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Future outlook for growth factors

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In the future improvements in the efficacy and safety profiles of the various growth factors in clinical use should be achievable through optimization of dosage schedules. The use of combinations of growth factors to provide hemopoietic support should enable considerable advances to be made in the treatment of hematological and non-hematological malignancies. Growth factors, such as granulocyte-macrophage colony stimulating factor may be used not only to maximize neutrophil recovery after myeloablative therapy, but also to mobilize peripheral blood stem cells prior to harvesting by leukapheresis. Growth inhibitory cytokines such as transforming growth factor-β and macrophage inflammatory protein-1α may be used to protect normal cells in the bone marrow and other sites where dose-limiting toxicities occur. Therefore, in the next few years, the whole approach to chemoradiotherapy will need to be reconsidered in the light of the dose intensification made possible by improved bone marrow support techniques and advances in other areas of supportive care.

Key words: Granulocyte-macrophage colony stimulating factor, growth-inhibitory cytokines, hemopoietic support, high-dose chemotherapy, peripheral blood stem cell rescue.

Introduction

In the future, optimization of dosage schedules for growth factors should result in improvements in their efficacy and safety profiles. This should enable considerable therapeutic advances to be achieved using appropriate combinations of growth factors to provide hemopoietic support. A number of key issues are likely to be addressed. The maximization of neutrophil and platelet recovery will be important goals, and the protection not only of normal bone marrow stem cells, but also the cells of the gastrointestinal tract, the lungs and other sites where dose-limiting toxicities occur, will also be a priority. Peripheral blood stem cell (PBSC) rescue has been shown to produce reliable hematopoietic reconstitution following myeloablative therapy, and it seems likely that it will replace autologous bone marrow transplantation (ABMT) in the future. Growth factors, such as granulocyte-macrophage colony stimulating factor (GM-CSF), may be used to mobilize PBSCs prior to harvesting by leukapheresis. The whole approach to chemo-radiotherapy will need to be reconsidered in the light of the availability of improved bone marrow support and advances in supportive care. The use of high-dose therapy will also need to be rationalized and treatment regimens will require simplification if they are to be used routinely and safely for the treatment of common tumours, without the need for specialized bone marrow transplantation facilities.

Maximization of neutrophil recovery

A study reported by Cebon *et al.*[1] showed that the variables which correlated with the hematological response to GM-CSF, dose, area under curve (AUC) and time >1 ng/ml, differed from those associated with toxic effects (C_{max} and intravenous administration; Figure 1). Thus, for maximal response, GM-CSF should be given in such a way that the cells are exposed to a concentration of not less than 1 ng/ml for a prolonged period of time. Subcutaneous administration, which effectively produces a gradually released depot, was found to be more effective and was associated with less toxicity than intravenous bolus injections or short (2 h) intravenous infusions. This supports the findings of an earlier study by Lieschke *et al.*[2] which reported that subcutaneous administration or continuous intravenous infusions of GM-CSF were more potent, and generally preferable to short intravenous infusions, and that GM-CSF was an ineffective stimulant of leukopoiesis when given as a bolus injection. By manipulation of the dose, route and dose frequency it may be possible to design more optimal therapeutic schedules for GM-CSF.

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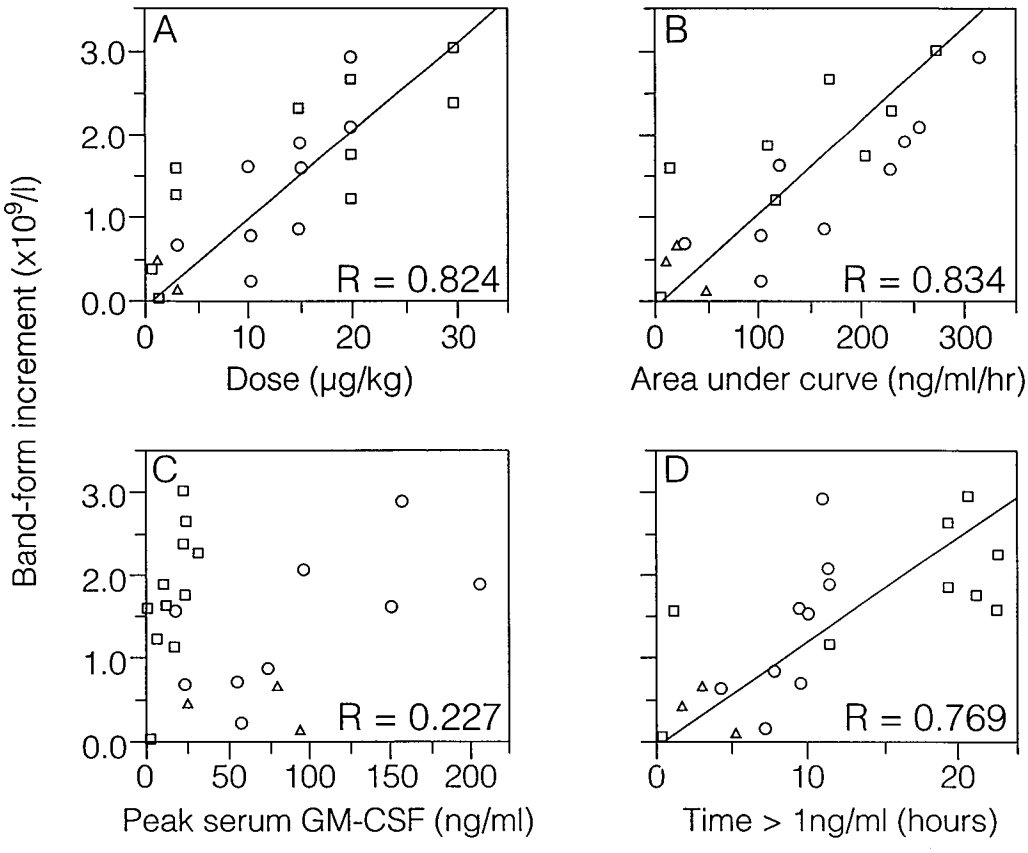

Figure 1. The relationship between the band-form increment, dose and pharmacokinetic variables and the method of GM-CSF administration. (A) The relationship between GM-CSF dose and 24 h band form increment; (B) The relationship between AUC and 24 h band form increment; (C) The relationship between C_{max} and 24 h band form increment. The *R*-value refers to all patients without separation on the basis of route of GM-CSF administration; (D) The relationship between time >1 ng/ml and 24 h band-form increment. Symbols denote the different routes of GM-CSF administration: □, s.c.; △, i.v. bolus injection; ○, short i.v. infusion. Patients with marrow infiltration by tumor and neutropenia have been excluded.

Mobilization of peripheral blood stem cells

PBSC rescue is probably the most rapidly growing area for use of growth factors. While ABMT is still the most commonly used method for bone marrow rescue following myeloablative therapy. Infusion of PBSCs has also been shown to produce reliable and durable hematopoietic reconstitution.[3–6] PBSCs may also be given repeatedly to support patients, so that they can then be given high-dose intensity treatments with less risk of severe toxicity. PBSCs may be harvested prior to treatment and then given after each course of dose intensive chemotherapy or after myeloablative treatment. The period of neutropenia and of thrombocytopenia, the number of platelet transfusions required, the number of days of hospitalization, and the antibiotic usage are reduced with the use of PBSCs (personal observation). Growth factors, such as GM-CSF, post-chemotherapy are essential for mobilization of sufficient PBSC to limit the harvest to one leukapheresis.

A recent study, reported by Elias *et al.*[7], demonstrated that GM-CSF-mobilized PBSCs provided rapid and sustained reconstitution of all cell lineages, following high-dose chemotherapy for breast cancer, in the majority of the patients studied. Recovery of granulocytes to $\geq 500/\mu l$ was observed on a median of day 14 (range 8–57), and transfusion independence (i.e. platelets to $\geq 20{,}000/\mu l$) occurred on a median of day 12 (range 8–134; Figure 2). Autologous PBSC rescue is an attractive alternative to ABMT for hematopoietic support after high-dose therapy, and it is likely to replace ABMT in the future.

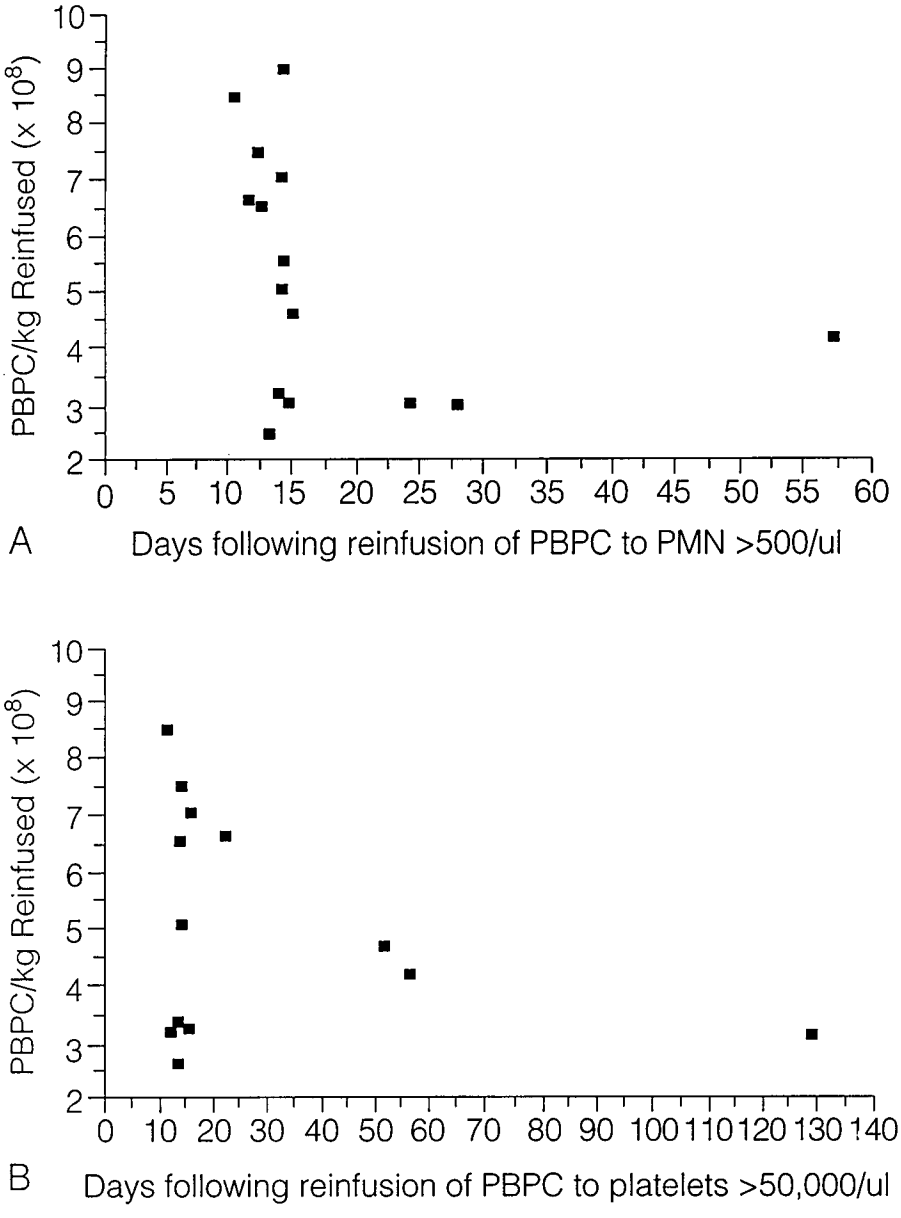

Figure 2. The dose of PBPCs per kilogram does not correlate with time to granulocyte (A) or platelet (B) recovery, but a threshold phenomenon may exist. The arrow in (B) indicates a patient who recovered >20 000/μl platelets by day +13, developed antiplatelet antibodies, and subsequently received bone marrow on day +136.

At present, autologous PBSC rescue represents the gold standard for recovery from intensive chemoradiotherapy, against which new potential treatments should be compared. In general, it is likely that combinations of two or more cytokines, rather than single agents, will provide the most effective hemopoietic support. For example, IL-3 alone produces a prompt effective recovery of platelet levels but has very little effect on white blood cells. However, if IL-3 is given for 4 days and then followed by a low dose of GM-CSF (1 μg/kg), a prompt increase in white cell counts is seen (personal observation).

Growth-inhibitory cytokines

It has been shown that growth factors can be used to improve the safety of chemoradiotherapy treatment regimens by increasing the rate of

recovery of neutrophil and platelet counts after treatment and after ABMT and PBSC rescue. However, cytokines can also be used to protect normal stem cells from the damaging effects of cytotoxic therapy. The bowel is often the site of limiting toxicity and patients who have received PBSC rescue may show hemopoietic recovery just 12 days after PBSC infusion but they may require hospitalization for several additional days due to poor nutritional status, resulting from severe diarrhea and stomatitis, which may prevent them from eating. Transforming growth factor (TGF-β) and macrophage inflammatory protein-1 (MIP-1α) are examples of growth-inhibitory cytokines. TGF-β inhibits the growth of stem cells in the bowel as well as in the bone marrow and could be used to stop these cells from cycling, thus protecting them from cycle-specific cytotoxic treatments, and allowing faster rates of recovery.

High-dose chemotherapy

The use of growth-stimulatory and growth-inhibitory cytokines should enable higher, and hopefully more effective, doses of chemotherapy to be given with greater safety. However, the use of high-dose chemotherapy requires careful consideration and regimens may need to be redesigned to take into account the pharmacokinetics of the agents involved. Considering, for example, the pharmacokinetics of carmustine (BCNU); the AUC can vary 10- to 20-fold, resulting in toxicity in some patients and less than optimal response in others. It may, therefore, be prudent to titrate the doses of the drugs used in each patient individually. The timing of administration of different chemotherapeutic agents is also important. Research involving the DNA repair enzyme, O^6-alkylguanine-DNA alkyltransferase, has shown that the time between administration of cyclophosphamide and BCNU is critical as far as DNA repair is concerned.[8] If high-dose therapy is to be used, it should be given at the optimal dose intensity and it should be given safely, utilizing appropriate rescue techniques as indicated. As for conventional treatments, high-dose chemotherapy should be carefully evaluated in each indication for non-additive toxicity and non-cross resistance and also for a steep dose–response curve (to maximize the difference between high and standard doses). It is not appropriate to simply assume that a regimen which is effective and safe when used to treat acute leukemia will have an identical profile of effects in patients with other malignancies.

Techniques which have been developed for use in patients with hematological malignancies may be employed in other areas of oncology. Antman *et al.*[9] achieved a 6-fold increase in the dose of chemotherapy in patients with advanced metastatic breast cancer, using autologous bone marrow support. This major dose escalation was achieved safely and a high response rate was seen in this group of patients with a very poor prognosis, who might normally have been 'written off'. Twenty-seven percent progression-free survival was seen after 2–4 years, a rate similar to that seen in acute myeloid leukemia, a condition which is generally treated aggressively, with intent to cure. In the future it may be possible to utilize other hematological treatment breakthroughs in patients with non-hematological malignancies.

Is autologous bone marrow support feasible on an out-patient basis?

While the use of ABMT is unlikely be possible on an out-patient basis, PBSC rescue may be feasible in this setting. A sufficient number of PBSCs must be available for collection and one could not, therefore, expect to collect PBSC after bone marrow damaging treatments such as widefield radiotherapy, melphalan or busulphan. Ideally one would like to be able to mobilize sufficient PBSCs that one or two pints of blood would be sufficient for reconstitution, thus avoiding the need for leukapheresis. If the preparative regimen could be given and cleared in 48 h the necessity for freezing the cells, with its associated cost, would be unnecessary. While this is not yet achievable, the use of combinations of growth factors may help to maximize the release of PBSCs and facilitate their collection. If a patient has insufficient autologous stem cells and no family donor, human umbilical cord blood may provide an alternative source of stem and progenitor cells for transplantation. Data from a recently published study by Broxmeyer *et al.*[10] suggests that there may be sufficient cells in a single cord blood collection to engraft the hemopoietic system of an adult.

Conclusion

During the last 5 years considerable research has been carried out into the actions and potential uses

of various growth factors. In addition to their well documented beneficial effects on hematopoietic recovery following myelotoxic chemotherapy, growth factors, such as GM-CSF can also be used to mobilize PBSCs prior to harvesting by leukapheresis, and this is possibly the most rapidly growing area for the use of growth factors. In the next 5 years the benefits of this research should be seen in terms of more effective and safer use of high-dose intensity chemoradiotherapy regimens for the treatment of hematological and non-hematological malignancies.

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