Quality; 2009. AHRQ publication no. 09-E015.
12. Drake MT, Maurer MJ, Link BK, et al. Vitamin D insufficiency and prognosis in non-Hodgkin's lymphoma. *J Clin Oncol.* 2010;28:4191-4198.
13. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Hood N. Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. *J Clin Oncol.* 2009;27:3757-3763.
14. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academics Press; 2011.
15. Amir E, Simmons CE, Freedman OC, et al. A phase 2 trial exploring the effects of high-dose (10,000 IU/day) Vitamin D3 in breast cancer patients with bone metastases. *Cancer.* 2010;116:284-291.

Eribulin: A New Option in the Treatment of Metastatic Breast Cancer

By Georgia Litsas, RN, NP
Dana-Farber/Brigham and Women's Cancer Center, Boston, Massachusetts

Breast cancer is the most common cancer among women. In 2010, there were an estimated 207,090 new cases and 39,840 deaths.[1] Despite many improvements in the treatment of breast cancer, about 20% to 30% of women with the disease will progress to metastatic breast cancer (MBC). Although MBC remains incurable, a variety of treatment options are available. The US Food and Drug Administration (FDA) recently approved eribulin (Halaven), providing an exciting new option for women with heavily pretreated MBC.

Eribulin is a synthetic analog of halichondrin B, a nontaxane microtubule dynamics inhibitor originally isolated from a sea sponge. Eribulin inhibits the growth phase of microtubules and sequesters tubulin into nonproductive aggregates, resulting in G2/M cell-cycle block, by disrupting mitotic spindles. It exerts its action at a site on the cellular level that is distinct from that targeted by taxanes, vinca alkaloids, and other existing microtubulin inhibitors.

FDA approval was based on data from the international, phase 3 EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin) clinical trial, which had a primary end point of overall survival (OS). To be eligible, all the women had to have been treated with 2 to 5 prior chemotherapy regimens and to have experienced disease progression within 6 months of completing their most recent chemotherapy regimen. Of the regimens administered previously in the adjuvant or metastatic setting, at least 1 had to have been anthracycline based and 1 had to have been taxane based to be eligible for enrollment. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and patients with preexisting neuropathy >grade 2 were ineligible.

Median OS was significantly prolonged for patients randomized to receive eribulin.

Investigators randomized 762 patients with MBC at a 2:1 ratio to eribulin (n = 508) or a single-agent therapy selected by their physician prior to randomization (n = 254). Randomization was stratified by geographic region, HER2 status, and prior capecitabine exposure. The physician's choice of treatment consisted of any single agent, whether a chemotherapy, hormonal, or biologic therapy, or supportive care only. Randomization was stratified by geographic region, HER2 status, and prior capecitabine exposure. Eribulin 1.4 mg/m^2 was administered on days 1 and 8 every 21 days, with dose reductions and delays for predetermined toxicities. The control arm therapies consisted of the following agents: vinorelbine (Navelbine; 26%), gemcitabine (Gemzar; 18%), a taxane (16%), capecitabine (18%), an anthracycline (9%), other chemotherapy (10%), and hormonal therapy (3%).

Median OS was significantly prolonged for patients randomized to receive eribulin compared with those who received the physician's choice of treatment (13.1 vs 10.6 mo, respectively; hazard ratio, 0.809; 95% confidence interval, 0.660-0.991; P = .041).

Eribulin treatment had a manageable safety profile. The most common adverse reactions in the eribulin arm, occurring in >25% of patients, were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common treatment-related adverse reactions ≥grade 3 experienced by >5% of patients were neutropenia (57%), asthenia/fatigue (10%), and peripheral neuropathy (8%). The most common serious adverse reactions reported in eribulin-treated patients were febrile neutropenia (4%) and neutropenia (2%). The most common toxicity leading to discontinuation of eribulin was peripheral neuropathy (5%).

These results were discussed at the 2010 ASCO Annual Meeting and published in *The Lancet* in March 2011.[2] These results are especially noteworthy because this is the first time a single agent has demonstrated survival benefit in this population.

The recommended dosage of eribulin is 1.4 mg/m^2 administered intravenously over 2 to 5 minutes on days 1 and 8 of a 21-day cycle. Eribulin may be administered undiluted or diluted in 100 mL of 0.9% sodium chloride injection, USP. The drug should not be administered through an intravenous line that is delivering a dextrose-containing solution.[3]

Eribulin offers new promise for women with heavily pretreated MBC. The results of the EMBRACE trial demonstrate that cytotoxic therapies directed at a well-defined target remain a viable area of continued study. Given the favorable results of the EMBRACE trial, future studies will examine the use of eribulin in the adjuvant setting and also as frontline therapy in the metastatic setting. It is important for nurses to be aware of the FDA's approval of eribulin, its mechanism of action, and its safety profile. Nurses are in a pivotal position to advocate for their patients, to provide consistent patient education, and to monitor adverse reactions. ●

References

1. Breast cancer overview. American Cancer Society. http://www.cancer.org/Cancer/BreastCancer/OverviewGuide/breast-cancer-overview-key-statistics. Updated September 2010. Accessed April 12, 2011.
2. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomized study. *Lancet*. 2011;377(9769):914-923.
3. Halaven [package insert]. Woodcliff Lake, NJ: Eisai, Inc.; 2010.

Update on PARP Inhibitors in Breast Cancer, 2010-2011

By Sarah Hopps, PharmD
College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City

Shubham Pant, MD
University of Oklahoma Health Sciences Center, Oklahoma City

Poly(ADP-ribose) polymerase (PARP) are a group of enzymes that are essential for base excision repair.[1] There are several members of the PARP family, of which PARP1 is the most extensively studied.[1,2] PARP1 only detects single-stranded DNA breaks and initiates repair; without PARP1, a single-stranded break is converted into a double-stranded break and repaired by homologous repair.[1] PARP inhibition shows promise in *BRCA1/2*-deficient tumors, which lack homologous repair capability, causing synthetic lethality (decrease in repair of both single- and double-stranded DNA breaks, leading to cell death).[3] Synergy has also been demonstrated when PARP inhibitors are combined with several traditional cytotoxic agents including temozolomide (Temodar), cyclophosphamide, topotecan, paclitaxel, cisplatin, gemcitabine (Gemzar), and irinotecan.[4-12] Several PARP inhibitors are in development, with iniparib (BSI-201), veliparib (ABT-888) and olaparib (AZD2281), being the furthest along. In the past year, PARP inhibitors have shown activity as single agents and in combination with chemotherapy, and data have been published in journals and presented as abstracts in meetings.

Iniparib

O'Shaughnessy and colleagues evaluated the efficacy of the intravenous small-molecule PARP inhibitor, iniparib, in women with triple-negative (estrogen receptor-, progesterone receptor-, and HER2-negative) metastatic breast cancer.[4] In this open-label phase 2 study, 123 patients were randomized to gemcitabine (1000 mg/m^2) and carboplatin (AUC 2) on days 1 and 8 of a 21-day cycle with or without iniparib, which was administered to patients in that group on days 1, 4, 8, and 11. Up to 2 prior chemotherapy regimens for metastatic disease were permitted. The study allowed for patients in the control arm to cross over to the iniparib group at the time of progression.

The overall response rate (ORR) was 52% in the iniparib arm versus 32% in the chemotherapy-only group (P = .002). The median progression-free survival (PFS) was 5.9 months for patients taking iniparib compared with 3.6 months for those on chemotherapy alone (P = .01). No significant differences were observed in the frequency of adverse events between the groups.

For the 51% of patients in the control

group who crossed over, iniparib demonstrated only minimal antitumor activity. The authors noted that the results are prone to biases and are being confirmed in a randomized phase 3 trial.

Earlier this year, sanofi-aventis announced that a phase 3 study of iniparib failed to meet its primary end points of significant improvement in overall survival (OS) and PFS but did not offer detailed findings.[13] A prespecified analysis of patients treated with iniparib in the second- and third-line settings reportedly demonstrated improvement in OS and PFS "consistent with what was seen in the phase 2 study," but specific data will not be offered until the upcoming annual meeting of the American Society of Clinical Oncology. It will be interesting to view data on the survival advantage for these patients and for those with a *BRCA1/2* mutation.

Oliparib

Two articles published in *The Lancet* evaluated the novel oral PARP inhibitor olaparib in patients with *BRCA1/2* mutations and advanced breast cancer or recurrent ovarian cancer.[14,15] Both studies compared a 400-mg twice-daily dose (cohort 1) with a 100-mg twice-daily dose (cohort 2). In patients with breast cancer, the ORR was 42% in cohort 1 and 25% in cohort 2. The median PFS also seemed to be lower in cohort 2 than in cohort 1 (2.8 vs 5.7 mo, respectively).

Patients progressing after platinum chemotherapy rarely had a confirmed response when treated with oliparib. This was also seen in patients with ovarian cancer who received olaparib 400 mg twice daily. Response was confirmed in 38% of platinum-sensitive patients versus 30% of platinum-resistant patients.

The most common toxicities seen with oliparib in these trials were nausea and fatigue. It is important to note that the cohorts were not randomized; hence, one has to exercise caution in interpreting the response rates.

Conclusion

Additional novel PARP inhibitors are being investigated in early-phase trials for breast and ovarian cancer and other solid tumors. In 2010, several abstracts were presented from early-stage trials that combine PARP inhibitors with cytotoxic chemotherapy agents. For example, a phase 2 study evaluated the efficacy of veliparib in combination with temozolomide in patients with metastatic breast cancer[8] and reported 1 complete response, 2 partial responses, 7 patients with stable disease (all unconfirmed), and 14 patients whose disease progressed. A number of phase 1 trials were also presented. Updated data from these and other trials could help determine the future rule for PARP inhibitors in breast cancer. ●

References

1. Underhill C, Toulmonde M, Bonnefoi H. A review of PARP inhibitors: from bench to bedside. *Ann Oncol.* 2011;22:268-279.

2. Ame JC, Splenlehauer C, de Murcia G. The PARP superfamily. *BioEssays*. 2004;26:882-893.

3. Leung M, Rosen D, Fields S, et al. Poly(ADP-ribose) polymerase-1 inhibition: preclinical and clinical development of synthetic lethality. *Mol Med.* 2011. [Epub ahead of print.]

4. O'Shaughnessy J, Osborne C, Pippen JE, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med.* 2011;364:205-214.

5. Blakeley JO, Ye X, Grossman SA, et al. Poly (ADP-ribose) polymerase-1 (PARP1) inhibitor BSI-201 in combination with temozolomide (TMZ) in malignant glioma. *J Clin Oncol.* 2010;28(15S):Abstract 2010.

6. Dent RA, Lindeman GJ, Clemons M, et al. Safety and efficacy of the oral PARP inhibitor olaparib (AZD2281) in combination with paclitaxel for the first- or second-line treatment of patients with metastatic triple-negative breast cancer: results from the safety cohort of a phase I/II multicenter trial. *J Clin Oncol.* 2010;28(15S):Abstract 1018.

7. Giaccone G, Rajan A, Kelly RJ, et al. A phase I combination study of olaparib (AZD2281; KU-0059436) and cisplatin (C) plus gemcitabine (G) in adults with solid

tumors. *J Clin Oncol.* 2010;28(15S):Abstract 3027.
8. Isakoff SJ, Overmoyer B, Tung NM, et al. A phase II trial of the PARP inhibitor veliparib (ABT888) and temozolomide for metastatic breast cancer. *J Clin Oncol.* 2010;28(15S):Abstract 1019.
9. Ji JJ, Kummar S, Chen AP, et al. Pharmacodynamic response in phase I combination study of ABT-888 and topotecan in adults with refractory solid tumors and lymphomas. *J Clin Oncol.* 2010;28(15S):Abstract 2514.
10. Kummar S, Chen AP, Ji JJ, et al. A phase I study of ABT-888 in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. *J Clin Oncol.* 2010;28(15S):Abstract 2605.
11. Moulder S, Mita M, Bradely C. A phase 1b study to assess the safety and tolerability of the PARP inhibitor iniparib (BSI-201) in combination with irinotecan for the treatment of patients with metastatic breast cancer (MBC). In: *Proceedings from the 33rd Annual CTRC-AACR San Antonio Breast Cancer Symposium*; December 8-15, 2010; San Antonio, TX. Abstract P6-15-01.
12. Tan AR, Givvon MN, Stein RA, et al. Preliminary results of a phase I trial of ABT-888, a poly(ADP-ribose) polymerase (PARP) inhibitor, in combination with cyclophosphamide. *J Clin Oncol.* 2010;28(15S):Abstract 3000.
13. Sanofi-aventis reports top-line results from phase III study with iniparib (BSI-201) in metastatic triple-negative breast cancer [press release]. Bridgewater, NJ: sanofi-aventis; January 27, 2011. http://sanofi-aventis.mediaroom.com/index.php?s=43&item=310. Accessed April 1, 2011.
14. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP)-ribose polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet.* 2010;376:235-244.
15. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP)-ribose polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet.* 2010;376:245-251.

Abstracts of Interest

33rd Annual San Antonio Breast Cancer Symposium

ACOSOG Z1031: Neoadjuvant Comparison between Letrozole, Anastrozole, and Exemestane for Postmenopausal Women with Estrogen Receptor–Rich Stage 2/3 Breast Cancer

ACOSOG Z1031 investigators identified 2 data sets that will help inform the design of larger adjuvant endocrine trials. One finding will help in the selection of agents: Letrozole, anastrozole, and exemestane showed no difference in efficacy in the neoadjuvant setting for postmenopausal women with estrogen receptor–rich (Allred 6-8) clinical stage 2/3 breast cancer. The other finding will help in patient selection: Patients with pretreatment intrinsic subtype luminal B had more favorable preoperative endocrine prognostic index scores than patients with subtype luminal A. This finding suggests that because approximately one-third of women with subtype luminal A may be able to avoid chemotherapy, they are not suitable for larger adjuvant endocrine trials. *Ellis M, et al. Abstract S1-2.*

Obesity at Diagnosis Is Associated with Inferior Outcomes in Hormone Receptor–Positive Breast Cancer

Evaluating the results of 3 Eastern Cooperative Oncology Group trials—E1199, E5188, and E3189—investigators identified a strong relationship between body mass index (BMI) and disease-free survival (DFS) and overall survival (OS). They found that a BMI >30 kg/m^2 at diagnosis is associated with significantly inferior DFS and OS in women with hormone receptor–positive operable breast cancer treated with adjuvant chemotherapy. The investigators concluded that their findings imply that factors associated with obesity may predispose this subset of patients to recurrence. *Sparano JA, et al; for the Southwest Oncology Group; Cancer and Leukemia Group B; North Central Cancer Treatment Group. Abstract S2-1.* ●

A Review of Investigational Drugs at HOPA

By Christin Melton

A review of promising investigational drugs at the annual Hematology/Oncology Pharmacy Association meeting shows the pharmaceutical industry is responding to the call for more targeted agents in oncology. While a few drugs in the pipeline offer little survival advantage over current standards of care, clinical trials suggest their greater selectivity results in less toxicity. Robert T. Dorr, PhD, RPh, a professor of pharmacology at the Arizona Cancer Center in Tucson, expects a handful of new agents to come to market in the United States in the next year.

Prostate Cancer Pipeline

The drug furthest along in the prostate cancer pipeline is abiraterone acetate, which studies show improves overall survival (OS) in men with metastatic castration-resistant prostate cancer (CRPC). Abiraterone is an orally administered, small-molecule, irreversible inhibitor of the CYP17A1 enzyme. Inhibiting CYP17A1 blocks the downstream synthesis of dehydroepiandrosterone (DHEA) and other androgen precursors into testosterone. Abiraterone is more selective and 10 to 30 times more potent than the commonly used ketoconazole. A pivotal, phase 3, randomized trial (N = 1195) demonstrated that adding abiraterone to prednisone improved OS by 3.9 months in men with CRPC previously treated with docetaxel chemotherapy. Adverse effects were "relatively minimal and easily managed," said Dorr, with the most common being fluid retention and hypertension. Dorr added that it is not yet clear whether abiraterone exacerbated underlying cardiovascular risk in this elderly patient population or produced it. Dorr expects the US Food and Drug Administration (FDA) to approve abiraterone later this year.

MDV3100 is another emerging therapy for metastatic CRPC, but Dorr said abiraterone's success has hindered recruitment for the phase 3 trials needed to support the manufacturer's New Drug Application. Preliminary study data show that the androgen-receptor antagonist produced fairly high rates of prostate-specific antigen response in chemotherapy-naive and previously treated patients, and he believes it will ultimately receive FDA approval.

Breast Cancer Therapies

TDM-1, a novel agent for HER2-positive breast cancer, suffered a setback when the FDA deferred approving the drug pending stronger evidence of its efficacy. TDM-1 combines trastuzumab and a derivative of the microtubule antibody maytansine, and Dorr considers it superior to trastuzumab. He expects forthcoming trial data to provide the FDA with enough evidence that TDM-1 improves response and OS to warrant approval.

Robert T. Dorr, PhD, RPh

"At the highest dose, you actually get regression with this construct. … In some breast tumors, you can get near-total suppression," he said. Although trastuzumab inhibits tumor growth, it does not typically spur tumor regression. Phase 2 studies suggest that TDM-1 is far less toxic than trastuzumab. "This is a big improvement for patients, that you can get the same outcome with markedly reduced toxicity," he said.

Crizotinib in Lung Cancer

Crizotinib, which Dorr called "a home run," is another drug he expects to see approved soon. Crizotinib is an oral small-molecule inhibitor, effective for the 5% of patients with non–small cell lung cancer who have chromosomal rearrangements of anaplastic lymphoma kinase. Phase 1/2 trial (N = 82) results published in the *New England Journal of Medicine* last year by Kwak and colleagues disclosed that 80% of heavily pretreated patients achieved partial response (PR), complete response (CR), or stable disease (SD).

A follow-up analysis slotted for the upcoming annual meeting of the American Society of Clinical Oncology is expected to show responses were fairly durable and is likely to report improvement in OS. Crizotinib appears to be relatively safe, with most toxicities ≤grade 1. "The only grade 3 toxicities we are seeing is AST [alanine aminotransferase] and ALT [aspartate aminotransferase] elevations, and 80% of these patients could go down to 200 mg twice daily," said Dorr. He added that dose-limiting fatigue was seen at a dose of 300 mg twice daily. Approval could be delayed if the FDA does not approve the companion diagnostic test submitted for consideration at the same time.

Drugs in Hematologic Malignancies

The pace of drug development in chronic myeloid leukemia (CML) does not appear to be slowing. Of the most promising investigational agents, bosutinib (SKI-606) is probably the furthest along. Like the currently approved tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib, bosutinib is not effective in patients with a *T315I* mutation. Bosutinib's primary targets are ABL, SRC, and CAMK26, and it has a maximum tolerated dose of 500 mg once daily. Bosutinib has demonstrated activity in phase 2 trials, which have reported CRs and major molecular response in nearly three-quarters (74%) of patients resistant to or unable to tolerate imatinib and in patients resistant to dasatinib or nilotinib. Trials report low rates of grade 3/4 toxicities, with diarrhea, neutropenia, and hypomagnesemia among the most common.

"The problem that happened with bosutinib is that the so-called pivotal 3000 trial that was supposed to show a superior cytogenetic response rate [over imatinib] at 1 year did not reach its primary end point," he said. Despite this, the manufacturer filed a New Drug Application with the FDA in the hopes that it might be approved as a second- or third-line agent, which Dorr believes is likely.

Dorr discussed 2 agents progressing down the multiple myeloma pipeline. Carfilzomib is a proteasome inhibitor undergoing investigation in a large, closely watched, phase 3 trial enrolling patients refractory to bortezomib. He expressed skepticism as to whether it would prove superior to existing agents in terms of efficacy but praised its lower toxicity profile. An added benefit of carfilzomib is that patients do not need steroid treatment while taking it.

Pomalidomide is another promising drug for refractory multiple myeloma. It is an oral immunomodulatory agent, and preliminary phase 1/2 trial data presented by Lacy and associates at the American Society of Hematology meeting in December 2010 indicated that it was highly active in patients with heavily pretreated disease. They reported an overall response rate (ORR) of 62%, and Dorr said 24% of PR fell into the "very good" category. One-third of patients experienced neutropenia ≥grade 3, which might be something to watch for in future analyses.

Is Axitinib Next in Kidney Cancer?

Patients with renal cell carcinoma (RCC) refractory to sorafenib could have a new option soon. A 2007 phase 2 trial of the oral drug axitinib, which Dorr described as a "pure" inhibitor of vascular endothelial growth factor (VEGF) 1, 2, and 3, demonstrated a 44% ORR using RECIST criteria, time to progression of 15.7 months, and median OS of 29.9 months. Rini and colleagues enrolled 62 heavily pretreated patients with refractory metastatic RCC in a single-arm trial of axitinib and found that most patients experienced PR or SD. Grade 3/4 adverse events included hand-foot syndrome, which he noted is a class effect of VEGF inhibitors.

"I think RCC is turning out to be a little like CML. You'll start on a drug and ultimately fail on it, move to another one and then another one, and there's a possibility you can later go back to an original drug and get response," said Dorr.

BRAF a Target in Melanoma

Constitutively active $BRAF^{V600E}$ mutations are found in 60% of patients with melanoma.

PLX4032 (also known as RG7204), a powerful inhibitor of $BRAF^{V600E}$, is the furthest along in development. Early trial results in advanced melanoma showed that most patients with a $BRAF^{V600E}$ mutation achieved PR or CR and that 81% of patients saw their tumors shrink by at least 30%, which prompted numerous headlines touting PLX4032 as a possible cure. Many patients ultimately become refractory to the drug, however, and some researchers are looking at whether combining it with a MET inhibitor might provide more durable responses. A January 2011 press release by the companies making PLX4032 announced that upcoming preliminary data would show improved OS and PFS for patients taking PLX4032 as part of a phase 3 trial. "I think the molecular drug will probably be approved sometime next year," Dorr said.

Dorr predicted that in the coming year, we would likely see many more novel targeted agents making their way out of the crowded oncology pipeline. He expects a number of RET and MET inhibitors and drugs that affect RAS signaling to start generating interest. We have "maybe 15 or 16 kinase inhibitors in the armamentarium now," he said, but with more than 500 protein kinases identified in humans, a tremendous amount of room remains for future discovery. ●

Robert T. Dorr receives a salary from AmpliMed Corporation, for which he is chief executive officer; owns interest in stock in AmpliMed; and has received royalties from Clinovel.

Ask the Experts

YOUR QUESTIONS ANSWERED

Newsletter Series

4th Annual Considerations in Multiple Myeloma

Editor in Chief
Sagar Lonial, MD
Associate Professor of
Hematology and Oncology
Emory University School of Medicine

Topics include:

- Newly Diagnosed Patients
- Maintenance Therapy
- Transplant-Eligible Patients
- Retreatment
- Transplant-Ineligible Patients
- Cytogenetics
- Side-Effect Management
- Bone Health

www.coexm.com/myeloma

This activity is supported by an educational grant
from Millennium Pharmaceuticals, Inc.

Takeda MILLENNIUM THE TAKEDA ONCOLOGY COMPANY

3rd Annual Considerations in Lymphomas

Editor in Chief
Stephanie A. Gregory, MD
The Elodia Kehm Chair of Hematology
Professor of Medicine
Director, Section of Hematology
Rush University Medical Center/Rush University

Topics include:

- Hodgkin Lymphoma
- Follicular Lymphoma
- Mantle Cell Lymphoma
- Waldenstrom's Macroglobulinemia
- Diffuse Large B-Cell Lymphoma
- T-Cell Lymphoma

www.coexm.com/lymphoma

This activity is supported by educational grant from Cephalon Oncology,
Millennium Pharmaceuticals, Inc., and Seattle Genetics, Inc.

Cephalon Oncology · Takeda MILLENNIUM THE TAKEDA ONCOLOGY COMPANY · SeattleGenetics

Submit your questions at www.coexm.com/ask-experts

Target Audience

These activities were developed for physicians, nurses, and pharmacists.

Accreditation

This activity has been approved for 1.0 *AMA PRA Category 1 Credit*™ (a total of 14.0 credit hours will be issued for completion of all activities). Nursing and Pharmacy credit hours will also be provided. For complete learning objectives and accreditation information, please refer to each activity.

This activity is jointly sponsored by Global Education Group and Medical Learning Institute, Inc.

Coordination for this activity provided by Center of Excellence Media, LLC.

global EDUCATION GROUP · Medical Learning Institute, Inc. LEADERS IN MEDICAL ACCREDITATION MLI · COE CENTER OF EXCELLENCE MEDIA, LLC

For information about the physician accreditation of this activity, please contact Global at 303-395-1782 or inquire@globaleducationgroup.com.

PROVENGE® (sipuleucel-T)

Suspension for Intravenous Infusion **Rx Only**

BRIEF SUMMARY – See full Prescribing Information for complete product information

INDICATIONS AND USAGE: PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

DOSAGE AND ADMINISTRATION

- **For Autologous Use Only.**
- The recommended course of therapy for PROVENGE is 3 complete doses, given at approximately 2-week intervals.
- Premedicate patients with oral acetaminophen and an antihistamine such as diphenhydramine.
- Before infusion, confirm that the patient's identity matches the patient identifiers on the infusion bag.
- **Do Not Initiate Infusion of Expired Product.**
- Infuse PROVENGE intravenously over a period of approximately 60 minutes. **Do Not Use a Cell Filter.**
- Interrupt or slow infusion as necessary for acute infusion reactions, depending on the severity of the reaction.

(See Dosage and Administration [2] of full Prescribing Information.)

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

- **PROVENGE is intended solely for autologous use.**
- **Acute infusion reactions** (reported within 1 day of infusion) included, but were not limited to, fever, chills, respiratory events (dyspnea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. In controlled clinical trials, 71.2% of patients in the PROVENGE group developed an acute infusion reaction.

  In controlled clinical trials, severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. The incidence of severe events was greater following the second infusion (2.1% vs 0.8% following the first infusion), and decreased to 1.3% following the third infusion. Some (1.2%) patients in the PROVENGE group were hospitalized within 1 day of infusion for management of acute infusion reactions. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

  Closely monitor patients with cardiac or pulmonary conditions. In the event of an acute infusion reaction, the infusion rate may be decreased, or the infusion stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed.

- **Handling Precautions for Control of Infectious Disease.** PROVENGE is **not** routinely tested for transmissible infectious diseases. Therefore, patient leukapheresis material and PROVENGE may carry the risk of transmitting infectious diseases to health care professionals handling the product. Universal precautions should be followed.
- **Concomitant Chemotherapy or Immunosuppressive Therapy.** Use of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) given concurrently with the leukapheresis procedure or PROVENGE has not been studied. PROVENGE is designed to stimulate the immune system, and concurrent use of immunosuppressive agents may alter the efficacy and/or safety of PROVENGE. Therefore, patients should be carefully evaluated to determine whether it is medically appropriate to reduce or discontinue immunosuppressive agents prior to treatment with PROVENGE.
- **Product Safety Testing.** PROVENGE is released for infusion based on the microbial and sterility results from several tests: microbial contamination determination by Gram stain, endotoxin content, and in-process sterility with a 2-day incubation to determine absence of microbial growth. The final (7-day incubation) sterility test results are not available at the time of infusion. If the sterility results become positive for microbial contamination after PROVENGE has been approved for infusion, Dendreon will notify the treating physician. Dendreon will attempt to identify the microorganism, perform antibiotic sensitivity testing on recovered microorganisms, and communicate the results to the treating physician. Dendreon may request additional information from the physician in order to determine the source of contamination.

(See Warnings and Precautions [5] of full Prescribing Information.)

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety evaluation of PROVENGE is based on 601 prostate cancer patients in the PROVENGE group who underwent at least 1 leukapheresis procedure in four randomized, controlled clinical trials. The control was non-activated autologous peripheral blood mononuclear cells.

The most common adverse events, reported in patients in the PROVENGE group at a rate ≥15%, were chills, fatigue, fever, back pain, nausea, joint ache, and headache. Severe (Grade 3) and life-threatening (Grade 4) adverse events were reported in 23.6% and 4.0% of patients in the PROVENGE group compared with 25.1% and 3.3% of patients in the control group. Fatal (Grade 5) adverse events were reported in 3.3% of patients in the PROVENGE group compared with 3.6% of patients in the control group.

Serious adverse events were reported in 24.0% of patients in the PROVENGE group and 25.1% of patients in the control group. Serious adverse events in the PROVENGE group included acute infusion reactions *(see Warnings and Precautions)*, cerebrovascular events, and single case reports of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare.

PROVENGE was discontinued in 1.5% of patients in Study 1 (PROVENGE group n=341; Control group n=171) due to adverse events. Some patients who required central venous catheters for treatment with PROVENGE developed infections, including sepsis. A small number of these patients discontinued treatment as a result. Monitoring for infectious sequelae in patients with central venous catheters is recommended.

Each dose of PROVENGE requires a standard leukapheresis procedure approximately 3 days prior to the infusion. Adverse events that were reported ≤1 day following a leukapheresis procedure in ≥5% of patients in controlled clinical trials included citrate toxicity (14.2%), oral paresthesia (12.6%), paresthesia (11.4%), and fatigue (8.3%).

Table 1 provides the frequency and severity of adverse events reported in ≥5% of patients in the PROVENGE group of randomized, controlled trials of men with prostate cancer. The population included 485 patients with metastatic castrate resistant prostate cancer and 116 patients with non-metastatic androgen dependent prostate cancer who were scheduled to receive 3 infusions of PROVENGE at approximately 2-week intervals. The population was age 40 to 91 years (median 70 years), and 90.6% of patients were Caucasian.

Table 1 Incidence of Adverse Events Occurring in ≥5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any Adverse Event	**591 (98.3)**	**186 (30.9)**	**291 (96.0)**	**97 (32.0)**
Chills	319 (53.1)	13 (2.2)	33 (10.9)	0 (0.0)
Fatigue	247 (41.1)	6 (1.0)	105 (34.7)	4 (1.3)
Fever	188 (31.3)	6 (1.0)	29 (9.6)	3 (1.0)
Back pain	178 (29.6)	18 (3.0)	87 (28.7)	9 (3.0)
Nausea	129 (21.5)	3 (0.5)	45 (14.9)	0 (0.0)
Joint ache	118 (19.6)	11 (1.8)	62 (20.5)	5 (1.7)
Headache	109 (18.1)	4 (0.7)	20 (6.6)	0 (0.0)
Citrate toxicity	89 (14.8)	0 (0.0)	43 (14.2)	0 (0.0)
Paresthesia	85 (14.1)	1 (0.2)	43 (14.2)	0 (0.0)
Vomiting	80 (13.3)	2 (0.3)	23 (7.6)	0 (0.0)
Anemia	75 (12.5)	11 (1.8)	34 (11.2)	7 (2.3)
Constipation	74 (12.3)	1 (0.2)	40 (13.2)	3 (1.0)
Pain	74 (12.3)	7 (1.2)	20 (6.6)	3 (1.0)
Paresthesia oral	74 (12.3)	0 (0.0)	43 (14.2)	0 (0.0)
Pain in extremity	73 (12.1)	5 (0.8)	40 (13.2)	1 (0.3)
Dizziness	71 (11.8)	2 (0.3)	34 (11.2)	0 (0.0)
Muscle ache	71 (11.8)	3 (0.5)	17 (5.6)	0 (0.0)
Asthenia	65 (10.8)	6 (1.0)	20 (6.6)	2 (0.7)
Diarrhea	60 (10.0)	1 (0.2)	34 (11.2)	3 (1.0)
Influenza-like illness	58 (9.7)	0 (0.0)	11 (3.6)	0 (0.0)
Musculoskeletal pain	54 (9.0)	3 (0.5)	31 (10.2)	3 (1.0)
Dyspnea	52 (8.7)	11 (1.8)	14 (4.6)	3 (1.0)
Edema peripheral	50 (8.3)	1 (0.2)	31 (10.2)	1 (0.3)
Hot flush	49 (8.2)	2 (0.3)	29 (9.6)	1 (0.3)
Hematuria	46 (7.7)	6 (1.0)	18 (5.9)	3 (1.0)
Muscle spasms	46 (7.7)	2 (0.3)	17 (5.6)	0 (0.0)
Hypertension	45 (7.5)	3 (0.5)	14 (4.6)	0 (0.0)
Anorexia	39 (6.5)	1 (0.2)	33 (10.9)	3 (1.0)
Bone pain	38 (6.3)	4 (0.7)	22 (7.3)	3 (1.0)
Upper respiratory tract infection	38 (6.3)	0 (0.0)	18 (5.9)	0 (0.0)
Insomnia	37 (6.2)	0 (0.0)	22 (7.3)	1 (0.3)
Musculoskeletal chest pain	36 (6.0)	2 (0.3)	23 (7.6)	2 (0.7)
Cough	35 (5.8)	0 (0.0)	17 (5.6)	0 (0.0)
Neck pain	34 (5.7)	3 (0.5)	14 (4.6)	2 (0.7)
Weight decreased	34 (5.7)	2 (0.3)	24 (7.9)	1 (0.3)
Urinary tract infection	33 (5.5)	1 (0.2)	18 (5.9)	2 (0.7)
Rash	31 (5.2)	0 (0.0)	10 (3.3)	0 (0.0)
Sweating	30 (5.0)	1 (0.2)	3 (1.0)	0 (0.0)
Tremor	30 (5.0)	0 (0.0)	9 (3.0)	0 (0.0)

*Control was non-activated autologous peripheral blood mononuclear cells.

Cerebrovascular Events. In controlled clinical trials, cerebrovascular events, including hemorrhagic and ischemic strokes, were reported in 3.5% of patients in the PROVENGE group compared with 2.6% of patients in the control group.

(See Adverse Reactions [6] of full Prescribing Information.)

To report SUSPECTED ADVERSE REACTIONS, contact Dendreon Corporation at 1-877-336-3736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Dendreon Corporation
3005 First Avenue
Seattle, Washington 98121

Dendreon
Targeting Cancer, Transforming Lives®

P-A-11.10-073.00

PROVENGE®
(sipuleucel-T)

In asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer

PROVENGE is the first in a new class of therapy

that is designed to activate a patient's own antigen-presenting cells to stimulate an immune response against prostate cancer.

- **Extends median survival beyond 2 years**—25.8 months compared with 21.7 months for patients in the control* group (*P*=.032)
- **Reduction in risk of death—22.5%** (HR=0.775, 95% CI: 0.614, 0.979)
- **Therapy completed in 3 cycles**—3 infusions, at approximately 2-week intervals†
- **Most common adverse events are primarily mild or moderate**—chills, fatigue, fever, back pain, nausea, joint ache, and headache

*Control was nonactivated, autologous, peripheral blood mononuclear cells.
†The dosing interval ranged from 1 to 15 weeks in controlled clinical trials.

INDICATION: PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

IMPORTANT SAFETY INFORMATION: PROVENGE is intended solely for autologous use and is not routinely tested for transmissible infectious diseases.

In controlled clinical trials, serious adverse events reported in the PROVENGE group include acute infusion reactions (occurring within 1 day of infusion) and cerebrovascular events. Severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

The most common adverse events (incidence ≥15%) reported in the PROVENGE group are chills, fatigue, fever, back pain, nausea, joint ache, and headache.

Please see Brief Summary of full Prescribing Information on the adjacent page.

Dendreon
Targeting Cancer, Transforming Lives®

P-A-02.11-007.00

www.PROVENGE.com

PROVENGE®
(sipuleucel-T)
Stimulate a Response