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Original Paper

GM-CSF in Haematopoietic Stem Cell Transplantation

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AFTER HEMATOPOIETIC stem cell transplantation (SCT) patients are exposed to a pancytopenia of an average 2–3 weeks duration. This period is accompanied by morbidity, due to infections and bleedings with a risk of mortality. The goals of using recombinant human granulocyte macrophage-colony stimulating factor (rhGM-CSF) after hematopoietic SCT may be 2-fold: a faster neutrophil recovery would hopefully be associated with less infections, less antibiotic use, shorter stay in hospital and costs reduction. Furthermore effects on immune recovery may be anticipated, leading to less infections and a higher graft versus leukaemia effect.

AUTOLOGOUS BONE MARROW TRANSPLANTATION

Randomised studies [1–6] demonstrated that administration of rhGM-CSF after autologous bone marrow transplantation (ABMT) shortened the duration of granulocytopenia by approximately 4–10 days compared with placebo. Apart from enhancing neutrophil recovery, rhGM-CSF has also been shown to favour CD4 regeneration after ABMT without effects on NK and B cell recovery [8]. A review of the literature on this subject [7] reveals that only three phase III placebo controlled studies in patients undergoing an ABMT [1–3] showed a reduced incidence of documented infections in rhGM-CSF treated patients. In most studies the reduction in duration of granulocytopenia was accompanied by a significant reduction in hospital stay and/or of duration of antibiotic use. Furthermore, Nemunaitis [1] reported statistically fewer infections in 65 patients with lymphoid malignancies receiving GM-CSF after ABMT compared with 63 placebo treated patients (17 versus 30%). Similarly, Link and colleagues [2] observed infectious events in 46% of patients treated with rhGM-CSF in comparison with 70% in the placebo group. Most other studies on this subject have not corroborated these findings. Moreover, none of the phase III studies could establish a lower treatment-related mortality, a reduction in non-myeloid toxicity, an enhanced tumour response nor a prolonged survival for the rhGM-CSF treated patients.

The reason for the apparent discrepancy between the positive effect of rhGM-CSF on granulocyte recovery and objective clinical benefits such as a reduction in the incidence of documented infections remains ambiguous in most studies. Several factors might be held responsible for the apparent lack of clinical benefit, and other factors may obscure clinical efficacy. One of the reasons may be that hard endpoints, i.e. documented infections, were not carefully monitored in the reported studies. Secondly, infections after ABMT are most likely to occur during the time period when absolute neutrophil counts (ANC) are $<100/\mu l$. Khwaja [5] showed that 96% of positive blood cultures occurred during the period when ANC was $<100/\mu l$ after ABMT. rhGM-CSF has no major impact on the duration of the episode of very severe granulocytopenia ($ANC<100/\mu l$) [1, 5, 9] rhGM-CSF does not promote early engraftment, but rather accelerates myelopoiesis once it is initially established, causing a more rapid rise of the neutrophils after a period of severe neutropenia. Thirdly, granulocytopenia is not the only reason that patients treated with chemotherapy and radiotherapy are prone to infections. Other factors, such as mucosal damage, the use of indwelling intravascular catheters, of antibacterials and of immunosuppressive drugs, enhance the risk of infections. In a subgroup of patients with a high risk of fungal infections, the use of rhGM-CSF is attractive from a theoretical point of view, since the risk for fungal infections increases with prolonged neutropenia [10]. It is known that antifungal therapy is more effective after recovery of the neutropenia.

In conclusion, it is questionable whether rhGM-CSF administration in all patients who are treated with high-dose therapy plus ABMT is truly cost saving, taking into consideration that the incidence of documented infections was not reduced in the vast majority of studies. The administration of rhGM-CSF seems to be indicated in those patients at high risk of prolonged neutropenia, e.g. with a duration of at least 3 weeks. Finally, it should of course be noted that there is an increasing use of autologous mobilised blood with its associated clinical benefits, in preference to bone marrow as a source of stem cells.

AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION

Peripheral blood stem cell (PBSC) collections have almost completely replaced bone marrow stem cell (BMSC) harvests because of the perceived advantages of more rapid engraftment with less tumour contamination in the inoculum. Spitzer [11] has shown that administration of a combination of recombinant human granulocyte-colony stimulating factor (rhG-CSF) and rhGM-CSF after PBSC infusion shortens

the duration of granulocytopenia by several days, but it has no influence on the duration of thrombocytopenia. Furthermore, clinical variables of febrile days, septic episodes and transfusion requirements were similar between study arms. Similarly, in another phase III double-blind placebo controlled randomised trial [12] the administration of rhGM-CSF in patients transplanted with rhGM-CSF-mobilised PBPC failed to demonstrate a clinical benefit in terms of tempo of engraftment, numbers of documented infections, transfusion requirements and mucositis grading. Therefore, the clinical benefit of HGF administration after PBSCT has not been demonstrated and may depend on individual clinical circumstances.

ALLOGENEIC BONE MARROW TRANSPLANTATION

Allogeneic bone marrow transplantation (BMT) involves infusion of donor marrow into a host whose own marrow has been preconditioned by myeloablative therapy. Graft-versus-host disease and graft failure due to regrowth of immunocompetent host lymphocytes which react against non-shared histocompatibility antigens expressed on donor cells are a theoretical concern when using rhGM-CSF to stimulate progenitor cell growth and differentiation. T cell depletion effectively reduced the incidence of severe forms of acute graft-versus-host disease (GVHD) after BMT, but is associated with a higher incidence of immunologically mediated rejection, a slower engraftment and a higher incidence of opportunistic infections. In an attempt to identify factors associated with graft failure, or death due to infection, haemorrhage or graft failure in 712 patients undergoing BMT, a leucocyte count of below 0.2×10^9/l was the most powerful predictor of graft failure or death [13]. Therefore, delay in hematological recovery after BMT may extend and amplify the risks of infection and haemorrhage, compromise patients' survival, and increase the duration and costs of hospitalisation. RhGM-CSF after BMT improves and accelerates engraftment of neutrophils and monocytes. Furthermore, rhGM-CSF may affect NK activity by counteracting the suppressing effects of monocytes [14], and hence improve the outcome after BMT. In the setting of T cell depleted grafts, administration of rhGM-CSF may counterbalance some of its negative consequences.

Only a few placebo-controlled randomised trials have investigated the use of rhGM-CSF in the setting of BMT [15, 16]. In a multicentre, double-blind randomised study involving 57 patients with leukaemia, aplastic anaemia or multiple myeloma receiving T cell depleted marrow from an HLA-identical sibling were enrolled [15]. Compared with placebo, rhGM-CSF accelerated leucocyte and neutrophil recovery significantly. The incidence of GVHD and transplant-related mortality were not different in both groups. However, the number of bronchopneumonias was significantly lower in the rhGM-CSF-treated group ($P=0.03$). Furthermore, the number of days on systemic antibiotics was 14 days in the rhGM-CSF group and 20 days in the control group in the centre with 30 evaluable patients ($P=0.03$). Side-effects were manageable and consisted of fever, myalgias and fluid retention. A second double-blind, placebo-controlled trial involving 40 patients with leukaemia confirmed that rhGM-CSF accelerated neutrophil recovery after BMT. This study did not report significant clinical benefits [16]. Antibiotic use was significantly greater in the rhGM-CSF group, which was attributed to the policy of using empirical antibiotics in patients with fever, a recognised side-effect of rhGM-CSF. Long-term follow-up showed that the administration of rhGM-CSF did not appear to be associated with an increased incidence of chronic GVHD or relapse [17].

As the multicentre study showed a trend to a lower relapse rate in the rhGM-CSF treated patients, the efficacy and safety of prolonged administration after T cell depleted BMT was further investigated but only preliminary results of this study have been published [18]. Low-doses of rhGM-CSF were needed to maintain leucocyte counts above 10×10^9/l.

In conclusion, current available data do not indicate a standard role for rhGM-CSF administration after BMT. rhGM-CSF may be considered in patients with bone marrow failure [19] and/or pulmonary infection. The role of rhGM-CSF role should be further explored; in particular prolonged GM-CSF treatment may contribute to our understanding of the role of rhGM-CSF to prevent infections and relapse after BMT.

ALLOGENEIC PERIPHERAL BLOOD STEM CELL TRANSPLANTATION

The use of rhGM-CSF following allogeneic peripheral blood stem cell transplantation may be of interest, but no data are available on its use in controlled clinical trials.

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