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The benefits of haematopoietic growth factors in the management of gynaecological oncology

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Summary

Neutropenia and anemia are important complications of cancer chemotherapy and can be prevented and treated with granulocyte colony-stimulating factor and erythropoietin.

Key words: Chemotherapy-related neutropenia; Chemotherapy-related anemia; Cancer and quality of life; Hematopoietic growth factors; Granulocyte colony-stimulating factor; Erythropoietin.

Introduction

Treating cancer with myelosuppressive chemotherapy agents damages the integrity of the bone marrow, impairing haematopoiesis. Reducing haematopoiesis decreases the number of circulating neutrophils and red blood cells, causing neutropenia and anaemia, respectively, which are common and serious complications of cancer treatment. Chemotherapy-induced neutropenia has significant consequences. These include increased risk of infection and mortality, chemotherapy dose delays and reductions that may compromise treatment effectiveness, increased costs through use of antibiotics and hospital admission, and a negative impact on patient quality of life. Anaemia causes fatigue and decreased quality of life, and may adversely affect patient outcome by reducing the anti-tumour activity of radiotherapy and some chemotherapeutic agents. Haematopoietic growth factors such as filgrastim (a granulocyte colony-stimulating factor) and recombinant human erythropoietin (an erythropoietic factor), developed in the 1980s and 1990s, significantly improved the management of neutropenia and anaemia in patients with cancer. Recently, a new generation of haematopoietic growth factors has been developed to simplify and optimise treatment of these complications. Once-per-cycle pegfilgrastim (Neulasta™) is as effective as daily filgrastim in reducing the duration of severe neutropenia (DSN). Darbepoetin alfa (Aranesp®), administered once per week or once every two weeks (Q2W), rapidly corrects anaemia in cancer patients, and has the potential to offer even more extended dosing intervals. These novel cytokines could simplify the management of neutropenia and anaemia with fewer injections and less disruption to patients' daily lives.

Neutropenia

a) Incidence of neutropenia

In healthy adults, the level of circulating neutrophils is between 1.5 and 7 x 109 cells/l. Moderate (World Health Organisation [WHO] grade 3) and severe neutropenia (WHO grade 4) are defined as absolute neutrophil counts (ANC) of 0.5-0.9 x 10^9/l, and ≤ 0.5 x 10^9/l, respectively. Definitions of febrile neutropenia (FN) vary, but it is commonly described as a temperature > 38.3°C with an ANC of < 0.5 x 10^9 cells/l [1].

In patients with cancer, the most common cause of neutropenia is myelosuppression caused by cytotoxic chemotherapy. The reported rates of neutropenia and neutropenic complications vary widely. The Canadian Database Initiative reported a 42% incidence of a least one neutropenic complication in breast cancer patients receiving a variety of chemotherapy regimens. Of these patients, 72% had further complications in subsequent cycles [2]. The American Society of Clinical Oncology (ASCO) reported a 25-40% incidence of FN with common chemotherapy regimens in patients receiving chemotherapy for the first time [3]. The

European Society for Medical Oncology (ESMO) noted that the reported rate of FN in Europe varies from 10-57% and grade 4 neutropenia from 2-8% for most patients receiving standard-dose chemotherapy regimens [4]. Unfortunately, it is difficult to assess the true extent of neutropenic complications from much of the available clinical trial data. Inconsistent reporting of haematologicial toxicities makes it difficult to evaluate a regimen's potential myelotoxicity. For example, in a retrospective analysis of 87 randomised clinical trials in early-stage breast cancer published from 1990-2000, only 46 studies reported haematological toxicity data [5]. The incidence of grade 3 or 4 neutropenia was 1-78% with cyclophosphamide, methotrexate, 5-fluorouracil (CMF, n = 7,206 patients), and 3-100% with cyclophosphamide, doxorubicin, 5-fluorouracil (CAF) or

5-fluorouracil, epirubicin and cyclophosphamide (FEC) (n = 2,870 patients). More standard reporting methods are needed.

b) Clinical consequences of chemotherapy-induced neutropenia

Chemotherapy-induced neutropenia (CIN) has significant clinical consequences. Low neutrophil levels compromise a patient's immune system and increase vulnerability to infection. The risk of infection is linked to the severity and duration of neutropenia [6]. Infection can be life threatening and patients very often require hospital admission for intravenous anti-infectives, which increases costs and the burden on the health care provider. The mortality rate among cancer patients with FN is approximately 10% [7].

Neutropenia is the most common cause of dose reduction and delay in patients receiving chemotherapy [8]. In a study of Stage I-III breast cancer patients (n = 444), approximately 40-50% of patients needed dose reductions or delays after the first or second cycle due to neutropenic complications [2]. In another study of breast cancer patients (n = 449), 32% of chemotherapy dose reductions were due to myelosuppression [9]. However, it is difficult to assess the true extent of dose delay and reduction caused by haematological toxicity from clinical trial data because the delivered dose intensity is reported inconsistently. A review of 72 randomised clinical trials in early-stage breast cancer noted that only 53% reported information on dose intensity [10].

Chemotherapy dose reductions are linked to significantly lower response rates and reduced survival rates in patients with cancer, including those with gynaecological cancers. The 5-year relapse-free survival rate in breast cancer patients treated with CMF was 77% for patients receiving ≥ 85% of the planned dose, but only 48% for those receiving < 65% of the planned dose [9]. A 20-year follow-up confirmed the survival benefits of maintaining planned doses [11]. In patients with ovarian cancer, survival was better with a high-dose cisplatin-based therapy than with a low-dose regimen (114 vs 69 weeks, respectively) [12].

Dose-intensification of chemotherapy may be associated with increased survival. Patients with breast cancer treated with dose-dense chemotherapy (doxorubicin, paclitaxel, cyclophosphamide with a 2-week dose interval) had higher survival rates at three years compared with patients receiving the same chemotherapy with a 3-week dose interval [13]. In this study, disease-free and overall survival rates at three years were 85% and 92%, respectively, for the dose-dense schedule, and 81% and 90%, respectively, for the conventional schedule [13].

Neutropenia is expensive to manage and the costs have increased dramatically in recent years. A survey of over 79,000 hospitalisations for FN in 115 large academic institutions in the USA during 1995-2000 showed that the mean length of stay was 12 days and the mean cost per episode was $22,622 [14]. In another study in the USA, over 60,000 FN episodes in a 6-year period cost more than US$1 billion and accounted for more than 600,000 days in hospital [7, 15]. In a study of 83 women with gynaecological cancers, CIN resulted in an estimated total cost of $11,380 (€ 12,860) per person [16].

Quality of life (QOL) is also negatively affected by CIN. Neutropenia adds to the already high levels of stress and anxiety in patients with cancer. An internet survey showed that FN had a significant negative impact on patients' well-being [17]. Hospital admission with FN is often at short notice, causing stress, disruption to domestic routine and isolation [18]. Delays in chemotherapy schedules due to neutropenia also cause increased anxiety and inconvenience for patients and reduce QOL [18]. The Awareness of Neutropenia in Chemotherapy Study Group is currently developing and validating a QOL instrument specifically for neutropenia [19, 20].

c) Current management of neutropenia

As the clinical consequences of CIN can be serious and costly, it is important to minimise the incidence of CIN and its complications. Until the 1990s, watchful waiting with aggressive antibiotic treatment for patients with FN was standard care [21]. However, prophylactic antibiotics are generally not effective. There are also well-founded concerns about the prolonged and widespread use of antibiotics, which can lead to bacterial resistance, opportunistic infections by fungi and disruptions to the physiological microenvironment [22].

A more effective way of managing CIN is with granulocyte colony-stimulating factors (G-CSFs), which directly stimulate the formation of neutrophils and reduce the transit time of polymorphonucleocytes into the blood. Filgrastim (r-metHuG-CSF) has been used for over ten years to reduce CIN in patients with cancer [23]. Prophylactic filgrastim reduces the DSN in patients with acute myeloid leukaemia by approximately five days compared with placebo [24]. Filgrastim also effectively minimises complications of CIN. Heil *et al.* report that filgrastim significantly reduces the duration of fever, parenteral antibiotic use and hospitalisation [24]. In breast cancer patients, filgrastim significantly reduces the rate of hospital admission for FN [25] and enables more patients to receive planned dose on time [25-27]. In a meta-analysis of controlled clinical trials, prophylactic G-CSF led to a reduced risk of FN (odds ratio = 0.38, $p < 0.001$), documented infection (odds ratio = 0.51) and infection-related mortality (odds ratio = 0.60) as well as fewer chemotherapy delays (odds ratio = 0.32, $p < 0.001$) [28].

The prophylactic use of G-CSFs, such as filgrastim, has a significant impact on CIN and its consequences. However, if all patients with cancer were given G-CSF routinely, then approximately half would be treated unnecessarily, as not all patients develop FN with standard chemotherapy regimens [3]. Specialist oncology groups such as ASCO, ESMO, the European Organisation for the Research and Treatment of Cancer (EORTC), and the National Comprehensive Cancer Network (NCCN), have published guidelines to facilitate the appropriate use of prophylactic G-CSFs [3, 4, 29, 30]. Generally, these guidelines recommend primary prophylaxis when the risk of developing FN is greater than 40%, and secondary prophylaxis for patients with previous FN [3, 4, 29].

The appropriateness of the 40% FN risk has been questioned. Recent economic analyses suggest that G-CSFs are cost-effective when the risk of FN is < 40%. When indirect costs (such as patient out-of-pocket expenses and lost productivity due to morbidity and mortality) are accounted for, G-CSF prophylaxis is cost-effective when the risk of FN is close to 20% [31, 32]. When prolonged management of FN is likely, and the hospital stay is long, then primary prophylaxis with G-CSF is cost-effective when the risk of developing FN is only 10% [31].

One of the challenges in using guidelines to aid the appropriate use of G-CSF is the difficulty in estimating the risk of developing FN in individual patients [33]. The risk of CIN varies widely among patients with the same health status receiving the same chemotherapy for the same tumour type [5]. Certain groups are known to be at high risk of CIN, for example, elderly patients [34]. Therefore, easy-to-use predictive models are needed to identify patients at high risk of neutropenia and neutropenic complications after chemotherapy. Several such risk models have been published. For example, Silber et al. reported that in breast cancer patients, blood counts at the predicted nadir during the first cycle of chemotherapy can be used to assess a patient's relative risk for severe neutropenia and its consequences in subsequent treatment cycles [35]. Other predictors of CIN in breast cancer patients are age, nitrogen index, type of chemotherapy and oestrogen receptor status [36-38]. Validated risk models will enable oncologists to identify high-risk patients and therefore provide optimum, cost-effective protection from CIN.

d) Neutropenia in elderly cancer patients

Elderly cancer patients are particularly vulnerable to complications of myelosuppressive chemotherapy. In breast cancer patients treated with four cycles of adjuvant chemotherapy (cyclophosphamide, doxorubicin [CA]), the mean nadir ANC by cycle 4 was significantly lower in those aged ≥ 65 years than in younger patients (94×10^6 cells/l vs 270×10^6 cells/l, $p < 0.01$, [39]). Elderly patients, therefore, appear to have a lower haematopoietic reserve and are more prone to severe haematological toxicity with various chemotherapies than younger patients. For example, patients ≥ 70 years treated with actinomycin-D had a 319% increase in risk of grade 3 haematological toxicity compared with patients < 60 years

[40]. The incidence of neutropenia in elderly patients with non-Hodgkin's lymphoma treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CHOP-like chemotherapy is high, from 9-50% [34]. Fortunately, age has little effect on the neutrophil response to G-CSF. In healthy volunteers, filgrastim increased the number of polymorphonuclear neutrophilic leucocytes in the blood to a similar extent in 20-30 and 70-80 year olds [41]. The NCCN guidelines aim to minimise the toxicity of chemotherapy in older cancer patients [30, 42] by recommending prophylactic G-CSF in patients ≥ 70 years receiving CHOP or a drug combination of similar dose intensity (CAF, FEC 100 [5-fluorouracil, etoposide, cisplatin], CA).

e) Development of pegfilgrastim

The development of pegfilgrastim represents a significant advance in the pharmacological management of CIN. Pegfilgrastim consists of a 20,000 dalton polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue of filgrastim. Because filgrastim is relatively small (approximate molecular weight 18,800 daltons), it is rapidly cleared by the kidneys, resulting in a short serum half-life (approximately 3.5 hours). Daily injections of filgrastim are needed therefore, to maintain an adequate neutrophil response. Pegfilgrastim is a much larger molecule (approximate molecular weight 39,000 daltons) and consequently its clearance via the kidneys is minimised resulting in a longer serum half-life. Concentrations of pegfilgrastim in the serum are therefore sustained, making once-per-chemotherapy-cycle dosing possible [43]. In a phase 2 study, women with breast cancer treated with four cycles of doxorubicin/docetaxel chemotherapy every 21 days were given pegfilgrastim as a single subcutaneous injection per chemotherapy cycle (30, 60 or 100 μg/kg). The pharmacokinetics of pegfilgrastim were non-linear and depended on both the dose and neutrophil count [44].

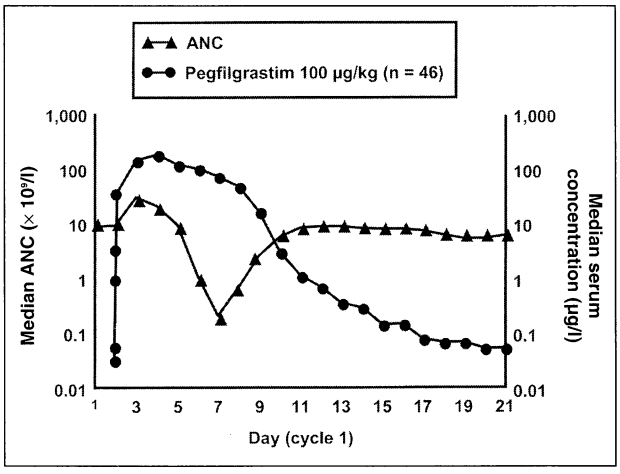

Figure 1. — Mean serum levels of pegfilgrastim and mean ANC. This graph shows that pegfilgrastim is cleared as neutrophil levels return to normal. Permission - *Clinical Journal of Oncology Nursing*, 2003, 7, 55.

The maximum serum concentration of pegfilgrastim occurred approximately 24 hours post-dosing and was sustained until the ANC nadir (Figure 1). As the neutrophil levels increased, pegfilgrastim serum concentrations decreased, consistent with a neutrophil-mediated clearance mechanism [44]. This 'self-regulating' pegfilgrastim clearance provides tailored protection for individual patients.

Pegfilgrastim was compared with filgrastim in two pivotal phase 3 trials in patients with breast cancer [46, 47]. Both studies were similar, enrolling patients with either high-risk early-stage (Stage II) breast cancer or advanced (Stage III or IV) breast cancer (n = 310 [46]; n = 157 [47]). The chemotherapy regimen was doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2) given as four 21-day cycles. Starting on day 2 of each cycle, patients received either a single subcutaneous injection of pegfilgrastim (100 μg/kg/cycle [46]; 6 mg/cycle [47]) followed by daily injections of placebo, or filgrastim (5 μg/kg/day) until the ANC reached 10 x 10^9/l or for 14 days whichever was the shortest. The primary efficacy endpoint in both studies was DSN (days with ANC <0.5 x 10^9/l) in cycle 1. These studies were designed to show that once-per-cycle pegfilgrastim was as effective as daily filgrastim in reducing DSN (noninferiority design). In the dose-by-weight (100 μg/kg/cycle) study, the DSN in cycle 1 was 1.7 and 1.8 days for pegfilgrastim and filgrastim, respectively [46]. Similar results were obtained in the fixed-dose (6 mg/cycle) study (mean DSN in cycle 1 was 1.8 and 1.6 days for pegfilgrastim and filgrastim, respectively [47]). These DSN values were much shorter than those reported for breast cancer patients receiving the same chemotherapy regimen when G-CSF was not used (range = 5-7 days [48]), indicating that primary prophylaxis with growth factors is effective in reducing CIN. The mean DSN in the fixed-dose study was similar across a broad range of patient body weights (46-132 kg), indicating that a single 6 mg fixed dose of pegfilgrastim does not affect efficacy in

heavier patients. In both studies, pegfilgrastim was well tolerated and its safety profile was similar to that of filgrastim.

In these two phase 3 studies, the incidence of FN, a pre-defined endpoint, was 9% vs 18% ($p < 0.05$ [46]) and 13% vs 20% (p = not significant [47]) for pegfilgrastim and filgrastim, respectively. A combined analysis of the data from these two studies showed that patients given a single injection of pegfilgrastim per cycle had a significantly lower observed risk of developing FN (relative risk = 0.56, 95% confidence intervals [CI] = 0.35, 0.89, $p < 0.05$) than those given daily filgrastim [49]) (Figure 2). Overall, only 11% of patients receiving pegfilgrastim developed FN compared with 19% of patients receiving filgrastim, suggesting that pegfilgrastim may have superior efficacy for the management of neutropenic complications compared with filgrastim. These findings warrant further investigation.

The combined analysis also showed a trend towards lower risk of hospital admission and intravenous anti-infective use in patients receiving pegfilgrastim than in those receiving filgrastim.

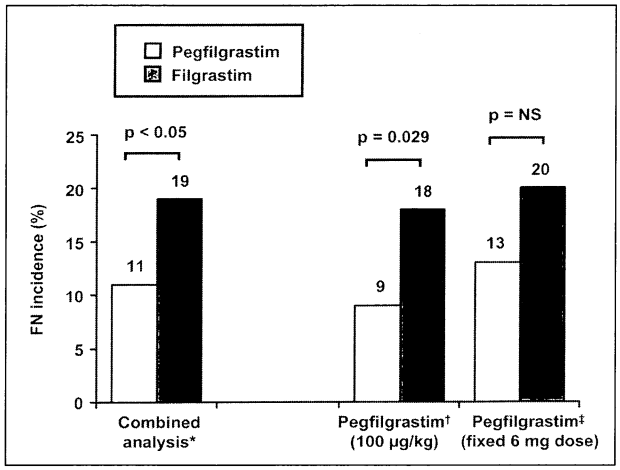

Figure 2. — Comparison of the incidence of febrile neutropenia in phase 3 randomised controlled trials with filgrastim and pegfilgrastim in breast cancer patients. Adapted from *[49], †[46], ‡[47].
Permission - *European Journal of Hospital Pharmacy*, 2002, 2, 56.

Anaemia

a) Background to anaemia

An imbalance between the production and destruction or loss of red blood cells (RBCs) causes anaemia. This imbalance reduces the number of RBCs or amount of Hgb in the blood resulting in an insufficient oxygen-carrying capacity. In healthy adults, Hgb concentrations range from 14-18 g/dl in men and 12-16 g/dl in women [51]. Several organisations, including the WHO, the National Cancer Institute (NCI) and many of the major oncology cooperative groups (e.g. Eastern Cooperative Oncology Group; Southwest Oncology Group; Cancer and Leukemia Group B; Gynecologic Oncology Group), have defined anaemia and its toxicity grading criteria [51]. Generally, mild anaemia is a Hgb concentration of 10-12 g/dl, moderate anaemia is a Hgb concentration of 8-10 g/dl, serious/severe anaemia is a Hgb concentration of 6.5-8 g/dl and life-threatening anaemia is a Hgb concentration of < 6.5 g/dl.

Anaemia is common in patients with cancer, often resulting from myelosuppressive chemotherapy or radiotherapy, or as a direct effect of the cancer itself. Several factors contribute to anaemia in patients with cancer, including type, duration and intensity of chemotherapy, age, infection, histology and stage of tumour, and other comorbid conditions. The incidence of anaemia in cancer also varies depending on the type of malignancy. It can be particularly high in women with gynaecological cancers. For example, in a review of 12 centres in Canada, the incidence of anaemia in patients with breast cancer (17%) was higher than those with colorectal cancer (13%). In women with ovarian cancer the incidence of anaemia was very high (51%) and similar to rates in patients with lung cancer (52%) and non-Hodgkin's lymphoma (53%) [52]. The incidence of mild-to-moderate anaemia was similar in patients with metastatic breast cancer (55%) and advanced ovarian cancer (44%), where the incidence of serious/life-threatening anaemia was approximately 13% and 16%, respectively [51].

The type of chemotherapy can also influence the severity of anaemia in patients with cancer. In early-stage breast cancer patients (Stage I-III) treated with four cycles of mainly AC, the mean change in Hgb levels over three months was –2.0 ± 1.4 g/dl [53]. Table 1 summarises the incidence of anaemia in some gynaecological cancers treated with various chemotherapy regimens. Most patients are likely to experience some degree of symptomatic anaemia, even those treated with the newer chemotherapeutic agents.

Table 1. — *Incidence and severity of anaemia in patients with gynaecological cancers treated with various chemotherapy regimens.*

Cancer type	Chemotherapy	Incidence of anaemia (patients %)
Advanced breast cancer*	Paclitaxel	36-51
	Docetaxel	60-97
	Doxorubicin/ docetaxel	84
Metastatic breast cancer†	Paclitaxel	93 (grade 1/2) 7 (grade 3/4)
	Docetaxel	97 (grade 1/2) 0-14 (grade 3/4)
	CAF-M	27 (grade 1/2) 1 (grade 3/4)
Advanced ovarian cancer†	Carboplatin	66 (grade 1/2) 0-26 (grade 3/4)
	Cisplatin	8 (grade 1/2) 2 (grade 3/4)
	Paclitaxel/cisplatin	58 (grade 1/2) 8 (grade 3/4)
	Cisplatin/ cyclophosphamide	32-97 (grade 1/2) 2-29 (grade 3/4)

*[54]; †Adapted from [51].
CAF-M = cyclophosphamide, doxorubicin, 5-fluorouracil, methotrexate.

Fatigue is the most common symptom of anaemia in patients with cancer. In the USA, a survey of 419 patients (48% of 282 women had breast/ gynaecological cancers) found that 78% suffered fatigue in the course of their disease and treatment. Patients also reported that fatigue negatively affected their daily life, including work, physical and emotional well-being and relationships with family and friends [55]. In a QOL study of patients with cancer (50% breast/ovarian) using the Functional Assessment of Cancer Therapy-General scale (FACT-G) with additional questions on fatigue and anaemia, a decrease in Hb levels to < 12 g/dL was linked to increased fatigue and a significant decrease in QOL [56]. Interestingly, the USA survey highlighted a major difference between patients and oncologists in perceptions of fatigue [55]. More patients (41%) than oncologists (5%) thought that fatigue was more important to treat than pain, and most oncologists (94%) thought that pain was more important.

There is increasing evidence to suggest that anaemia can adversely affect patient outcome and survival. A literature review of 60 papers reported the survival of patients with cancer according to either Hgb levels or to the presence of anaemia [57]. In the diverse group of cancers studied (including lung, head and neck, prostate and cervical carcinoma, multiple myeloma, leukaemia and lymphoma), anaemia increased the overall relative risk of death by 65%. There are also data to suggest that anaemia can compromise patient survival by reducing the anti-tumour activity of radiotherapy and some cytotoxic chemotherapeutic agents. In patients receiving radiotherapy for head and neck cancers, a 5-year survival rate of 28% was reported in anaemic patients and 58% in non-anaemic patients ($p < 0.0001$). The 5-year local tumour control was 21% and 76% in anaemic and non-anaemic patients, respectively ($p < 0.0001$) [58]. In a recent study in patients receiving non-platinum chemotherapy for solid or non-myeloid haematological malignancies, there was a reduction in transfusion requirement and an improvement in QOL in patients randomised to receive recombinant human erythropoietin (rHuEPO) [59]. There was a trend to improved survival (not statistically significant) for the rHuEPO treated group of patients, and the median survival times were 17 months with rHuEPO and 11 months with placebo.

Anaemia also has many hidden costs, such as those incurred in the treatment of comorbid conditions, additional resource/staff time, and time off from work.

b) Undertreatment of anaemia

There are data to indicate that cancer- and chemotherapy-related anaemias are undertreated. In a USA survey of 3,472 cancer patients (including 42% with breast cancer and 6% with ovarian cancer), a significant number of anaemic patients (52-70%) did not receive rHuEPO, a treatment for anaemia [60]. In a further market research study of over 3,000 cancer patients treated by 60 cancer specialists in five European countries, approximately 60% of anaemic patients received no treatment for their anaemia in 1998-2000. For patients with Hgb levels of 10-12 g/dl (mild anaemia), fewer than 15% were treated [61]. Reasons for non-treatment included lack of recognition, lack of awareness of the incidence of anaemia and its impact, and limited treatment options.

c) Limitations of current therapies for cancer anaemia

Prior to 1990, the main focus of anaemia management was on treatment for severe anaemia (Hgb concentration < 8.5 g/dl) with RBC transfusions [62]. Although transfusions rapidly relieve anaemia, the effects are transient and do not address the underlying causes. In addition, RBC transfusions are associated with significant risks, including infections (from the transfer of bacteria, viruses or protozoa), immunosuppression, allergic reactions and haemolytic transfusion reactions [62]. There are further limitations such as inconvenience, limited blood supply and time-consuming handling.

Between 1991 and 1997, the main therapeutic focus was still the treatment of severe anaemia, but the introduction of rHuEPO provided a valuable alternative to RBC transfusions. Since 1997, there has been increasing interest in the treatment of mild-to-moderate anaemia, in recognition of its impact on patient QOL. rHuEPO has been shown to improve QOL and reduce the need for RBC transfusions, although transfusions are still used to treat severe anaemia and in emergency cases (e.g. severe haemorrhage).

There are limitations to the widespread use of erythropoietic agents to treat anaemia in patients with cancer. These include cost, limited effectiveness, long response time, no adequate predictors of response, lack of a clear dose-response relationship and the need for frequent injections and visits [63].

d) Development of darbepoetin alfa

Recombinant DNA technology was used to create darbepoetin alfa (Aranesp®). The development of darbepoetin alfa stemmed from an understanding of the relationship between the number of sialic acid-containing carbohydrate moieties and the clearance and therefore activity of the erythropoietin molecule. Darbepoetin alfa is biochemically distinct from rHuEPO: five amino acids were changed allowing two additional carbohydrate moieties to be bound to the protein, which increases the sialic acid content (from a maximum of 14 residues to a possible 22 residues) [64, 65]. Like rHuEPO and endogenous EPO, darbepoetin alfa stimulates erythropoiesis by promoting the proliferation, maturation and differentiation of RBCs. However, the increased sialic acid content of the darbepoetin alfa molecule results in a three-fold longer serum half-life than rHuEPO [66, 67], and increased in vivo biological activity [65]. Darbepoetin alfa therefore has the potential to improve response rates, shorten the time to response and to be given less frequently than rHuEPO.

Darbepoetin alfa is licensed in the European Union for the treatment of anaemia associated with chronic renal failure in adults and children ≥ 11 years of age, and for the treatment of anaemia in adult cancer patients with solid tumours (non-haematological malignancies) receiving chemotherapy.

e) Clinical experience with darbepoetin alfa

An extensive international clinical programme studied the efficacy and safety of darbepoetin alfa in a wide range of malignancies (non-myeloid solid tumours and lymphoproliferative malignancies) in patients receiving diverse therapies. Included are phase 1 and 2 studies, evaluating the pharmacokinetics and the dose-response relationship of darbepoetin alfa administered at different frequencies (from once a week up to once every four weeks), and two pivotal phase 3 studies in lung cancer and lymphoproliferative malignancies. The overall programme includes patients with breast cancer and ovarian cancer. Below is a summary of the key results from the clinical trials.

Analysis of the data was carried out according to the intent-to-treat principle.

The dose-response relationship of darbepoetin alfa administered once per week (0.5-4.5 μg/kg/week) has been studied in randomised phase 2 studies in patients with solid tumours [68, 69] or with lymphoproliferative malignancies [70]. The primary efficacy endpoint was the proportion of patients achieving a haemoglobin response, defined as an increase in Hgb of at least 2 g/dl from baseline Hgb in the absence of any RBC transfusion in the previous 28 days. Glaspy and colleagues reported a Hgb response ranging from 23% (95% CI = 0-46%) for the 0.5 μg/kg/week group to 76% (95% CI = 59-94%) for the 4.5 μg/kg/week group over the 12-week treatment period [68, 69]. Patients receiving 1.5 μg/kg/week darbepoetin alfa showed a mean change in Hgb both after four weeks and after 12 weeks that was comparable to that observed in the rHuEPO control arm, despite dose increases of rHuEPO (150-300 IU/kg three times per week [TIW]) at week 8 in patients who showed an inadequate initial response. Darbepoetin alfa doses of 2.25 μg/kg/week and above appeared to be associated with greater Hgb increases and enhanced efficacy relative to rHuEPO (Table 2).

Table 2. — *Mean change in Hgb with darbepoetin alfa (1.5-4.5 μg/kg/week) and rHuEPO (150 IU/kg TIW*). Adapted from [69].*

	rHuEPO (150 IU/kg TIW*)	Darbepeotin alfa (μg/kg/week) 1.5	2.25	4.5
n	53	35	59	29
Mean change in Hgb after 4 weeks (g/dl) (SE)	0.30 (0.20)	0.30 (0.19)	0.70 (0.16)	0.90 (0.20)
Mean change in Hgb after 8 weeks (g/dl) (SE)	0.90 (0.30)	1.00 (0.30)	1.20 (0.20)	1.70 (0.30)
Mean change in Hgb after 12 weeks (g/dl) (SE)	1.10 (0.25)	1.10 (0.28)	1.30 (0.23)	1.90 (0.32)

*Dose increased to 300 IU/kg TIW if inadequate response by week 8.
SE = standard error.
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In the study of anaemic patients with lymphoproliferative malignancies receiving chemotherapy, more patients had a Hgb response in the darbepoetin alfa 1.0 μg/kg/week (45%), 2.25 μg/kg/week (55%) and 4.5 μg/kg/week (62%) groups than in the placebo group (10%, $p < 0.01$) [70].

A pivotal, phase 3, randomised, double-blind, placebo-controlled clinical trial further evaluated the efficacy and safety of darbepoetin alfa [71]. Patients with lung cancer receiving multicycle, platinum-containing chemotherapy were randomised to receive either darbepoetin alfa (2.25 μg/kg/week, n = 156) or placebo (n = 158) for 12 weeks. The dose of darbepoetin alfa was increased to 4.5 μg/kg/week after six weeks if patients did not respond (Hgb increase ≤1 g/dl over baseline). The primary efficacy endpoint was the proportion of patients requiring a RBC transfusion from week 5 until the end of the treatment period. The study confirmed the efficacy of darbepoetin alfa 2.25 μg/kg/week, as suggested in the phase 2 studies. Between weeks 5 and 12, significantly fewer patients receiving darbepoetin alfa required RBC transfusions than those receiving placebo (27% vs 52%, $p < 0.001$) (Figure 3). Furthermore, significantly fewer patients receiving darbepoetin alfa required RBC transfusions than those receiving placebo ($p < 0.001$) throughout the entire treatment period (weeks 1-12).

The proportion of patients achieving a haematopoietic response, defined as an increase in Hgb of at least 2 g/dl from baseline Hgb in the absence of any RBC transfusion in the previous 28 days or a Hgb level of ≥12 g/dl, was also significantly higher in the darbepoetin alfa group than the placebo group (66% vs 24%, $p < 0.001$). Adverse events were similar between the groups, and there was no evidence of antibody formation due to administration of darbepoetin alfa.

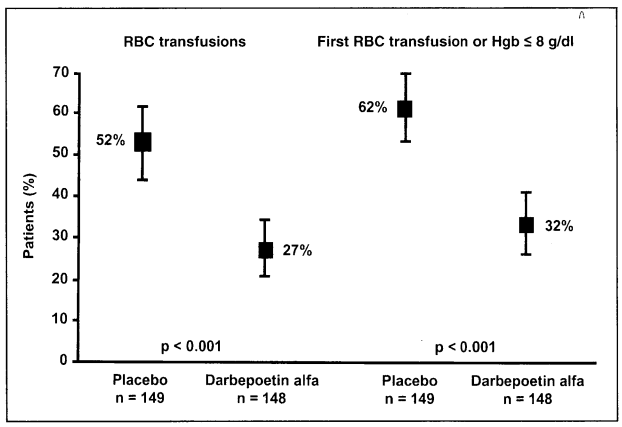

Figure 3. — The incidence of red blood cell transfusions in patients receiving placebo or darbepoetin alfa from week 5 until the end-of-treatment phase. This graph shows that darbepoetin alfa significantly reduces the proportion of patients requiring RBC transfusion. Adapted from [71].
Permission - *Journal of the National Cancer Institute*, 2002, 94, 1211.

Several phase 2 clinical trials in patients with solid tumours have demonstrated the efficacy of darbepoetin alfa with increased dosing intervals. In patients with solid tumours receiving chemotherapy (n = 128, 23% with breast cancer and 13% with gynaecological cancers), darbepoetin alfa was administered at 3.0, 5.0, 7.0 or 9.0 μg/kg Q2W for 12 weeks [68, 69]. The minimally effective doses of darbepoetin alfa were 3.0 and 5.0 μg/kg Q2W, with no increased benefit observed at higher doses. A haematopoietic response was achieved in 66% and 84% of patients in the 3.0 and 5.0 μg/kg Q2W groups, respectively. In a multicentre, randomised, double-blind, placebo-controlled study, patients with solid tumours receiving chemotherapy were given darbepoetin alfa once every three weeks (Q3W; 4.5, 6.75, 9.0, 12.0, 13.5 or 15.0 μg/kg) or once every four weeks (Q4W; 9.0, 12.0, 15.0 or 18.0 μg/kg) or placebo [72]. The proportion of patients with a haematopoietic response ranged from 51-71% (Q3W) and 49-73% (Q4W). Darbepoetin alfa also has efficacy in treating chronic anaemia in patients with cancer (non-myeloid malignancies) who are not receiving chemotherapy [73]. In this study, a haematopoietic response was achieved in 72% and 100% of patients receiving darbepoetin alfa at 1.0 and 4.5 μg/kg/week for 12 weeks. There was also a haematopoietic response with longer dosing inter-

vals in 60% of patients receiving darbepoetin alfa at 6.75 μg/kg Q3W, in 61% of patients receiving darbepoetin alfa at 6.75 μg/kg Q4W, and in 70% of patients receiving darbepoetin alfa at 10 μg/kg Q4W [73].

To evaluate the relationship between Hgb concentration and QOL, and the effects of treatment for anaemia, data from two clinical trials [68, 71] were combined (n = 517) [74]. Patients completed the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) questionnaire at baseline and at the end of treatment. Fatigue improved by four points when Hgb concentrations increased by ≥2 g/dl. Patients' physical, functional, emotional well-being, and anaemia symptoms also improved as Hgb concentrations increased [74]. This suggests that treating anaemia in patients with cancer improves their overall QOL.

The optimal dose and schedule of darbepoetin alfa were explored in a recent clinical trial using a novel 'front-loading' concept [75]. A scheme of this concept is illustrated in Figure 4.

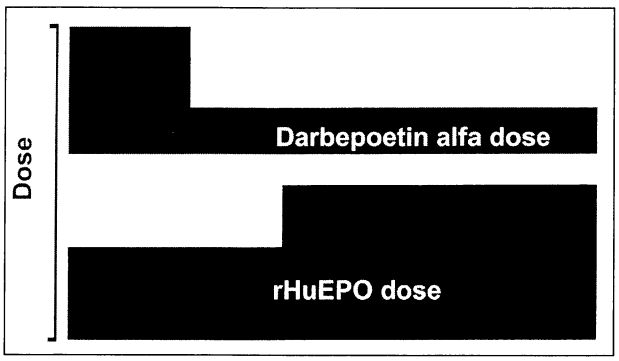

Figure 4. — Schematic illustration of the front-loading concept.

The aim of this trial was to optimise treatment by producing higher and faster response rates to darbepoetin alfa, and simplifying dosing schedules for patients and health care professionals. Darbepoetin alfa was given to patients with solid tumours receiving chemotherapy according to a correction phase/maintenance phase design. Three groups of patients were given an initial correction dose of darbepoetin alfa (4.5 μg/kg/week). In one group, when the Hgb concentrations were ≥12 g/dl, the dose was reduced to a maintenance dose of 1.5 μg/kg/week (n = 32). For the other two groups, the dose of darbepoetin alfa was reduced after four weeks to 2.25 μg/kg/week (n = 30), or 3.0 μg/kg Q2W (n = 30). A control group (n = 30) received rHuEPO (40,000 IU/week, increased to 60,000 IU/week in patients with an inadequate response). The mean change in Hgb at week 4 was 80% greater in patients on darbepoetin alfa (all groups combined) than in the rHuEPO control group. By week 12, the change in Hgb concentration was still higher (approximately 30%) with darbepoetin alfa than with rHuEPO, despite the reduction in darbepoetin alfa dose. The time to Hgb response appeared to be faster with darbepoetin alfa than with rHuEPO. Fewer than 50% of the patients on rHuEPO responded, so their median time to Hgb response could not be estimated. In two of the darbepoetin alfa groups, the median time to Hgb response was seven weeks [75]. Overall, this study showed that darbepoetin alfa correction for four weeks followed by a lower and/or less frequent maintenance schedule may increase the speed of response and increase the proportion of patients responding to darbepoetin alfa compared with standard rHuEPO therapy.

Conclusions

Neutropenia and anaemia are common and serious complications of myelosuppressive chemotherapy. Haematopoietic growth factors such as filgrastim and rHuEPO provide physicians with a pharmacological option to manage these conditions in patients with cancer. However, these first generation recombinant proteins have some shortcomings. Understanding the structure-function relationship has aided in the development of the novel agents pegfilgrastim and darbepoetin alfa. The long-acting format of pegfilgrastim and enhanced therapeutic activity of darbepoetin alfa can simplify and optimise the management of neutropenia and anaemia, respectively.

References

[1] Hughes W. T., Armstrong D., Bodey G. P., Brown A. E., Edwards J. E., Feld R. *et al.*: "1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever". *Clin. Infect. Dis.*, 1997, *25*, 551.

[2] Chang J.: "Chemotherapy dose reduction and delay in clinical practice: evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer". *Eur. J. Cancer*, 1999, *36 suppl. 1*, S11.

[3] Ozer H., Armitage J. O., Bennett C. L., Crawford J., Demetri G. D., Pizzo P. A. *et al.*: "Update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines". *J. Clin. Oncol.*, 2000, *18*, 3558.

[4] ESMO: "ESMO recommendations for the application of haematopoietic growth factors (hGFs)". *Ann. Oncol.*, 2001, *12*, 1219.

[5] Dale D., Crawford J., Lyman G.: "Chemotherapy-induced neutropenia and associated complications in randomized clinical trials: an evidence-based review". *Proc. Am. Soc. Clin. Oncol.*, 2001, *20*, 410a (Abstract 1638).

[6] Bodey G. P., Buckley M., Sathe Y. S., Freireich E. J.: "Quantitative relationships between circulating leukocytes and infection in patients with acute leukaemia". *Ann. Intern. Med.*, 1966, *64*, 328.
[7] Kuderer N. M., Cosler L., Crawford J., Dale D. C., Lyman G.: "Cost and mortality associated with febrile neutropenia in adult cancer patients". *Proc. Am. Soc. Clin. Oncol.*, 2002, *21*, 250a (Abstract 998).
[8] Trillet-Lenoir V., Green J., Manegold C., Von Pawel J., Gatzemeier U., Lebeau B. *et al.*: "Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy". *Eur. J. Cancer*, 1993, *29A*, 319.
[9] Bonadonna G., Valagussa P.: "Dose-response effect of adjuvant chemotherapy in breast cancer". *N. Eng. J. Med.*, 1981, *304*, 10.
[10] Dale D. C., McCarter G., Crawford J., Lyman G. H.: "Delivered dose intensity in randomized clinical trials (RCTs) of chemotherapy in early-stage breast cancer (ESBC) and non-Hodgkin's lymphoma (NHL): a need for improved reporting". *Proc. Am. Soc. Clin. Oncol.*, 2002, *21*, 252a (Abstract 1004).
[11] Bonadonna G., Valagussa P., Moliterni A., Zambetti M., Brambilla C.: "Adjuvant cyclophosphamide, methotrexate and fluorouracil in node-positive breast cancer". *N. Eng. J. Med.*, 1995, *332*, 901.
[12] Kaye S. B., Lewis C. R., Paul J., Duncan I. D., Gordon H. K., Kitchener H. C. *et al.*: "Randomised study of two doses of cisplatin with cyclophosphamide in epithelial ovarian cancer". *Lancet*, 1992, *340*, 329.
[13] Citron M., Berry D., Cirrinicione C., Carpenter J., Hudis C., Gradishar W. *et al*: "Superiority of dose-dense (DD) over conventional scheduling (CS) and equivalence of sequential (SC) vs. combination adjuvant chemotherapy (CC) for node-positive breast cancer (CALGB 9741, INT C9741)". *Oral presentation at the 25th Annual San Antonio Breast Cancer Symposium, December 11-13, 2002* (Abstract 15).
[14] Lyman G. H., Kuderer N. M., Agboola O., Crawford J., Dale D. C.: "The epidemiology and economics of neutropenia in hospitalized cancer patients: data from the University HealthSystem Consortium". *Blood*, 2001, *98*, 432a (Abstract 1813).
[15] Kuderer N. M., Crawford J., Dale D., Lyman G.: "Cost distributions and length of stay associated with febrile neutropenia in adult cancer patients". *Supportive Care in Cancer*, 2002, *10*, 372 (Abstract P-71).
[16] Calhoun E. A., Welshman E. E., Change C-H., Lurain J. R., Bennett C. L.: "Cost of chemotherapy-induced neutropenia, thrombocytopenia and neurotoxicity". *Proc. Am. Soc. Clin. Oncol.*, 2001, *20*, 242a (Abstract 964).
[17] Erder M. H., Fridman M., Weaver C. H.: "Cancer patients (CPs) perspectives about the impact of febrile neutropenia morbidity (FNM) on their well being (WB) and preferences for filgrastim treatment vs dose reduction to prevent FN: an internet survey". *Proc. Am. Soc. Clin. Oncol.*, 2001, *20*, 210b (Abstract 2589).
[18] Traynor B.: "Quality of life with filgrastim (r-metHuG-CSF)". In: "Filgrastim (r-metHuG-CSF) in Clinical Practice". Morstyn G., Dexter T. M. (eds). 1st edition. New York: Marcel Dekker, 1994, 319.
[19] Calhoun E. A., Chang C.-H., Welshman E. E., Cella D.: "Development and validation of the FACT-Neutropenia". *Blood*, 2001, *98*, 427a (Abstract 1791).
[20] Calhoun E. A., Chang C.-H., Welshman E. E., Cella D.: "A neutropenia-specific quality of life instrument: rationale for the development of the FACT-N". *Proc. Am. Soc. Clin. Oncol.*, 2002, *21*, 375a (Abstract 1498).
[21] Pizzo P. A.: "Fever in immunocompromised patients". *N. Engl. J. Med.*, 1999, *341*, 893.
[22] Dale D.: "Management of febrile neutropenia: The shift from treatment to prevention". *Oncol. Spectrums*, 2002, *3*, 6.
[23] Welte K. W., Gabrilove J., Bronchud M. H., Platzer E., Morstyn G.: "Filgrastim (r-metHuG-CSF): The first 10 years". *Blood*, 1996, *88*, 1907.
[24] Heil G., Hoelzer D., Sanz M. A., Lechner K., Yin J. A. L., Papa G. *et al.*: "A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia". *Blood*, 1997, *90*, 4710.
[25] Rivera E., Erder M. H., Fridman M., Brannan C., Frye D., Hortobagyi G. N.: "Delivering full planned dose on time (PDOT) chemotherapy (CT) while lowering the incidence of febrile neutropenia (FN) hospitalizations: initial results form a prospective study (N=528) providing filgrastim support to high risk breast cancer patients (BCP)". *Breast Cancer Res. Treat.*, 2001, *69*, 209 (Abstract 3).
[26] De Graaf H., Willemse P. H. B., Bong S. B., Piersma H., Tjabbes T., van Veelen H. *et al.*: "Dose intensity of standard adjuvant CMF with granulocyte colony-stimulating factor for premenopausal patients with node-positive breast cancer". *Oncology*, 1996, *53*, 289.
[27] Ribas A., Albanell J., Bellmunt J., Solé-Calvo L.-A., Bermejo B., Gallardo E. *et al.*: "Five-day course of granulocyte colony-stimulating factor in patients with prolonged neutropenia after adjuvant chemotherapy of breast cancer is a safe and cost-effective schedule to maintain dose-intensity". *J. Clin. Oncol.*, 1996, *14*, 1573.
[28] Lyman G. H., Kuderer N. M., Djulbegovic B.: "Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis". *Am. J. Med.*, 2002, *112*, 406.
[29] Croockewit A. J., Bronchud M. H., Aapro M. S., Bargetzi M. J., Crown J., Gratwohl A. *et al.*: "A European perspective on haematopoietic growth factors in haemato-oncology: report of an expert meeting of the EORTC". *Eur. J. Cancer*, 1997, *33*, 1732.
[30] Balducci L., Yates J.: "General guidelines for the management of older patients with cancer". *Oncology*, 2000, *14*, 221.
[31] Lyman G. H., Kuderer N., Greene J., Balducci L.: "The economics of febrile neutropenia: implications for the use of colony-stimulating factors". *Eur. J. Cancer*, 1998, *34*, 1857.
[32] Sivasubramaniam V., Dale D., Crawford J., Agboola Y., Lyman G.: "Impact of outpatient treatment of febrile neutropenia (FN) on risk thresholds for G-CSF prophylaxis in cancer chemotherapy". *Proc. Am. Soc. Clin. Oncol.*, 2001, *20*, 392a. Abstract 1563.
[33] Bennett C. L., Weeks J. A., Somerfield M. R., Feinglass J., Smith T. J.: "Use of hematopoietic colony-stimulating factors; comparison of the 1994 and 1997 American Society of Clinical Oncology surveys regarding ASCO clinical practice guidelines". *J. Clin. Oncol.*, 1999, *17*, 3676.
[34] Balducci L., Hardy C. L., Lyman G. H.: "Hemopoietic reserve in the older cancer patient: clinical and economic considerations". *Cancer Control*, 2000, *7*, 539.
[35] Silber J. H., Fridman M., DiPaola R. S., Erder M., Pauly M., Fox K.: "First-cycle blood counts and subsequent neutropenia, dose reduction or delay in early-stage breast cancer therapy". *J. Clin. Oncol.*, 1998, *16*, 2392.
[36] Aslani A., Smith R., Allen B., Pavlakis N., Levi J.: "The predictive value of body protein for chemotherapy-induced toxicity". *Cancer*, 2000, *15*, 796.
[37] Lininger L., Crawford J., Dale D., Chen H., Agboola Y., Stump E. *et al.*: "Predicting risk of neutropenic complications: a point-of-care assessment tool". *Proc. Am. Soc. Clin. Oncol.*, 2001, *20*, 411a (Abstract 1640).
[38] Lyman G. H., Crawford J., Dale D., Chen H., Agboola Y., Lininger L.: "Clinical prediction models for febrile neutropenia (FN) and relative dose intensity (RDI) in patients receiving adjuvant breast cancer chemotherapy". *Proc. Am. Soc. Clin. Oncol.*, 2001, *20*, 394a (Abstract 1571).

[39] Dees E. C., O'Reilly S., Goodman S. N., Sartorius S., Levine M. A., Jones R. J. *et al.*: "A prospective pharmacologic evaluation of age-related toxicity of adjuvant chemotherapy in women with breast cancer". *Cancer Invest.*, 2000, *18*, 521.
[40] Begg C. B., Elson P. J., Carbone P. P.: "A study of excess hematologic toxicity in elderly patients treated on cancer chemotherapy protocols". In: "Cancer in the elderly; approaches to early detection and treatment". New York, Springer, 1989, 149.
[41] Chatta G. S., Price T. H., Stratton J. R., Dale D. C.: "Aging and marrow neutrophil reserves". *J. Am. Geriatr. Soc.*, 1994, *42*, 77.
[42] Bokemeyer C., Honecker F., Wedding U., Späth-Schwalbe E., Lipp H. P., Kolb G.: "Use of hematopoietic growth factors in elderly patients receiving cytotoxic chemotherapy". *Onkologie*, 2002, *25*, 32.
[43] Molineux G., Kinstler O., Briddell B., Hartley C., McElroy P., Kerzic P. *et al.*: "A new form of filgrastim with sustained duration in vivo and enhanced ability to mobilise PBPC in both mice and humans". *Exp. Hematol.*, 1999, *27*, 1724.
[44] Holmes F. A., Jones S. E., O'Shaughnessy J., Vukelja S., George T., Savin M. *et al.*: "Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer". *Ann. Oncol.*, 2002, *13*, 903.
[45] Bedell C.: "Pegfilgrastim for chemotherapy-induced neutropenia". *Clin. J. Oncol. Nurs.*, 2003, *7*, 55.
[46] Holmes F. A., O'Shaughnessy J. A., Vukelja S., Jones S. E., Shogan J., Savin M. *et al.*: "Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer". *J. Clin. Oncol.*, 2002, *20*, 727.
[47] Green M. D., Koelbl H., Baselga J., Galid A., Guillem V., Gascon P. *et al.*: "A randomized, double-blind, phase 3 study of fixed-dose, single-administration pegfilgrastim vs daily filgrastim in patients receiving myelosuppressive chemotherapy". *Ann. Oncol.*, 2003, *14*, 29.
[48] Misset J. L., Dieras V., Gruia G., Bourgeois H., Cvitkoic E., Kalla S. *et al.*: "Dose-finding study of docetaxel and doxorubicin in first-line treatment of patients with metastatic breast cancer". *Ann. Oncol.,* 1999, *10*, 553.
[49] Siena S., Piccart M. J., Holmes F. A., Glaspy J., Hackett J., Renwick J.: "A combined analysis of two pivotal randomized trials of a single dose of pegfilgrastim per chemotherapy cycle and daily filgrastim in patients with stage II-IV breast cancer". *Oncol. Rep.*, 2003, *10*, 715.
[50] Pettengell R.: "Advances in haematological support of cancer treatments". *Eur. J. Hosp. Pharm.*, 2002, *2*, 56.
[51] Groopman J. E., Itri L. M.: "Chemotherapy-induced anemia in adults; incidence and treatment". *J. Natl. Cancer Inst.*, 1999, *91*, 1616.
[52] Skillings J. R., Rogers-Melamed I., Nabholtz J.-M., Sawka G., Gwardry-Sridhar P., Moquin J.-P. *et al.*: "An epidemiological review of anaemia in cancer chemotherapy in Canada". *Eur. J. Cancer*, 1995, *31a (suppl. 5)*, S5 (Abstract 879).
[53] O'Shaughnessy J., Vukelja S., Savin M., Holmes F. A., Jones M., Royall D. *et al.*: "Effects of epoetin alfa (Procrit) on cognitive function, mood, asthenia, and quality of life in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy: a double-blind, randomised, placebo-controlled trial". *Proc. Am. Soc. Clin. Oncol.*, 2002, *21*, 363a (Abstract 1449).
[54] Demetri G. D., Gabrilove J. L., Blasi M. V., Hill R. J., Glaspy J.: "Benefits of epoetin alfa in anemic breast cancer patients receiving chemotherapy". *Clin. Breast Cancer*, 2002, *3*, 45.
[55] Vogelzang N. J., Breitbart W., Cella D., Curt G. A., Groopman J. E., Horning S. J. *et al.*: "Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey". *Semin. Hematol.*, 1997, *34 (suppl. 2)*, 4.
[56] Cella D.: "The functional assessment of cancer therapy-anemia (FACT-An) scale: a new tool for the assessment of outcomes in cancer anemia and fatigue". *Semin. Hematol.*, 1997, *34 (suppl. 2)*,13.
[57] Caro J. J., Salas M., Ward A., Goss G.: "Anemia as an independent prognostic factor for survival in patient with cancer: a systematic, quantitative review". *Cancer*, 2001, *91*, 2214.
[58] Frommhold H., Guttenberger R., Henke M.: "The impact of blood haemoglobin content on the outcome of radiotherapy. The Freiburg experience". *Strahlenther. Onkol.*, 1998, *174 (suppl. 4)*, 31.
[59] Littlewood T. J., Bajetta E., Nortier J. W., Vercammen E., Rapoport B.: "Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results or a randomised, double-blind, placebo-controlled trial". *J. Clin. Oncol.*, 2001, *19*, 2865.
[60] Lawless G., Royalty M. W., Meyers J.: "Epoetin practice pattern usage in community practice". *Blood*, 2000, *96*, 390b (Abstract 5446).
[61] ISIS. Research conducted by ISIS Research Ltd. 2000. Data on file.
[62] Koeller J.: "Clinical guidelines for the treatment of cancer-related anaemia". *Pharmacother*, 1998, *18*, 156.
[63] Demetri G. D.: "Anaemia and its functional consequences in cancer patients: current challenges in management and prospects for improving therapy". *Br. J. Cancer*, 2001, *84 (suppl. 1)*, 31.
[64] Elliott S. G., Lorenzini T., Strickland T., Delorme E., Egrie J. C.: "Rational design of novel erythropoiesis stimulating protein (Aranesp™): a super-sialyted molecule with increased biological activity". *Blood*, 2000, *96*, 82a. Abstract 352.
[65] Egrie J. C., Browne J. K.: "Development and characterization of novel erythropoiesis stimulating protein (NESP)". *Br. J. Cancer*, 2001, *84 (suppl. 1)*, 3.
[66] Heatherington A., Schuller J., Dittrich C., Mercer A. J., Rossi G.: "Intravenous (IV) administration of darbepoetin alfa to patients with nonmyeloid malignancies receiving multicycle chemotherapy; pharmacokinetic profiles". *Proc. Am. Soc. Clin. Oncol.*, 2002, *21*, 256b (Abstract 2844).
[67] Macdougall I. C., Gray S. J., Elston O., Breen C., Jenkins B., Browne J. *et al.*: "Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients". *J. Am. Soc. Nephrol.*, 1999, *10*, 2392.
[68] Glaspy J. A., Jadeja J. S., Justice G., Kessler J., Richards D., Schwartzberg L. *et al.*: "Darbepoetin alfa given every 1 or 2 weeks alleviates anaemia associated with cancer chemotherapy". *Br. J. Cancer*, 2002, *87*, 268.
[69] Glaspy J. A., Tchekmedyian N. S.: "Darbepoetin alfa administered every 2 weeks alleviates anemia in cancer patients receiving chemotherapy". *Oncology*, 2002, *16 (suppl. 11)*, 23.
[70] Hedenus M., Hansen S., Taylor K., Arthur C., Emmerich B., Dewey C. *et al.*: "Randomized, dose-finding study of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies". *Br. J. Haematol.*, 2002, *119*, 79.
[71] Vansteenkiste J., Pirker R., Massuti B., Barata F., Font A., Fiegl M. *et al.*: "Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving cancer chemotherapy". *J. Natl. Cancer Inst.*, 2002, *94*, 1211.
[72] Kotasek D., Albertsson M., Mackey J., Berg R., Robinson J., Colowick A.: "Randomized, double-blind, placebo-controlled, dose-finding study of darbepoetin alfa administered once every 3 (Q3W) or 4 (Q4W) weeks in patients with solid tumours". *Proc. Am. Soc. Clin. Oncol.*, 2002, *21*, 356a (Abstract 1421).

[73] Smith R. E., Tchekmedyian S., Richards D., Klarnet J., Fleishman A., Gayko U. *et al.*: "Darbepoetin alfa effectively alleviates anemia in patients with chronic anemia of cancer; efficacy and pharmacokinetic results of a dose-escalation study". *Proc. Am. Soc. Clin. Oncol.*, 2002, *21*, 367a (Abstract 1465).
[74] Kallich J., Erder H., Glaspy J., Vansteenkiste J., Rossi G., Poulsen E. *et al.*: "Improvement in haemoglobin levels improves health-related quality of life (HRQOL) of anaemic cancer patients". *Hematol. J.*, 2001, *1 (suppl. 1)*, 185 (Abstract 688).
[75] Glaspy J., Jadeha J., Justice G., Fleishman A., Armstrong S., Colowick A.: "Optimizing the management of anemia in cancer patients: a randomised, active-controlled, study investigating the dosing of darbepoetin alfa". *Proc. Am. Soc. Clin. Oncol.*, 2002, *21*, 362a (Abstract 1446).

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