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Reduction of Infection Rates in Cancer Patients Associated With the Use of Haematopoietic Growth Factors

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As the risk of infection associated with chemotherapy is related to the depth of the fall in neutrophil counts, protection from neutropenia has been used as an endpoint for growth factors in this setting. However, the functional status of these and other myeloid cells are also important. Therefore, more direct measurements of clinical improvement will also be useful. Several studies have suggested that the use of granulocyte-macrophage colony-stimulating factor (GM-CSF) can result in improvements in hospital stay, days of fever, antibiotic use and thrombocytopenia. Similar findings have been confirmed by our own work which indicates that GM-CSF not only shortens the period of leukopenia, but also reduces the complications of infection. More sensitive and appropriate endpoints should be included in future trials, including rate of and survival from infection as well as overall and disease-free survival.
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INTRODUCTION

THERE HAVE been few clinical studies which have been designed specifically to evaluate the effects of varying dose intensity on response and survival [1]. However, the use of high-dose regimens has been associated with a statistically significant survival advantage in three randomised clinical trials, in acute lymphocytic leukaemia in children [2], in small-cell carcinoma of the lung [3] and in testicular cancer [4]. In a randomised trial in patients with metastatic breast cancer higher response rates and better palliation were achieved by using full-dose chemotherapy [5]. Also, in trials using high-dose chemotherapy with bone marrow support, relatively high response rates and prolonged disease-free survival have been reported in patients with malignant lymphoma [6], breast cancer [7] and testicular cancer [8]. Finally, a number of retrospective analyses have suggested a positive correlation between dose-intensity and treatment outcome in a number of human malignancies [9].

Thus, although increased dose or dose intensity of chemotherapy may not always improve clinical response, it is likely that in certain cancers these factors may be correlated with response, degree of palliation and possibly survival. In most cases the major dose-limiting toxic effect of chemotherapeutic regimens is myelosuppression. Therefore, the ability to reduce the severity and duration of drug-induced pancytopenia has considerable potential to affect the prospects of high-dose chemotherapy and chemoradiotherapy. For curative approaches this has curtailed attempts to maintain the dose and schedule of therapy or to apply more agressive regimens to improve survival. The abrogation of side effects in essentially palliative regimens is also important if the rationale for such treatment is to be preserved.

Bone marrow transplantation (BMT) (autologous, syngeneic and allogenic) has allowed the use of more intensive myeloablative therapies [10]. Infection-related morbidity and mortality, however, are high during the period of haematopoietic reconstitution [11]. Bone marrow recovery after allogenic BMT is generally faster than after autologous BMT (ABMT) but the occurrence of acute graft-versus-host disease (GVHD) is a major limitation [12]. T-cell depletion effectively reduces the incidence of severe forms of acute GVHD [13] but it may be associated with slower marrow recovery and more opportunistic infections [14].

A second technique now being employed, either alone or in combination with BMT, to promote haematopoietic recovery after myeloablative therapy is the autografting of peripheral blood stem cells (PBSCs) or progenitors, which have been harvested by leukapheresis before chemotherapy. It has been reported that these cells generally induce a faster haematopoietic recovery than bone marrow autografts [15]. A third possible approach to limiting the severity and duration of drug-induced myelosuppression is the use of haematopoietic growth factors, either alone or in combination with bone marrow or PBSC reinfusion of PBSC.

USE OF GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR IN CANCER

Appropriate endpoints

Studies addressing the myelotoxicity of cancer chemotherapy have demonstrated a consistently beneficial effect of granulocyte-macrophage colony-stimulating factor (GM-CSF) on the severity and duration of neutropenia [16, 17]. GM-CSF has also been shown to significantly increase the yields of peripheral blood progenitors when given prior to leukapheresis [18, 19]. When given after BMT, GM-CSF has resulted in significantly faster recovery of leucocyte and neutrophil counts and lower use of systemic antibiotics compared with BMT alone [20].

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The neutropenia experienced by patients shortly after cytotoxic therapy often results in bacterial and secondary fungal infections which are a major cause of morbidity and may be fatal [17]. As the risk of infection, fever and sepsis associated with chemotherapy are related to the depth and duration of the nadir in neutrophil counts, protection from neutropenia has been employed as an endpoint for the efficacy of myeloid growth factors in this setting. However, the functional status of the restored neutrophils will also be important, as will the role they play within the network of adequate humoral, cellular and antibody-mediated immune responses. Furthermore the function and number of other myeloid cells may also be important in controlling infection. Therefore, while a measure of absolute neutrophil count may be useful, more direct measures of clinical improvement are also important. The management of febrile neutropenic patients is costly because of the prolonged hospitalisation and intravenous antibiotic therapy required. Restoration of cellular mechanisms of host defence might be expected to improve the response to other therapeutic measures and in the setting of infection, due to chemotherapy-induced neutropenia endpoints such as use of antibiotics, days of hospitalisation and periods of neutropenic fever should be considered.

Consideration of the biological profile of GM-CSF provides an illustration of this point. While there is good clinical evidence that GM-CSF can safely and effectively restore the neutrophil count after various chemotherapy regimens, the direct effects of this molecule on other cells and through the secondary release of other cytokines, suggests that GM-CSF may provide greater clinical benefit than would be achieved by simply restoring the number of neutrophils (see T. Jones pages S10-S13).

Early dose-ranging trials have provided firm evidence that GM-CSF can promote recovery of cell counts after chemotherapy [21, 22]. However, some of these studies have also given preliminary indications of other benefits. Antman and colleagues achieved an improved tumour response rate of 79% compared with 52% in a previous study [21]. In a study by Herrmann and others, the duration of hospital stay and the requirement for parenteral antibiotics were also reduced [23]. Ho *et al.* have reported shorter periods of thrombocytopenia (from 7 to 3 days) with reduced rates of infection and stomatitis [24]. Steward *et al.* have been able to attenuate the duration of thrombocytopenia and neutropenia induced by melphalan (120 mg/m^2), to times at least as short as those reported in a historical series receiving ABMT [25, 26].

We have conducted a phase II trial of 60 patients randomised to receive GM-CSF (2-32 μg/kg equivalent to glycosylated drug) or placebo for chemotherapy-induced neutropenia [27]. This study has been reported elsewhere but, briefly, rhGM-CSF (CHO-fully glycosylated) was given for 5 days by either continuous intravenous infusion (20 patients) or twice daily by subcutaneous (s.c.) injections (20 patients). A third group received rhGM-CSF (*E. Coli* non-glycosylated) by s.c. injections once a day (20 patients) .

This study showed that while low doses given for 5 days were sufficient to enhance leucocyte recovery in some patients, a clear dose-response relationship existed with higher doses (Fig. 1). The increase in white blood cell (WBC) count derived mainly from neutrophils, but the recovery of monocytes and eosinophils was also significantly enhanced, although to a lesser degree. No consistent difference was seen with respect to platelet recovery, reticulocyte counts, or the recovery of basophils and lymphocytes. These findings compare well with

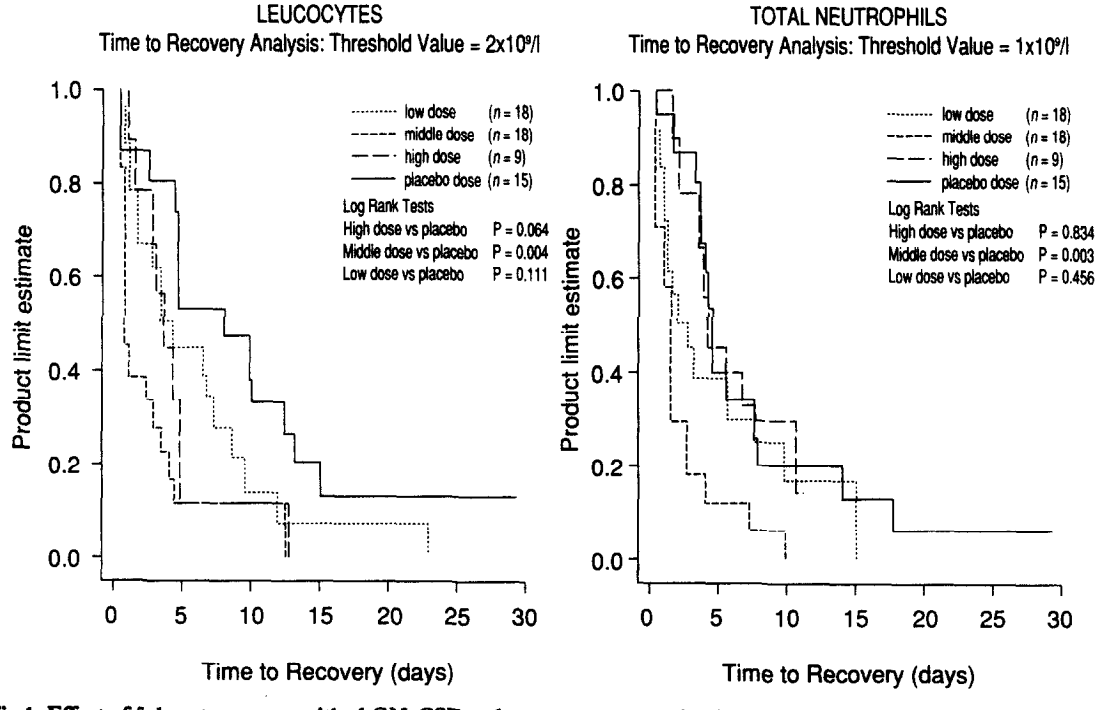

Fig 1. Effect of 5 days treatment with rhGM-CSF on leucocyte recovery in chemotherapy-induced leucopenia. Pooled low, middle and high-dose groups of rhGM-CSF and pooled placebo groups. Low: 1.3, 2.7 μg, Middle: 5.5, 11 μg, High: 22 μg protein per kg body weight per day.

other studies of chemotherapy-induced neutropenia, without placebo controls, using either rhGM-CSF [21] or rhG-CSF [28]. Placebo-controlled trials conducted in small cell lung cancer [29], febrile neutropenia [30], relapsed or refractory acute leukaemia [31] and ABMT [32], gave similar results with respect to neutrophil recovery.

Whether the increase in absolute neutrophil count (ANC) is accompanied by clinical benefit is less clear. However, although the numbers are relatively low, analysis of some of the secondary parameters described earlier do provide an indication that this is so. In the group given *E. coli*-derived rhGM-CSF significantly ($P < 0.001$) fewer days of antibiotic use (mean 1.1 range 0-7 vs. 8.0 days range 0-20) and fever were experienced compared with controls. Similar although non-significant trends were obtained in the groups receiving CHO derived GM-CSF. While these data suggest that rhGM-CSF helped to prevent complications of infection, the design of the study does not allow definite conclusions to be drawn.

SUMMARY

The data presented in this review indicate that rhGM-CSF shortens the period of leukopenia following chemotherapy and suggests that the course of infections may be modified. Similar observations have been made by others in some cases of cyclic neutropenia [33] and neutropenia following a radiation accident [34]. This accumulating clinical experience with rhGM-CSF suggests that it is an effective drug and makes it difficult to withhold this treatment from patients suffering life-threatening infections during periods of severe neutropenia. However, the design of clinical studies of growth factors should bear in mind their full repertoire of biological effects and the status of host-defence network within which they will operate. These may indicate potential benefits other than numerical increases in cell counts. By anticipating and monitoring potentially beneficial effects, it may be possible to exploit these in future trials, especially where combinations with cytokines (such as interleukins) or other agents (antibacterial, antifungal, antitumour) are considered. A more practical and perhaps sensitive range of endpoints are also required if such opportunities are to be identified. As candidates for such trials may already be aggressively treated with antibiotics and antifungal agents more sophisticated and ingenious study designs will be required.

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