Abstract. Anemia has a high prevalence and incidence in patients with cancer and is associated with a range of symptoms, including fatigue, which affect the vast majority of patients receiving chemotherapy exerting a considerable impact on patients' quality of life. The development of the erythropoiesis-stimulating agent epoetin represented a major step forward in the treatment of chemotherapy-related anemia, providing an effective and safe alternative to red blood cell transfusions. The subsequently introduced epoetin analogue, darbepoetin alpha, with a prolonged serum half-life, allowed for extended dosing intervals and less frequent administration. Recently published large prospective trials provided the oncology community with new important information on the use of currently available erythropoietic agents to improve anemia in patients suffering from cancer. However, it is also clear from recent reports that scrutiny on the safe use of these drugs is still required.

Mild or moderate anemia (haemoglobin, Hb <11 g/dL) can affect up to 100% of patients with cancer, with the incidence of severe or life-threatening anemia (Hb <8 g/dL) reaching as high as 80%, depending on the type of malignancy and chemotherapy (1). Hypoxia due to anemia contributes to increased morbidity and reduced quality of life (QoL). In particular, fatigue affects an estimated 60% to almost 100% of patients receiving chemotherapy causing functional impairment and a deterioration in the sense of well-being (2). Red blood cell (RBC) transfusions have been the traditional method of alleviating symptoms of cancer-associated anemia. However, transfusions are associated with short-lived benefits and a risk of infections/disease transmission and allergic reactions. In addition, stringent transfusion guidelines have lowered the threshold Hb level for transfusion from 10 to 7-8 g/dL (3).

Cloning of the human erythropoietin gene during the 1980s (4) allowed viable quantities of recombinant human erythropoietin (epoetin) to be produced commercially and paved the way for the use of erythropoietic agents (EAs) in several clinical conditions first of all anemia of chronic kidney disease (5). The efficacy of epoetin (alpha and beta) in chemotherapy-related anemia (CRA) in terms of Hb levels, decreased RBC transfusion requirements and QoL parameters has been shown in numerous clinical trials (6-8). Dosing of epoetin three times per week is the originally approved regimen, which is associated with some inconvenience for patients and healthcare providers.

To further improve anemia treatment, attempts have been made to extend the dosing interval of EAs, both for epoetin and for its recently developed analogue darbepoetin alpha, the latter being the first EA to be approved for once weekly (QW) dosing. Epoetin and darbepoetin share the same native protein sequence, but the molecules have distinct glycosylation patterns, resulting in a three-fold longer serum half-life and a greater biological activity for darbepoetin compared with its predecessor (9). Because of differences in the pharmacokinetic properties of darbepoetin and epoetin,

*Present address: Medical Oncology Unit, Perrino General Hospital, Brindisi.

Correspondence to: Nicola Silvestris, MD, Medical and Experimental Oncology Unit, National Cancer Center, Via Hahnemann, 209, 70126 Bari, Italy. Tel: +39 080 5555621, e-mail: nicolasilvestris@virgilio.it

Key Words: Chemotherapy-related anemia, erythropoietic agents, review.
Darbepoetin can be administered less frequently. In fact, while epoetin was shown to ameliorate CRA also when given QW (10, 11), darbepoetin was further examined and proved effective at extended dosing intervals, including dosing once every three weeks (Q3W) (12). Albeit differences in practice patterns exist between Europe and North America (13, 14), it is now common clinical practice (and guidelines acknowledge this) to consider regimens of less frequent administration of EAs (3, 15).

Until recently, there have been few reports of clinical trials formally comparing the effectiveness of: i) extended Q3W dosing schedule of darbepoetin vs. standard weekly dosing; ii) darbepoetin vs. epoetin administered in the doses and schedules commonly used in oncology practice. In fact, most of the published comparative analyses until around mid 2006 have been retrospective, have been limited to historical controls, or were pilot studies using multiple dose levels of darbepoetin (16, 17). For this reason decisions about which EA to use and how and when to administer it when trying to ameliorate anemia in patients suffering from cancer are (were) based on a limited evidence pool (18, 19). To further complicate this matter, recent reports have raised safety concerns about the use of EAs in cancer patients (20).

Efficacy and Safety of Darbepoetin Alpha

Based on several dose-ranging studies showing a dose-dependent efficacy of darbepoetin in improving anemia in patients with nonmyeloid malignancies (21-24), a weekly darbepoetin dose of 2.25 μg/kg was chosen for two large placebo-controlled, double blind, phase III trials. Vansteenkiste et al. randomly assigned 320 anemic (Hb<11 g/dL) patients with lung cancer receiving platinum-containing chemotherapy to receive either placebo or darbepoetin for 12 weeks (25). This study demonstrated a statistically significant decrease of both the incidence of transfusion and the number of units transfused (both p<0.001). The proportion of patients achieving a hematopoietic response (2 g/dL rise in Hb or the achievement of a Hb level of 12 g/dL) also significantly favour darbepoetin (66% vs. 24%; p<0.001). Moreover, improvement in fatigue symptoms (measured using the Functional Assessment of Cancer Therapy-Fatigue scale, FACT-F) was greater in the darbepoetin arm (56% versus 44%), with borderline statistical significance. Similar results were achieved in a parallel study conducted by Hedeneus et al. in 344 patients with lymphoid malignancies undergoing chemotherapy (26). It is worth noting that the difference in efficacy between darbepoetin and placebo in these two trials was almost equal to that described in previous similar studies with epoetin (27, 28). In a retrospective analysis of the dataset of a phase III trial with darbepoetin in lung cancer patients evaluating the Hb level at which treatment should be initiated, darbepoetin significantly reduced red blood cell transfusions compared with placebo, irrespective of the Hb level at treatment initiation (≥10-11 g/dL vs. <10 g/dL) (29).

Like epoetin, darbepoetin is a well-tolerated drug, irrespective of tumor type, dose and schedule of administration. The adverse events reported in clinical trials were generally those expected in the patient population studied (30). Only venous thromboembolism events may represent a significant risk associated with EA therapy (3). This is likely to be related to a rapid or excessive rise in Hb levels which can be avoided or minimize by strictly adhering to labeled indications and current guidelines.

Several studies initially suggested that therapy with EAs may improve survival and tumor control in patients with solid tumors receiving chemotherapy or radiotherapy (31). In contrast, recent randomized trials suggest that EAs may negatively alter patient survival (32-35). In one of these studies this finding has been suggested to be correlated with the expression of erythropoietin receptors on tumor cells (36). It is important to underline that all these studies evaluated EA treatment outside standard guidelines and approved indication (i.e. patients did not receive active cancer treatment or were given EAs to avoid the occurrence of anemia). An updated systematic review of 57 trials of EAs including 9353 cancer patients (37), while confirming that the administration of epoetin and darbepoetin increases the risk of thrombo-embolic events (RR=1.67), no effects (either positive or negative) on tumor response or overall survival were demonstrated. Nevertheless, further scrutiny of the use of EAs is mandatory and the FDA has recently provided additional recommendations on the use of EAs (38).

Extended Dosing Intervals

Several studies focused on the possible extension of the dosing interval for darbepoetin beyond the originally approved QW schedule. In a dose-finding study of Glaspy et al. a clear relationship was evident between the dose and the magnitude of the mean increase in Hb in each cohort until a dose of 4.5 μg/kg QW or 9 μg/kg Q2W was reached (21). The minimally effective dose of darbepoetin Q2W (3.0 μg/kg) exhibited a similar efficacy to the standard dose of epoetin.

The possibility to administer darbepoetin Q3W has also been widely explored. A double-blind, placebo-controlled, dose-response study evaluated several weight-based doses of Q3W darbepoetin (39). The drug was shown to be effective at all doses, with limited incremental benefit at doses greater than 6.75 μg/kg. More recently, Glaspy et al. (40) provided further evidence of the effectiveness of darbepoetin 6.75 μg/kg Q3W for the treatment of CRA.
demonstrating that response to darbepoetin is irrespective of the timing of administration relative to concurrent chemotherapy. Moreover, a phase II randomized controlled trial of darbepoetin (41) indicated that, in keeping with the pharmacokinetic-pharmacodynamic modelling of this molecule, the efficacy profile was not affected if a fixed (vs. weight-based) dose was used.

In a recent Phase III randomized, double-blind, active-controlled trial, Canon et al. (42) compared the efficacy and safety of QW and Q3W regimens of darbepoetin treatment in anemic patients with nonmyeloid malignancies receiving cyclic chemotherapy. The fixed 500 µg dose selected for the Q3W treatment arm of this study approximated the approved Q3W dose in Europe of 6.75 µg/kg as well as an equivalent exposure to the standard QW 2.25 µg/kg dose, for an average weight patient of approximately 74 kg. This important study showed no statistically significant differences between the two arms in terms of transfusion requirement and Hb level achieved. However, a trend favouring patients treated with 500 µg of darbepoetin was observed for both the endpoints. The frequency of cardiovascular/thromboembolic adverse events was the same in both groups, and safety was comparable. These results demonstrate that patients receiving chemotherapy who develop anemia can safely and effectively be treated with darbepoetin Q3W. The fixed Q3W dosing represents a convenient schedule that permits the synchronization of anemia treatment with the administration of many chemotherapy regimens enhancing patient convenience and reducing resource utilization.

**Direct Comparison of Darbepoetin and Epoetin**

Oncologists can rely on both epoetin and darbepoetin when trying to ameliorate CRA but, until recently, no conclusive information from direct-comparison studies (43-47) were available. This is no more the case after the recent publication of the largest randomized study of EAs in CRA (1,209 patients received protocol therapy) by Glaspy et al. This remarkable trial was designed to test the hypothesis that darbepoetin 200 mg Q2W is comparable (i.e not inferior) to epoetin 40,000 U QW as a starting dose (48).

The outcome in terms of the primary endpoint, which was the proportion of patients who required RBC transfusion, was equivalent from the standpoint of a noninferiority analysis, with a trend in favour of epoetin. In both groups, the mean Hb concentrations improved from approximately 10.2 g/dL at baseline to 11.8 g/dL by the end of the treatment phase. The number of patients achieving and maintaining target Hb concentration (11 g/dL to 13 g/dL) was slightly superior (86% vs. 80%), but not statistically significant, in the epoetin group. In contrast, the trend in the study in terms of QoL changes favoured darbepoetin, probably as a consequence of patients receiving an injection less frequently. Overall, despite some criticisms because of the noninferiority design of the study (49), darbepoetin 200 µg Q2W was shown to be as effective as epoetin 40,000 U QW. It is worth noting that the dose of darbepoetin used in the study (and frequently in the US) is considered the minimum effective dose. Indeed, the approved (and more effective) regimens of darbepoetin involve starting dosages of 2.25 µg/Kg QW or 6.75 µg/Kg or 500 mg Q3W.

Finally, in a pooled analysis of 20 clinical trials, Glaspy et al. evaluated whether a different dosing interval of darbepoetin affected its efficacy compared with weekly epoetin (50). End-points of the study included the percentage of patients requiring transfusions, reaching a target Hb ≥11 g/dL, and achieving ≥3 point change in FACT-F score from baseline. The results from this analysis suggested that the type of EA used did not affect the percentage of patients who achieved clinically meaningful endpoints. Indeed, the dosing interval at which darbepoetin was administered (QW, Q2W, or Q3W) did not affect its efficacy.

**Conclusion**

Large prospective studies published recently and discussed in this article have clearly demonstrated that there are no meaningful differences between epoetin and darbepoetin when administered to patients with CRA and that darbepoetin administered Q3W achieves clinical outcomes comparable to those with the current labelled weekly starting dose. Oncologists now possess additional information to guide decisions on how to utilize EAs for treatment of CRA.

Notwithstanding continuous advances in the treatment of CRA with EAs, there are still a number of key questions. The suggestion that EAs may negatively alter tumor behaviour or patient survival (32-35, 51) despite reassuring data from a recent meta-analysis (38), require a clear definition of what biological activities epoetin and darbepoetin have that are physiologically and clinically relevant, beyond merely supporting the developing erythron. As a "positive" example, a recent report suggests the protective effect of erythropoietin in doxorubicin-induced cardiomyopathy (52).

Both epoetin and darbepoetin are approved specifically for anemia associated with chemotherapy and not for anemia of cancer per se. Because of the negative survival indications noted above, clinicians should strictly adhere to current approved indication and consider 12 g/dL the optimum Hb level to be reached. Higher Hb levels are neither desirable nor proven to be safe from the current clinical data.

Finally, a crucial point that remains to be elucidated is how to optimize use of EAs as 30% to 50% of patients with CRA do not respond to epoetin or darbepoetin as they are currently used. A hallmark of anemia in cancer patients is the
development of disturbances of iron homeostasis (53) which leads to functional iron deficiency (54) despite elevated total-body iron stores. When functional iron deficiency is present in cancer patients receiving EAs, iron repletion by i.v. infusion is recommended based on both indirect evidence (18) and the results of one controlled trial (55). It still remains to be seen whether response to EAs is augmented with concomitant administration of parenteral iron in patients without iron deficiency (56). Owing to the increased erythropoietic activity stimulated by EAs, adequate delivery of iron to the bone marrow from the beginning of erythropoietic therapy may well optimize response, i.e. by avoiding the development of iron deficiency, whose occurrence during erythropoietic therapy represents a major limitation to its efficacy (54). Three studies (57-59) of i.v. iron supplement in anemic cancer patients receiving EAs support this hypothesis.

While epoetin is in its full maturity of years and darbepoetin has come of age, a number of erythropoiesis-stimulating agents, including several that are orally bioavailable, are in their infancy (60, 61). Additionally, recent discoveries about the biology of erythropoiesis, including novel inhibitory proteins (62), promise more targeted agents to come.

In the near future it is likely that anemic cancer patients will benefit by further refinements of treatment with currently available EAs (if given adhering to current guidelines) and by the introduction of promising agents now under active investigation.

Acknowledgements

Partially supported by Oncologia Ca’ Granda Onlus and Associazione Italiana per la Ricerca sul Cancro (AIRC).

References


Received June 20, 2007
Revised September 5, 2007
Accepted October 2, 2007