Guidelines for the Use of Erythropoietic Growth Factors in Patients With Chemotherapy-Induced Anemia

By George M. Rodgers, MD

The use of erythropoietic growth factors to treat chemotherapy-induced anemia (CIA) has been increasing as clinicians become more aware of the ability of these drugs to improve the quality of life of patients with cancer. The cost associated with erythropoietic growth factor therapy makes its appropriate use a practical issue for physicians and hospitals. Clinical practice guidelines can benefit physicians by increasing practice efficiency, reducing medical errors, increasing the quality of medical care, and decreasing reimbursement problems. The American Society of Clinical Oncology and the American Society of Hematology, the European Organisation for Research and Treatment of Cancer, and the National Comprehensive Cancer Network (NCCN) have all published guidelines for using erythropoietic growth factors to treat CIA, and this article reviews and summarizes those guidelines. Of the three guidelines for the use of erythropoietic growth factors in CIA, the NCCN guidelines are based on the most recent data. Current evidence indicates that erythropoietic growth factors can increase hemoglobin levels, reduce the need for red blood cell transfusions, and improve quality of life; the effect of erythropoietic therapy on outcomes in patients with CIA is still being investigated.

ASCO/ASH Guidelines
In 1997, the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) began discussions on developing clinical practice guidelines for the use of erythropoietic therapy in patients with cancer. At that time, epoetin was the only erythropoietic growth factor available. The two organizations established a panel of experts to develop guidelines that were based on the Agency for Healthcare Research and Quality topic review of epoetin, which was released in 2001.

That review covered the medical literature on erythropoiesis-stimulating agents published between January 1985 and October 1999; epoetin alfa (Procrit) was the primary drug evaluated. Evidence was weighted such that the results of large randomized controlled trials and meta-analyses were given greater weight. In the absence of compelling evidence, panel conclusions were reached by consensus. The resulting ASCO/ASH guidelines, published in 2002 and summarized in Table 1, are "a blend of evidence, the opinion of experienced practitioners, and their interpretation of the evidence."[3]

Epoetin alfa was recommended in patients with CIA and a hemoglobin (Hgb) level less than 10 g/dL, administered according to the prescribing information—150 U/kg tiw, escalated to 300 U/kg tiw if there is no response after 4 weeks—or at the recommended dose of 40,000 U/wk, with dose escalations in nonresponders.[4] The target Hgb level was established at (or near) 12 g/dL, with the dose of epoetin alfa adjusted to maintain it at that level. In patients who do not respond to escalated doses, the guidelines suggest that iron deficiency be evaluated.[3]

EORTC Guidelines
More recently, the European Organisation for Research and Treatment of Cancer (EORTC) published its guidelines for the use of erythropoietic growth factors in patients with cancer and CIA. The EORTC literature search covered the years 1996 through 2003; epoetin alfa, epoetin beta, and darbepoetin...
alfa (Aranesp) were reviewed. The evidence levels and weighting methods were similar to those used by ASCO and ASH. The EORTC panel focused on addressing specific questions, including the threshold Hgb level for initiating therapy, the target Hgb level, the utility of dose escalation, the prevention of red blood cell transfusions, the effects on quality of life and survival, the optimal regimens, and the adverse effects of erythropoietic growth factors.[5] The EORTC guidelines, summarized in Table 2, were published in 2004.

Erythropoietic growth factor therapy was recommended to improve quality of life and prevent red blood cell transfusions in patients with cancer and anemia. It was suggested that treatment be initiated at Hgb levels of 9 to 11 g/dL, on the basis of the patient's symptoms. The target Hgb level was 12 to 13 g/dL. There was support in the literature for the use of all three growth factors (epoetin alfa, epoetin beta, and darbepoetin alfa). The risks for pure red cell aplasia and thrombosis were discussed, but the latter risk appeared to be related to the Hgb level achieved.

NCCN Guidelines
The National Comprehensive Cancer Network (NCCN) is an alliance of 19 major cancer centers in the United States whose primary focus is on disseminating information on cancer care to patients and health-care workers. To this end, it has developed numerous practice guidelines in oncology, including guidelines for supportive care. The most recently published guidelines (in 2006) for the management of cancer- and treatment-related anemia are available on the NCCN website (www.nccn.org) and on CD-ROM.[6] Panel members from NCCN institutions reviewed an updated Cochrane database on the use of erythropoietic growth factors in patients with cancer as the basis for the 2006 guidelines. Most of the recommendations in the guidelines are based on categories of consensus, either level 1-uniform consensus based on high-level evidence (large randomized controlled trials and meta-analyses)—or level 2A-uniform consensus based on low-level evidence, including clinical experience. The NCCN guidelines are summarized in Table 3.

Either erythropoietic growth factors or red blood cell transfusions are recommended to correct anemia in cancer patients. Because there are data that show maximal incremental improvements in quality of life when Hgb levels increase from 11 to 12 g/dL,[7] it is recommended that erythropoietic growth factor be initiated at Hgb levels of 10 to 11 g/dL. The target Hgb level is 12 g/dL. The recommended erythropoietic growth factors are epoetin alfa and darbepoetin alfa, given in the dosages recommended in the prescribing information (epoetin alfa 150 U/kg tiw or 40,000 U/wk[4]; darbepoetin alfa 2.25 µg/kg/wk or 500 µg q3wk[8]). Dose titration recommendations are also suggested (see Table 3). The NCCN guidelines also include information on parenteral iron therapy to treat functional iron deficiency of cancer and discuss potential adverse events with erythropoietic growth factor therapy, including hypertension, thrombosis, pure red cell aplasia, and the possibility of decreased survival.

The Guidelines Compared
The differences in the three guidelines relate primarily to the published literature that was available when they were prepared. The ASCO/ASH guidelines are based on older literature, and they have not been updated; consequently, they do not include recommendations for the use of darbepoetin alfa. The EORTC guidelines, based on more-recent data, have also not been updated in 2 years. In contrast, the NCCN guidelines are updated annually, and their recommendations are based on the most recent data.

In all three guidelines, the target Hgb level is 12 g/dL, but the threshold levels for initiating therapy differ (ASCO-ASH, 10 g/dL; EORTC, 9-11 g/dL; NCCN, 10-11 g/dL). This is an important issue for physicians and patients because insurance payers may have different criteria for reimbursement, depending on which guidelines are used. Features of the three guidelines are shown for comparison in Table 4.

A common question concerns which erythropoietic agent is preferred—epoetin alfa or darbepoetin alfa. The EORTC and NCCN guidelines both have recommendations based on clinical trial results showing equivalence of the two agents.

Parenteral Iron Therapy
The use of intravenous iron to optimize the response to erythropoietic growth factors is discussed in the NCCN guidelines. The current basis for using parenteral iron derives from results reported in the study by Auerbach and colleagues[9] in which intravenous iron dextran, but not oral iron, significantly increased the Hgb levels and improved the quality of life of patients treated with chemotherapy and epoetin alfa. Research in this area is ongoing, and the optimal parenteral agent...
and its dose and schedule remain to be determined.

Conclusions
Clinical guidelines offer the possibility of summarizing clinical trial data for practitioners in a concise, practical fashion. To remain useful, guidelines must be reviewed and updated when new information becomes available. Of the three guidelines for use of erythropoietic growth factors in CIA, the NCCN guidelines are based on the most recent data. The more recent guidelines recommend a threshold Hgb level of 9 to 11 g/dL (EORTC) and 10 to 11 g/dL (NCCN). All three guidelines recommend a target Hgb level of 12 g/dL. The EORTC and NCCN guidelines recommend both epoetin alfa and darbepoetin alfa as treatment options. This is supported by the results of large community trials that compared the two drugs; three of four such prospective studies reported similar clinical outcomes.[10-13] Clinical trials have shown that erythropoietic growth factor therapy can increase Hgb levels, reduce the need for red blood cell transfusions, and improve quality of life. Likewise, in patients with renal anemia who are undergoing hemodialysis, treatment according to guidelines aimed at maintaining adequate Hgb levels has been shown to improve their outcomes.[14] It will be useful to show similar benefits with treatment according to the guidelines developed for patients with cancer and CIA.

Disclosures:
Dr. Rodgers is on the speakers bureau of and has participated in clinical trials for Amgen.

References:


11. Waltzman R, Croot C, Justice GR, et al: Randomized comparison of epoetin alfa (40,000 U weekly) and darbepoetin alfa (200 microgm q2w) in anemic patients with cancer receiving chemotherapy.


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