Appendix I. (Continued)

Osterborg A, Brandberg Y. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer.* 2003;97:3125–3126; author reply, 3126–3127.

Pedrazzoli P, Tullio C, Cerea G, Siena S. Iron supplement in cancer patients receiving erythropoietin. *J Clin Oncol.* 2004;22:4428; author reply, 4428–4429.

Perillo A, Ferrandina G, Pierelli L, et al. Cytokines alone for PBPC collection in patients with advanced gynaecological malignancies: G-CSF vs G-CSF plus EPO. *Bone Marrow Transplant.* 2004;34:743–744.

Ponchio L, Zambelli A, De Stefano A, et al. Transfusion requirement can be abolished by epoietin-a and autologous platelet predeposit in patients receiving high dose chemotherapy with stem cell support. *Haematologica.* 2000;85:219–220.

Powles T, Shamash J, Liu W. Erythropoietin to treat anaemia in patients with head and neck cancer. *Lancet.* 2004;363:82.

Reed N, Morere JF. Optimising anaemia management with epoetin beta. *Oncology.* 2004;67(Suppl 1):12–16.

Straus DJ. Epoetin alfa therapy for patients with hematologic malignancies and mild anemia. *Clin Lymphoma.* 2003;4(Suppl 1):S13–S17.

VanAudenrode M. Re: Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J Natl Cancer Inst.* 2003;95:761–762; author reply, 762–763.

Vansteenkiste J, Poulsen E, Rossi G, Glaspy J. Darbepoetin alfa: Impact on treatment for chemotherapy-induced anemia and considerations in special populations. *Oncology (Williston Park).* 2002;16(Suppl 11):45–55.

Vaupel P, Mayer A. Erythropoietin to treat anaemia in patients with head and neck cancer. *Lancet.* 2004;363:992; author reply, 993.

Waltzman RJ. A randomized, active-control, pilot trial of front-loaded dosing regimens of darbepoetin-alfa for the treatment of patients with anemia during chemotherapy for malignant disease. *Cancer.* 2004;100:1545–1546; author reply, 1546.

Fewer than 10 Patients

Kerridge I, Spencer A, Azzi A, Seldon M. Response to erythropoietin in chronic myelomonocytic leukaemia. *Intern Med J.* 2001;31:371–372.

Fewer than 10 Patients per Treatment Arm

Chang J, Phippard L, Sharma D, Lau CY. A phase II randomized trial of three loading doses of epoetin alfa followed by every three-week (Q3W) dosing in cancer patients receiving chemotherapy. Abstract presented at: American Society of Clinical Oncology 41st Annual Meeting; May 13–17, 2005; Orlando, Fla. Abstract 8219.

Csaki C, Ferencz T, Schuler D, Borsi JD. Recombinant human erythropoietin in the prevention of chemotherapy-induced anaemia in children with malignant solid tumours. *Eur J Cancer.* 1998;34:364–367.

Tsukuda M, Yuyama S, Kohno H, et al. Effectiveness of weekly subcutaneous recombinant human erythropoietin administration for chemotherapy-induced anemia. *Biotherapy.* 1998;11:21–25.

Ineligible Study Design

Hunault-Berger M, Tanguy-Schmidt A, Rachieru P, et al. rHuEpo before high-dose therapy allows autologous peripheral stem-cell transplantation without red blood cell transfusion: A pilot study. *Bone Marrow Transplant.* 2005;35:903–907.

Kaupke CJ, Butler GC, Vaziri ND. Effect of recombinant human erythropoietin on platelet production in dialysis patients. *J Am Soc Nephrol.* 1993;3:1672–1679.

(continued)

Appendix I. (Continued)

Nordyke R, Chang C-H, Chiou C-F, et al. Validation of a patient satisfaction questionnaire for anemia treatment (PSQ-An). Abstract presented at: American Society of Hematology 46th Annual Meeting and Exposition; December 2–6, 2004; San Diego, Calif. Abstract 5297.

Scott SN, Boeve TJ, McCulloch TM, et al. The effects of epoetin alfa on transfusion requirements in head and neck cancer patients: A prospective, randomized, placebo-controlled study. *Laryngoscope*. 2002;112:1221–1229.

Vercammen E, Ludwig H, Liu K, et al. Analysis of the effect of body weight on the efficacy and safety of epoetin alfa. Abstract presented at: American Society of Clinical Oncology 41st Annual Meeting; May 13–17, 2005; Orlando, Fla. Abstract 8184.

No Comparator of Interest

Berns JS, Rudnick MR, Cohen RM, et al. Effects of normal hematocrit on ambulatory blood pressure in epoetin-treated hemodialysis patients with cardiac disease. *Kidney Int*. 1999;56:253–260.

Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339:584–590.

Bommer J, Kugel M, Schoeppe W, et al. Dose-related effects of recombinant human erythropoietin on erythropoiesis. Results of a multicenter trial in patients with end-stage renal disease. *Contrib Nephrol*. 1988;66:85–93.

Bommer J, Samtleben W, Koch KM, et al. Variations of recombinant human erythropoietin application in hemodialysis patients. *Contrib Nephrol*. 1989;76:149–156.

Caravaca F, Lopez-Minguez JR, Arrobas M, et al. Haemodynamic changes induced by the correction of anaemia by erythropoietin: Role of antiplatelet therapy. *Nephrol Dial Transplant*. 1995;10:1720–1724.

Conlon PJ, Kovalik E, Schumm D, et al. Normalization of hematocrit in hemodialysis patients does not affect silent ischemia. *Ren Fail*. 2000;22:205–211.

Conlon PJ, Kovalik E, Schumm D, et al. Normalization of hematocrit in hemodialysis patients with cardiac disease does not increase blood pressure. *Ren Fail*. 2000;22:435–444.

Foley RN, Parfrey PS, Morgan J, et al. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int*. 2000;58:1325–1335.

Furuland H, Linde T, Ahlmen J, et al. A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol Dial Transplant*. 2003;18:353–361.

Grutzmacher P, Bergmann M, Weinreich T, et al. Beneficial and adverse effects of correction of anaemia by recombinant human erythropoietin in patients on maintenance haemodialysis. *Contrib Nephrol*. 1988;66:104–113.

Kuhn K, Nonnast-Daniel B, Grutzmacher P, et al. Analysis of initial resistance of erythropoiesis to treatment with recombinant human erythropoietin. Results of a multicenter trial in patients with end-stage renal disease. *Contrib Nephrol*. 1988;66:94–103.

Linde T, Ekberg H, Forslund T, et al. The use of pretransplant erythropoietin to normalize hemoglobin levels has no deleterious effects on renal transplantation outcome. *Transplantation*. 2001;71:79–82.

Navarro JF, Mora C, Macia M, Garcia J. Randomized prospective comparison between erythropoietin and androgens in CAPD patients. *Kidney Int*. 2002;61:1537–1544.

Nissenson AR, Lindsay RM, Swan S, et al. Sodium ferric gluconate complex in sucrose is safe and effective in hemodialysis patients: North American Clinical Trial. *Am J Kidney Dis*. 1999;33:471–482.

Samtleben W, Baldamus CA, Bommer J, et al. Blood pressure changes during treatment with recombinant human erythropoietin. *Contrib Nephrol*. 1988;66:114–122.

(continued)

Appendix I. (Continued)

Teplan V, Schuck O, Votruba M, et al. Metabolic effects of keto acid-amino acid supplementation in patients with chronic renal insufficiency receiving a low-protein diet and recombinant human erythropoietin—a randomized controlled trial. *Wien Klin Wochenschr.* 2001;113:661-669.

No Outcome of Interest

Allon M, Kleinman K, Walczyk M, et al. Pharmacokinetics and pharmacodynamics of darbepoetin alfa and epoetin in patients undergoing dialysis. *Clin Pharmacol Ther.* 2002;72:546-555.

Boccia RV, Liu D, Silberstein P, et al. An evaluation of the effectiveness of darbepoetin alfa 300 mcg every 3 weeks (Q3W) on clinical outcomes in cancer patients with chemotherapy-induced anemia. Abstract presented at: American Society of Hematology 46th Annual Meeting and Exposition; December 2-6, 2004; San Diego, Calif. Abstract 5310.

Coleman EA, Anaissie E, Coon SK, et al. A randomized trial of home-based exercise for patients receiving aggressive treatment and epoetin alfa for multiple myeloma: Hemoglobin (Hb) transfusion, fatigue and performance as outcomes. Abstract presented at: American Society of Clinical Oncology 40th Annual Meeting; June 5-8, 2004; New Orleans, La. Abstract 8026.

Estrin JT, Schocket L, Kregenow R, Henry DH. A retrospective review of blood transfusions in cancer patients with anemia. *Oncologist.* 1999;4:318-324.

Glossmann JP, Engert A, Wassmer G, et al. Recombinant human erythropoietin, epoetin beta, in patients with relapsed lymphoma treated with aggressive sequential salvage chemotherapy—results of a randomized trial. *Ann Hematol.* 2003;82:469-475.

Kallich JD, Tchekmedyian NS, Damiano AM, et al. Psychological outcomes associated with anemia-related fatigue in cancer patients. *Oncology (Williston Park).* 2002;16:117-124.

Lundholm K, Daneryd P, Bosaeus I, et al. Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignant disease: Effects on survival, metabolism, and function. *Cancer.* 2004;100:1967-1977.

Martino M, Oliva E, Console G, et al. Administration of recombinant human erythropoietin alpha before autologous stem cell transplantation reduces transfusion requirement in multiple myeloma patients. *Support Care Cancer.* 2005;13:182-187.

Voulgari PV, Hatzimichael EC, Tsiara S, et al. Investigation for the presence of anti-erythropoietin antibodies in patients with myelodysplastic syndromes. *Eur J Haematol.* 2001;66:31-36.

No Population of Interest

Abels R. Rate of progression of chronic renal failure in predialysis patients treated with erythropoietin. *Semin Nephrol.* 1990;10(Suppl 1):20-25.

Canadian Erythropoietin Study Group. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. *BMJ.* 1990;300:573-578.

Canadian Erythropoietin Study Group. Effect of recombinant human erythropoietin therapy on blood pressure in hemodialysis patients. *Am J Nephrol.* 1991;11:23-26.

Christopoulou M, Derartinian H, Hatzidimitriou G, Iatrou L. Autologous blood transfusion in oral and maxillofacial surgery patients with the use of erythropoietin. *J Craniomaxillofac Surg.* 2001;29:118-125.

Clyne N, Jogestrand T. Effect of erythropoietin treatment on physical exercise capacity and on renal function in predialytic uremic patients. *Nephron.* 1992;60:390-396.

(continued)

Appendix I. (Continued)

Corwin HL, Gettinger A, Pearl RG, et al, for the EPO Critical Care Trials Group. Efficacy of recombinant human erythropoietin in critically ill patients: A randomized controlled trial. *JAMA*. 2002;288:2827–2835.

Corwin HL, Gettinger A, Rodriguez RM, et al. Efficacy of recombinant human erythropoietin in the critically ill patient: A randomized, double-blind, placebo-controlled trial. *Crit Care Med*. 1999;27:2346–2350.

Donnelly SM, Ali MA, Churchill DN. Bioavailability of iron in hemodialysis patients treated with erythopoietin: Evidence for the inhibitory role of aluminum. *Am J Kidney Dis*. 1990;16:447–451.

Ehrenreich H, Hasselblatt M, Dembowski C, et al. Erythropoietin therapy for acute stroke is both safe and beneficial. *Mol Med*. 2002;8:495–505.

Hyllner M, Avall A, Bengtson JP, Bengtsson A. IL-6 and IL-8 response to erythropoietin therapy in radical hysterectomy. *Acta Anaesthesiol Scand*. 2005;49:47–51.

Kleinman KS, Schweitzer SU, Perdue ST, et al. The use of recombinant human erythropoietin in the correction of anemia in predialysis patients and its effect on renal function: A double-blind, placebo-controlled trial. *Am J Kidney Dis*. 1989;14:486–495.

Klinkmann H, Wieczorek L, Scigalla P. Adverse events of subcutaneous recombinant human erythropoietin therapy: Results of a controlled multicenter European study. *Artif Organs*. 1993;17:219–225.

Kokot F, Wiecek A, Mesjasz J, et al. Influence of long-term recombinant human erythropoietin (rHuEpo) therapy on plasma leptin and neuropeptide Y concentration in haemodialysed uraemic patients. *Nephrol Dial Transplant*. 1998;13:1200–1205.

Kosmadakis N, Messaris E, Maris A, et al. Perioperative erythropoietin administration in patients with gastrointestinal tract cancer: Prospective randomized double-blind study. *Ann Surg*. 2003;237:417–421.

Kristal B, Shurtz-Swirski R, Shasha SM, et al. Interaction between erythropoietin and peripheral polymorphonuclear leukocytes in hemodialysis patients. *Nephron*. 1999;81:406–413.

Laporte JP, Yeshurun M, Fouillard L, et al. A long-term follow-up of 33 patients with non-Hodgkin's lymphoma who received the BEAM high-dose intensification regimen with cytokine support only and no transplant. *Leukemia*. 2004;18:1717–1721.

Larson B, Bremme K, Clyne N, Nordstrom L. Preoperative treatment of anemic women with epoetin beta. *Acta Obstet Gynecol Scand*. 2001;80:559–562.

Laupacis A, for the Canadian Erythropoietin Study Group. A randomized double-blind study of recombinant human erythropoietin in anaemic hemodialysis patients. *Transplant Proc*. 1991;23:1825–1826.

Laupacis A, for the Canadian Erythropoietin Study Group. Changes in quality of life and functional capacity in hemodialysis patients treated with recombinant human erythropoietin. *Semin Nephrol*. 1990;10:11–19.

Lim VS, DeGowin RL, Zavala D, et al. Recombinant human erythropoietin treatment in pre-dialysis patients. A double-blind placebo-controlled trial. *Ann Intern Med*. 1989;110:108–114.

Lim VS, Kirchner PT, Fangman J, et al. The safety and the efficacy of maintenance therapy of recombinant human erythropoietin in patients with renal insufficiency. *Am J Kidney Dis*. 1989;14:496–506.

Locatelli F, Olivares J, Walker R, et al, for the European/Australian NESP 902020 Study Group. Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. *Kidney Int*. 2001;60:741–747.

Muirhead N, Laupacis A, Wong C. Erythropoietin for anaemia in haemodialysis patients: Results of a maintenance study (the Canadian Erythropoietin Study Group). *Nephrol Dial Transplant*. 1992;7:811–816.

Nissenson AR, Korbet S, Faber M, et al. Multicenter trial of erythropoietin in patients on peritoneal dialysis. *J Am Soc Nephrol*. 1995;5:1517–1529.

(continued)

Appendix I. (Continued)

Nissenson AR, Swan SK, Lindberg JS, et al. Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. *Am J Kidney Dis.* 2002;40:110–118.

Revicki DA, Brown RE, Feeny DH, et al. Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. *Am J Kidney Dis.* 1995;25:548–554.

Rodriguez RM, Corwin HL, Gettinger A, et al. Nutritional deficiences and blunted erythropoietin response as causes of the anemia of critical illness. *J Crit Care.* 2001;16:36–41.

Roth D, Smith RD, Schulman G, et al. Effects of recombinant human erythropoietin on renal function in chronic renal failure predialysis patients. *Am J Kidney Dis.* 1994;24:777–784.

Shand BI, Buttimore AL, Hurrell MA, et al. Hemorheology and fistula function in home hemodialysis patients following erythropoietin treatment: A prospective placebo-controlled study. *Nephron.* 1993;64:53–57.

Sheingold S, Churchill D, Muirhead N, et al. The impact of recombinant human erythropoietin on medical care costs for hemodialysis patients in Canada. *Soc Sci Med.* 1992;34:983–991.

Silverberg DS, Blum M, Agbaria Z, et al. The effect of i.v. iron alone or in combination with low-dose erythropoietin in the rapid correction of anemia of chronic renal failure in the predialysis period. *Clin Nephrol.* 2001;55:212–219.

Singh NP, Aggarwal L, Singh T, et al. Anaemia, iron studies and erythropoietin in patients of chronic renal failure. *J Assoc Physicians India.* 1999;47:284–290.

Sobota JT. Recombinant human erythropoietin in patients with anemia due to end-stage renal disease. US multicenter trials. *Contrib Nephrol.* 1989;76:166–178.

Stone WJ, Graber SE, Krantz SB, et al. Treatment of the anemia of predialysis patients with recombinant human erythropoietin: A randomized, placebo-controlled trial. *Am J Med Sci.* 1988;296:171–179.

Teplan V, Schuck O, Knotek A, et al. Effects of low-protein diet supplemented with ketoacids and erythropoietin in chronic renal failure: A long-term metabolic study. *Ann Transplant.* 2001;6:47–53.

Teplan V, Schuck O, Knotek A, et al. Enhanced metabolic effect of erythropoietin and keto acids in CRF patients on low-protein diet: Czech multicenter study. *Am J Kidney Dis.* 2003;41:S26–S30.

Thadhani R, Cheriyan R, Brenner R, et al. Treatment of anemia with Aranesp™ (darbepoetin alfa) improves health related quality of life (HRQOL) in patients with chronic kidney disease (CKD). *J Am Soc Nephrol.* 2002;13:637A. Abstract 0802.

The US Recombinant Human Erythropoietin Predialysis Study Group. Double-blind, placebo-controlled study of the therapeutic use of recombinant human erythropoietin for anemia associated with chronic renal failure in predialysis patients [published correction appears in *Am J Kidney Dis.* 1991;18:420]. *Am J Kidney Dis.* 1991;18:50–59.

van Iperen CE, Gaillard CA, Kraaijenhagen RJ, et al. Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. *Crit Care Med.* 2000;28:2773–2778.

Vanrenterghem Y, Barany P, Mann JF, et al, for the European/Australian NESP 970200 Study Group. Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients. *Kidney Int.* 2002;62:2167–2175.

Vaziri ND, Ritchie C, Brown P, et al. Effect of erythropoietin administration on blood and plasma viscosity in hemodialysis patients. *ASAIO Trans.* 1989;35:505–508.

William J, Saad N, Salib M, et al. The acute effect of intravenously administered recombinant human erythropoietin on the immune response of uremic patients maintained on regular hemodialysis. *Artif Organs.* 1998;22:192–196.

(continued)

Appendix I. (Continued)

Not Anemia Treatment

Baron F, Sautois B, Baudoux E, et al. Optimization of recombinant human erythropoietin therapy after allogeneic hematopoietic stem cell transplantation. *Exp Hematol.* 2002;30:546–554.

Outcomes Not Extractable

Daneryd P. Epoetin alfa for protection of metabolic and exercise capacity in cancer patients. *Semin Oncol.* 2002;29(Suppl 8):69–74.

Huddart RA, Welch RS, Chan S, et al. A prospective randomised comparative-group evaluation of epoetin alfa for the treatment of anaemia in UK cancer patients receiving platinum-based chemotherapy. *Ann Oncol.* 2002;13(Suppl 5):177. Abstract 652P.

Mattiuzzi GN, Kantarjian H, Cortes J, et al. Epoetin alfa (EPO) vs standard of care (SOC) decreases number of PRBC transfusions (tx) in patients (pts) receiving hyper-CVAD for acute lymphocytic leukemia (ALL), lymphoblastic lymphoma (LL), and Burkitt's lymphoma (BL). Abstract presented at: American Society of Clinical Oncology 41st Annual Meeting; May 13–17, 2005; Orlando, Fla. Abstract 6703.

Michael U, Jackisch C, Lenhard MS, et al. Epoetin-alpha reduces red blood cell (RBC) transfusions in high-risk breast cancer patients with adjuvant dose-dense, sequential chemotherapy with epirubicin (E), paclitaxel (T) and cyclophosphamide (C) (ETC). Abstract presented at: American Society of Clinical Oncology 41st Annual Meeting; May 13–17, 2005; Orlando, Fla. Abstract 613.

Studies of Renal Anemia

Abraham PA, Macres MG. Blood pressure in hemodialysis patients during amelioration of anemia with erythropoietin. *J Am Soc Nephrol.* 1991;2:927–936.

Bennett WM. A multicenter clinical trial of epoetin beta for anemia of end-stage renal disease. *J Am Soc Nephrol.* 1991;1:990–998.

Kohler M, Morsdorf S, Jung F, et al. Recombinant human erythropoietin (rh-EPO) in chronic, dialysis-dependent renal failure: Effects on macro- and microcirculation and hematologic parameters [in German]. *Beitr Infusionsther.* 1990;26:89–95.

Kuriyama S, Tomonari H, Yoshida H, et al. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. *Nephron.* 1997;77:176–185.

Study Design Other than Randomized Clinical Trial

Aguilera A, Bajo MA, Diez JJ, et al. Effects of human recombinant erythropoietin on inflammatory status in peritoneal dialysis patients. *Adv Perit Dial.* 2002;18:200–205.

Grzegorzewska AE, Leander M. Lymphocyte subset counts in CAPD patients in relation to administration of recombinant human erythropoietin and angiotensin-converting enzyme inhibitors. *Perit Dial Int.* 2002;22:625–628.

Hirayama A, Nagase S, Gotoh M, et al. Reduced serum hydroxyl radical scavenging activity in erythropoietin therapy resistant renal anemia. *Free Radic Res.* 2002;36:1155–1161.

McMahon LP, Mason K, Skinner SL, et al. Effects of haemoglobin normalization on quality of life and cardiovascular parameters in end-stage renal failure. *Nephrol Dial Transplant.* 2000;15:1425–1430.

Nitta K, Akiba T, Takei T, et al. Inflammation and resistance to erythropoietin in hemodialysis patients. *Acta Haematol.* 2002;108:168–170.

Schwartzberg L, Yee L, Senecal F, et al. Darbepoetin alfa (DA) 200 mcg every 2 weeks (Q2W) vs epoetin alfa (Epo) 40,000 U weekly (QW) in anemic patients (pts) receiving chemotherapy (ctx). Abstract presented at: American Society of Clinical Oncology 40th Annual Meeting; June 5–8, 2004; New Orleans, La. Abstract 8063.

Appendix II. Non-cancer-induced anemia treatment studies.

Bamias A, Aravantinos G, Kalofonos C, et al. Prevention of anemia in patients with solid tumors receiving platinum-based chemotherapy by recombinant human Erythropoietin (rHuEpo): A prospective, open label, randomized trial by the Hellenic Cooperative Oncology Group. *Oncology*. 2003;64:102–110.

Chang J, Couture F, Young S, et al. Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy [published correction appears in *J Clin Oncol*. 2005;23:5276]. *J Clin Oncol*. 2005;23(12):2597–2605.

de Campos E, Radford J, Steward W, et al. Clinical and in vitro effects of recombinant human erythropoietin in patients receiving intensive chemotherapy for small-cell lung cancer. *J Clin Oncol*. 1995;13:1623–1631.

Dunphy FR, Harrison BR, Dunleavy TL, et al. Erythropoietin reduces anemia and transfusions: A randomized trial with or without erythropoietin during chemotherapy. *Cancer*. 1999;86:1362–1367.

Gamucci T, Thorel MF, Frasca AM, et al. Erythropoietin for the prevention of anaemia in neoplastic patients treated with cisplatin. *Eur J Cancer*. 1993;29A(Suppl 2):S13–S14.

Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. *Lancet*. 2003;362:1255–1260.

Kronberger M, Fischmeister G, Poetschger U, et al. Reduction in transfusion requirements with early epoetin alfa treatment in pediatric patients with solid tumors: A case-control study. *Pediatr Hematol Oncol*. 2002;19:95–105.

O'Shaughnessy JA, Vukelja SJ, Holmes FA, et al. Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. *Clin Breast Cancer*. 2005;5:439–446.

Rades D, Schild SE, Yekebas EF, et al. Epoetin-alpha during radiotherapy for stage III esophageal carcinoma. *Cancer*. 2005;103:2274–2279.

ten Bokkel Huinink WW, de Swart CA, van Toorn DW, et al. Controlled multicentre study of the influence of subcutaneous recombinant human erythropoietin on anaemia and transfusion dependency in patients with ovarian carcinoma treated with platinum-based chemotherapy. *Med Oncol*. 1998;15:174–182.

Thatcher N, De Campos ES, Bell DR, et al. Epoetin alpha prevents anaemia and reduces transfusion requirements in patients undergoing primarily platinum-based chemotherapy for small cell lung cancer. *Br J Cancer*. 1999;80:396–402.

Wolchok JD, Klimek VM, Williams L, Chapman PB. Prophylactic recombinant epoetin alfa markedly reduces the need for blood transfusion in patients with metastatic melanoma treated with biochemotherapy. *Cytokines Cell Mol Ther*. 1999;5:205–206.

original *contribution*

Treatment of Chemotherapy-Induced Anemia in Breast Cancer: Results of a Randomized Controlled Trial of Darbepoetin Alfa 200 μg Every 2 Weeks Versus Epoetin Alfa 40,000 U Weekly

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Abstract

Background: Current chemotherapy regimens for breast cancer result in high incidences of anemia, which can be treated with erythropoietic agents. The relative efficacy of darbepoetin alfa and epoetin alfa was explored in this phase II, open-label, randomized, multicenter trial in anemic patients with breast cancer receiving chemotherapy. **Patients and Methods:** Patients were randomized at a 1:1 ratio to receive darbepoetin alfa 200 μg every 2 weeks (n = 72) or epoetin alfa 40,000 U weekly (n = 69) for ≤ 16 weeks. Clinical and hematologic endpoints and validation of a novel patient satisfaction questionnaire for anemia treatment were evaluated for all patients randomized to receive ≥ 1 dose of study drug. **Results:** Baseline characteristics were generally similar between treatment groups. Mean changes in hemoglobin (Hb) level from baseline were similar at 1.9 g/dL for darbepoetin alfa and 1.7 g/dL for epoetin alfa. Hematopoietic responses (≥ 2 g/dL increase in Hb level from baseline or Hb level ≥ 12 g/dL) were also similar between groups (88% for darbepoetin alfa and 81% for epoetin alfa). The proportions of patients who received a transfusion during treatment were 6% (95% CI, 0-11%) for darbepoetin alfa and 16% (95% CI, 7%-25%) for epoetin alfa. Most patients (67 patients receiving darbepoetin alfa [93%]; 61 patients receiving epoetin alfa [90%]) exhibited a clinically meaningful target Hb level ≥ 11 g/dL. No differences in safety were observed. **Conclusion:** These results suggest that, in patients with breast cancer, darbepoetin alfa 200 μg every 2 weeks and epoetin alfa 40,000 U weekly result in comparable clinical outcomes for the treatment of chemotherapy-induced anemia.

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Key words: Erythropoietin, Quality of life, Target hemoglobin level, Transfusion

Introduction

The American Cancer Society has estimated that 212,930 new cases of breast cancer will be diagnosed in the United States in 2005, with > 40,000 patients dying from the disease.[1] Currently available therapy for breast cancer includes myelosuppressive chemotherapy agents that result in significant toxicities and reduce patients' quality of life (QOL) and can also impact the completion of a recommended course of therapy.[2-7] In a recent survey of > 15,000 European patients with cancer, nearly 30% of patients with breast cancer were anemic (hemoglobin [Hb] level < 12 g/dL) at enrollment, and > 70% of patients breast cancer receiving chemotherapy experienced some degree of anemia during the course of chemotherapy.[8]

Even with these high rates of anemia, the incidence of anemia in patients with breast cancer is likely to increase in the near term given the recent advances in adjuvant therapy in early-stage breast cancer that are particularly myelosuppressive. In the Intergroup study INT-C9741, which compared the efficacy of dose-dense sequential therapy of AC (doxorubicin/cyclophosphamide) followed by paclitaxel with granulo-

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cyte colony-stimulating factor support versus every-3-week therapy in breast cancer, disease-free survival improved with dose-dense therapy (response rate, 0.74; $P = 0.01$); however, dose-dense therapy was associated with an increased transfusion rate of 13%, compared with < 4% in the every-3-week group.[9] In clinical practice, the use of this regimen has been reported to result in severe anemia; in 73 patients receiving dose-dense AC chemotherapy, mean Hb levels decreased by 1.5 g/dL after 2 cycles of therapy and decreased by 2.1 g/dL after 4 cycles, with 68% of patients requiring erythropoietic therapy.[10]

Compared with other patients with cancer, patients with breast cancer tend to be younger (mean age, 50-60 years), are more likely to be working, and, in many cases, are the primary caregivers for their families.[11] Consequently, treatment of their disease and associated fatigue present a substantial burden on the normal daily activities of the patients and their families.[11-14] For this reason, erythropoietic therapies have been used extensively in patients with breast cancer to alleviate the signs and symptoms of anemia and to decrease the number of red blood cell transfusions.[15-19] To optimize treatment and QOL, less frequent dosing of erythropoietic agents and the ability to synchronize dosing with chemotherapy (eg, every-2-week dosing in patients receiving dose-dense chemotherapy regimens) may provide significant benefits for patients with breast cancer. Darbepoetin alfa, a novel erythropoietic therapy with an extended serum half-life compared with recombinant human erythropoietin, is commonly administered in the United States using a weekly or an every-2-week dosing regimen.[20-24] In Europe, every-3-week administration of darbepoetin alfa has recently been approved in patients with nonmyeloid malignancies receiving chemotherapy[25] and offers the convenience of synchronization with every-3-week chemotherapy regimens.

It has been hypothesized that patients with chemotherapy-induced anemia treated with erythropoietic agents may exhibit decreased survival. This concern arose largely because of 2 recent clinical trial reports of epoetin alfa and epoetin beta in which an increased incidence of thromboembolic events was observed.[26,27] Study design may have contributed to the observation of these events because treatment was initiated in nonanemic patients (Hb level > 12 g/dL)[26] and Hb levels were allowed to increase to 15 g/dL during the study period.[27] Although these observations are important to note, it is also important to note that these studies may have been compromised by insufficient data collection, thereby precluding definitive conclusions about any risk regarding the use of erythropoietic agents. However, results emerging from randomized controlled trials specifically designed to evaluate the impact of erythropoietin therapy on survival (including a trial in advanced breast cancer) have not observed any difference in overall survival or disease progression.[28-30] The thrombotic events observed in these randomized controlled trials have been consistent with previous studies in this area.

Despite the routine use of darbepoetin alfa and epoetin alfa in this patient population, no randomized controlled trials of these agents have been conducted in patients with breast cancer, which represent approximately 20%-25% of anemic patients with cancer. To this end, we designed and conducted a prospective, randomized trial of darbepoetin alfa 200 μg every 2 weeks and epoetin alfa 40,000 U weekly for ≤ 16 weeks to provide information regarding the relative efficacy and safety of these 2 agents in patients with breast cancer.

Patients and Methods

Patients

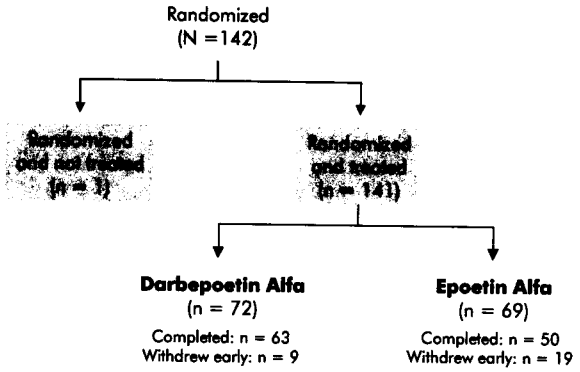
This open-label, phase II descriptive trial enrolled female patients with anemia (Hb level < 11 g/dL) and histologically confirmed breast cancer at 20 centers in the United States. Data from this study were previously included in an integrated analysis of 3 studies.[31] Further key eligibility criteria for the trial were patients age ≥ 18 years, anemia induced by chemotherapy, ≥ 8 planned additional cycles of chemotherapy, Karnofsky performance status ≥ 50%, and adequate liver and renal function. Exclusion criteria included history of anemia caused by factors unrelated to chemotherapy, uncontrolled hypertension, active bleeding, red blood cell transfusion within 4 weeks of screening, erythropoietic therapy within 2 weeks of randomization, history of red cell aplasia, or known hypersensitivity to recombinant mammalian red cell growth factor product. The study protocol was approved by the institutional review boards at participating centers, and patients' informed consent was obtained before the initiation of study procedures.

Study Design

Patients were randomized at a 1:1 ratio centrally to receive darbepoetin alfa 200 μg every 2 weeks or epoetin alfa 40,000 U weekly for ≤ 16 weeks. The randomization was stratified by the patients' screening Hb levels (< 10 g/dL or ≥ 10 g/dL). Treatment efficacy and safety were monitored during treatment, at the end of treatment (2 weeks after the final dose of darbepoetin alfa or 1 week after the final dose of epoetin alfa), and at a 2-week follow-up visit. Hemoglobin levels, transfusions, and adverse events were assessed every 2 weeks for both study drugs.

The Patient Satisfaction Questionnaire for Anemia (PSQ-An), a disease- and treatment-specific instrument for measuring satisfaction with anemia treatment in patients with cancer, was administered every 4 weeks during the trial.[32] This instrument includes domains assessing patient satisfaction with the treatment itself and domains pertaining directly to anemia treatment, which include the following: patient's general satisfaction with treatment, convenience of treatment for patient and family/friends, patient's pain and discomfort, and financial aspects of treatment for the patient. This instrument consisted of 2 parts: a descriptive part (11 items) that included questions about resources devoted to treatment and a scale part (10 items) that included questions about treatment burden and overall satisfaction.

Figure 1 Patient Disposition



Dose modifications were prespecified to maintain appropriate Hb levels during the trial. After 4 weeks of treatment, if Hb did not increase ≥ 1 g/dL from baseline, doses were increased to 300 μg every 2 weeks for darbepoetin alfa or 60,000 U weekly for epoetin alfa. Study drug was withheld if Hb levels exceeded 13 g/dL and was restarted at the previous level when Hb levels were ≤ 13 g/dL. Supplemental iron therapy was permitted according to institutional standards. Red blood cell transfusions were also recommended if Hb levels decreased to < 8 g/dL.

Study Drugs

Darbepoetin alfa was supplied as a clear, colorless, sterile protein solution containing 200 μg or 325 μg of darbepoetin alfa per milliliter. Commercially available epoetin alfa was obtained by the clinical sites.

Study Objectives and Endpoints

The trial was designed as an exploratory (phase II) investigation that had a number of descriptive objectives but did not have a prespecified formal hypothesis testing. The objectives were the following: to quantify the efficacy of darbepoetin alfa compared with epoetin alfa in patients with breast cancer; to provide information regarding the feasibility, internal consistency, and validity of the PSQ-An; and to describe the safety profile of darbepoetin alfa compared with epoetin alfa in patients with breast cancer.

Study endpoints included mean change in Hb during treatment, mean Hb level at the end of treatment, and proportion of patients exhibiting a hematopoietic response (Hb level ≥ 12 g/dL or increase in Hb level from baseline ≥ 2 g/dL). We additionally analyzed data evaluating the ability to achieve and maintain a target Hb range of 11-13 g/dL. This range is consistent with those recommended by the American Society of Hematology (ASH)/American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Organization of Research and Treatment of Cancer (EORTC), which specify target Hb ranges of near 12 g/dL,[32] 11-12 g/dL,[33] and 12-13 g/dL,[34] respectively; these are evidence-based guidelines, as these ranges have been shown to be associated with lowered transfusion risks and maximum QOL benefits. Furthermore, the Food and Drug Administration (FDA)–approved package instructions for darbepoetin alfa and epoetin alfa recommend that Hb values > 12 g/dL should not be used as a therapeutic target and provide recommendations for dose reduction and dose withholding to prevent Hb levels > 13 g/dL.[35,36] The endpoints reported herein include the exploratory endpoint of the proportion of patients exhibiting and maintaining a target Hb level (≥ 11 g/dL) and the median time to achieve target Hb level.

Safety was assessed by summarizing the incidence of adverse events by treatment group. All adverse events were summarized by the system organ class affected based on Medical Dictionary for Regulatory Activities adverse event preferred terms. The Medical Dictionary for Regulatory Activities is the international medical terminology developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Antibody formation was assessed at baseline and at the end of study (2 weeks after the last dose of study drug).

Statistical Analysis

Statistical analyses were conducted on all patients who were randomized and received ≥ 1 dose of study drug. Baseline demographics and clinical characteristics were summarized as the mean and standard deviation (SD) for continuous measures and as the number and percentage for categoric measures. Proportion endpoints were presented as crude percentages and Kaplan-Meier estimates.

Hemoglobin-based endpoints were summarized as the mean and 95% CI calculated using Greenwood's estimate of variance.[37] To handle missing Hb data, 2 statistical approaches were used: the first approach ensured that all patients randomized received study drug were included in the analysis, with missing Hb values imputed using the last available Hb value (termed the last value carried forward [LVCF] analytical approach). Similarly, Hb values in the 28 days after a red blood cell transfusion were excluded from the analyses and replaced using the last Hb value before transfusion. An alternative method (available data approach) was performed as a sensitivity analysis in which missing Hb values and values in the 28 days after a red blood cell transfusion were excluded but not imputed. Crude proportions were calculated for the overall and monthly incidence of transfusions.

To evaluate the timeliness of response to darbepoetin alfa relative to epoetin alfa, the time to achieve the target Hb range (11-13 g/dL) was reported using the Kaplan-Meier estimate of the median and 95% CIs. Kaplan-Meier curves depicting the time to target Hb levels ≥ 11 g/dL were plotted over time. The crude proportion of patients exhibiting Hb levels ≥ 11 g/dL in the absence of a transfusion in the previous 28 days was reported. Each patient's mean Hb levels and duration of treatment after exhibiting the target Hb level were summarized. The percentage of patients within each

mean Hb category (< 11 g/dL, 11-13 g/dL, and > 13 g/dL) after achievement of target Hb was also provided.

Feasibility of the PSQ-An was summarized as the mean patient completion rate throughout treatment and 95% CI. Descriptive outcomes were analyzed by treatment group.

Mean weekly dose of study drug was calculated as the cumulative dose divided by the weeks of exposure. Duration of exposure were the number of weeks between the last dose (including dose any withheld) and the first dose, adding 1 week for epoetin alfa and 2 weeks for darbepoetin alfa.

Results

Baseline Patient Characteristics

From 20 participating US centers between October 2002 and December 2003, a total of 141 patients (72 receiving darbepoetin alfa [51%] and 69 receiving epoetin alfa [49%]) were enrolled and received study drug (Figure 1). Of these patients, 63 patients receiving darbepoetin alfa (88%) and 50 patients receiving epoetin alfa (72%) completed the study. The reasons for discontinuation (eg, withdrawal of informed consent, investigator decision, death, loss to follow-up) were similar between treatment groups; however, fewer patients in the darbepoetin alfa group compared with the epoetin alfa group withdrew consent (3 patients [4%] vs. 8 patients [12%], respectively).

Generally, no major differences in baseline demographics or clinical characteristics were observed between treatment groups (Table 1). Mean baseline Hb concentrations were 10.5 g/dL ± 0.8 for the darbepoetin alfa group and 10.6 g/dL ± 0.7 for the epoetin alfa group. Approximately 20% of both groups had baseline Hb levels < 10 g/dL.

Table 1 Patient Demographics and Baseline Characteristics

Characteristic	Darbepoetin Alfa (n = 72)	Epoetin Alfa (n = 69)
Female Sex, n (%)	72 (100)	69 (100)
Mean Age ± SD, Years (Range)	53.6 ± 11.4 (35-81)	58.4 ± 12.5 (34-81)
Ethnicity, n (%)		
White	58 (81)	57 (83)
Other	14 (19)	12 (17)
Disease Stage, n (%)		
I/II	37 (51)	26 (38)
III	11 (15)	13 (19)
IV	22 (31)	26 (38)
Unknown	2 (3)	4 (6)
Karnofsky Performance Status, n (%)		
100	9 (13)	9 (13)
90	36 (50)	36 (52)
80	17 (24)	17 (25)
70	9 (13)	5 (7)
60	1 (1)	2 (3)
Previous Radiation Therapy, n (%)	9 (13)	10 (14)
Previous Chemotherapy, n (%)		
≥ 1 Previous regimen	23 (32)	32 (46)
> 2 Previous regimens	8 (11)	15 (22)
Chemotherapy Regimen Received, n (%)		
Taxane	53 (73)	48 (70)
Anthracycline	40 (55)	32 (47)
Alkylating agents	37 (51)	28 (41)
Antimetabolites	16 (22)	19 (28)
Monoclonal antibodies	10 (14)	11 (16)
Other	37 (51)	36 (53)
Mean Hemoglobin Level ± SD (g/dL)	10.5 ± 0.8	10.6 ± 0.7
Hemoglobin Level, n (%)		
< 10 g/dL	14 (19)	11 (16)
≥ 10 g/dL	58 (81)	58 (84)
Mean Serum Ferritin ± SD (ng/mL)	336.3 ± 319.8	290 ± 260.3
Mean Transferrin Saturation ± SD (%)	27.32 ± 17.11	29.28 ± 21.82
Iron Supplementation (Any Route), n (%)	72 (100)	69 (100)

Efficacy

Drug Use. Most patients in both treatment groups had a dose modification (increase, decrease, and/or withholding) during the trial (93% of the darbepoetin alfa group and 88% of the epoetin alfa group). The mean every-2-week dose for darbepoetin alfa was 211 μg ± 61 and the mean weekly dose for epoetin alfa was 38,863 U ± 12,074. Mean durations of exposure were 14.1 weeks ± 3.2 weeks for patients receiving darbepoetin alfa and 13.8 weeks ± 3.9 for patients receiving epoetin alfa.

Transfusions. Six percent of the patients who received darbepoetin alfa had a transfusion, compared with 16% of the epoetin alfa group (Table 2). The difference between groups was –10% with an upper bound of the 95% CI of < 0. Similar profiles were observed between the baseline Hb strata. These results indicate that it is highly unlikely that future

Table 2 Incidence of Transfusions During Treatment by Baseline Hemoglobin Strata and Overall Analyses

Transfusion Parameter	Hb < 10 g/dL		Hb ≥ 10 g/dL		Overall	
	Darbepoetin Alfa (n = 14)	Epoetin Alfa (n = 11)	Darbepoetin Alfa (n = 58)	Epoetin Alfa (n = 58)	Darbepoetin Alfa (n = 72)	Epoetin Alfa (n = 69)
Incidence of Transfusions, % (95% CI)*	14 (0-33)	36 (8-65)	3 (0-8)	12 (4-20)	6 (0-11)	16 (7-25)
Difference, % (95% CI)†	–22 (–56 to 12)		–9 (–18 to 1)		–10 (–20 to 0)	
Monthly Rate, n (%)‡						
Month 1	2 (14)	2 (18)	0	0	2 (3)	2 (3)
Month 2	0	2 (20)	0	4 (7)	0	6 (9)
Month 3	1 (8)	0	0	2 (4)	1 (1)	2 (3)
Month 4	0	0	2 (4)	3 (6)	2 (3)	3 (6)

*Crude proportion.
†Incidence with darbepoetin alfa minus incidence with epoetin alfa.
‡Includes all patients with data available at the end of each month.

studies will show that epoetin alfa is more effective than darbepoetin alfa with respect to transfusion requirements.

Monthly transfusion rates were low in both groups throughout treatment (Table 3). No differences in transfusion rates within the Hb strata were observed.

Mean Change in Hemoglobin. Mean change in Hb increased similarly between patients treated with darbepoetin alfa and epoetin alfa at weeks 9 and 17 (Figure 2). Using the LVCF method, which included all patients randomized and treated, mean changes in Hb level from baseline were 1.9 g/dL ± 1.5 for the darbepoetin alfa group and 1.7 g/dL ± 1.4 for the epoetin alfa group at the end of treatment (week 17). From the sensitivity analysis using the available data approach, no major differences were observed between treatment groups. At week 17, mean change in Hb level was 2.3 g/dL for patients treated with darbepoetin alfa and 2.5 g/dL for patients treated with epoetin alfa.

Consistent results were found within baseline Hb strata (Figure 3). In the < 10-g/dL stratum, mean changes in Hb level were 2.4 g/dL for patients receiving darbepoetin alfa and 2 g/dL for patients receiving epoetin alfa. In the ≥ 10-g/dL stratum, mean changes in Hb level were 1.8 g/dL for patients receiving darbepoetin alfa and 1.7 g/dL for patients receiving epoetin alfa. The sensitivity analysis using the available data approach confirmed the robustness of the LVCF analysis with no differences observed between darbepoetin alfa and epoetin alfa.

Hematopoietic Response. Hematopoietic response rates (increase in Hb ≥ 2 g/dL or Hb level ≥ 12 g/dL) were 88% (95% CI, 80%-95%) for the darbepoetin alfa group and 81% (95% CI, 72%-90%) for the epoetin alfa group (Figure 4; Table 3). The difference between the groups was 6%, with a lower bound of the 95% CI of –6% and an upper bound of 18%. Within each Hb strata, similar rates were observed between treatment groups. The overall median time to hematopoietic response was 7 weeks for both treatment groups. Similar median response times were observed for both stratified Hb subsets.

Achievement and Maintenance of Target Hemoglobin Level. To further describe the efficacy of these agents, the ability of either agent to achieve and maintain a clinically meaningful Hb level (based on evidence-based guidelines) was explored. Nearly all patients exhibited the Hb target range (93% for

Table 3 Proportion of Patients Exhibiting a Hematopoietic Response by Baseline Strata and Overall Analyses

Response Parameter	Hb < 10 g/dL		Hb ≥ 10 g/dL		Overall	
	Darbepoetin Alfa (n = 14)	Epoetin Alfa (n = 11)	Darbepoetin Alfa (n = 58)	Epoetin Alfa (n = 58)	Darbepoetin Alfa (n = 72)	Epoetin Alfa (n = 69)
Patients with a Hematopoietic Response, % (95% CI)*	79 (57-100)	64 (35-92)	90 (82-97)	84 (75-94)	88 (80-95)	81 (72-90)
Difference, % (95% CI)†	15 (–21 to 51)		5 (–7 to 17)		6 (–6 to 18)	
Median Time to Response, Weeks (95% CI)‡	7 (6-11)	9 (6-14)	7 (5-11)	7 (5-8)	7 (6-9)	7 (6-9)

*Crude proportion.
†Incidence with darbepoeitin alfa minus incidence with epoetin alfa.
‡Kaplan-Meier estimate.

the darbepoetin alfa group and 90% for the epoetin alfa group; Table 4). Mean Hb concentrations after achieving the target range were similar between patients receiving darbepoetin alfa (12.1 g/dL) and those receiving epoetin alfa (12.3 g/dL). Median time to target was similar for both groups, at 3 weeks (95% CI, 3-5 weeks) for the darbepoetin alfa group and 4 weeks (95% CI, 3-5 weeks) for the epoetin alfa group (Table 4; Figure 5). When stratified by baseline Hb, no major differences between treatment groups were observed.

Patient Satisfaction Questionnaire for Anemia Treatment. The PSQ-An instrument has been reported to be feasible, reliable, and valid.[38] In patients with breast cancer, completion rates of the PSQ-An exceeded 80% at each time point during the trial (range, 88%-94%). In general, outcomes from the descriptive part of the PSQ-An were similar over the treatment period between patients who received darbepoetin alfa and those who received epoetin alfa. The cumulative number of clinic visits during the treatment period was lower for patients treated with darbepoetin alfa than for patients who received epoetin alfa. To travel to and from the clinic for each injection, patients treated with darbepoetin alfa spent a mean of 1.7 hours ± 1.4 and patients treated with epoetin alfa spent a mean of 2.2 hours ± 2.6. The mean time spent in the clinic to receive each injection was 1.6 hours ± 1.7 for patients who received darbepoetin alfa and 2.4 hours ± 2.4 for patients who received epoetin alfa. To receive each injection, patients in either group spent approximately $20-$30 in out-of-pocket expenses.

Safety

Of 141 patients, 11 in the darbepoetin alfa group (15%) and 16 in the epoetin alfa group (24%) had ≥ 1 serious adverse event. These events were consistent with those reported in other studies of erythropoietic therapies in cancer treated with chemotherapy and included general disorders, administration-site conditions, blood and lymphatic system disorders, and gastrointestinal disorders. No major differences in safety were observed between the 2 treatment groups. No thrombotic events were reported for either group during treatment. No neutralizing antibodies against either study drug were detected in any samples at screening or at the end of treatment.

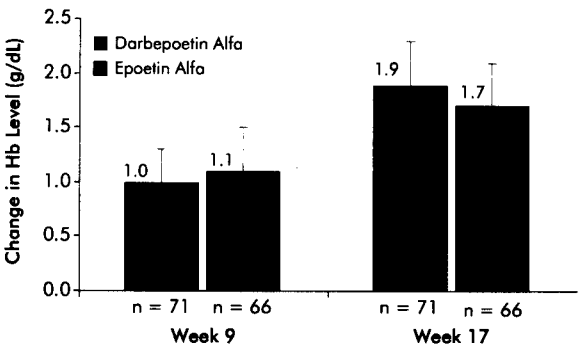
Discussion

Patients with breast cancer represent a specific cancer population with unique demographics. With increasingly higher incidences of all grades of anemia with newer adjuvant chemotherapy regimens for the treatment of breast cancer, the need for data on the efficacy of erythropoietic agents in breast cancer is underscored. This report presents results from the first comparative phase II randomized trial that describes the relative efficacy of the most commonly used dosages of darbepoetin alfa and epoetin alfa in patients with breast cancer.

Our findings support the comparability in efficacy and safety between darbepoetin alfa 200 μg every 2 weeks and epoetin alfa 40,000 U weekly in patients with breast cancer for the treatment of chemotherapy-induced anemia. In both treatment groups and within each baseline Hb stratum, Hb levels improved approximately 2 g/dL from baseline at the end of treatment, hematopoietic responses were high, and transfusion requirements were low. Overall, no differences between darbepoetin alfa and epoetin alfa were observed in any hematologic or transfusion-based endpoints. In general, safety profiles were similar between groups in this study, with adverse events that were consistent with those reported in other studies of erythropoietic therapies in patients with cancer receiving chemotherapy. No patients had thrombotic events during the study.

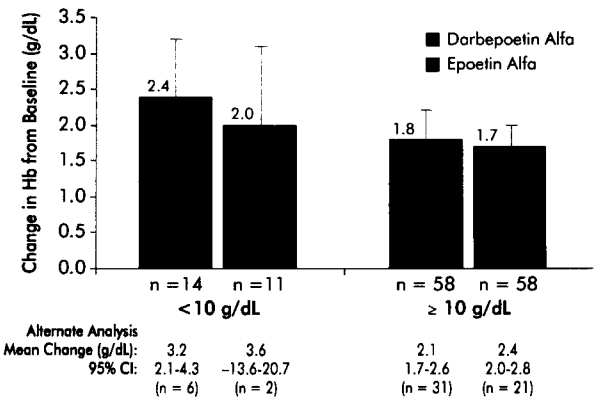
These findings of efficacy are similar to those previously reported for erythropoietic agents for the treatment of chemotherapy-induced anemia[15-19,22,23]; however, our results are unique because the relative efficacy of these 2 agents can be compared in a setting in which many confounding factors have been eliminated. By using a single cancer population, the inherent heterogeneity in tumor types, a variable found to be a covariate affecting response in

Figure 2 Mean (95% CI) Change in Hemoglobin from Baseline at Weeks 9 and 17 (LVCF Approach)



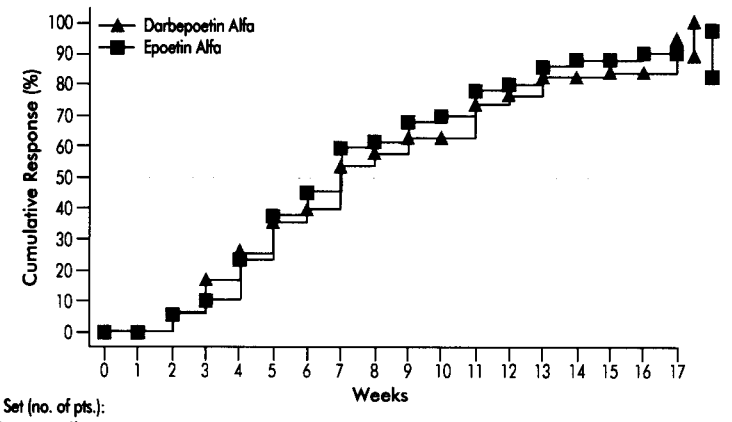
Vertical bars represent 95% CIs.

Figure 3 Change in Hemoglobin from Baseline at End of Treatment Stratified by Baseline Hemoglobin Level (LVCF Approach)



Vertical bars represent 95% CIs.

Figure 4 Time to Hematopoietic Response (Kaplan-Meier Estimate)



Risk Set (no. of pts.):

Darbepoetin Alfa	72	72	72	68	58	51	44	40	31	27	24	24	17	15	11	11	10	9
Epoetin Alfa	69	69	68	64	60	55	40	34	25	23	19	18	11	10	7	6	5	1

Error bars represent 95% CI at week 17. Weekly values were available because some patients received treatment at different times than those specified in the protocol because of clinic scheduling conflicts.

a recent study by Vadhan-Raj et al,[39] has been removed in our study. Further, confounding factors arising from the heterogeneity in chemotherapy regimens, such as use of platinum versus nonplatinum compounds, have also been minimized.

In order to formally determine noninferiority or equivalence for comparisons of active treatments, large numbers of patients are generally required with a formal noninferiority/equivalence margin prespecified in the protocol. Although no predefined noninferiority margin was specified in this trial, some observations regarding the statistical comparability of these 2 agents can be made. For transfusion requirements, the mean difference between groups favored darbepoetin alfa (–10%; 95% CI, –20% to 0), with the upper limit of the 95% CI of the difference excluding zero, indicating that darbepoetin alfa is very unlikely to have a higher transfusion requirement than epoetin alfa in this population. For hematopoietic response, the lower limit of the 95% CI of the difference between groups was –6%, indicating that differences favoring epoetin alfa > 6% should be rare (occurring in < 2.5% of cases). Although the trials were not formally powered to conclusively demonstrate noninferiority of darbepoetin alfa, the overall results strongly suggest that darbepoetin alfa 200 μg every 2 weeks achieves comparable clinical outcomes compared with epoetin alfa 40,000 U weekly. To confirm these findings, a trial with a prespecified noninferiority margin should be conducted.

In evaluating clinical characteristics that are important for the comparison of active therapies, the length of time between initiation of erythropoietic therapy and achievement of a clinically relevant response was considered to be an important measure of therapeutic success. However, this temporal relationship could not be addressed using the standard validated endpoints discussed herein. To address this, an endpoint measuring the achievement and maintenance of a clinically meaningful target Hb range of 11-13 g/dL was selected. This target Hb range is consistent with those recommended by the ASH/ASCO (12 g/dL or near to 12 g/dL), NCCN (11-12 g/dL), and EORTC (12-13 g/dL) evidence-based guidelines; patients with Hb levels > 11 g/dL are considered to have minimal transfusion risk and maxi-

Table 4 Achievement and Maintenance of Target Hemoglobin Level ≥ 11 g/dL

Hemoglobin Result	Hb < 10 g/dL		Hb < 10 g/dL		Overall	
	Darbepoetin Alfa (n = 14)	Epoetin Alfa (n = 11)	Darbepoetin Alfa (n = 58)	Epoetin Alfa (n = 58)	Darbepoetin Alfa (n = 72)	Epoetin Alfa (n = 69)
Patients Exhibiting Target Hb Level ≥ 11 g/dL, n (%)*	11 (79)	7 (64)	56 (97)	54 (95)	67 (93)	61 (90)
Median Time to Target, Weeks (95% CI)†	7 (5-8)	7 (6-12)	3 (3-4)	3 (3-4)	3 (3-5)	4 (3-5)
Mean ± SD Hemoglobin Level After Achieving Target (g/dL)	11.7 ± 0.8	11.9 ± 1.0	12.2 ± 0.7	12.4 ± 0.7	12.1 ± 0.8	12.3 ± 0.8
Mean ± SD Duration of Treatment After Achieving Target Hb Level (Weeks)	9.5 ± 1.9	7.7 ± 4.6	10.4 ± 3.5	10.5 ± 3.6	10.2 ± 3.4	10.1 ± 3.8
Maintained Mean Hb Categories After Achievement of Target Hb Level, n (%)*						
< 11 g/dL	3 (27)	1 (14)	2 (4)	4 (7)	5 (7)	5 (8)
11-13 g/dL	7 (64)	4 (57)	45 (80)	39 (72)	52 (78)	43 (70)
> 13 g/dL	1 (9)	2 (29)	9 (16)	11 (20)	10 (15)	13 (21)

*Crude proportion.
†Kaplan-Meier estimate.

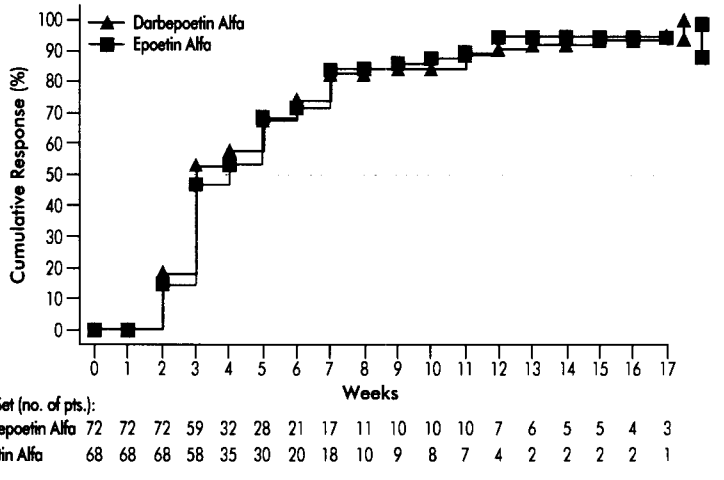
mized health-related QOL benefits.[32-34] The upper limit conforms to the FDA-approved package insert for each product that requires withholding therapy if the Hb concentration exceeds 13 g/dL.[35,36] In this trial, no differences in the ability to achieve, time to achieve, or ability to maintain the therapeutic target range were observed between darbepoetin alfa and epoetin alfa. After achievement of the target Hb range, dose titration rules (withholding therapy if the Hb level exceeds 13 g/dL) in this trial stabilized Hb concentrations at approximately 12 g/dL in both groups; only a few patients in either group maintained Hb levels greater than the 13 g/dL threshold.

Endpoints based on the target Hb range were specifically chosen because these endpoints not only measure clinically relevant success over time but also to ensure that patients whose Hb levels exceed the 13-g/dL limit are not counted as treatment successes. Other time-sensitive methods such as the area under the Hg level/time curve; continuous variables, such as Hb change; or binary outcomes, such as hematopoietic response, for example, are insensitive to the determination of a target therapeutic range or of a threshold concentration above which possible safety concerns may alter the risk/benefit relationship.[18]

The PSQ-An was reliable, feasible, and valid.[32] These findings support the use of the PSQ-An in the breast cancer population and may allow formal comparisons of the impact of anemia therapy on the daily lives of patients and caregivers.

A few limitations existed for this trial. First, no formal hypothesis testing to compare efficacy between these 2 agents was prespecified. Our findings provide information of response and patient satisfaction with erythropoietic treatment in breast cancer. Formal hypothesis testing will need to be conducted to confirm these initial results. Second, the generalizability of these results to other tumor types need to be confirmed in larger, formal trials; however, our findings are consistent with large, well-conducted medication-use evaluation studies in heterogeneous populations that demonstrated the comparability of these 2 agents at these dosages.[20-22,24]

Figure 5 Achievement of Target Hemoglobin Level ≥ 11 g/dL (Kaplan-Meier Estimate)



Error bars represent 95% CI at week 17. Weekly values were available because some patients received treatment at different times than those specified in the protocol because of clinic scheduling conflicts.

Conclusion

Darbepoetin alfa 200 μg every 2 weeks and epoetin alfa 40,000 U weekly appear to achieve similar hematologic and transfusion-based outcomes as well as patient satisfaction with erythropoietic treatment in patients with breast cancer.

Acknowledgements

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References

1. Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2005. *CA Cancer J Clin* 2005; 55:10-30.
2. Carrick S, Ghersi D, Wilcken N, et al. Platinum containing regimens for metastatic breast cancer. *Cochrane Database Syst Rev* 2004; (3):CD003374.
3. Cristofanilli M, Hortobagyi GN. Breast cancer highlights: key findings from the San Antonio Breast Cancer Symposium: a U.S. perspective. *Oncologist* 2004; 9:471-478.
4. Carlson R. NCCN Clinical practice guidelines in oncology: breast cancer, vol. 1. Jenkintown, PA: NCCN, 2004.
5. Kirshner J, Hatch M, Hennessy DD, et al. Anemia in stage II and III breast cancer patients treated with adjuvant doxorubicin and cyclophosphamide chemotherapy. *Oncologist* 2004; 9:25-32.
6. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. *J Clin Oncol* 2003; 21:4524-4531.
7. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment [published erratum in *J Natl Cancer Inst* 2000; 92:497]. *J Natl Cancer Inst* 1999; 91:1616-1634.
8. Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *Eur J Cancer* 2004; 40:2293-2306.
9. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741 [published erratum in *J Clin Oncol* 2003; 21:2226]. *J Clin Oncol* 2003; 21:1431-1439.
10. Schwartzberg L, Tauer K, Barry FV. Dose dense chemotherapy (DDC) supported by pegfilgrastim (peg) and an erythropoietic agent (EA) in operable breast cancer. Presented at the 27th Annual San Antonio Breast Cancer Symposium; December 8-11, 2004; San Antonio, TX. Abstract #6035.
11. Ganz PA, Kwan L, Stanton AL, et al. Quality of life at the end of primary treatment of breast cancer: first results from the moving beyond cancer randomized trial. *J Natl Cancer Inst* 2004; 96:376-387.
12. Chung CT, Carlson RW. Goals and objectives in the management of metastatic breast cancer. *Oncologist* 2003; 8:514-520.
13. Osoba D, Slamon DJ, Burchmore M, et al. Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic

breast cancer. *J Clin Oncol* 2002; 20:3106-3113.
14. Beveridge RA, Rifkin RM, Moleski RJ, et al. Impact of long-acting growth factors on practice dynamics and patient satisfaction. *Pharmacotherapy* 2003; 23(suppl):101S-109S.
15. Chang J, Couture F, Young S, et al. Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy. *J Clin Oncol* 2005; 23:2597-2605.
16. Glaspy J, Patel R, Tchekmedyian N, et al. Darbepoetin alfa given once every 3 weeks (Q3W) either synchronously or asynchronously with Q3W chemotherapy (ctx) improves anaemia in patients (pts) with breast cancer: results of a randomised, open-label study. Presented at: the 4th Annual European Breast Cancer Conference; March 20, 2004; Hamburg, Germany.
17. Blayney D, Vadhan-Raj S, Mirtsching B, et al. Darbepoetin alfa 3.0 mcg/kg every 2 weeks improves hemoglobin and quality of life in a subset of breast cancer patients in a community-based trial of patients with chemotherapy-induced anemia. *Breast Cancer Res Treat* 2003; 85(suppl):640a.
18. Leyland-Jones B, O'Shaughnessy JA. Erythropoietin as a critical component of breast cancer therapy: survival, synergistic, and cognitive applications. *Semin Oncol* 2003; 30(5 suppl 16):174-184.
19. Demetri GD, Gabrilove JL, Blasi MV, et al. Benefits of epoetin alfa in anemic breast cancer patients receiving chemotherapy. *Clin Breast Cancer* 2002; 3:45-51.
20. Patton J, Reeves T, Wallace J. Effectiveness of darbepoetin alfa versus epoetin alfa in patients with chemotherapy-induced anemia treated in clinical practice. *Oncologist* 2004; 9:451-458.
21. Thames WA, Smith SL, Scheifele AC, et al. Evaluation of the US Oncology Network's recommended guidelines for therapeutic substitution with darbepoetin alfa 200 microg every 2 weeks in both naive patients and patients switched from epoetin alfa. *Pharmacotherapy* 2004; 24:313-323.
22. Schwartzberg L, Shiffman R, Tomita D, et al. A multicenter retrospective cohort study of practice patterns and clinical outcomes of the use of darbepoetin alfa and epoetin alfa for chemotherapy-induced anemia. *Clin Ther* 2003; 25:2781-2796.
23. Glaspy J, Jadeja J, Justice G, et al. Darbepoetin alfa given every 1 or 2 weeks alleviates anaemia associated with cancer chemotherapy. Br *J Cancer* 2002; 87:268-276.
24. Herrington JD, Davidson SL, Tomita DK, et al. Utilization of darbepoetin alfa and epoetin alfa for chemotherapy-induced anemia. *Am J Health Syst Pharm* 2005; 62:54-62.
25. Aranesp® [package insert]. Breda, Netherlands: Amgen Inc; 2004
26. Leyland-Jones B; BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol* 2003; 4:459-460.
27. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 2003; 362:1255-1260.
28. Möbus VJ, Untch M, Du Bois A, et al. Dose-dense sequential chemotherapy with epirubicin(E), paclitaxel (T) and cyclophosphamide (C) (ETC) is superior to conventional dosed chemotherapy in high-risk breast cancer patients (≥ 4 +LN). First results of an AGO-trial. *Proc Am Soc Clin Oncol* 2004; 23:6a (Abstract #513).
29. Micheal U, Jackisch C, Lenhard MS, et al. Epoetin-alpha reduces red blood cell transfusions (RBC) in high-risk breast cancer patients with adjuvant dose-dense, sequential chemotherapy with epirubicin (E), paclitaxel (T) and cyclophosphamide (C) (ETC). *Proc Am Soc Clin Oncol* 2005; 23:31a (Abstract #613).
30. Blohmer JU, Hauschild M, Hilfrich J, et al. Safety and efficacy of first-line epirubicin-docetaxel (ED) versus epirubicin-cyclophosphamide (EC): a multicenter randomized phase III trial in metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 2004; 23:33a (Abstract #627).
31. Schwartzberg LS, Yee LK, Senecal FM, et al. A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. *Oncologist* 2004; 9:696-707.
32. Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 2002; 20:4083-4107.
33. Sabbatini P. NCCN Guidelines (NCCN practice guidelines in oncology: cancer and treatment-related anemia), vol. 2. Jenkintown, PA: NCCN, 2004.
34. Bokemeyer C, Aapro MS, Courdi A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. *Eur J Cancer* 2004; 40:2201-2216.
35. Aranesp® [package insert]. Thousand Oaks, CA: Amgen Inc; 2005.
36. Patton J, Kuzur M, Liggett W, et al: Epoetin alfa 60,000 U once weekly followed by 120,000 U every 3 weeks increases and maintains hemoglobin levels in anemic cancer patients undergoing chemotherapy[published erratum in *Oncologist* 2004; 9:240]. *Oncologist* 2004; 9:90-96.
37. Collette D. *Modeling Survival Data in Medical Research*. London, UK: Chapman and Hall/CRC; 1994.
38. Nordyke R, Chang CH, Chiou CF, et al. Validation of a patient satisfaction questionnaire for anemia treatment, the PSQ-An. In press.
39. Vadhan-Raj S, Mirtsching B, Gregory SA, et al: Baseline (BL) covariates of response to darbepoetin alfa (DA) every 2 weeks (Q2W) in pa-

[3556] Randomized, Double-Blind, Placebo-Controlled Study of Darbepoetin alfa Every 3 Weeks for the Treatment of Chemotherapy-Induced Anemia. Session Type: Poster Session 807-III

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Background: Darbepoetin alfa (Aranesp®; DA) has been shown to be safe and effective for treating chemotherapy-induced anemia (CIA). The ability to administer darbepoetin alfa every 3 weeks (Q3W) (coincident with chemotherapy) would simplify the treatment of CIA. We report results from the first multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial evaluating efficacy and safety of fixed Q3W administration of an erythropoietic agent.

Methods: This study enrolled subjects ≥18 years, diagnosed with anemia (hemoglobin [Hb]<11g/dL) and a nonmyeloid malignancy with ≥12 weeks of planned chemotherapy. Patients (N=391) were randomized 1:1 to receive DA 300 µg or placebo Q3W for 15 weeks. Dose adjustment rules included: increase (to 500 µg Q3W) if Hb concentration was <9 g/dL at week 4 or <10 g/dL (and had <1-g/dL increase) at week 7, or decrease (dependent on previous dose) if Hb concentration was ≥13 g/dL or had ≥1-g/dL increase in any 2-week period. Efficacy was assessed by incidence of red blood cell (RBC) transfusions and achievement of target Hb of ≥11 g/dL (not exceeding 13 g/dL), consistent with ASH/ASCO, NCCN, EORTC evidence-based practice guidelines.

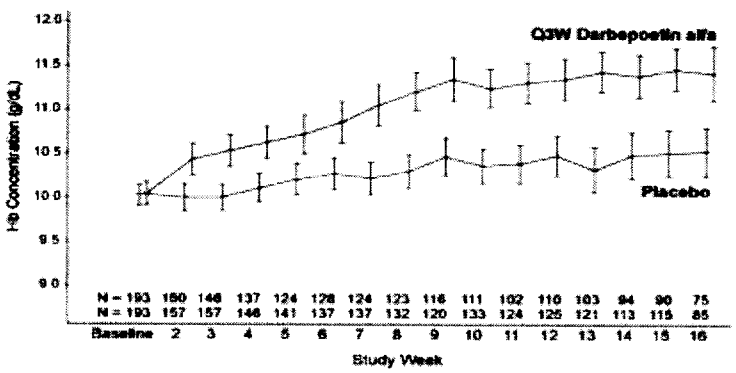
Results: A total of 386 randomized patients were included in the analysis. Demographic characteristics were similar between the 2 groups. Mean (SD) Hb levels at baseline were 10.03 (0.86) and 10.05 (0.92) g/dL in the placebo and DA groups, respectively. The most common tumor types were breast (23%), colon (11%), nonsmall-cell-lung cancer (10%), and hematologic malignancies (11%; 8% Non-Hodgkin's Lymphoma). The incidence of RBC transfusions from week 5 to the end of treatment phase (EOTP) (the primary endpoint) was significantly lower for the DA group than for the placebo group (P<0.001) (see Table). Hb levels rose steadily in the DA group through approximately week 9, increasing by a mean (SD) of 1.08 (1.28) g/dL from baseline, and then remained relatively stable (see Figure). The proportion of patients achieving Hb target range from week 5 to EOTP was significantly higher for the DA group than for the placebo group (P<0.001). Dose adjustment rules helped to maintain Hb levels within target range. The safety profile of DA was consistent with that observed in previous studies. Rapid increases in Hb concentration or increases to ≥13 g/dL were not associated with adverse events.

Conclusions: Fixed Q3W administration of DA is well tolerated and effective for the treatment of CIA.

Summary of Results

	Placebo	Darbepoetin alfa
Week 5 to EOTP	N=185	N=181
Transfusions, KM (95% CL) (primary endpoint)	41% (34, 49)	24% (18, 30)
Achievement of target Hb, KM (95% CL)	48% (41, 56)	82% (76, 88)
Week 1 to EOTP	N=193	N=193
Transfusions, KM (95% CL)	47% (40, 54)	30% (23, 36)
Median time to target Hb, weeks (95% CL)	12 (9, 16)	6 (3, 7)

KM = Kaplan-Meier estimate



Abstract #3556 appears in Blood, Volume 106, issue 11, November 16, 2005
Keywords: Clinical trial|Growth factor|Hemoglobin

Monday, December 12, 2005 10:30 AM

Poster Session: Pathophysiology of Erythropoiesis and Related Disorders (10:30 AM-6:30 PM)

Abstract # 3556

Randomized, Double-Blind, Placebo-Controlled Study of Darbepoetin alfa Every 3 Weeks for the Treatment of Chemotherapy-Induced Anemia

Kerry Taylor,[1] Peter Ganly,[2] Veena Charu,[3] Joseph DiBenedetto,[4] Irene Ferreira,[5] Greg Rossi,[5] and Enrique Hernandez[6]

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INTRODUCTION

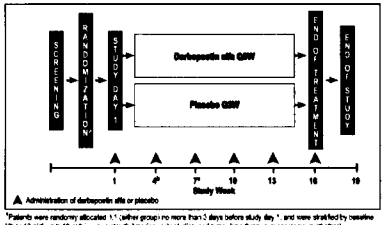
- Chemotherapy-induced anemia (CIA) is common in patients with cancer receiving myelosuppressive chemotherapy[1] and can be effectively alleviated by increasing hemoglobin (Hb) levels with the erythropoiesis-stimulating proteins, darbepoetin alfa (Aranesp®) and epoetin alfa (Procrit®).[2,3]
- Darbepoetin alfa has a half life of approximately 74 hours[4] that allows it to be administered at extended dosing intervals of up to once every 3 weeks (Q3W).[4,5]
- Darbepoetin alfa therapy is effective at alleviating the symptoms associated with chemotherapy-induced anemia when administered Q3W.[4,5]
- Chemotherapy is usually administered Q3W. Administration of darbepoetin alfa Q3W may permit the synchronization of anemia therapy with chemotherapy, potentially offering added convenience to patients and their caregivers.
- We report the preliminary, final results from the first multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial evaluating the efficacy and safety of a fixed dose (300 mcg) of darbepoetin alfa administered Q3W.

STUDY OBJECTIVE

- To evaluate the efficacy and safety of darbepoetin alfa administered at 300 mcg Q3W in treating anemia in patients with non-myeloid malignancies receiving cyclic chemotherapy

PATIENTS AND METHODS

Study Schema



[a]Patients were randomly allocated 1:1 (within group) no more than 3 days before study day 1, and were stratified by baseline Hb (< 10 g/dL vs ≥ 10 g/dL), region (North America vs Australia), and tumor type (lung vs gynecologic vs all other).
[b]If a patient's Hb concentration was < 9 g/dL, the dose of darbepoetin alfa was increased to 500 mcg.
[c]If a patient's Hb concentration was < 10 g/dL and the increase in Hb was < 1 g/dL, the dose of darbepoetin alfa was increased to 500 mcg.

Darbepoetin alfa was withheld if a patient's Hb was > 13 g/dL, and was reinstated at a lower dose at the next administration visit.

The dose of darbepoetin alfa was decreased if Hb increased by > 1 g/dL in any 2-week period in the absence of an RBC transfusion during the previous 14 days. For patients receiving 500 mcg Q3W, 300 mcg Q3W, or 200 mcg Q3W, the dose was reduced to 300 mcg Q3W, 200 mcg Q3W, or 150 mcg Q3W, respectively.

REFERENCES

1. Groopman JE, Itri LM. *J Natl Cancer Inst*. 1999;91(19):1616-1634.
2. Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B. *J Clin Oncol*. 2001;19(11):2865-2874.
3. Vansteenkiste J, Pirker R, Massuti B, Barata F, Font A, Fiegl M, et al. *J Natl Cancer Inst*. 2002;94(19):1211-1220.
4. Glaspy J, Henry D, Patel R, Timmerwilder S, Applebaum S, Bercovici D, et al. *Eur J Cancer*. 2005;41:1145-1154.
5. Kotasek D, Steger G, Faught W, Uscinska C, Pauber T, Calvacki AB, et al. *Eur J Cancer*. 2003;39(14):2028-2034.
6. Rizzo JD, Lichtin AE, Woolf SH, Seidenfeld J, Bennett CL, Cella D, et al. *J Clin Oncol*. 2002;20(19):4083-4107.
7. Rodgers GM. Available online at: http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf. Accessed 2005.
8. Bokemeyer C, Aapro MS, Courdi A, Foubert J, Lee H, Osterborg A, et al. *Eur J Cancer*. 2004;40(15):2201-2216.

PATIENTS AND METHODS *(continued)*

Key Patient Eligibility Criteria

- Anemic (Hb < 11 g/dL) within 24 hours before randomization
- ≥ 18 years old
- Non-myeloid malignancy
- At least 12 additional weeks of chemotherapy
- Adequate liver and renal function
- No more than 2 red blood cell (RBC) transfusions in the 4 weeks before randomization, or any RBC transfusion in the 2 weeks before randomization, or planned RBC transfusions between randomization and study day 1
- No erythropoietic therapy in the 4 weeks before randomization or planned erythropoietic therapy between randomization and study day 1

Study Endpoints

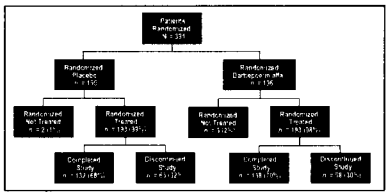
- The primary endpoint was the percentage of patients who received RBC transfusions from week 5 to the end of the treatment period (EOTP)
- Other endpoints included the percentage of patients who achieved a Hb concentration ≥ 11 g/dL (not exceeding 13 g/dL, in accordance with evidence-based guidelines[6,7,8]) from week 1 to EOTP in the absence of RBC transfusions in the preceding 28 days
- Safety endpoints included:
  - The incidence and severity of adverse events
  - The percentage of patients with Hb > 13 g/dL
  - The percentage of patients with an increase in Hb of 1 g/dL in ≤ 4 days, or 2 g/dL in 28 days
  - The presence of antibodies to darbepoetin alfa

Statistical Analysis

- Analyses of transfusion endpoints were stratified by baseline Hb concentration (< 10 g/dL or ≥ 10 g/dL) and tumor type (lung/gynecologic and other cancers)
- The percentages of patients receiving ≥ 1 RBC transfusion and who achieved a Hb concentration ≥ 11 g/dL were estimated using the Kaplan-Meier (KM) estimate
- Transfusion results are presented as KM estimates adjusted for stratification factors used at randomization (tumor type, screening Hb category, and geographic region)
- The difference (darbepoetin alfa – placebo) in the proportion of patients experiencing at least one RBC transfusion was calculated based on the adjusted KM estimates
- The sensitivity and specificity of a ≥ 1-g/dL rise in Hb concentration within 4 weeks of treatment (early response) to the incidence of RBC transfusions and the proportion of patients who achieved the target Hb were determined
  - For the incidence of RBC transfusions, sensitivity is the percentage of patients who had an early response and did not receive an RBC transfusion, specificity is the percentage of patients who did not have an early response and did receive an RBC transfusion
  - For the achievement of target Hb, sensitivity is the percentage of patients who had an early response and achieved target Hb, specificity is the percentage of patients who did not have an early response and did not achieve target Hb

RESULTS

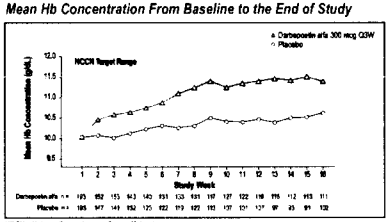
Patient Disposition



Baseline Demographics and Disease Characteristics

	Placebo (n = 192)	Darbepoetin alfa 300 mcg Q3W (n = 193)	All Patients (n = 385)
Number of women – n (%)	117 (61)	117 (61)	234 (61)
Race – n (%)			
White	152 (79)	153 (79)	305 (79)
Black	23 (12)	24 (12)	44 (11)
Other	21 (11)	16 (8)	37 (10)
Mean (SD) age, years	63.6 (12.3)	64.5 (12.1)	64.1 (12.2)
Geriatric age group – n (%)			
≥ 65	99 (52)	108 (56)	208 (53)
Tumor Type – n (%)			
Lung/gynecologic	48 (25)	46 (24)	94 (24)
Ovarian	13 (7)	19 (10)	32 (8)
Nonsmall-cell lung	24 (12)	16 (8)	40 (10)
Other lung/gynecologic	11 (6)	11 (6)	22 (6)
Non-lung/gynecologic	145 (75)	147 (76)	292 (76)
Breast	39 (20)	50 (26)	89 (23)
Large intestine/Colon	24 (12)	19 (10)	43 (11)
Non-Hodgkin's Lymphoma	17 (9)	13 (7)	30 (8)
Other	65 (34)	65 (34)	130 (34)
Mean (SD) baseline Hb (g/dL)	10.3 (0.9)	10.1 (0.9)	10.0 (0.9)

Mean Hb Concentration From Baseline to the End of Study



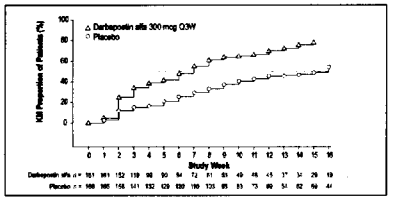
NCCN = National Comprehensive Cancer Network

Achievement and Maintenance of Target Hb Concentration

	Placebo (n = 192)	Darbepoetin alfa 300 mcg Q3W (n = 193)
KM percentage of patients achieving Hb ≥ 11 g/dL week 1 to EOTP – % (95% CL) [n]	55 (46, 64) [108]	77 (70, 84) [151]
Median time to target Hb, weeks (95% CL)	16 (11, NE)	7 (6, 8)
Mean (95% CL) Hb after achieving target (g/dL) [n]	11.0 (10.8, 11.1) [104]	11.5 (11.3, 11.7) [146]
Patients maintaining Hb concentration after achieving target – n (%)		
< 11 g/dL	49 (45)	42 (28)
11 to 13 g/dL	54 (52)	98 (67)
> 13 g/dL	1 (1)	6 (4)

NE = not estimable

Time to Target Hb Concentration (≥ 11 g/dL)



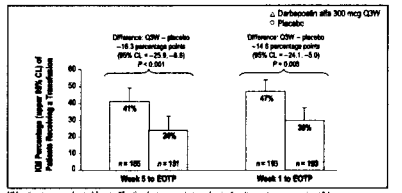
Sensitivity and Specificity of ≥ 1-g/dL Increase in Hb After 4 Weeks of Dosing

	Placebo (n = 193)	Darbepoetin alfa 300 mcg Q3W (n = 193)
Patients with a ≥ 1 g/dL increase in Hb after 4 weeks		
Crude percentage – % (95% CL) [n]	20 (15, 27) [172]	48 (40, 55) [178]
RBC Transfusions		
Sensitivity – %	21.5	55.6
Specificity – %	81.5	75.5
Target Hb Concentration		
Sensitivity – %	31.2	51.7
Specificity – %	93.4	81.5

Darbepoetin alfa Dosing

	Placebo (n = 192)	Darbepoetin alfa 300 mcg Q3W (n = 193)
Average (SD) weekly dose (mcg)	0 (0)	94.6 (24.5)
Mean (SD) total number of doses	4.2 (1.2)	4.1 (1.2)
Mean (SD) weeks of dosing	13.5 (3.8)	13.4 (3.7)
Patients with ≥ 1 dose reduction – n (%)	43 (22)	76 (39)
Patients with ≥ 1 dose withheld – n (%)	3 (2)	25 (13)
Patients who had a dose increase – n (%)	72 (38)	46 (24)

Patients Receiving an RBC Transfusion



KM estimates are adjusted for stratification factors used at randomization (tumor type, screening Hb)

SAFETY

- Darbepoetin alfa was well tolerated in both treatment groups; there were no clinically important differences in the incidence of adverse events and serious adverse events
- The incidence of cardiovascular and thromboembolic events were similar in the 2 treatment groups

Cardiovascular and Thromboembolic Events

	Placebo (n = 192)	Darbepoetin alfa 300 mcg Q3W (n = 193)
Number of patients – n (%)		
Arrhythmia	7 (4)	11 (6)
Congestive Heart Failure	3 (2)	3 (2)
Cerebrovascular Accident	3 (2)	3 (2)
Hypertension	4 (2)	6 (3)
Myocardial Infarction, Ischemic and Coronary Artery Disease	2 (1)	1 (1)
Seizure	0 (0)	1 (1)
Embolism/Thrombosis (Arterial and Venous)	11 (6)	15 (8)
Death (Any Reason)	26 (10)	17 (9)

- No patients had neutralizing antibodies to darbepoetin alfa

CONCLUSIONS

- Darbepoetin alfa administered at 300 mcg Q3W is well tolerated and effective for treating cancer patients with CIA.
- The percentage of patients receiving RBC transfusions from week 5 to EOTP was almost 2-fold less for the darbepoetin alfa group compared with the placebo group
- Darbepoetin alfa 300 mcg Q3W increased Hb to within the range recommended by current evidence-based guidelines (11 to 13 g/dL).[6,7,8]
- Although approximately 50% of patients receiving darbepoetin alfa 300 mcg Q3W achieved a ≥ 1-g/dL increase in Hb after 4 weeks of treatment, this endpoint is not a good predictor of whether a patient will achieve the target Hb or avoid RBC transfusion.
- The dosing regimen of Q3W may simplify the treatment of CIA in the oncology practice by synchronizing darbepoetin alfa therapy with chemotherapy administered Q3W, thereby minimizing disruption to the lives of patients and their caregivers.