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Darbepoetin Alfa

In Patients with Chemotherapy-Related Anaemia

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Contents

Abstract

- Darbepoetin alfa, novel erythropoiesis stimulating protein closely related to human erythropoietin, has been developed for the treatment of chemotherapy-related anaemia in patients with non-myeloid malignancies.
- In three 12-week, phase II studies in patients with cancer and chemotherapy-related anaemia, subcutaneous darbepoetin alfa, administered in once-weekly or 2-, 3- or 4-weekly regimens, dose-dependently increased the mean haemoglobin levels.
- In a randomised, double-blind, phase III study in 320 patients with lung cancer and chemotherapy-related anaemia, recipients of subcutaneous darbepoetin alfa 2.25 μg/kg once weekly, received red blood cell (RBC) transfusion ≈2-fold less frequently than placebo recipients ($p < 0.001$).
- In the same study, patients receiving darbepoetin alfa also received fewer standard units of RBC for transfusion and had greater haematopoietic response rate than placebo recipients (both $p < 0.001$).
- Subcutaneous darbepoetin alfa 2.25 μg/kg once weekly also reduced patient-reported fatigue (assessed by a quality-of-life questionnaire) [$p = 0.019$ vs placebo].
- Darbepoetin alfa was generally well tolerated in clinical trials. The most frequent darbepoetin alfa-related adverse events were: body oedema, arthralgia and skin rash.

Features and properties of darbepoetin alfa (novel erythropoiesis stimulating protein, Aranesp®)	
Indication	
Chemotherapy-related anaemia in patients with non-myeloid malignancies	
Mechanism of action	
Erythropoiesis-stimulating protein; erythropoietin receptor agonist	Stimulates red blood cell production by supporting survival, proliferation and differentiation of erythroid progenitor cells in bone marrow
Recommended dosage and administration	
Starting dose[a]	2.25 μg/kg
Route of administration	Subcutaneous injection
Frequency of administration	Once weekly
Recommended guidelines for dosage adjustment in the US	
If Hb increase <1 g/dL after 6w	Increase dose up to 4.5 μg/kg
If Hb increase >1 g/dL within 2w or Hb level >12 g/dL	Reduce dose by ≈25%
If Hb level >13 g/dL	Withhold treatment until Hb level <12 g/dL; then reinstate with dose reduced by ≈25% from previous dose
Recommended guidelines for dosage adjustment in Europe	
If Hb increase <1 g/dL after 4w	Increase dose to 4.5 μg/kg
If Hb level >14 g/dL	Withhold treatment until Hb level <13 g/dL; then reinstate with dose reduced by ≈50% from previous dose
Adverse events (treatment-related)[b]	
Most frequent[c]	Body oedema, arthralgia and skin rash
Other clinically significant	Venous thrombosis, pulmonary embolism
a Minimal effective starting dose in clinical trials was 1.5 μg/kg.	
b According to the US prescribing information.	
c ≥5% incidence and >2-fold greater frequency compared with placebo.	

Cancer-related anaemia, sometimes referred to as the 'anaemia of chronic disease',[1] is an important contributor to the morbidity related to malignancy. This form of anaemia is primarily caused by impaired erythropoietin production (probably a consequence of excessive release of proinflammatory cytokines in malignant disorders[2]) in response to decreased serum haemoglobin (Hb) levels.[3] In patients with cancer receiving chemotherapy the aetiology of anaemia is, however, multifactorial.[4,5]

Chemotherapy aggravates cancer-related anaemia and contributes to inappropriately low serum erythropoietin levels for the degree of anaemia.[6] It also contributes to the loss of the inverse linear relationship between serum Hb and erythropoietin levels in patients with cancer.[6] In this respect, chemotherapy-related anaemia and anaemia associated with chronic kidney disease share a similar pathogenesis[1] and could potentially be responsive to the same treatment (i.e. replacement with exogenous erythropoietin or its analogues).[6] Severe anaemia requiring red blood cell (RBC) transfusions is a common complication of myelosuppressive chemotherapy affecting up to 60% of treated patients with solid tumours.[7]

Anaemia impairs health-related quality of life (HR-QOL) in patients with cancer[8] and is associated with numerous symptoms, including fatigue.[9] Fatigue, which is the most frequently reported symptom in patients with cancer,[10] affects an estimated 80% to almost 100% of patients receiving chemotherapy.[7] Hence, the treatment of anaemia in patients with cancer undergoing chemotherapy is important for the relief of fatigue and improvement of HR-QOL in this patient population.

Until now, treatment options for iatrogenic, chemotherapy-related anaemia included administration of RBC transfusions if the anaemia was severe (i.e. Hb <8 g/dL),[7] or subcutaneous recombinant human erythropoietin (rHuEPO) if the anaemia was moderate to mild [i.e. Hb from 8 g/dL to within normal limits (i.e. 12–16 g/dL for women and 14–18 g/dL for men)].[7] Subcutaneous rHuEPO was also indicated if symptoms of anaemia were sufficient to require RBC transfusion but where transfusion was not considered an acceptable treatment option.[11]

Transfusion of allogeneic RBCs still carries extremely low but significant risks of acute transfusion reactions and of transmission of infectious agents. This treatment strategy may also adversely affect the immune system of patients with cancer, thereby increasing the risk of postoperative infections and cancer recurrence and shortening patients' survival.[9,12]

In patients with chemotherapy-related anaemia, adequate Hb levels can be achieved and maintained with subcutaneous rHuEPO administered once weekly.[13] Beneficial effects on Hb levels in this patient population can also be achieved with subcutaneous darbepoetin alfa (Aranesp®[1]), a novel erythropoiesis-stimulating protein. Importantly, darbepoetin alfa has the advantage of a longer serum elimination half-life ($t_{1/2}$) than rHuEPO.[4] This may allow for less frequent administration of the drug that could be synchronised with chemotherapy cycles (e.g. once every 2, 3 or 4 weeks).[14] The longer $t_{1/2}$ of darbepoetin alfa may also confer greater biological activity of the drug.[15]

The clinical use and tolerability of darbepoetin alfa for the treatment of anaemia associated with chronic kidney disease has been recently reviewed in *Drugs*.[16] This review focuses on the use of darbepoetin alfa in chemotherapy-related anaemia.

1. Pharmacodynamic Profile

The pharmacodynamic properties of darbepoetin alfa have been recently reviewed in *Drugs*.[16] This section provides a brief summary of the same information with inclusion of data from two recent studies, reported as abstracts, in mice with chemotherapy-induced anaemia.[17,18]

- Darbepoetin alfa is a glycoengineered protein analogue of rHuEPO consisting of 165 amino acids.[4,15] It has different primary structure from rHuEPO, which allows for an increased carbohy-

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

drate content (≈51% vs 40%). This results in an increased molecular weight (37.1 vs 30.4kD).[19] Darbepoetin alfa stimulates erythropoiesis through the same mechanism as endogenous erythropoietin[4,20] (i.e. binds to surface receptors on RBC precursors in the bone marrow, supporting their survival, differentiation and proliferation[19,21,22]). It is produced by recombinant DNA technology in Chinese hamster ovarian cells.[4,15,20]

- Substitution of five amino acids (Ala30Asn, His32Thr, Pro87Val, Trp88Asn and Pro90Thr) in rHuEPO allows for two additional oligosaccharide attachments in darbepoetin alfa at asparagine 30 and 88. Each of these two additional N-linked carbohydrate chains adds up to four sialic acid residues, thus increasing the maximum number of sialic acid residues within the molecule from 14 (in rHuEPO) to 22 (in darbepoetin alfa).[15,19]
- Since the amino acid sequence of darbepoetin alfa differs from that of endogenous erythropoietin, there is at least a theoretical possibility that darbepoetin alfa could be immunogenic. This risk is, however, minimised by the carbohydrate shield comprising sialic acid residues on the five dissimilar amino acid positions in darbepoetin alfa.[15,19] In all clinical trials to date development of antibodies against darbepoetin alfa was not detected and the sequelae indicating antibody formation were not clinically observed (see section 4).
- Long-term *in vivo* bioassays in mice have confirmed a direct relationship between the sialic acid content, $t_{1/2}$ and *in vivo* biological activity of various rHuEPO isoforms.[15,19,23] Increasing the sialic acid content was also shown to prolong $t_{1/2}$ of darbepoetin alfa by approximately 3-fold compared with rHuEPO.[15,19,24] This, consequently, contributed to increased *in vivo* biological activity of darbepoetin alfa in animal models[15,19,24] and in patients with chronic kidney disease.[15,25,26]

Animal Studies

- Two studies in murine models investigated the effects of darbepoetin alfa on erythropoiesis for the prevention and treatment of anaemia induced by chemotherapy (i.e. fluorouracil or cyclophosphamide)[17] or combined chemo- and radiotherapy (i.e. carboplatin injection followed by exposure to gamma irradiation).[17,18]
- In the first study, mice receiving darbepoetin alfa 100 μg/kg 10, 7 or 5 days before exposure to chemo/radiotherapy had mean peak Hb levels of 19 g/dL on day 1, which returned to normal (i.e. 14 g/dL) by day 11 and remained such for the remainder of the study. Haemoglobin levels in untreated control mice decreased to 7.4 g/dL by day 15. Similar results were obtained in the other two chemotherapy models.[17]
- The second study utilised a model of repeated exposure to combined chemo- and radiotherapy to examine the role of darbepoetin alfa (dosage not stated) in supporting Hb levels through multiple treatment cycles. The best results were achieved with administration of darbepoetin alfa once every 2 weeks. This regimen increased Hb levels by 2–3 g/dL during four chemo/radiotherapy cycles. In addition, it eliminated the Hb overshoot that occurred with once-weekly administration of darbepoetin alfa, when such treatment was initiated 7 days before the first chemo/radiotherapy cycle.[18]

2. Pharmacokinetic Profile

The pharmacokinetics of darbepoetin alfa in chemotherapy-receiving patients with non-myeloid malignancies have been investigated in three studies. Most data are available in abstract form[27,28] with the exception of a fully published report from a study using subcutaneous darbepoetin alfa 2.25 μg/kg.[29]

Absorption

- In a nonblind, dose-escalating study, a single dose of darbepoetin alfa 0.5 μg/kg administered subcutaneously during the first chemotherapy cycle produced a mean peak plasma drug concentration (C_{max}) of 1.77 μg/L (n = 3) after 72 hours (t_{max}) [n = 2]. In the same study, 48 hours after subcutaneous administration of darbepoetin alfa 0.5 and 1.0 μg/kg the respective mean drug concentrations were 1.6 (n = 9) and 3.3 μg/L (n = 2).[27]

- After a single subcutaneous dose of darbepoetin alfa 2.25 μg/kg administered during chemotherapy cycle 1 to patients with cancer (n = 14) in another study, the mean C_{max} and t_{max} of darbepoetin alfa were 8.96 μg/L and 86.1 hours.[29]
- In the third pharmacokinetic study, in a similar patient population treated with subcutaneous darbepoetin alfa (4.5, 6.75, 9.0 and 13.5 μg/kg) once every 3 weeks, predicted mean drug plasma concentrations (14.7, 22.1, 29.4 and 44.1 μg/L) at 48 hours after administration at week 10 (n = 16) were within one standard deviation of the observed mean values (9.67, 22.7, 28.1 and 38.3 μg/L) for the respective drug doses. Thus, the pharmacokinetics of darbepoetin alfa appeared to be dose- and time-linear and predictable and were described by a one-compartment model.[28]

Elimination

- In patients with non-myeloid malignancies who received a single subcutaneous dose of darbepoetin alfa 0.5 μg/kg during the first chemotherapy cycle, the mean plasma clearance (CL) and $t_{1/2}$ were 0.003 L/h/kg and 49.7 hours.[27]
- Following a single subcutaneous dose of darbepoetin alfa 2.25 μg/kg given in the first chemotherapy cycle to seven patients with cancer in another study, the mean CL corrected for bioavailability and $t_{1/2}$ were 0.004 L/h/kg and 32.6 hours.[29]

3. Therapeutic Trials

The efficacy of subcutaneous darbepoetin alfa, administered once weekly or once every 2-, 3- or 4-weeks, for the treatment of chemotherapy-related anaemia has been investigated in two phase I/II clinical trials[14,30-34] and one phase III trial[35,36] in patients with solid tumours and in one phase II trial in patients with lymphoproliferative malignancies.[33,34] Following section presents the results of intent-to-treat analyses from these trials.

These 12-week trials have assessed the efficacy of darbepoetin alfa in correcting and maintaining Hb levels[14,30-35] and in reducing the incidence of RBC transfusions (the incidence was calculated using the Kaplan-Meier method).[14,30-33,35,36] In phase I/II studies, Hb response was defined as an increase of ≥2 g/dL from baseline in the absence of RBC transfusion in the preceding 4 weeks.[30,31,33,34] Final reports from two phase II trials[14,30-32] and a phase III trial,[35] defined 'haematopoietic response' as a clinical endpoint in patients who either had an Hb response or Hb ≥12 g/dL in the absence of RBC transfusion in the preceding 4 weeks.

Final reports from one phase II[30,31] and a phase III[35] trial have been fully published. The most recent results from the other phase II trials are currently available only as abstracts.[14,33,34]

All patients participating in the clinical trials of darbepoetin alfa were anaemic (Hb ≤11 g/dL), were receiving chemotherapy for cancer, had an Eastern Cooperative Oncology Group performance status of 0–2, were not iron deficient and had not received >2 RBC transfusions within 4 weeks of randomisation. The patients were randomised to receive either the study drug (at various doses and frequencies) or the control drug in the form of either placebo[14,33,35,36] or rHuEPO (150 IU/kg three times weekly; dose doubled at week 8 if Hb increase was <1 g/dL or 40 000 U/week; dose increased to 60 000 U/week at week 6 if Hb increase was <1 g/dL).[30-32] In all trials, dose increase for non-responders was not allowed for recipients of darbepoetin alfa.

An analysis[35] of the effects of darbepoetin alfa on fatigue and HR-QOL (i.e. through increase in Hb levels) has been conducted in patients with chemotherapy-related anaemia in a phase III study. Patients completed the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) questionnaire[8] at baseline and at the end of the treatment.[35] This assessment instrument consists of FACT-General questionnaire plus 13 questions addressing issues related specifically to fatigue. FACT-F is also part of a broader FACT-Anaemia assessment tool.[8]

Phase I/II Trials

- Three randomised phase I/II studies investigated the optimal dose and frequency of darbepoetin alfa for the treatment of chemotherapy-related anaemia. In these studies, darbepoetin alfa was administered

either once weekly[30-34] or once every 2,[30] 3[14] or 4[14] weeks.

- In two studies with the once-weekly regimen, patients receiving darbepoetin alfa 2.25 μg/kg (n = 22[33] and 59[30]) had greater mean increases from baseline in Hb level at week 12 (1.7[33] and 1.3 g/dL[30]) than patients receiving placebo (1.1 g/dL; n = 11)[33] or rHuEPO 150 IU/kg three times weekly (1.1 g/dL; n = 53),[30] in respective studies. Likewise, patients receiving darbepoetin alfa required RBC transfusions ≈2-fold less frequently during weeks 5–12 (27%[33] and 13%[30]) than patients receiving placebo (45%)[33] or rHuEPO (23%),[30] in respective studies.

- The former study was conducted in patients with lymphoproliferative malignancies (n = 66; 73% with lymphoma and 23% with myeloma)[33] while the latter included patients with solid tumours (n = 269).[31] Patients in both studies who received darbepoetin alfa 1.0, 2.25 or 4.5 μg/kg once weekly had comparable and dose-dependent Hb response rates (figure 1).[34]

- In the latter study, once-weekly darbepoetin alfa 1.5–4.5 μg/kg resulted in a haematopoietic response in 53–84%[32] of patients (n = 123), in a dose-dependent manner.[31] This study also compared the efficacy of darbepoetin alfa 3–9 μg/kg administered once every 2 weeks with that of rHuEPO 40,000 U/week, in patients with solid tumours.[30] Haematopoietic response rates were 66%, 84%, 58% and 71%, respectively, in patients receiving darbepoetin alfa 3, 5, 7 and 9 μg/kg (n = 33, 31, 32 and 32) compared with 63% in patients receiving rHuEPO (n = 32).[30] The incidence of RBC transfusion during weeks 5–12 among evaluable patients receiving darbepoetin alfa (n = 119) ranged from 4–23% compared with 36% in the comparator rHuEPO group (n = 30).[30]

- In a double-blind, placebo-controlled trial in 405 patients, recipients of darbepoetin alfa 4.5–15.0 and 9–18 μg/kg, administered once every 3 (n = 198) and 4 (n = 125) weeks, respectively, had similar range of haematopoietic response rates (51–71% vs 49–73%) and of RBC transfusion rates (30–19% vs 35–20%). Patients in the respective placebo groups, for the 3- and 4-weekly regimens, had lower haematopoietic response rates (31% and 16%) and higher transfusion rates (46% and 36%) than the study drug groups.[14]

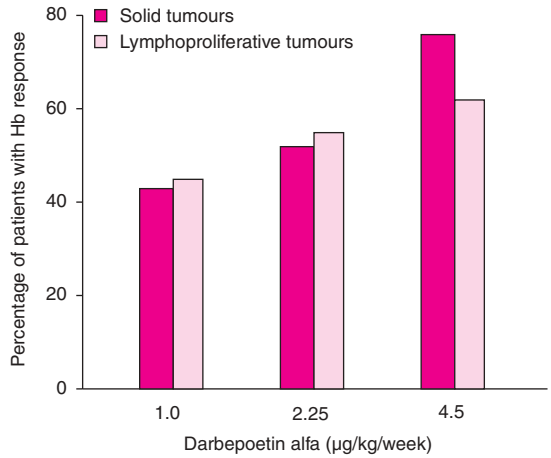

Fig. 1. Comparative efficacy of darbepoetin alfa in patients with solid or lymphoproliferative malignancies. Results from two randomised, phase II clinical trials in patients with solid tumours (n = 124) or lymphoproliferative malignancies (n = 55). All patients were anaemic [haemoglobin (Hb) ≤11 g/dL], had an Eastern Cooperative Oncology Group performance status of 0–2, were not iron deficient, had not received red blood cell transfusions within 4 weeks of randomisation and were receiving chemotherapy. All patients also received subcutaneous darbepoetin alfa 1.0, 2.25 or 4.5 μg/kg once weekly for 12 weeks.[34] Hb response was defined as ≥2 g/dL increase in Hb level from baseline.

Phase III Trial

- A randomised (1 : 1 ratio), double-blind, placebo-controlled, phase III clinical trial was conducted in 320 patients with lung cancer (29% small-cell and 71% non-small-cell type) and anaemia receiving platinum-containing chemotherapy using subcutaneous darbepoetin alfa 2.25 μg/kg administered once weekly for 12 weeks. The proportion of patients receiving RBC transfusion was ≈2-fold lower among recipients of darbepoetin alfa than among placebo recipients (27% vs 52% during weeks 5–12; $p < 0.001$) [figure 2].[35]

- Patients treated with darbepoetin alfa also received fewer standard units of RBC for transfusion (0.67 vs 1.92 units during weeks 5–12; $p < 0.001$)

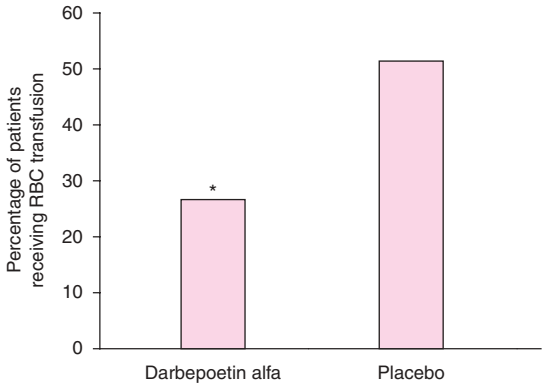

Fig. 2. Efficacy of darbepoetin alfa in reducing the incidence of red blood cell (RBC) transfusions. Proportion of patients receiving RBC transfusion during weeks 5–12 of the study. Results from a randomised (1 : 1 ratio), double-blind, placebo-controlled, phase III study of subcutaneous darbepoetin alfa 2.25 μg/kg administered once weekly, in 320 patients with lung cancer and anaemia receiving platinum-containing chemotherapy.[35] *$p < 0.001$ vs placebo.

and had a higher haematopoietic response rate (66% vs 24%; $p < 0.001$) than placebo recipients.[35]

- The proportion of patients hospitalised for an overnight stay (10.3 vs 13.0 days; $p = 0.13$) and the median duration of progression-free survival (22 vs 20 weeks; 95% CI = 18–31 and 17–23 weeks, respectively) were similar in the darbepoetin alfa and the placebo groups.[35] However, an earlier report from the same study showed that patients with the small-cell type of lung cancer who received darbepoetin alfa had longer median duration of progression-free survival than placebo recipients (33 vs 23 weeks).[36]
- An HR-QOL analysis from the same study demonstrated that a higher proportion of patients receiving darbepoetin alfa had a ≥25% increase in the FACT-F scale score than placebo recipients (32% vs 19%, $p = 0.019$). This suggests that darbepoetin alfa may produce significant relief from fatigue in patients with chemotherapy-related anaemia.[35]

4. Tolerability

In all clinical trials, darbepoetin alfa administered subcutaneously at various doses and frequencies was reported to be generally well tolerated;[14,30-33,36] quantitative data were reported in three studies.[21,29,35] The manufacturer's prescribing information package for the US market reports tolerability data compiled from seven active- and/or placebo-controlled studies of darbepoetin alfa in a total of 873 patients with cancer. All patients in these studies were concomitantly receiving cyclic chemotherapy.[4]

- In a fully published preliminary report of a phase II study in patients with solid tumours and anaemia receiving chemotherapy, 16 of 107 (15%) patients had treatment-related adverse events which included injection-site pain (7%), fever, pain and limb pain (2% each) and one case of rectal bleeding (<1%).[21]
- In a phase III trial, the tolerability profile of darbepoetin alfa was reported to be similar to that of placebo. The incidence of hypertension was 6% and 4% and that of thrombotic events was 5% and 3%, respectively, among recipients of darbepoetin alfa and placebo.[35]
- According to the manufacturer's US prescribing information, adverse events that occurred in ≥5% of cases and more than twice as frequently with darbepoetin alfa than with placebo were: body oedema of any type (21% vs 10%), arthralgia (13% vs 6%) and skin rash (7% vs 3%). Among other clinically significant adverse events, patients receiving darbepoetin alfa more frequently had pulmonary embolism (1.3% vs 0%) and various forms of thrombosis (5.6% vs 4.1%) than patients receiving placebo. [4]
- In all clinical trials to date,[19,21,29,31,35,37,38] development of antibodies against darbepoetin alfa was not detected and the sequelae indicating antibody formation were not clinically observed (see section 1). However, the manufacturer's US prescribing information states that the incidence of antibody development in patients receiving darbepoetin alfa has not yet been adequately determined.[4]

5. Dosage and Administration

In a clinical trial with once-weekly administration in patients with chemotherapy-related anaemia, minimal effective starting dose of darbepoetin alfa, in respect to Hb response, was 1.5 μg/kg with a plateau effect observed at 4.5 μg/kg.[4,31]

The recommended dosage of darbepoetin alfa for the treatment of chemotherapy-related anaemia in patients with cancer is 2.25 μg/kg once weekly administered via subcutaneous injection. The dosage should, however, be adjusted for each patient to achieve and maintain a target Hb level (see table).[4,5]

Darbepoetin alfa is formulated as a sterile, colourless, preservative-free protein solution supplied in single-use vials[4] or prefilled syringes.[5] The drug should be kept refrigerated at 2–8°C until use.[4,5]

6. Darbepoetin Alfa: Current Status in Patients with Chemotherapy-Related Anaemia

Darbepoetin alfa is a novel erythropoiesis-stimulating protein that has been previously approved in the US and Europe for the treatment of anaemia associated with chronic kidney disease.[4,5] It is now approved in the US for use in patients with non-myeloid malignancies in whom anaemia is related to concomitantly administered chemotherapy.[4] Likewise, the drug is approved in the European Union for the treatment of anaemia in adult patients with solid tumours (i.e. non-haematological malignancies) receiving chemotherapy.[5]

Data from phase II/III clinical trials indicate that subcutaneous darbepoetin alfa, administered in once-weekly or 2-, 3- or 4-weekly regimens, is generally well tolerated and effective in correcting and maintaining Hb levels and in reducing the need for RBC transfusions in anaemic patients with solid tumours or lymphoproliferative malignancies. It also reduces fatigue and improves the HR-QOL in patients with chemotherapy-related anaemia. Its long $t_{1/2}$ allows for less frequent administration that could be synchronised with chemotherapy cycles (i.e. once every 2, 3 or 4 weeks) in this patient population.

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