Review

Haematological toxicities associated with dose-intensive chemotherapy, the role for and use of recombinant growth factors

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Summary

High-dose chemotherapy is increasingly accepted as a treatment approach in a number of tumour types. However, there are controversies surrounding its efficacy and there is a need to consider its safety. In view of this, much effort has been directed towards the provision of adequate supportive care strategies to prevent toxicities and to ameliorate myelosuppression. Severe anaemia and its associated symptoms, for example, fatigue can have a debilitating effect on a patient's quality of life and often necessitates red blood cell transfusions. Erythropoietin, a glycoprotein hormone which stimulates red blood cell production, has been established for the treatment of anaemia in patients with chronic renal insufficiency. It is currently approved in most countries for treating anaemia associated with cancer, and its role is emerging especially in patients undergoing high-dose chemotherapy. This paper gives an overview of the studies conducted to date with epoetin alfa (recombinant human erythropoietin) in patients receiving allogeneic and autologous bone marrow transplants or peripheral blood stem cells in conjunction with high-dose chemotherapy. In addition, there are some novel clinical applications for epoetin alfa: for example, in delayed anaemia, as a supportive strategy prior to high-dose chemotherapy and as a synergistic enhancer of blood progenitor cell mobilisation in combination with granulocyte-colony-stimulating factor (G-CSF).

Key words: anaemia, epoetin alfa, high-dose chemotherapy, progenitor cell mobilisation, red blood cell transfusion

Introduction

The dose and schedule of chemotherapy are essential to treatment success. Pre-clinical and clinical trial data from studies treating a variety of tumour types support this view. For example, dose reductions of 20%, which are not infrequent in clinical oncology practice and are usually related to myelosuppression, can lead to a 50% reduction in cure rate. High-dose chemotherapy takes advantage of a theoretical dose-response relationship; its rationale being that by increasing the dose of chemotherapeutic agent, response rates will also be increased. The provision of adequate supportive care strategies (e.g., bone marrow transplant or peripheral blood stem cell support) to prevent haematological and non-haematological toxicities associated with high-dose chemotherapy is a major issue in defining the overall benefits of this approach to cancer therapy. In the past decade much research has been conducted into dose-intensification; however, its clinical benefits versus its risks still require confirmation through randomised trials before it can be considered for mainstream clinical practice.

In this setting, severe anaemia is a consequence of myelosuppression. The resulting fatigue can have a debilitating effect on the patient's quality of life. Furthermore, it often requires the use of packed red blood cell transfusions, adding to the burden of treatments the patient must endure. The need for and extent of red blood cell transfusion during the first 30 days after high-dose chemotherapy is variable, depending on the chemotherapy used, the underlying disease, whether bone marrow transplant was allogeneic or autologous or whether peripheral blood stem cell support was used [1]. As many as 30 units of red blood cells can be used within the first 30 days of treatment with high-dose chemotherapy, with an average of four units in patients with solid tumours.

The effect of high-dose chemotherapy on serum erythropoietin

Immediately after the administration of high-dose chemotherapy, bone marrow erythropoiesis shuts down for a period of one to two weeks. During these two weeks the erythropoietin levels become disproportionally high followed by a recovery in erythroid production. The initial increase in erythropoietin levels is independent of haemoglobin level, chemotherapeutic regimen or whether autologous or allogeneic bone marrow transplantation has been employed. By four weeks post-high-dose chemotherapy, circulating reticulocytes reappear (reaching 2% or more). However, the erythropoietin level may now fall and can remain disproportionately low for up to one year [2, 3]. In view of these observations, and the well established role of
Erythropoietin in stimulating committed erythroid precursors [4-6], studies were conducted to determine whether bone marrow transplant procedures affected erythropoietin levels.

In 31 patients undergoing bone marrow transplant (autologous, n = 14; allogeneic, n = 17), mean serum levels of erythropoietin peaked on day 7 post-high-dose chemotherapy and fell steadily thereafter [7]. There were no significant differences in average haematocrit levels between days 7 and 28 post-transplant (due to red blood cell transfusions), whereas the average serum erythropoietin levels decreased four-fold (P < 0.1) during the same period. Ireland et al. reported similar results from a longer-term study in which sequential changes in serum erythropoietin levels were measured over a period of 130 days in 17 patients receiving bone marrow transplant [8]. These authors noted that erythropoietin levels remained inappropriately low even after 14 days follow-up in patients receiving allogeneic support, whereas levels had returned to normal within 14 days post-transplant in those patients receiving autologous support. As a consequence, the red blood cell transfusions required were greater in the allogeneic group than in the autologous group (5.5 units per patient versus 1 unit per patient). These data suggest that there are differences in these two settings, and that anaemia in the allogeneic group may be more like the anaemia of chronic disease.

Epoetin alfa as a supportive strategy in bone marrow transplantation

Erythropoietin is a glycoprotein hormone crucial to the regulation of erythropoiesis; it stimulates red blood cell production by binding to receptors on erythroid progenitors [9]. The cloning of the erythropoietin gene [10, 11] has enabled production of recombinant human erythropoietin (epoetin alfa) in sufficient quantities for use in the clinical setting. Epoetin alfa has an established role in the treatment of anaemia associated with chronic renal failure, leading to its investigation in a number of other settings. The early findings in anaemia of chronic diseases, that serum erythropoietin levels are sometimes inadequate for the degree of anaemia, provided a rationale for clinical investigations into the use of epoetin alfa in patients receiving high-dose chemotherapy, particularly in the allogeneic bone marrow transplant setting. Positive results have been reported in randomised, placebo-controlled trials involving patients receiving allogeneic bone marrow transplants.

Steegman et al. conducted a single-centre, prospective, randomised, controlled study of epoetin alfa in 28 allogeneic bone marrow transplant patients; 16 with acute leukaemia and 12 with chronic myeloid leukaemia [12]. Of the 24 evaluable patients, 13 received epoetin alfa as a single bolus, intravenous injection (100 units/kg/day on days 0-7 and 150 units/kg/day on days 7-30) and 11 received placebo. Serum erythropoietin levels were significantly higher in the epoetin alfa group than in the control group on days 7, 14 and 21 after bone marrow transplantation. Red blood cell transfusion requirements were significantly lower in the epoetin alfa treatment group compared with the control group (4 units versus 12 units; P < 0.05).

Klaesson et al. randomised 50 patients with haematological malignancies undergoing allogeneic bone marrow transplantation to receive either epoetin alfa (200 units/kg/day; n = 25) or placebo (n = 25) [13]. During eight weeks’ follow-up there were no significant differences in the haemoglobin levels between the two groups, but the epoetin alfa group required only half as many red blood cell transfusions as the control group (epoetin alfa group five units/person; control group 10 units/person).

Having established the efficacy of epoetin alfa in the allogeneic setting, studies were carried out in patients receiving autologous bone marrow transplants. In one study, epoetin alfa (75 units/kg/day for 30 days) was given to patients receiving allogeneic transplants (n = 10) or autologous transplants (n = 10) and compared with historical controls [14]. As in other studies, there were significant differences in total red blood cell and platelet transfusion requirements in the allogeneic group - those patients receiving epoetin alfa required significantly fewer transfusions than the control group. However, there were no differences in the autologous group compared with controls (Table 1). Similar results have also been reported in two further studies investigating epoetin alfa in the autologous and allogeneic settings [15, 16]. These results indicate that epoetin alfa in the early post-transplant period appears to be of benefit only in patients receiving allogeneic bone marrow transplants.

Novel supportive care roles for epoetin alfa

Further studies have been carried out to investigate the effects of epoetin alfa in a number of other settings. In some patients who have anaemia post-transplant (either autologous or allogeneic), serum erythropoietin levels may remain reduced for up to one year, making them a potential target for clinical intervention.

| Abbreviations: BMT – bone marrow transplant; RBC – red blood cell; PLT – platelet, NS – not statistically significant. |  }

Table 1. The effect of epoetin alfa treatment on transfusion requirements in patients receiving either allogeneic or autologous bone marrow transplants [14].

<table>
<thead>
<tr>
<th>Allogeneic BMT patients</th>
<th>Epoetin alfa group</th>
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<table>
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suitable candidates for epoetin alfa treatment. Peliska et al., therefore, conducted a small study to assess the effects of epoetin alfa in 20 patients who had remained anaemic for more than 30 days after allogeneic or autologous transplantation [17]. Patients received epoetin alfa 150 units/kg three times a week for three weeks by subcutaneous injection, starting a median of 44 days post-transplant. The results revealed a response rate (defined as an increase of 1 g/dl in haemoglobin concentration) in 83% of patients. Furthermore, the best response was seen in those patients whose serum erythropoietin levels were lowest (88% of patients with pre-treatment erythropoietin levels < 50 mU/ml responded versus only 22% with levels > 50 mU/ml). These results suggest that delayed anaemia (> 30 days post-transplant) could be an appropriate indication for epoetin alfa.

Even though they may be ideal candidates for high-dose chemotherapy, some patients are unable to accept blood transfusions, for example, for religious reasons. Although Jehovah's witnesses allow stem cell transplantation, they typically do not receive this treatment because of their refusal to receive transfusions for haematologic toxicity. Our study group recently conducted a small trial to assess whether epoetin alfa given prior to high-dose chemotherapy would reduce red blood cell transfusion requirements and/or increase haemoglobin levels after peripheral blood stem cell transplant. Preliminary analysis of the study results has revealed that epoetin alfa 10,000 units s.c. given for seven days before and seven days after high-dose chemotherapy greatly reduced red blood cell transfusion requirements compared with controls. Patients receiving erythropoietin required a total of four units of red blood cells (average 0.57 units per person) versus 36 units (average of four units per person) in the control group, despite the average haemoglobin levels being comparable in both groups throughout the duration of the study (Figure 1).

These results in high-dose chemotherapy patients suggest two situations in which epoetin alfa could be of value: delayed anaemia and in patients unable to accept blood product transfusions. Further investigations are required to clarify these roles.

Epoetin alfa – synergistic role in blood progenitor cell mobilisation

Although the main target for erythropoietin is the committed erythroid progenitor cell [9], in vitro experiments have revealed that it may also have a multi-lineage effect [18–20] and that there may be a cooperative effect between erythropoietin and other growth factors in early progenitor cell proliferation and differentiation [21, 22]. These findings have been confirmed in the clinical setting; several studies have reported increases in circulating colony-forming units – granulocyte macrophage (CFU-GM) and bone marrow megakaryocytes in haemodialysis patients receiving epoetin alfa [5, 23, 24]. On the strength of these results, Oliveri et al. assessed the effectiveness of epoetin alfa plus G-CSF versus G-CSF alone to enhance blood progenitor cell mobilisation after high-dose chemotherapy [25]. Thirty-four patients underwent priming chemotherapy followed by either G-CSF 5 µg/kg/day (n = 18) or G-CSF 5 µg/kg/day plus epoetin alfa 50 units/kg/day (n = 16). There were no differences between groups in the main clinical characteristics thought to affect blood progenitor cell mobilisation (previous chemotherapy, time span between chemotherapy and priming, diagnosis, bone marrow involvement and age). The combination of epoetin alfa plus G-CSF was significantly more effective than G-CSF alone in stimulating the mobilisation of progenitor cells and CD34 cells (Figure 2). Furthermore, apheresis collections gave significantly better yields for total progenitor cells/kg for the epoetin alfa plus G-CSF group compared with the G-CSF only group. These findings suggest that epoetin alfa has a synergistic activity with G-CSF in the mobilisation of haematopoietic progenitor cells. These investigators are currently conducting a controlled, prospective randomised study to confirm their findings. This and other investigations are required to establish the clinical relevance of these results in terms of reduction in red blood
cell transfusions post-high-dose chemotherapy. Results from studies in breast cancer patients treated with accelerated cyclophosphamide, epirubicin and 5-fluorouracil adjuvant therapy support these findings. When patients were treated with epoetin alfa (150 units/kg; three times a week) they did not develop significant anaemia and required no blood transfusions [26]. Furthermore, patients receiving GM-CSF plus epoetin alfa showed less anaemia and thrombocytopenia than patients receiving only GM-CSF [27].

Conclusion

The data available to date suggest that epoetin alfa has a role in the support of patients receiving bone marrow transplantation. In the allogeneic setting, epoetin alfa is of value in preventing or reducing the anticipated anaemia and red blood cell transfusion requirements. It can contribute to a patient’s quality of life by reducing the degree of anaemia and the need for blood transfusions. In addition, epoetin alfa may have other roles, such as in delayed anaemia (> 30 days) post-transplant, stem cell mobilisation, or prior to high-dose chemotherapy; however, these indications require further investigation before their value can be fully defined.

References


