

Current Challenges and Future Strategies in the Management of Patients With Hematologic Malignancies

Based on data presented at:

The CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Ortho Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Ortho Biotech Products, L.P.; and preceding the 45th Annual Meeting of the American Society of Hematology (ASH) December 6-9, 2003/San Diego, California

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Guest Editor

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Drugs discussed in this report:

Generic Name	Brand Name(s)
Alkylating Agent Cyclophosphamide	Cytosan®, Neosar®
Analgesic (and other uses) Acetylsalicylic acid (aspirin)	Multiple brand names
Antimetabolites Cytarabine Methotrexate sodium	Cytosar-U® Methotrexate sodium injection and sodium tablets, Trexall® tablets
Antibiotics/Antineoplastics Amoxicillin Bleomycin sulfate Dacarbazine Doxorubicin HCl (conventional doxorubicin) Doxorubicin HCl liposome injection (pegylated liposomal doxorubicin) Etoposide Mechlorethamine HCl Procarbazine HCl Vinblastine sulphate Vincristine	Amoxil® capsules, tablets, chewable tablets, and powder for oral suspension Blenoxane® for injection DTIC-Dome® Adriamycin® PFS/RDF injection Caelyx®, Doxil® Etopophos®, Toposar®, VePesid® Mustargen® for injection Matulane® capsules Velban® Oncovin®, Vincasar PFS®, Vincrex®
Antiviral Acyclovir sodium	Zovirax® for injection
Corticosteroids Dexamethasone Prednisolone sodium phosphate	Decadron® elixir and tablets Orapred®, Pediapred® oral solutions
Hematopoietic Agents Darbepoetin alfa Granulocyte colony-stimulating factor (G-CSF; filgrastim) Granulocyte/macrophage-colony stimulating factor (GM-CSF; sargramostim) Recombinant human erythropoietin (epoetin alfa) Recombinant human erythropoietin (epoetin beta)	Aranesp® for injection Neupogen® for injection Leukine® Procrit® for injection Neorecormon®
Immunomodulatory Agent Thalidomide	Thalomid® capsules
Laxative Standardized senna concentrate and docusate sodium	Senokot-S®, Ex-Lax®, and other brand names
Monoclonal Antibodies Gemtuzumab ozogamicin Rituximab	Mylotarg™ for injection Rituxan® for infusion, I.V.
<i>The following are in phase 1, 2, or 3 trials:</i>	
Farnesyltransferase Inhibitor Tipifarnib (R115777)	Zarnestra™

Welcome to The Foundation for Better Health Care CME.

Needs Assessment

Through needs assessment surveys, literature searches, advisory board suggestions, and previous meeting evaluations, The Foundation for Better Health Care (FBHC) has determined a need to address current challenges and future strategies in hematology.

Overall Goal

This comprehensive report was designed to educate physicians who treat hematologic malignancies or hematologic complications.

Learning Objectives

The FBHC supports the recent Institute of Medicine's recommendations that "All healthcare professionals should be educated to deliver patient-centered care as members of an interdisciplinary team, emphasizing evidence-based practice, quality improvement approaches and informatics."¹

Upon completion of this CME activity, participants should have improved overall knowledge, skills, and attitudes concerning the current challenges and future strategies in hematology. Specifically, participants should be able to:

- 1) Reflect on new treatment strategies for multiple myeloma in order to apply these in their clinical practice
- 2) Outline the current goals and anticipated benefits of established and new treatment strategies for chemotherapy-related anemia in order to recognize patients who would benefit from therapy
- 3) Summarize potential future applications of erythropoietic agents to identify new areas of research
- 4) Discuss present and future challenges in lymphoma management in order to properly assess and treat patients with this hematologic malignancy

Clinical recommendations are based upon evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications to care for your patients.

¹ Greiner AC, Knebel E, eds. *Health Professions Education: A Bridge to Quality*. Washington, DC: National Academy Press; 2003.

Intended Audience

This activity is designed for US-based hematologists, oncologists, and other healthcare professionals who treat hematologic malignancies or hematologic complications.

Method of Clinician Participation

Read the comprehensive report carefully and complete the post-test (see p. 21). A minimum score of 80% on the post-test must be obtained in order to be awarded credit. There is no fee for this activity. Credit for the post-test is available until June 28, 2005.

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FBHC Medical Director Catherine Bozeman, MD	Nothing to disclose
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- Once-weekly dosing of epoetin alfa (40,000-60,000 U subcutaneously) is not approved by the United States Food and Drug Administration (FDA) for treatment of chemotherapy-induced anemia (see pp. 9, 10, 11, 12, 14, 15, 16).
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- Epoetin beta dosed at 300 IU/kg, 3 times a week, is not approved by the FDA for anemia correction in patients with solid tumors (see pp. 15, 16).
- Pegylated liposomal doxorubicin is not approved by the FDA for treatment of multiple myeloma (see pp. 6, 7, 8, 9).

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**Editorial:**

Current Challenges and Future Strategies in the Management of Patients With Hematologic Malignancies

Mohamad A. Hussein, MD, Director, Myeloma Research Program, Cleveland Clinic Taussig Cancer Center, Cleveland, Ohio

The management of hematologic malignancies is entering a new era in which patients are being treated based on both the origin and clinical presentation of their cancer as well as its genotype and molecular behavior. The goal in the management of hematologic malignancies is to prolong survival while maintaining the patient's quality of life. Drug resistance remains a major barrier to achieving treatment goals. Importantly, we are now beginning to understand some of the mechanisms whereby hematologic malignant cells evade drug-induced apoptosis. Greater understanding of the underlying processes and pathways that occur at the molecular level in the malignant process have allowed us to develop targeted cytostatic agents with the potential to be more specific, more effective, and less toxic. Some of these agents include monoclonal antibodies, tyrosine kinase inhibitors, antiangiogenic therapies, and farnesyltransferase inhibitors.

Perhaps one of the best examples of the advances resulting from targeted therapies is in the treatment of acute myeloid leukemia (AML). Current induction regimens for AML are controversial, with no single agent considered a standard of care. Phase 2 studies of gemtuzumab ozogamicin, a recently introduced CD33-targeted monoclonal antibody, demonstrated a 31% remission rate (defined as $\leq 5\%$ blasts in the bone marrow, neutrophils $\geq 1,500/\mu\text{L}$, hemoglobin ≥ 9 g/dL, and red blood cell and platelet transfusion independence), a 14% early mortality rate, and a median overall survival of 5.4 months in younger patients and 5.9 months in older patients, but with significant hematologic toxicities (Stadtmauer EA et al. *Proc Am Soc Clin Oncol*. 2001;20:301a. Abstract 1203). In contrast, the novel agent tipifamib, an oral farnesyltransferase inhibitor, has resulted in an overall response rate (complete plus partial responses) of 33%, positive overall survival with the majority of responders ($>60\%$) alive at 15 months, and a

favorable side-effect profile in a phase 2 trial (CTEP/NCI-1754) of newly diagnosed adults with poor-risk AML and myelodysplastic syndrome (Lancet JE et al. *Blood*. 2003;102 [suppl 11]: Abstract 613). One of the important aspects of the study is the high median age (74 years) of the patients participating. Traditionally, this age population does not tolerate aggressive chemotherapeutic regimens. In this trial with tipifamib, patients over 75 years of age had an overall response rate of 36%, and a relatively low 13% of all patients had grade 4 toxicity—usually infection secondary to neutropenia.

This report will discuss new treatment approaches for multiple myeloma. The Waltzman article will review current considerations in the management of anemia in patients with hematologic malignancies. The Lewis article reports emerging data surrounding potential future applications for erythropoietic agents. Finally, the Canellos article will describe present and future challenges in the management of lymphoma. The underlying theme of these articles is that the overall goal in the treatment of hematologic malignancies is to achieve the best possible response rates and extend survival time with limited toxicity, so that patients will enjoy close to normal survival with minimal impact on their quality of life. ■

New Treatment Strategies for Multiple Myeloma

Based on data presented by Mohamad A. Hussein, MD, Director, Myeloma Research Program, Cleveland Clinic Taussig Cancer Center, Cleveland, Ohio

Multiple myeloma is the second most common hematologic malignancy, accounting for approximately 10% of all hematologic malignancies. The American Cancer Society (ACS) estimates there will be 15,270 new cases in the United States in 2004 (ACS Cancer Reference Information. Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_multiple_myeloma_30.asp?sitearea=. Accessed May 14, 2004). Multiple myeloma is characterized by increased plasma cells in the bone marrow, lytic bone lesions, and increased produc-

tion of monoclonal immunoglobulin (M-protein). Median age at diagnosis is 65 years, which is important since patient age and status play a major role in determining treatment approach. The myeloma cell inherits the many intrinsic systems that are characteristic of a normal plasma cell to adapt, grow, survive, and overcome drug-induced apoptosis (Figure 1, p. 6).

Median survival is 3 to 4 years for patients with multiple myeloma, and the ACS estimates 11,070 people will die from this disease in 2004 (ACS Cancer Reference Information.

Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_multiple_myeloma_30.asp?sitearea=. Accessed May 14, 2004). Multiple myeloma remains incurable despite the availability of many conventional and high-dose chemotherapy regimens. Since the myeloma cell has various mechanisms whereby it can resist drug-induced apoptosis, no major impact on overall survival has been achieved with any particular regimen or treatment strategy. New treatment approaches for multiple myeloma are presented in this article.

■ **Modifying Conventional Therapy: DvD**

Research has been conducted at the Cleveland Clinic to investigate the

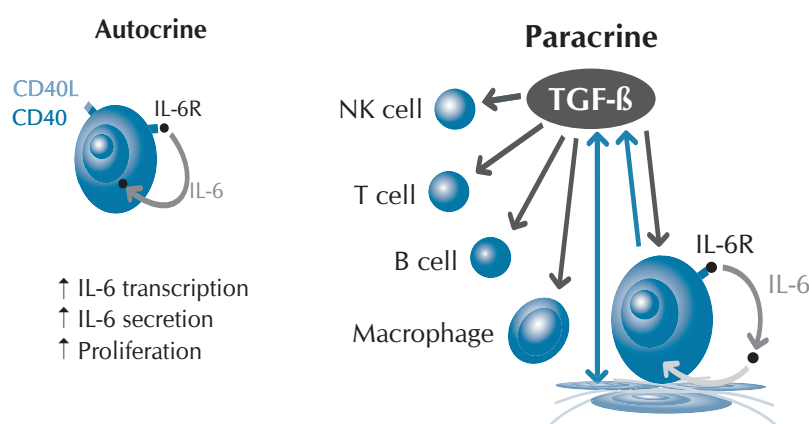
feasibility of modifying one of the conventional chemotherapy regimens of VAd therapy (0.4 mg vincristine daily, 9.0 mg/m² conventional doxorubicin daily over 24 hours for 4 consecutive days, and 40 mg dexamethasone orally on days 1-4, 9-12, and 17-20, with treatment repeated every 4 weeks). In this modified regimen, called DVd, pegylated liposomal doxorubicin (40 mg/m² intravenous [IV] on day 1) has been used as a replacement for conventional doxorubicin. Pegylated liposomal doxorubicin consists of doxorubicin that has been encapsulated in

liposomes to alter the pharmacokinetics and pharmacology of the chemotherapy agent. As a result, the pegylated formulation remains in the circulation longer than conventional doxorubicin. Because it also permits extravasation (leakage) from the permeable vasculature of tumors, leading to greater accumulation of doxorubicin in the tumor tissue, it can potentially reduce associated toxicities (Hussein MA et al. *Cancer*. 2002;95:2160-2168; Yuan F et al. *Cancer Res*. 1994;54:3352-3356; Schueller JJS et al. 24th SABCS. Abstract 436). The slow-dividing nature of plasma cells and increased

angiogenesis in the bone marrow of patients with multiple myeloma allows the malignant plasma cell to be exposed to a high concentration of doxorubicin for a lengthy period of time, which, according to in vitro data, increases malignant plasma cell kill and could overcome multidrug resistance. In addition, the convenience of administering this formulation in the outpatient setting provides the rationale for integrating the long-acting liposomal encapsulated form of doxorubicin—pegylated liposomal doxorubicin—into this regimen (Hussein MA et al. *Cancer*. 2002;95:2160-2168). In the DVd regimen, the dexamethasone schedule is reduced (40 mg/day administered orally only during the first 4 days of each cycle); vincristine 2 mg IV is given on day 1.

With the above rationale in mind, a phase 2 study was conducted to investigate the efficacy and tolerability of the DVd regimen in patients with newly diagnosed multiple myeloma (Hussein MA et al. *Cancer*. 2002;95:2160-2168). Thirty-three patients received IV pegylated liposomal doxorubicin (40 mg/m²) and vincristine (2 mg) on day 1, and 40 mg oral or IV dexamethasone on days 1 to 4 only. This regimen was repeated every 4 weeks for a minimum of 6 cycles; 2 more cycles were administered after best response was achieved. Prophylactic use of growth factors was prohibited, but growth factor support could be given to patients who had developed prolonged neutropenia during a previous DVd cycle. Subsequently, vitamin B₆ (200 mg/day) was added to the protocol to minimize the risk of developing hand-foot syndrome (HFS). Overall response rate was 88%: 4 patients (12%) achieved complete response (CR) (complete disappearance of M-protein from serum and urine by immune fixation, along with < 3% plasma cells in the bone marrow by biopsy, and absence of monoclonal plasma cells by immune staining of the bone marrow on 2 different occasions 4 weeks apart); 7 patients (21%) achieved ≥ 75% decrease in M-protein; 13 patients (39%) achieved ≥ 50% to < 75% decrease in M-protein; and 5 patients (15%) achieved ≥ 25% to < 50%

Figure 1. Mechanisms of Myeloma Cell Growth



NF-κB activation
Cytokine production
– IL-6, IGF-1, TNF-α
MM growth, survival, anti-apoptosis,
drug resistance, migration

JUXTACRINE SIGNALING

MM CELL	BM SC	ECM
CD56	HSP	
LFA-1	ICAM-1	
VLA-4	VCAM-1	Fibronectin
VLA-5		Fibronectin
Syndecan		Type I Collagen

BM SC: bone marrow stromal cell; CD40L: CD40 ligand; ECM: extracellular matrix; HSP: heparin sulfate proteoglycan; IGF-1: insulin-like growth factor-1; IL-6: interleukin-6; IL-6R: interleukin-6 receptor; ICAM-1: intercellular adhesion molecule-1; LFA-1: lymphocyte function-associated antigen-1; MM: multiple myeloma; NK cell: natural killer cell; TGF-β: transforming growth factor-beta; TNF-α: tumor necrosis factor-alpha; VCAM-1: vascular adhesion molecule-1; VLA-4: very late antigen-4; VLA-5: very late antigen-5.

Urashima M et al. *Blood*. 1995;85:1903-1912; Urashima M et al. *Blood*. 1996;87:1928-1938; Chauhan D et al. *Blood*. 1996;87:1104-1112.

Source: Based on data presented by Mohamad A. Hussein, MD, at the CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Ortho Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Ortho Biotech Products, L.P., and preceding the 45th Annual Meeting of the American Society of Hematology (ASH), December 6-9, 2003, San Diego, California.

decrease in M-protein. Three patients (9%) had stable disease and 1 patient (3%) had progressive disease. "Patients who achieve stable disease and show no evidence of disease progression experience progression-free survival rates comparable to, if not better than, patients who achieve response [Browman GP et al. *J Clin Oncol*. 1995;13:2354-2369]; therefore, DVd can be considered beneficial even in these patients," Dr. Hussein noted. Median time to maximal response was 5.8 months (range, 0.7-13.6 months). The median time to progression was 23.1 months, and the median survival had not yet been reached at 60 months. Progression-free survival was 42% at 2 years and 23% at 3 years. Two-year and 3-year survival rates are estimated to be 79% and 67%, respectively. Median follow-up among the patients still alive is 62.0 months (range, 50.9-70.3 months).

No patients discontinued treatment due to adverse events, and the occurrence of HFS was less than 10% in patients who received education and supplemental vitamin B₆. Upon further analysis, it was the opinion of the investigators that the intensive patient education, rather than the addition of vitamin B₆, was responsible for the decrease in the incidence of HFS.

Interestingly, mean microvascular density (MVD) was significantly reduced from 3.8 ± 3.3 to 1.6 ± 2.3 ($P < .001$) in 17 patients with pre- and post-treatment evaluations. High pretreatment MVD was significantly associated with poor prognosis ($P = .02$). Despite the significant reduction in MVD, this finding did not significantly correlate with progression-free survival ($P = .88$). Antiangiogenic effects of DVd require further study.

DVd Versus VAd Randomized Trial

Because of the positive findings from the first phase 2 study of DVd, a confirmatory phase 2b, multicenter, randomized study was undertaken with an accrual goal of 250 evaluable patients to compare DVd ($n = 87$) with VAd ($n = 88$) in patients with newly diagnosed active multiple myeloma (Hussein MA et al. *Blood*. 2003;102. Abstract 1653). The doses

used in the phase 2b study were the same as those used in phase 2. Primary endpoints included objective response and clinical benefit (defined as reduced hospitalization, documented sepsis, antibiotic use, and grade 3 or 4 neutropenia or neutropenic fever). Patient demographics and clinical characteristics were similar between groups; mean age was 60 years in both groups. Response rates were comparable in both arms (DVd vs VAd: complete remission, 3.4% vs 0%; remission, 14.9% vs 13.6%; and partial remission, 25.3% vs 25.0%). In contrast, substantially less toxicity was seen in patients receiving DVd compared with VAd (Table 1). Notably, grade 3/4 neutropenia occurred in significantly fewer patients (8.0% vs 22.7%, respectively; $P < .05$) and rates of sepsis showed a trend toward statistical significance (3.4% vs 8.0%, respectively). In addition, hospitalizations for drug administration were less frequent and hospital days for complications were reduced by a mean of 1 day (7.4 vs 8.4) with DVd versus VAd.

Based on this body of data, the recently published National Comprehensive

Cancer Network (NCCN) multiple myeloma treatment guidelines recommended the use of DVd as one of the first-line conventional therapies.

Thalidomide (T) and DVd in Newly Diagnosed and Relapsed/Refractory Patients

Thalidomide is an attractive agent because of its multiple effects, which include direct inhibition of multiple myeloma cell growth and survival; direct stimulation of the cellular immune system; modulation of integrins compromising the adhesive interactions between the multiple myeloma cells and bone marrow stroma, resulting in alteration of secretion of cytokines such as interleukin-6 (IL-6); sensitizing myeloma cells to chemotherapy; and thalidomide's anti-angiogenic effects (Raje N, Anderson K. *N Engl J Med*. 1999;341:1606-1609). Thalidomide does not reverse the angiogenic activity in the multiple myeloma patients' bone marrows; yet it prevents new angiogenic vessels from forming.

Table 1. Multicenter Trial in Newly Diagnosed Multiple Myeloma: Toxicity Comparison of DVd and VAd

	DVd (n = 87)	VAd (n = 88)
Hospitalization* (%) (95% CI)	37.9 (27.7-48.1)	35.2 (25.2-45.2)
Mean days of hospitalization (95% CI)	7.4 (6.3-8.5)	8.4 (6.8-10.0)
Receiving antibiotics (%) (95% CI)	59.8 (49.5 - 70.1)	68.2 (58.5 - 77.9)
Documented sepsis (%) (95% CI)	3.4 (0.0-7.3)	8.0 (2.3-13.6)
Grade 3/4 neutropenia (%) (95% CI)	8.0 (2.3-13.8)[†]	22.7 (14.0-31.5)

*Hospitalization due to adverse events.

[†] $P < .05$.

CI: confidence interval; n: number of patients; DVd: pegylated liposomal doxorubicin + vincristine + reduced-dose dexamethasone; VAd: vincristine + conventional doxorubicin + reduced-dose dexamethasone.

Adapted from Hussein M et al. 45th Annual Meeting of the ASH. Poster 1653.

Source: Based on data presented by Mobamad A. Hussein, MD, at the CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Ortho Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Ortho Biotech Products, L.P.; and preceding the 45th Annual Meeting of the American Society of Hematology (ASH), December 6-9, 2003, San Diego, California.

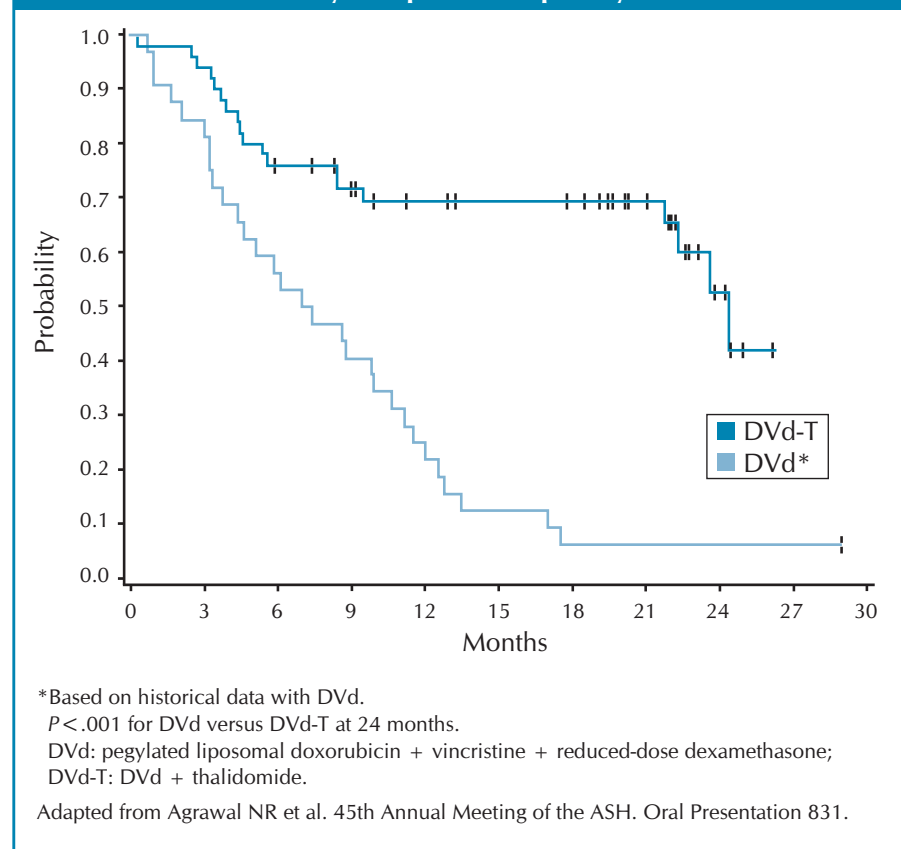
The standard treatment schedule of thalidomide at the Cleveland Clinic multiple myeloma research program is to start patients on thalidomide at 50 mg every night before sleep and increase by 50 mg weekly to the maximal tolerated dose, not to exceed 400 mg (Farray D et al. *Proc Am Soc Clin Oncol.* 2002;21:276a. Abstract 1103). Due to its side-effect profile, supportive therapies should include senna laxative, increased fluid intake, and supplementing vitamin B₁₂ and folates for deficient patients (Beckmann MJ et al. *Am J Clin Pathol.* 1995;104:305. Abstract; Baz R et al. *Blood.* 2002;100. Abstract 2368). Preliminary data from ongoing single-agent studies of thalidomide in patients with newly diagnosed multiple myeloma show response rates of approximately 30%; in combination with steroids, response rates are approximately 60%.

The ability of thalidomide to sensitize the myeloma cells to chemotherapy and steroids in addition to the theoretical benefit of maintaining the antiangiogenic activity achieved by the DVd regimen provides the rationale for combination of thalidomide with DVd. This was the impetus for a study evaluating DVd-T in newly diagnosed and relapsed/refractory multiple myeloma patients (Agrawal NR et al. *Blood.* 2003;102. Abstract 831). Patients received standard DVd and thalidomide regimens followed by prednisolone 50 mg every other day and the maximum tolerated dose of thalidomide until disease progression or intolerable toxicity. One hundred patients have been enrolled, with data available on 90 patients (45 newly diagnosed and 45 relapsed/refractory). Response was assessed according to Southwest Oncology Group (SWOG) criteria; near-complete response (NCR)

was defined as $\geq 90\%$ reduction of the M-protein and $< 10\%$ plasma cells in the bone marrow. A deep-vein thrombosis (DVT) diagnostic algorithm and neuropathy dose reduction schema were utilized. Reviewing patient demographics, relapsed/refractory patients were older than newly diagnosed patients (median, 64 vs 58 years), tended to have worse performance status (PS 0, 22% vs 42%), and had a higher baseline $\beta 2$ microglobulin level (mean, 6.6 vs 4.6 mg/L). Both groups received a median of 6 cycles of treatment.

The first 31 patients showed increased grade 3/4 toxicities (neutropenia, bacterial and viral infections, paresthesia, and deep venous thrombosis (DVT). Therefore, the following supportive measures were implemented: prophylactic amoxicillin 250 mg twice daily (BID), acyclovir 400 mg BID, aspirin 81 mg/day; sargramostim (granulocyte/macrophage colony-stimulating factor; GM-CSF) or filgrastim (granulocyte colony-stimulating factor; G-CSF) if the total white blood cell count was less than 5,000/L on day 1 of therapy; and a more aggressive vincristine dose reduction schema. After the amendments, neutropenic fevers and pneumonia dropped from 8 cases in the refractory patients to none in the next 74 patients enrolled; there were no neutropenic fevers requiring therapy; and DVT was reduced from an overall rate of 33% to 10%. Complete and near-complete response rates to DVd-T were impressive and virtually identical in newly diagnosed patients and relapsed/refractory patients (46% vs 47%, respectively). Stable disease or better occurred in 84% of newly diagnosed patients and 89% of refractory/relapsed patients. Median time to first response was 1.1 months and 1.8 months, in the newly diagnosed and relapsed/refractory patients, respectively. Best response was noted at a median of 4.2 months for patients in both groups. Comparison of time to progression in newly diagnosed patients receiving DVd-T versus historical data for newly diagnosed patients receiving DVd alone did not demonstrate any significant difference at 9 months ($P = .79$); however, longer follow-up is needed. In marked contrast, a significant ($P < .001$) benefit

Figure 2. Time to Progression/Relapse in Refractory/Relapsed Multiple Myeloma



Source: Based on data presented by Mohamad A. Hussein, MD, at the CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Ortho Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Ortho Biotech Products, L.P.; and preceding the 45th Annual Meeting of the American Society of Hematology (ASH), December 6-9, 2003, San Diego, California.

was seen in time to progression in relapsed/refractory patients receiving DVd-T versus DVd (Figure 2, p. 8). Longer follow-up is needed to clarify the effects of DVd-T on progression-free and overall survival. ■

Key Points in Focus

- Multiple myeloma remains an incurable disease, with drug resistance being a major contributor. New treatment approaches are needed that produce increased response rates and improved survival with minimal toxicity in patients with newly diagnosed and relapsed/refractory disease.
- In a phase 2 trial of DVd (pegylated liposomal doxorubicin, vincristine, reduced-schedule dexamethasone), an 88% overall response rate and a 12% complete response (CR) rate were seen in newly diagnosed patients. In addition, significant ($P < .001$) reductions in mean microvascular density were observed following DVd treatment; further study of this effect is warranted. In a confirmatory multicenter randomized phase 2b study in newly diagnosed patients, DVd compared with VAd (vincristine, conventional doxorubicin, reduced-dose dexamethasone) had comparable response rates but substantially less toxicity, and required less time in hospital for drug administration and side effects.
- Thalidomide (T) and DVd have different and complementary mechanisms of action, providing the rationale for studying the combination. Early research has shown that DVd-T results in relatively high CR/near-CR rates in both newly diagnosed (46%) and relapsed/refractory (47%) multiple myeloma patients, similar to the responses achieved by single autologous stem cell transplantation.
- When compared with historical control patients who had received DVd alone, adding T appeared to significantly improve time to progression in patients with relapsed or refractory disease. It is too early, however, to determine its effect on newly diagnosed patients and overall survival.

Erythropoietic Agents: Current Considerations

Based on data presented by Roger J. Waltzman, MD, Assistant Professor, Medical Oncology, St. Vincent's Cancer Center, and Assistant Professor, St. Vincent's Hospital, New York, New York

Anemia is a common complication in patients with hematologic malignancies, resulting in increased transfusion requirements and decreased quality of life (QOL) (Coiffier B et al. *Eur J Cancer*. 2001;37:1617-1623; Cella D. *Semin Oncol*. 1998;25:43-46). Anemia results primarily from the myelosuppressive effects of cytotoxic treatments or radiation therapy, although it can also be related to the disease itself—especially in patients with hematologic malignancies. Current considerations in the treatment of anemia, including standard of care, criteria for anemia treatment, and dosing strategies, are discussed in this article.

■ Standard of Care: Epoetin Alfa

Epoetin alfa (recombinant human erythropoietin [r-HuEPO]) was approved in 1993 for the treatment of anemia

in patients with nonmyeloid malignancies where anemia is due to effect of concomitantly administered chemotherapy, and has been the standard of care over the last decade (Procrit® [package insert]. Bridgewater, NJ: Ortho Biotech Products, L.P.; 2003; NCCN 9th Annual Conference Clinical Practice Guidelines & Outcomes Data in Oncology, 2004. Available at: http://www.nccn.org/professionals/physician_gls/default.asp. Accessed May 14, 2004). The United States Food and Drug Administration (FDA)-approved dose is 150 U/kg subcutaneously (SC) 3 times weekly (TIW); however, the dose most commonly used in oncology clinical practice is 40,000 U once weekly (QW) (NCCN 9th Annual Conference Clinical Practice Guidelines & Outcomes Data in Oncology, 2004. Available at: http://www.nccn.org/professionals/physician_gls/default.asp).

Table 1. Chemotherapy-Related Anemia: Efficacy of Epoetin Alfa

Study	Starting Dose	Study Duration (Weeks)	Mean Hb Δ at 4 Weeks (g/dL)	Mean Hb Δ at Study End (g/dL)	QOL Assessment Tool
Littlewood (N = 244)	150 U/kg TIW	28	0.8*	2.2*	LASA, SF-36, FACT-An
Gabrilove (N = 2,964)	40,000 U QW	16	1.0	1.8	LASA, FACT-An
Demetri (N = 2,289)	10,000 U TIW	16	1.0	2.0	LASA, FACT-An
Glaspy (N = 2,030)	150 U/kg TIW	16	1.1	1.8	LASA, FACT-An
Sloan (N = 172)	40,000 U QW	16	1.2	3.1	LASA, FACT-An
Shasha (N = 442)	40,000 U QW	16	1.1	1.7	LASA

*Estimated values based on graph of mean Hb over time.

Δ: change; FACT-An: Functional Assessment of Cancer Therapy-Anemia; Hb: hemoglobin; LASA: linear analog scale assessment; N: number of study patients; QOL: quality of life; QW: once weekly; SF-36: Short Form 36 health survey; TIW: three times weekly; U: units.

Littlewood TJ et al. *J Clin Oncol*. 2001;19:2865-2874. Gabrielove JL et al. *J Clin Oncol*. 2001;19:2875-2882. Demetri GD et al. *J Clin Oncol*. 1998;16:3412-3425. Glaspy J et al. *J Clin Oncol*. 1997;15:1218-1234. Sloan JA et al. *J Clin Oncol*. In press. Sasha D et al. *Cancer*. 2003;98:1072-1079.

Source: Based on data presented by Roger J. Waltzman, MD, at the CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Ortho Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Ortho Biotech Products, L.P.; and preceding the 45th Annual Meeting of the American Society of Hematology (ASH), December 6-9, 2003, San Diego, California.

Accessed May 14, 2004). These dosing regimens have been demonstrated to be clinically equivalent (NCCN 9th Annual Conference Clinical Practice Guidelines & Outcomes Data in Oncology, 2004. Available at: http://www.nccn.org/professionals/physician_gls/default.asp. Accessed May 14, 2004; Cheung W et al. *Eur J Clin Pharmacol.* 2001;57:411-418). Epoetin alfa dosed TIW and QW has been shown to increase hemoglobin (Hb) levels by approximately 1 g/dL after 4 weeks of therapy and approximately 2 g/dL after 8 weeks, to improve QOL, and to reduce transfusion requirements in controlled clinical trials, large community-based studies, and clinical practice (Table 1, p. 9) (NCCN 9th Annual Conference Clinical Practice Guidelines & Outcomes Data in Oncology, 2004. Available at: http://www.nccn.org/professionals/physician_gls/default.asp. Accessed May 14, 2004). In a randomized, multicenter, controlled study of cancer patients

receiving nonplatinum chemotherapy, significantly ($P = .006$) fewer patients treated with epoetin alfa 150 to 300 U/kg SC TIW for 12-24 weeks required transfusions after 28 days of treatment compared with patients who received placebo (24.7% vs 39.5%) (Littlewood TJ et al. *J Clin Oncol.* 2001;19:2865-2874).

The Hb increases seen in 2 large, community-based studies of epoetin alfa 40,000 U SC QW in anemic cancer patients receiving chemotherapy (Gabrilove JL et al. *J Clin Oncol.* 2001; 19:2875-2882) or chemoradiation (Shasha D et al. *Cancer.* 2003;98:1072-1079) were virtually unchanged even after accounting for the impact on Hb levels of transfusion within 28 days before Hb was recorded (Data on file, Ortho Biotech Products, L.P.). In addition, in a large, community-based study evaluating epoetin alfa dosed at 40,000 U QW in anemic cancer patients receiving chemotherapy, significant linear analog scale assess-

ment (LASA) QOL improvements were seen (19.4%-30.0%; $P < .001$) that significantly correlated with the magnitude of Hb increase ($P < .001$; $r = 0.173$) (Gabrilove JL et al. *J Clin Oncol.* 2001; 19:2875-2882). "Based on these data from about 8,000 patients, we have come to expect a clinically and statistically significant Hb increase of 1 g/dL at week 4 and 2 g/dL at week 8 with epoetin alfa TIW or QW and sustained Hb increases to week 16 (end of study) that relate to significant overall transfusion reductions and QOL improvements. We utilize early Hb response as a measure of efficacy of erythropoietic agents, especially since we know that this increase correlates with clinical improvements in QOL," Dr. Waltzman noted.

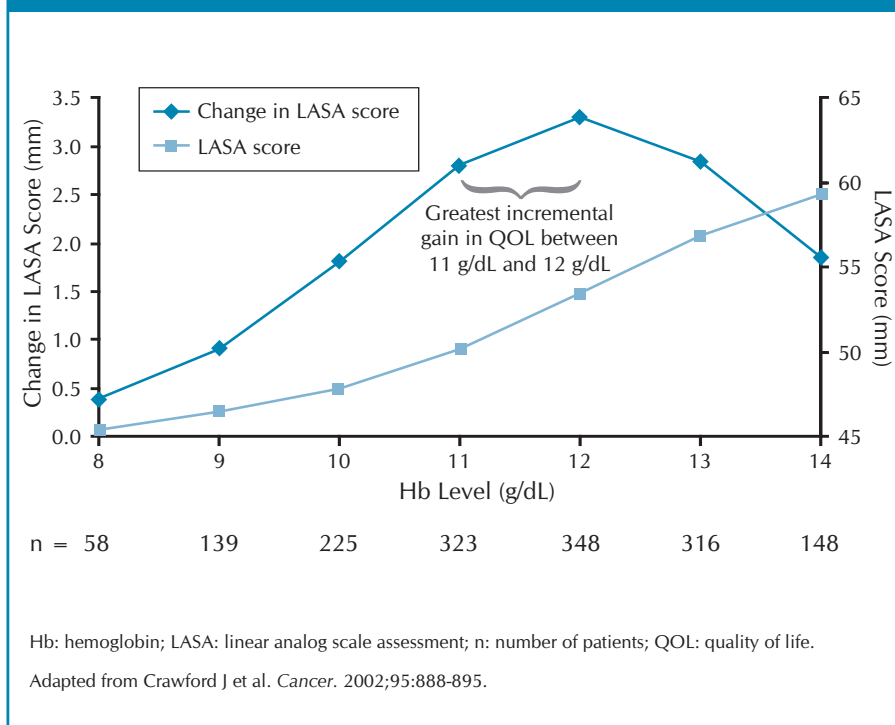
Target Hb for Anemia Correction

A subject of ongoing research and interest is the optimal target Hb level for optimizing patient QOL and ameliorating symptoms of anemia. An incremental analysis of LASA QOL data from 2 large, community-based studies evaluating epoetin alfa for the treatment of anemia in cancer patients receiving chemotherapy found the relationship between incremental change in QOL and 1-g/dL increases in Hb to be nonlinear (Crawford J et al. *Cancer* 2002; 95:888-895). The greatest incremental gain in QOL occurred as Hb increased from 11 g/dL to 12 g/dL (Figure 1).

Weighing the Options: Darbepoetin Alfa

Darbepoetin alfa was recently introduced into clinical practice with an FDA approval in July 2002 for the treatment of anemia in patients with nonmyeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy (Aranesp® [package insert]. Thousand Oaks, CA: Amgen Inc.; 2003). The indicated dose is 2.25 µg/kg QW; however, 3.0 µg/kg (about 200 µg) every 2 weeks (Q2W) is the dose most commonly used in clinical oncology practice in the United States (Blayney DW et al. *Proc Am Soc Clin Oncol.* 2003; 22:747. Abstract 3003; Vadhan-Raj S et al. *Proc Am Soc Oncol.* 2003;22:732. Abstract 2942). Structural and pharmacokinetic differences between

Figure 1. Change in Hemoglobin Level Correlates With Change in QOL: Incremental Analysis



Source: Based on data presented by Roger J. Waltzman, MD, at the CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Ortho Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Ortho Biotech Products, L.P.; and preceding the 45th Annual Meeting of the American Society of Hematology (ASH), December 6-9, 2003, San Diego, California.

darbepoetin alfa and endogenous erythropoietin or epoetin alfa, respectively, include (Egrie JC, Browne JK. *Br J Cancer*. 2001;84[suppl 1]:3-10):

- 5 versus 3 N-linked sugar chains
- Increased negative charge due to increased number of sialic acid residues
- 51% versus ~40% carbohydrate content
- Molecular weight 37.1 kDa versus 30.4 kDa

Darbepoetin alfa has an increased serum half-life (33-48 hours vs 16-19 hours for epoetin alfa after SC administration) and a decreased binding affinity for the erythropoietin receptor (1:4 ratio) versus epoetin alfa (Cheung W et al. *Eur J Clin Pharmacol*. 2001;57:411-418; Egrie JC, Browne JK. *Br J Cancer*. 2001;84[suppl 1]:3-10). In clinical trials, Hb increases seen with darbepoetin alfa have been comparable to those seen with epoetin alfa at the end of study—typically 12 to 16 weeks (Table 2). The proportion of

patients with early response (Hb increase of at least 1 g/dL after 4 weeks) has either not been reported or has been relatively low in these trials (Table 2). A recent study evaluated the time spent, number of clinic visits, and other QOL issues in 140 patients receiving darbepoetin alfa or epoetin alfa (and long- or short-acting white blood cell growth factors) while undergoing chemotherapy (Beveridge RA et al. *Pharmacotherapy*. 2003;23[12 pt 2]:101S-109S). Over the approximately 3-week period, the researchers found that the number of clinic visits was comparable (4.0 vs 3.8 per chemotherapy cycle) regardless of whether patients were receiving darbepoetin alfa (primarily given Q2W) or epoetin alfa (usually given QW). Compared with epoetin alfa, Q2W dosing of darbepoetin alfa led to a reduction in the number of injections per cycle (2.5 vs 1.3); however, the results of a related patient satisfaction survey indicated that patients generally tolerated the injections well, moderately disagreeing

with the statement that "receiving injections is a painful experience."

An interim analysis was conducted on data from 1,173 anemic (Hb \leq 11 g/dL) cancer patients receiving chemotherapy and darbepoetin alfa 3.0 μ g/kg Q2W enrolled in a randomized open-label study (Successful Outcomes in Anemia Research [SOAR]) (Blayney DW et al. *Proc Am Soc Clin Oncol*. 2003;22:747. Abstract 3003; Vadhan-Raj S et al. *Proc Am Soc Oncol*. 2003;22:732. Abstract 2942). A mean Hb increase from baseline of approximately 1 g/dL was achieved after 8 weeks of therapy and the mean Hb increase was approximately 1.7 g/dL at week 16 (end of treatment) ($P < .001$) in the intent-to-treat (ITT) population (Blayney DW et al. *Proc Am Soc Clin Oncol*. 2003;22:747. Abstract/Oral Presentation 3003). Quality of life results in this study were promising, with a 19% improvement in Functional Assessment of Cancer Therapy-Fatigue (FACT-F) and Energy Numerical Rating Grade (ENRG) at week 17 ($P < .001$) (Vadhan-Raj S et al. *Proc Am Soc Oncol*. 2003;22:732. Abstract/Oral Presentation 2942). Further research is warranted to determine darbepoetin alfa's effect on overall QOL.

Table 2. Chemotherapy-Related Anemia: Efficacy of Darbepoetin Alfa

Study	Starting Dose	Study Duration (Weeks)	Mean Hb Δ at 4 Weeks (g/dL)	Mean Hb Δ at Study End (g/dL)	QOL Assessment Tool
Vansteenkiste (N = 156)	2.25 μ g/kg QW	12	Not reported	Not reported	FACT-F
Hedenus* (N = 17)	2.25 μ g/kg QW	12	0.4	1.6	FACT-F
Glaspay* (N = 216)	0.5-8.0 μ g/kg QW	12	0-1.5	1.4-2.75	FACT-F
Kotasek (N = 198)	4.5-15.0 μ g/kg Q3W	12	Not reported	0.7-2.25	FACT-F
Vadhan-Raj (N = 1,173)	3.0 μ g/kg Q2W	16	Not reported	1.7 (ITT)	FACT-F ENRG

*Dose-finding study.

ENRG: Energy Numerical Rating Grade; FACT-F: Functional Assessment of Cancer Therapy-Fatigue; Hb: hemoglobin; ITT: intent to treat; N: number of study patients; QOL: quality of life; QW: once weekly; Q2W: every 2 weeks; Q3W: every 3 weeks.

Vansteenkiste J et al. *J Natl Cancer Inst*. 2002;94:1211-1220.

Hedenus M et al. *Br J Haematol*. 2002;119:79-86.

Glaspay JA et al. *Br J Cancer*. 2002;87:268-276.

Kotasek D et al. *Eur J Cancer*. 2003;39:2026-2034.

Vadhan-Raj S et al. 39th Annual Meeting of the ASCO. Abstract/Oral Presentation 2942.

Source: Based on data presented by Roger J. Waltzman, MD, at the CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Ortho Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Ortho Biotech Products, L.P.; and preceding the 45th Annual Meeting of the American Society of Hematology (ASH), December 6-9, 2003, San Diego, California.

Optimizing Efficacy in Anemia Treatment: Front-Loading Strategies

Erythropoietic agents are also being studied in novel dosing schedules, such as front-loading (ie, higher starting doses) followed by maintenance (ie, less frequent) dosing. "The hypothesis is that with front-loading dosing strategies there is a potential for achieving more timely increase in Hb and/or higher response rates and identifying nonresponders earlier, while maintaining cost neutrality with standard dosing," noted Roger J. Waltzman, MD. A proof-of-concept study was conducted in 20 anemic (Hb \leq 11 g/dL; mean baseline Hb, 10.1 g/dL) patients receiving chemotherapy for nonmyeloid malignancies (Patton J et al. *Oncologist*. 2004; 9:90-96). The study evaluated a 60,000-U QW initial dose of epoetin alfa followed by 120,000 U every 3 weeks (Q3W) in patients whose Hb

increased by at least 2 g/dL after at least 8 weeks. Treatment was continued for a maximum of 24 weeks. Mean Hb had increased by 1.0 ± 1.1 g/dL at week 4 and by 2.9 ± 1.9 g/dL at week 8 to 13.0 g/dL. Of the patients who went on to receive maintenance dosing, mean Hb levels were maintained at approximately 13.0 g/dL until end of study. A similar study was conducted with darbepoetin alfa in 241 anemic (Hb < 11 g/dL; mean baseline Hb, 10.2 g/dL) patients receiving chemotherapy for non-myeloid malignancies (Hesketh PJ et al. *Proc Am Soc Clin Oncol*. 2003;22:731. Abstract 2941). The study evaluated a QW darbepoetin alfa 325- μ g fixed dose versus a 4.5- μ g/kg weight-based dose followed by a Q3W maintenance dose of 325 μ g or 4.5 μ g/kg after first achievement of Hb ≥ 12 g/dL. Treatment duration was 16 weeks. After approximately 9 weeks, a mean Hb of 12 g/dL was reached and this mean Hb level was maintained with the Q3W dose until study end (week 16).

■ Head-to-Head Trials Comparing Epoetin Alfa and Darbepoetin Alfa

While it appears that there may be differences in the timing and magnitude of responses with these 2 agents in individual studies, direct comparisons are confounded by variations in clinical trial design and patient populations. "An important measure of efficacy that needs to be compared is time to Hb response and importance of early Hb response in

terms of transfusion requirements and QOL endpoints," Dr. Waltzman noted. Head-to-head trials with somewhat different designs and endpoints are ongoing. One such study is a phase 3, multicenter, open-label comparison in 300 anemic (Hb ≤ 11 g/dL) patients receiving chemotherapy for solid tumors. The study will evaluate epoetin alfa 40,000 to 60,000 U QW versus darbepoetin alfa 200 to 300 μ g Q2W with dose escalation according to National Comprehensive Cancer Network (NCCN) cancer- and treatment-related anemia guidelines. The trial is powered for comparison of hematologic and QOL endpoints between agents and stratifies patients by platinum versus nonplatinum chemotherapy. Preliminary results suggest some differences in hematologic outcomes favoring epoetin alfa, including Hb change at weeks 4, 8, and 12 (Data on file, Ortho Biotech Products, L.P.). A second ongoing trial is a pooled analysis of 3 phase 2 studies (100 patients each), which evaluates epoetin alfa 40,000 U QW versus darbepoetin alfa 200 μ g Q2W, with dose escalation at 4 weeks in nonresponders for each agent. These individual trials are not powered for comparison between agents, do not stratify patients by chemotherapy type, and do not include QOL endpoints. Updated results were presented at the 40th Annual Meeting of the American Society of Clinical Oncology (ASCO) in June 2004 (Waltzman RJ et al. 40th Annual Meeting of the ASCO. Abstract 8153; Schwartzberg L. 40th Annual Meeting of the ASCO. Abstract 8063). ■

Key Points in Focus

- Anemia is a frequent complication associated with hematologic malignancies and their treatment. Epoetin alfa 3 times weekly (TIW) or once weekly (QW) has been associated with hemoglobin (Hb) increases of approximately 1 g/dL after 4 weeks and approximately 2 g/dL after 8 weeks; significant reductions in transfusion requirements; and significant quality of life (QOL) improvements.
- Incremental analysis of linear analog scale assessment (LASA) QOL data from 2 large, community-based studies showed that the greatest incremental improvement in patient QOL occurred when Hb increased from 11 to 12 g/dL, indicating that 12 g/dL represents an important target for maximizing patient QOL.
- Darbepoetin alfa was recently introduced for the treatment of chemotherapy-related anemia. Both QW and every-2-week (Q2W) dosing studies have demonstrated Hb increases and reduction in transfusion requirements that are at best comparable to epoetin alfa at study end, but early Hb increases (1 g/dL at week 4) have not been consistently demonstrated. A recent study did not show a difference in clinic visits with QW or Q2W dosing of both erythropoietic agents.
- To achieve goals such as more timely increase in Hb, higher response rates, and ability to identify nonresponders sooner, front-loading doses of epoetin alfa or darbepoetin alfa followed by less frequent maintenance doses are being investigated. Results from studies of both agents are promising.
- Updated results of head-to-head trials comparing the efficacy of epoetin alfa and darbepoetin alfa were presented at the ASCO meeting in June 2004.

Future Applications of Erythropoietic Agents

Based on data presented by Lionel D. Lewis, MA, MBBCh, MD, FRCP (London), Professor of Medicine/Pharmacology & Toxicology, Dartmouth Medical School, Hanover, New Hampshire, and Co-Director, Phase I Oncology Program, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Preclinical and early clinical research has been conducted to determine the role of erythropoietin (EPO) and the erythropoietin receptor (EPO-R) in various tissues. These data and potential future applications of erythropoietic agents are the focus of this article.

EPO and EPO-R Tissue Distribution and Cellular Action

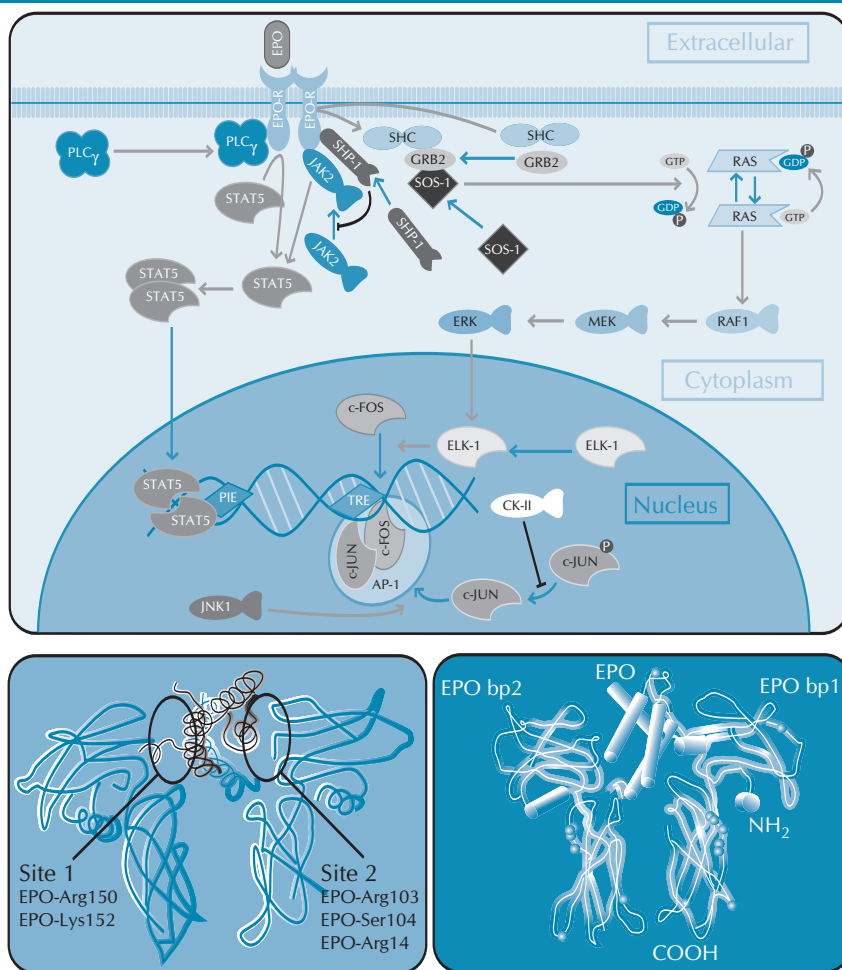
Erythropoietin receptors have been detected in a variety of cells and tissues (Juil SE et al. *Early Hum Dev.* 1998;52:235-249; Lappin TR et al. *Stem Cells.* 2002;20:485-492). In one study evaluating tissue distribution in the developing human fetus, EPO-Rs were detected in endothelial cells; myocardiocytes; macrophages; retinal cells; and cells of the adrenal cortex and medulla, small bowel, spleen, liver, kidney and lung (Juil SE et al. *Early Hum Dev.* 1998;52:235-249). In addition, although EPO was more prominent in the kidney, expression was seen in the liver parenchymal cells, neural retina of the eye, and adrenal cortex. An understanding of the mechanism of action of EPO provides insight into its potential function in other systems (Syed RS et al. *Nature.* 1998;395:511-516) (Figure 1). Erythropoietin binds to 2 adjacent EPO-Rs on the membrane of target cells and triggers several intracellular signaling pathways, including Janus family kinase 2 (JAK2)/signal transducer and activator of the transcription protein 5 (STAT5) and mitogen-activated protein kinase (MAPK), which regulate cell survival, proliferation, and differentiation. "Importantly, epoetin alfa has the same molecular structure, weight, carbohydrate content, sialic acid residues, amino acid sequence, and receptor binding affinity as endogenous EPO, and both compounds stimulate erythropoiesis in precisely the same way," commented Lionel D. Lewis, MD.

Non-Chemotherapy-Related Anemia

"A growing population that requires special attention is the elderly, especially because they are at increased

risk for cancer and anemia," Dr. Lewis noted. Anemia can be caused by iron deficiency or chronic disease in the elderly; it has also been suggested that an imbalance develops between inhibitory cytokines, particularly tumor necrosis factor (TNF) and interleukin-6 (IL-6) and the stimulatory cytokines EPO, interleukin-3 (IL-3), and granulocyte/macrophage colony-stimulating factor (GM-CSF) in bone marrow progenitors

Figure 1. Erythropoietin Receptor and Signaling



Arg: arginine; bp: base pair; CK-II: casein kinase II; EPO: erythropoietin; EPO-R: erythropoietin receptor; ERK: extracellular signal-regulated kinase; GDP: guanosine 5'-diphosphate; Grb2: growth factor receptor-binding protein 2; GTP: guanosine 5'-triphosphate; JAK2: Janus family kinase 2; JNK1: c-Jun N-terminal kinase 1; Lys: lysine; MEK: mitogen-activated ERK kinase; Ser: serine; PLC γ : Phospholipase C-gamma; PIE: prolactin inducible element; SHP-1: Src homology domain 2 (SH2)-containing tyrosine phosphatase-1; SOS-1: son of sevenless homolog protein; STAT5: signal transducer and activator of the transcription protein 5; TRE: TPA responsive element.

Adapted from Syed RS et al. *Nature.* 1998;395:511-516.

Source: Based on data presented by Lionel D. Lewis, MD, at the CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Ortho Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Ortho Biotech Products, L.P.; and preceding the 45th Annual Meeting of the American Society of Hematology (ASH), December 6-9, 2003, San Diego, California. Lower panels reprinted by permission from *Nature* (Syed RS et al. *Nature.* 1998;395:511-516) © 1998, Macmillan Publishers Ltd.

(Ershler WB. *J Am Geriatr Soc.* 2003; 51[3 suppl]:S18-S21). Research is ongoing to delineate the prevalence and consequences of anemia in the elderly, and studies evaluating erythropoietic agents are warranted. Patients undergoing radiation therapy also frequently experience anemia. In a recent open-label, community-based study, epoetin alfa administered 40,000 to 60,000 U once weekly (QW) for 16 weeks resulted in a significant increase in mean hemoglobin (Hb) (1.9 g/dL; $P < .05$) in 442 evaluable anemic (Hb ≤ 11 g/dL) patients receiving radiation therapy concomitantly or sequentially with chemotherapy for nonmyeloid malignancies. Among 407 of the patients who were on the study for 30 or more days, there was a 74% overall response rate (Hb increase ≥ 2 g/dL or Hb ≥ 12 g/dL). Additionally, there were reductions in transfusion requirements, and significant linear analog scale assessment (LASA) quality of life (QOL) improvements ($P < .05$) in the 359 patients evaluable for QOL (Shasha D et al. *Cancer.* 2003; 98:1072-1079). Epoetin alfa QW was well tolerated, and the safety profile was similar to that seen among anemic cancer patients receiving chemotherapy.

■ Effects on Tumor Hypoxia and Treatment Outcomes

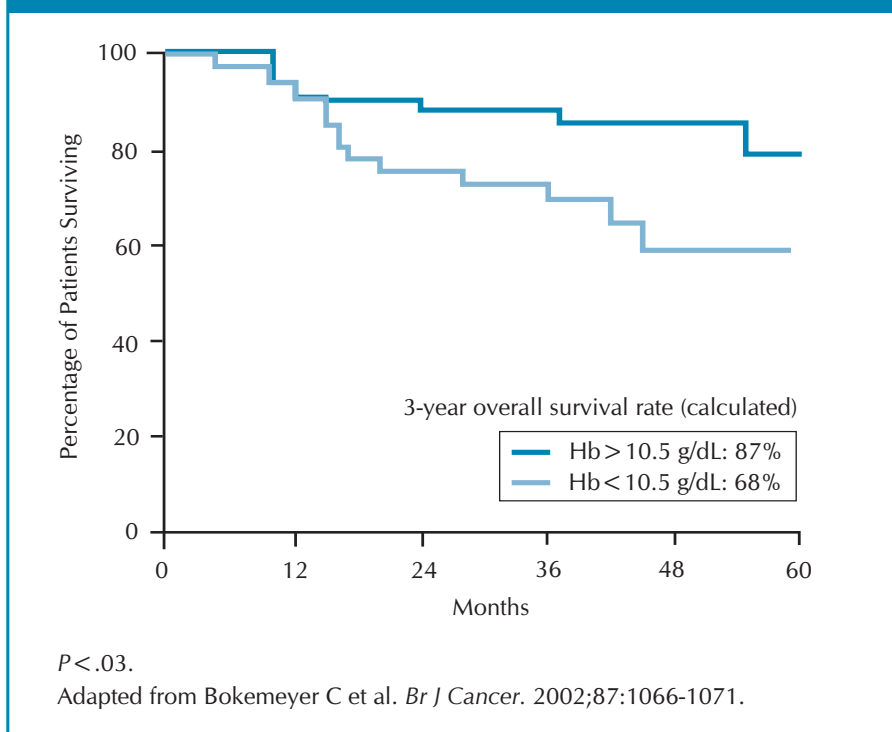
Hypoxia is a common attribute of solid tumors and often occurs as a result of anemia (Vaupel P et al. *Med Oncology.* 2001;18:243-259). This disorder results in tumor cells that have increased resistance to radiotherapy and some forms of chemotherapy and tend to be more aggressive (Vaupel P et al. *Med Oncology.* 2001;18:243-259). In an analysis of data from 89 patients receiving radiotherapy for advanced cancer of the uterine cervix, overall survival probabilities were significantly greater ($P = .004$) in patients with median $pO_2 \geq 10$ mm Hg versus $pO_2 < 10$ mm Hg treated with curative intent by primary radiation ($n = 42$; $P = .06$) or primary surgery ($n = 47$; $P = .01$) (Hockel M et al. *Cancer Res.* 1996;56:4509-4515).

Hemoglobin level has been shown to be a prognostic factor for progression-free survival and overall survival in many tumor types (Caro JJ et al. *Cancer.* 2001;91:2214-2221; Bokemeyer C et al. *Br J Cancer.* 2002;87:1066-1071) (Figure 2), as well as a predictive factor for treatment outcomes (Dunphy EP et al. *Int J Radiat Oncol Biol Phys.* 1989;16:1173-1178; Fein DA et al. *J Clin Oncol.* 1995;13:2077-2083; Lee WR et al. *Int J Radiat Oncol Biol Phys.* 1998;42:1069-1075; Obermair A et al. *Cancer.* 2001;92:903-908). Primarily preclinical and retrospective studies have been conducted to test the hypothesis that correcting anemia may influence treatment outcomes. In a recent preclinical study of 30 non-anemic female Fischer 344 rats, significantly fewer hypoxic measurements ($P = .008$) were seen in mammary carcinomas of rats randomized to epoetin alfa (2,000 U/kg/subcutaneous [SC] thrice weekly [TIW] for 2 weeks) versus placebo after tumor implantation (median pO_2 , 24.50 mm Hg vs

14.98 mm Hg) (Blackwell KL et al. *Cancer Res.* 2003;63:6162-6165). "The importance of these preclinical results is that the dose-response curve for tumor radiosensitivity is very linear and very steep between 1 and 10 mm Hg pO_2 ; based on this model, epoetin alfa certainly has the potential to yield beneficial effects on tumor oxygenation," Dr. Lewis added.

In a retrospective analysis of data from 191 patients undergoing pre-operative chemoradiation for squamous cell carcinoma of the oral cavity, patients with a pretreatment Hb ≥ 14.5 g/dL not treated with epoetin alfa and patients with pretreatment Hb < 14.5 g/dL treated with epoetin alfa had significantly ($P < .05$ and $P < .001$, respectively) higher complete response, locoregional control, and survival rates than patients with a pretreatment Hb < 14.5 g/dL not treated with epoetin alfa (Glaser CM et al. *Int J Radiat Oncol Biol Phys.* 2001; 50:705-715). The results of these

Figure 2. Anemia as a Prognostic Factor in Survival of Patients Receiving High-Dose Chemotherapy for Metastatic Testicular Cancer



Source: Based on data presented by Lionel D. Lewis, MD, at the CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Ortho Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Ortho Biotech Products, L.P.; and preceding the 45th Annual Meeting of the American Society of Hematology (ASH), December 6-9, 2003, San Diego, California. Reprinted by permission from [Nature](#) (Bokemeyer C et al. *Br J Cancer.* 2002;87:1066-1071) © 2002, Macmillan Publishers Ltd.

analyses and several others in patients with lung cancer, metastatic testicular cancer, cervical cancer, and mixed solid and nonmyeloid hematologic malignancies provide support for the benefit of maintaining normal Hb levels with epoetin alfa on treatment outcomes. These data are preliminary and, further, results of other studies are conflicting.

Recently, a double-blind, randomized, placebo-controlled, ex-US multicenter study designed to evaluate 12-month survival in metastatic breast cancer patients (N = 939) treated with epoetin alfa to maintain Hb between 12 and 14 g/dL showed a survival benefit in favor of the placebo group at 12 months, leading to early termination of the trial upon recommendation by the Independent Data Monitoring Committee; however, the survival curves converged at 19 months (Leyland-Jones B, BEST Investigators and Study Group. *Lancet Oncol.* 2003; 4:459-460).

In addition, another study evaluating the effects of epoetin beta (a formula of recombinant human erythropoietin not available in the United States) versus placebo on locoregional progression-free survival in 351 patients with head and neck cancer undergoing curative-intent radiotherapy suggested a deleterious effect of epoetin beta (Henke M. et al. *Lancet.* 2003;362:1255-1260). However, imbalances in the treatment groups and a large number of protocol violations (39% of the intent-to-treat population) may have contributed to the negative results and a lack of statistical power. The investigators of the study have acknowledged that baseline imbalances occurred, notably, more smokers and patients with relapsed cancer in the epoetin beta group than in the placebo group. Additionally, the population was highly heterogeneous with regard to resection status at baseline. While a significant difference was noted in progression-free survival between treatment groups for the intent-to-treat population, the largest subgroup (patients with completely resected tumors, comprising about half of the study population) demonstrated no difference between treatment groups ($P = .9$).

Overall, it is important to interpret the survival data with caution, as some of the studies discussed in this section were not prospectively designed to analyze the effect of erythropoietic agents on survival and treatment outcomes.

■ Potential Neurologic Applications

Preclinical research indicates that astrocytes are capable of producing EPO and that neurons have EPO-Rs. In a study conducted by Sakanaka et al, gerbils that received recombinant human erythropoietin (r-HuEPO) 2.5 to 25.0 U/day infused into their lateral ventricles were protected from ischemia-induced learning disabilities and insult to hippocampal CA1 neurons versus ischemic controls ($P < .05$) (Sakanaka M et al. *Proc Natl Acad Sci USA.* 1998;95:4635-4640). Recombinant human erythropoietin 5.0 U/day also reduced the number of degenerating synapses in the ischemic hippocampal CA1 field versus controls ($P < .01$). In another preclinical study conducted by Brines et al, mice given r-HuEPO (5,000 U/kg intraperitoneally [IP]) 24 hours before, during, or 3 hours after carotid artery occlusion showed significant ($P < .01$) and equivalent reduction of necrosis volume versus control mice (Brines ML et al. *Proc Natl Acad Sci USA.* 2000; 97:10526-10531). These results may have future implications for clinical practice.

Ehrenreich and colleagues studied the safety and efficacy of epoetin alfa in stroke patients in a 2-part evaluation (Ehrenreich H et al. *Mol Med.* 2002;8:495-505). In the phase 1 safety study, 13 patients received 33,000 U epoetin alfa infused intravenously for 30 minutes once daily for the first 3 days following a stroke. In the phase 2, double-blind, randomized, placebo-controlled efficacy study, 40 patients received the same dose of epoetin alfa within 5 hours of onset of symptoms. Overall, no safety concerns were identified and cerebrospinal fluid EPO reached 60 to 100 times that of control patients, proving that epoetin alfa reached the brain. Of particular interest, epoetin alfa treatment was associated with an improvement in clinical outcome at 1 month and a strong

trend for reduction in infarct size versus controls.

Several studies have found an association between cognitive deficits and chemotherapy (Schagen SB et al. *Cancer.* 1999;85:640-650; Phillips KA et al. *Proc Am Soc Clin Oncol.* 1999; 18:74a. Abstract 277; Ahles TA et al. *J Clin Oncol.* 2002;20:485-493). Problems related to verbal skills, short-term memory, concentration, and other aspects of cognitive function may persist for as long as 10 years after completion of chemotherapy (van Dam FS et al. *J Natl Cancer Inst.* 1998;90:210-218; Schagen SB et al. *Cancer.* 1999;85:640-650; Brezden CB et al. *J Clin Oncol.* 2000;18: 2695-2701; Ahles TA et al. *J Clin Oncol.* 2002;20:485-493). In a recent controlled, randomized pilot study, stage I-III breast cancer patients (N = 94) being treated with 4 cycles of anthracycline-based adjuvant or neoadjuvant chemotherapy for over 3 months were administered epoetin alfa 40,000 U QW SC or placebo and evaluated for change in cognitive function, mood, QOL, and asthenia (O'Shaughnessy J et al. *Breast Cancer Res Treat.* 2002;76[suppl 1]:S138. Abstract 550). Patients in the epoetin alfa arm maintained normal baseline Hb levels (+0.8 g/dL, baseline to pre-cycle 4), whereas placebo patients had a mean Hb decrease > 2 g/dL (O'Shaughnessy JA et al. 25th SABCS. Poster 550). As assessed by the 25-item Executive Interview (EXIT-25), in which lower scores represent better cognitive function, patients who received epoetin alfa had improvements in executive function compared with the deterioration observed in patients receiving placebo (-1.3 and +0.3, respectively, baseline to pre-cycle 4). Clock Drawing Task (CLOX) results were comparable between groups, with small improvements seen in both arms (O'Shaughnessy JA et al. 25th SABCS. Poster 550).

Early clinical data suggest that treatment with epoetin alfa may have positive effects on the peripheral nervous system as well. Nerve conduction studies were performed on 46 anemic predialytic patients with advanced chronic renal failure pre- and post-treatment with epoetin alfa

(80 U/kg/week SC for 5 months) (Hassan K et al. *J Nephrol.* 2003; 16:121-125). Motor nerve conduction velocity of the median, peroneal, and tibial nerves improved significantly ($P < .05$) (Table 1). In addition, compound muscle action potentials of the median nerve rose significantly to the normal range ($P < .05$). The investigators concluded that this nonhematopoietic effect of epoetin alfa may be related to some direct action through EPO-Rs on peripheral neuronal cells.

On the whole, this preliminary research showing potential neuro-protective effects of erythropoietic agents suggests that the utility of these drugs in cancer patients is likely to surpass their known effects in maintaining Hb levels, improving QOL, and reducing transfusion requirements. In particular, the O'Shaughnessy pilot study suggests a role for these agents in preserving cognitive function during chemotherapy. ■

Key Points inFocus

- Erythropoietin receptors (EPO-Rs) are broadly distributed in human tissues and EPO is a pleiotropic cytokine with cytoprotective, anti-apoptotic effects.
- Nonchemotherapy-related anemia is common, especially in the elderly and in patients undergoing radiation therapy. Erythropoietic agents should be evaluated in these populations. One study showed significant hemoglobin and quality of life benefits of epoetin alfa once weekly in radiotherapy-treated patients.
- Tumor hypoxia, often caused by anemia, is associated with increased tumor aggressiveness and resistance to cancer treatment. Studies evaluating the benefits of recombinant human erythropoietin (r-HuEPO; epoetin alfa or epoetin beta) on treatment outcomes have yielded conflicting results, with patient randomization imbalances and study design flaws complicating the interpretation of results in some cases.
- Preclinical studies confirm that epoetin alfa has neuroprotective properties. Early clinical studies suggest that epoetin alfa is associated with improvement in clinical outcome and reduction in infarct size in stroke patients, improved cognitive function in breast cancer patients, and improved nerve conduction in predialytic chronic renal failure patients.

Table 1. Effects of 5 Months of Therapy in Predialytic Patients

A. Effects of 5 Months of EPO Therapy on SCR, BUN, Hemoglobin and Hematocrit

	0 Months	5 Months	P Value
Creatinine (mg/dL)	4.0 ± 1.6	4.2 ± 1.7	.64
BUN (mg/dL)	67.1 ± 20.9	68.6 ± 12.9	.53
Hemoglobin (g/dL)	9.5 ± 0.8	11.0 ± 0.8	.0001
Hematocrit (%)	28.1 ± 2.7	32.9 ± 1.7	.0001

B. Effects of 5 Months of EPO Therapy on Nerve Conduction Velocity and Action Potentials on Polyneuropathy

Nerve	MNCV ₀	MNCV ₅	P Value	CMAP ₀	CMAP ₅	P Value
Ulnar	50.1 ± 4.9	51.5 ± 3.9	.19	7.8 ± 2.4	7.9 ± 2.0	.46
Median	43.0 ± 4.6	45.6 ± 5.8	.04	4.7 ± 1.4	6.0 ± 1.9	<.05
Peroneal	37.2 ± 3.1	40.0 ± 5.6	.03	1.5 ± 1.4	1.6 ± 1.6	.45
Tibial	32.8 ± 10.3	35.1 ± 10.5	.04	2.5 ± 2.0	2.7 ± 2.2	.26
	SNCV ₀	SNCV ₅	P Value	SNAP ₀	SNAP ₅	P Value
Ulnar	33.1 ± 19.6	35.3 ± 19.9	.09	8.17 ± 6.5	8.3 ± 7.0	.45
Median	33.8 ± 15.3	36.0 ± 11.1	.18	7.2 ± 5.7	8.9 ± 4.8	.16
Sural	19.1 ± 21.6	25.3 ± 21.8	.08	1.9 ± 2.8	3.0 ± 4.3	.07

BUN: blood urea nitrogen; CMAP: compound muscle action potentials; EPO: erythropoietin; MNCV: motor nerve conduction velocity; SCR: serum creatinine; SNAP: sensory nerve action potentials; SNCV: sensory nerve conduction velocity.

The values are means ± SD; MNCV₀, CMAP₀, SNCV₀: before EPO therapy; MNCV₅, CMAP₅, SNCV₅: after 5 months of EPO therapy.

Adapted from Hassan K et al. *J Nephrol.* 2003;16:121-125.

Source: Based on data presented by Lionel D. Lewis, MD, at the CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Ortho Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Ortho Biotech Products, L.P.; and preceding the 45th Annual Meeting of the American Society of Hematology (ASH), December 6-9, 2003, San Diego, California. Adapted with permission from *J Nephrol.* 2003;16:121-125.

Lymphoma: Present and Future Challenges

Based on data presented by George P. Canellos, MD, William Rosenberg Professor of Medicine, Harvard Medical School, and Senior Physician, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, Massachusetts

Since the 1970s, the incidence of non-Hodgkin's lymphoma (NHL) in the United States has nearly doubled, stabilizing in the 1990s primarily due to a decline in acquired immune deficiency syndrome (AIDS)-related NHL (American Cancer Society Cancer Facts and Figures 2003. Available at: <http://www.cancer.org/downloads/STT/CAFF2003PWSecured.pdf>. Accessed May 14, 2004). Mean age at diagnosis has been rising over time and is currently 60 years. Recent research conducted to delineate the fundamental processes and basic biology occurring on a cellular level has facilitated the development of many new targeted agents. Until the full potential of these agents is explored, the treatment of patients with lymphoma will continue to be challenging. Some of the challenges and strategies for improving outcome and minimizing toxicity in patients with lymphoma are discussed in this article.

Low-Grade Non-Hodgkin's Lymphoma

Treatment of low-grade NHL is controversial. Overall survivorship has not changed over the past 40 years despite the integration of steroids, cytotoxics, and radiation therapy (RT) into the treatment armamentarium, with median survival being approximately 10 years (Data on file, Stanford University, California). This can be explained by the fact that both single-agent and combination-agent studies have not demonstrated an overall survival advantage versus the watch-and-wait approach after median follow-up periods ranging from 3.5 to 10 years (Cavallin-Stahl E, Moller TR. *Semin Oncol.* 1986;13[1 suppl 1]:19-22; Young RC et al. *Semin Hematol.* 1988;25[2 suppl 2]:11-16; Kimby E et al. *Ann Oncol.* 1994;5 suppl 2]:67-71; Brice P et al. *J Clin Oncol.* 1997;15:1110-1117; Tsimberidou AM et al. *Blood.* 2002;100:4351-4357; Ardeschna KM et al. *Lancet.* 2003;362:516-522; Peterson

BA et al. *J Clin Oncol.* 2003;21:5-15). "A potential explanation for our inability to achieve improved survival rates with these regimens may very well be that none of them are directed at the natural history and fundamental biology of low-grade NHL cells," commented George P. Canellos, MD.

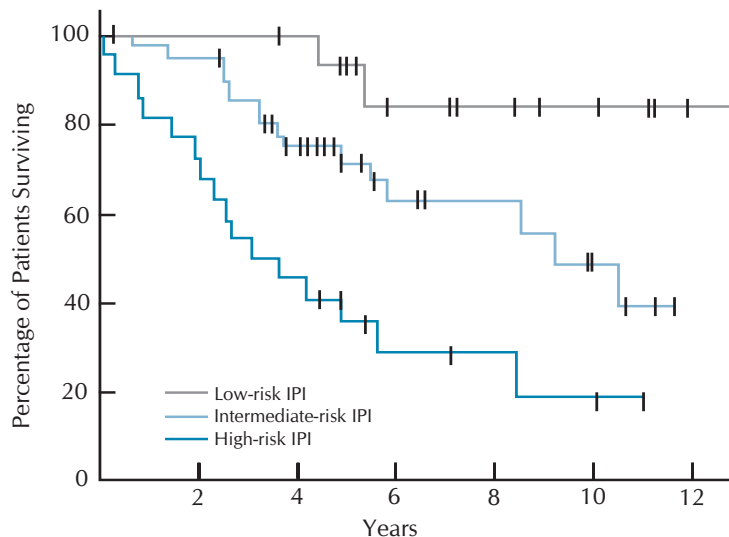
Because a survival benefit from treating asymptomatic low-grade NHL has not been demonstrated, measuring and monitoring patient prognosis and disease progression is critical to defining which patients are candidates for treatment. Prognostic factors associated with poor survival are advanced stage, bone marrow involvement, 2 or more extranodal sites, high lactate dehydrogenase level, and absence of interfollicular fibrosis (Bastion Y et al. *Ann Oncol.* 1991;

[2 suppl 2];123-129). Figure 1 shows patient survival by low-, intermediate-, and high-risk international prognostic index (IPI) characteristics (Bastion Y et al. *Ann Oncol.* 1991;[2 suppl 2]:123-129).

Options for the treatment of lymphomas have changed radically over the last several years with the discovery of new agents including monoclonal antibodies, immunotoxins, radioimmunotherapy, vaccines, cytotoxic lymphocytes, graft-versus-tumor effect via mini-transplants, and antisense nucleotides. Graft-versus-host disease rates (38%-68%) and treatment mortality rates (22%-46%) are considerable in patients who receive conventional allogeneic transplant, and although mini-allotransplant has resulted in lower treatment mortality rates (0%-30%), graft-versus-tumor effect is still high (40%-64%), Dr. Canellos said.

In a recent randomized European trial in 89 patients with low-grade NHL, high-dose therapy followed by autologous stem cell transplantation (ASCT)

Figure 1. Prognostic Factor Model Also Predicts Outcome in Follicular Lymphoma*



* $P = .0001$.

IPI: international prognostic index.

Survival of 127 patients with follicular lymphoma according to the IPI for aggressive lymphomas based on stage, mass size, number of extranodal sites, and lactate dehydrogenase level.

Adapted from Bastion Y et al. *Ann Oncol.* 1991;2(suppl 2):123-129.

Source: Based on data presented by George P. Canellos, MD, at the CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Ortho Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Ortho Biotech Products, L.P.; and preceding the 45th Annual Meeting of the American Society of Hematology (ASH), December 6-9, 2003, San Diego, California. Adapted with permission from *Ann Oncol.* 1991;2(suppl 2):123-129.

(with or without purging) resulted in substantial improvements in 4-year overall survival versus standard salvage chemotherapy (77% and 71% vs 46%, respectively) with this benefit extending to 84+ months (Schouten HC et al. *J Clin Oncol.* 2003;21:3918-3927). "New therapies and strategies are being uncovered faster than they can be evaluated in clinical trials. However, because some of these agents target and interfere with the anti-apoptotic mechanisms in cancer cells, they have the potential to enhance sensitization to cytotoxic agents and improve disease response and patient outcome," Dr. Canellos concluded.

High-Grade and Aggressive Large-Cell Lymphomas

Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) remains the standard chemotherapy regimen for patients with large-cell NHL. In a landmark Southwest Oncology Group (SWOG) randomized phase 3 study, patients with intermediate- or high-grade NHL receiving CHOP achieved similar overall survival and time to treatment failure and less severe toxicity than patients receiving more complex regimens including m-BACOD (moderate-dose methotrexate–bleomycin, doxorubicin,

cyclophosphamide, vincristine, dexamethasone), ProMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide, etoposide–cytarabine, bleomycin, vincristine, methotrexate), and MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone–bleomycin) after a median follow-up of 49 months (218-233 patients per treatment arm) (Fisher RI et al. *Ann Oncol.* 1994; 5[suppl 2]:91-95). Many modifications to the standard CHOP regimen have been explored over the last several years, with few demonstrating a survival advantage in large-cell lymphoma (Table 1).

One exception is the addition of rituximab to standard CHOP (R-CHOP), which has demonstrated promising results. Recent research has also centered on the benefit of high-dose chemotherapy and ASCT as consolidation of first complete remission. Results of 5 randomized European trials showed no survival advantage for consolidation with high-dose chemotherapy and ASCT versus conventional chemotherapy alone (Santini G et al. *J Clin Oncol.* 1998;16: 2796-2802; Kluin-Nelemans HC et al. *J Natl Cancer Inst.* 2001;93:22-30; Gisselbrecht C et al. *J Clin Oncol.* 2002;20:2472-2479; Kaiser U et al. *J Clin Oncol.* 2002;20:4413-4419;

Martelli M et al. *J Clin Oncol.* 2003; 21:1255-1262). In 4 of 5 trials, patients received abbreviated chemotherapy regimens prior to high-dose therapy and ASCT, and in the fifth trial by Santini et al, patients received full-course therapy. New agents under investigation include protein kinase C inhibitors, cyclin inhibitors, histone deacetylase inhibitors, proteasome inhibitors, and multifunctional folic acid antagonists. Clearly, developing new strategies for improving patient survival in high-grade large-cell lymphoma is a major challenge.

Many biologic factors have been shown to have prognostic significance in large-cell NHL, including circulating factors (eg, lactate dehydrogenase), cloned genes (eg, BAL), mutated genes (eg, p53), and excessive protein expression (eg, Bcl-2). A key area for future research will be to determine the relative importance of these factors in a single multifactorial analysis since their prognostic significance has been established only in individual studies. A sophisticated new technology that has allowed us to focus on the genetic expression and behavior of malignant cells is DNA microarray analysis. This technology has revealed that diffuse large B-cell lymphomas with activated B-cell like features confer a significantly worse prognosis than those with germinal-center B-cell like features ($P < .001$) (Alizadeh AA et al. *Nature.* 2000;403:503-511). A more readily accessible and simple prognostic model categorizes low-risk patients as those who have low or intermediate IPI without Bcl-2 expression but with germinal center phenotype, and high-risk patients as those with high IPI or intermediate IPI with Bcl-2 expression (regardless of phenotype); the model significantly predicts survival and improves risk stratification ($P \leq .02$) (Barrans SL et al. *Blood.* 2002; 99:1136-1143). "While it is evidently important to improve assessment of patient prognosis, DNA microarray technology may not provide additional benefit beyond IPI; rather, it will be most important in defining the targets that are critical to cellular function and for which novel therapeutic agents should be developed," Dr. Canellos remarked.

Table 1. Large-Cell Lymphoma: CHOP and Its Variants

Chemotherapy Regimen	Survival Advantage in Randomized Trials
CHOP plus MTX, bleomycin (m-BACOD)	No
Intensified CHOP (MEGA-CHOP)	No trial
Infusional (CHOPE, EPOCH)	Under study
CHOP + rituximab (GELA trial)	Yes
Chemotherapy to CR + ASCT (5 European trials)	No
CHOEP vs CHOP in low-risk young patients only (German trial)	Yes
Dose-dense CHOP or CHOEP (German trial)	No (same CR, better TTF)

ASCT: autologous stem cell transplantation; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CHOPE/CHOEP/EPOCH: CHOP + etoposide; CR: complete response; GELA: Groupe d'Etude des Lymphomes de l'Adulte; m-BACOD: moderate-dose methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; MEGA-CHOP: high-dose cyclophosphamide in CHOP regimen; MTX: methotrexate; TTF: time to treatment failure.

Source: Based on data presented by George P. Canellos, MD, at the CME-Certified symposium entitled, "Hematology: Current Challenges & Future Strategies," held on Friday, December 5, 2003, jointly sponsored by The Foundation for Better Health Care and DVC HealthCare Communications and supported by an educational grant from Orto Biotech Clinical Affairs, LLC, and Tibotec Therapeutics, a division of Orto Biotech Products, L.P.; and preceding the 45th Annual Meeting of the American Society of Hematology (ASH), December 6-9, 2003, San Diego, California.

■ Hodgkin's Disease

The current standard treatment of Hodgkin's disease (HD) is ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). A key challenge in treating HD is the frequency and associated mortality of intercurrent illnesses related to RT, such as secondary malignancies and cardiac toxicities. In fact, probability of death 35 years after diagnosis due to HD itself is 19%, versus 64% due to intercurrent illnesses (Data on file, Stanford University, California). Recent research has demonstrated that patients with localized HD receiving ABVD for non-bulky disease can achieve a 94% to 100% complete response (CR) rate at 5 years, 81% freedom from progression, and 92% to 97% overall survival rate without RT (Straus S et al. *Blood*. 2001;98:769a. Abstract 3201; Rueda A

et al. *Ann Oncol*. 2002;13:62. Abstract). In advanced HD, one study demonstrated no significant difference in 5-year event-free survival after median follow-up of 79 months in 333 patients treated with no consolidation RT versus consolidation RT after initial CR (84% vs 79%, respectively; $P = .35$) (Aleman BM et al. *N Engl J Med*. 2003;348:2396-2406). Chemotherapy regimens have also been explored. In a study of 856 patients with advanced disease, a failure-free survival benefit at 5 years was not seen with 8 to 10 cycles of MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine) versus ABVD (66% vs 63%; $P = .42$) in patients who were stratified by age, stage, and RT (Duggan DB et al. *J Clin Oncol*. 2003; 21:607-614). In addition, toxicity,

particularly the incidence of secondary neoplasms and infectious complications, was high. Several ongoing prospective, randomized trials are comparing newer regimens, including BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and Stanford V (bleomycin, doxorubicin, etoposide, mechlorethamine, prednisone, vinblastine, vincristine), versus ABVD in advanced HD. "Clearly, the future holds a vast research effort. However, one cannot overlook the success story in HD: that there has been a dramatic decrease in patient mortality over the last 30 years, primarily due to advances in treatment that we hope to continue to achieve," Dr. Canellos concluded. ■

Key Points in Focus

- Lymphoma is primarily a disease of the elderly. Development and study of targeted therapies that are more effective and less toxic is ongoing. In the meantime, strategies for improving outcome should focus on determining patient prognosis and need for intervention, identifying surrogate markers for survival, and balancing benefit of treatment versus associated toxicities.
- Survivorship for patients with low-grade non-Hodgkin's lymphoma has not changed over the last several decades. Single-agent and combination therapy approaches have not been proven to improve overall survival versus the watch-and-wait approach. However, aggressive therapy is warranted in patients with high-risk international prognostic index (IPI). New agents under investigation include monoclonal antibodies, radioimmunotherapy, and antisense oligonucleotides. Data on autologous stem cell transplantation (ASCT) in this setting are controversial, although a recent study demonstrated a survival benefit versus conventional chemotherapy.
- Standard treatment for high-grade aggressive large-cell lymphoma is CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Modifications to CHOP are being studied in an effort to improve response rates and overall survival, with R-CHOP (rituximab-CHOP) demonstrating the most promising results. Results of several randomized trials showed no survival advantage for consolidation of first complete remission with high-dose chemotherapy and ASCT versus conventional chemotherapy. DNA microarray technology has provided information to support development of a simple and effective prognostic model based on the IPI.
- Standard treatment for Hodgkin's disease is ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). In patients with localized disease, this regimen results in high response and freedom-from-progression rates. In patients with advanced disease, consolidation radiation therapy (RT) after complete or near-complete response with ABVD has not been demonstrated to improve event-free survival and has been associated with a high rate of secondary malignancies and cardiac toxicity. In addition, MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine) has not demonstrated an improved failure-free survival benefit versus ABVD and is associated with toxicities. Newer regimens being investigated include BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and Stanford V (bleomycin, doxorubicin, etoposide, mechlorethamine, prednisone, vinblastine, vincristine).

CME Post-Test, Post-Test Answer Key, and Evaluation Forms

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CME Post-Test: Please write your answers in the post-test answer key below.

1. Median age at diagnosis of multiple myeloma is:
 - a) 39 years
 - b) 45 years
 - c) 57 years
 - d) 65 years
2. In a phase 2b trial comparing DVd (pegylated liposomal doxorubicin, vincristine, reduced-schedule dexamethasone) with VAd (vincristine, conventional doxorubicin, reduced-dose dexamethasone), the 2 regimens elicited comparable response rates but VAd treatment was associated with substantially less toxicity, and required less time in hospital for drug administration and side effects:
 - a) True
 - b) False
3. When compared with historical control patients who had received DVd alone, adding thalidomide appeared to significantly improve time to progression in patients with relapsed or refractory disease:
 - a) True
 - b) False
4. Administration of epoetin alfa 3 times weekly or once weekly has been associated with the following results:
 - a) Hemoglobin increases of approximately 1 g/dL after 4 weeks and approximately 2 g/dL after 8 weeks
 - b) Significant reductions in transfusion requirements
 - c) Significant quality of life (QOL) improvements
 - d) All of the above
 - e) None of the above
5. Incremental analysis of linear analog scale assessment (LASA) QOL data from 2 large, community-based studies showed that the greatest incremental improvement in patient QOL occurred when Hb increased from:
 - a) 8 to 9 g/dL
 - b) 9 to 10 g/dL
 - c) 11 to 12 g/dL
 - d) 12 to 13 g/dL
6. Hemoglobin level has been shown to be a prognostic factor for progression-free survival and overall survival in many tumor types, as well as a predictive factor for treatment outcomes:
 - a) True
 - b) False
7. Among cancer patients, anemia is a concern only in patients who are receiving chemotherapy:
 - a) True
 - b) False
8. Early clinical studies suggest that treatment with epoetin alfa is associated with:
 - a) Improvement in clinical outcome and reduction in infarct size in stroke patients
 - b) Improved cognitive function in breast cancer patients
 - c) Improved nerve conduction in predialytic chronic renal failure patients
 - d) All of the above
 - e) None of the above
9. In low-grade non-Hodgkin's lymphoma, single-agent and combination-agent studies have not demonstrated an overall survival advantage versus the watch-and-wait approach after median follow-up periods ranging from 3.5 to 10 years:
 - a) True
 - b) False
10. A prognostic factor associated with poor survival in asymptomatic low-grade non-Hodgkin's lymphoma is:
 - a) Advanced stage
 - b) Bone marrow involvement
 - c) Two or more extranodal sites
 - d) High lactate dehydrogenase level
 - e) All of the above

Post-Test Answer Key: Please write in your answers to the 10 CME questions in this key.

1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____ 7. _____ 8. _____ 9. _____ 10. _____

Current Challenges and Future Strategies in the Management of Patients With Hematologic Malignancies
CME Comprehensive Report
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Needs Assessment



I am interested in educational activities in the following topic areas:

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
Multiple myeloma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Non-Hodgkin's lymphoma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Liposomal anthracyclines	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anemia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Erythropoietic agents	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Neutropenia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Angiogenesis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Immunomodulators	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Quality of life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hodgkin's disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Depression	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stem-cell transplantation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Myelodysplastic syndrome	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chronic myeloid leukemia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Monoclonal antibodies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cytogenetics	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Immunotherapy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Educational Objectives

After completing this activity, I am better able to:

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
1. Reflect on new treatment strategies for multiple myeloma in order to apply these to my clinical practice.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Outline the current goals and anticipated benefits of established and new treatment strategies for chemotherapy-related anemia in order to recognize patients who would benefit from therapy.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Summarize potential future applications of erythropoietic agents to identify new areas of research.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Discuss present and future challenges in lymphoma management in order to properly assess and treat patients with this hematologic malignancy.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. The goal of FBHC CME is to provide information that will help improve your practice. As a result of participating in this activity, please list change(s) you are willing to commit to make in your practice.	_____				

Program Evaluation

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
1. My overall rating of the activity is positive.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. This activity addressed significant scientific/medical questions or unmet medical needs.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I would recommend this educational activity to a colleague/peer.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I will share the content of this educational activity with a colleague/peer.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. The information provided in this activity may help health care providers enhance the delivery of health care.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I was adequately informed of faculty disclosures.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. The monograph was fairly balanced and free of commercial bias.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. If you chose Strongly Disagree, Disagree, or Neither Agree nor Disagree, for question 7, please clarify what you felt was not fairly balanced in the monograph.	_____				

9. Additional comments:

If you wish to receive credit for this activity, please fill in your name and address, and mail or fax the completed form to:
The Foundation for Better Health Care, 6 East 32nd Street, 9th Floor, New York, NY 10016 • Fax to: (212) 545-1378

Request for Credit

Name: _____ Degree (MD, DO, PharmD, RN, PA, BS, Other): _____
 Organization: _____ Specialty: _____
 Street Address: _____ City, State, Zip: _____
 Phone: _____ Fax: _____ E-Mail: _____

I certify my actual time spent to complete this educational activity to be:

- I participated in the entire activity and claim 1 credit
- I participated in only part of the activity and claim ____ credit(s)

Signature: _____ Date: _____

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Moving Clinicians from Knowledge to Action

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