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News: Reports of an ESO Task Force on Growth Factors

(Further reports from this task force will be published in future issues)

Haematopoietic Growth Factors in Clinical Medicine

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INTRODUCTION

HUMAN HAEMATOPOIETIC growth factors (HGFs) have now entered the clinical setting, and have provided invaluable help in treating a number of hitherto unresolved therapeutic problems [1–3]. At the same time, recombinant DNA technology has emerged as a safe and economic way of producing a new generation of drugs. Now that the first general benefits of this group of therapeutic agents have been well established, physicians can deal with the considerable number of issues involved in refining the use of these drugs.

THERAPEUTIC AIMS

An outline of the principle aims for the clinical use of HGFs in patients is given in Table 1. One of the most frequent clinical problems addressed worldwide is the improvement in chemotherapy-related cytopenias. Within a short period of time, the use of HGFs has led to a markedly reduced incidence of neutropenia-related complications, e.g. bacterial infection, in a large variety of different malignancies [4]. At the same time, the number of platelet transfusions required has decreased, and in many cases, the average duration of hospitalisation has been shortened. This has been mainly achieved by the use of the colony-stimulating factors (CSFs): recombinant human granulocyte CSF (rHuG-CSF), recombinant human granulocyte–macrophage CSF (rHuGM-CSF), multi-CSF/interleukin 3 (IL-3) and erythropoietin (EPO).

These factors have also allowed clinical trials using dose-escalated chemotherapy to be conducted, regimens that would, without the use of CSFs, be beyond acceptable levels of bone marrow toxicity. The possibility of the therapeutic benefit of dose-intensified chemotherapy has been demonstrated in terms of tumour response for certain diagnoses. However, the use of CSFs in dose-escalated chemotherapy requires further detailed therapeutic evaluation.

Table 1. Principle aims for the clinical use of HGFs

I	Mitigate cancer and chemotherapy-related side-effects
II	Augment non-specific mechanisms of host resistance in order to strengthen antitumour responses
III	Reduce toxicity to enable the use of higher doses of chemotherapy
IV	Influence constitutional defects in haematopoiesis
V	Facilitate and improve stem cell transplantation

Another important use of HGFs has evolved in transplantation of human haematopoietic stem cells. CSFs have generally proven to be capable of mobilising haematopoietic stem cells into peripheral blood to a degree that makes collection and use for transplantation safe and economically attractive. In bone marrow, and possibly also in peripheral stem cell transplantation, engraftment can be improved by application of CSFs. Interestingly, autologous transplantation of peripheral blood stem cells resulted in earlier engraftment and shorter platelet and neutrophil nadirs compared to classical autologous bone marrow transplantation in several clinical trials [5, 6].

Other than overcoming therapy-related toxicity, there are a number of clinical conditions involving constitutively subnormal haematopoieses, where, based upon current data, CSFs will have a substantial role. These include the congenital cytopenias [7], AIDS, myelodysplastic syndromes (MDS) and preleukaemias. In terms of numbers of patients, treatment of EPO-responsive anaemias is certainly one of the most valuable achievements of HGF use in clinical medicine.

Thirdly, induction of cell differentiation is an area requiring further definition of the therapeutic potential of HGFs. Although CSFs are already under investigation in myelodysplastic disorders and acute leukaemias, the effects of these factors on the differentiation status of the haematopoietic cells need to be critically studied before arriving at general criteria for the use of CSFs in these disease entities.

Lastly, improvement of effector function may prove to be an important principle in CSF application in patients. In addition to congenital functional defects of leucocytes, AIDS and infection are conditions where HGFs have already been shown to be beneficial.

APPLICATION SCHEMES

Whereas the preceeding text states the need for more phase III and IV studies, the use of cytokine combinations has not yet reached satisfactory phase I and II evaluation. G-CSF and

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EPO gave encouraging results in AIDS patients treated with zidovudine and in patients with MDS [8]. When applied in a sequential fashion, IL-3 and GM-CSF were able to recruit peripheral blood progenitors in a highly synergistic fashion compared to single agents [9]. Acceleration of platelet recovery has remained a constant cause of concern with all CSFs used so far. Here a combination of thrombopoietic factors such as IL-6, with the more "classic" CSFs may be of particular interest. Also, factors such as stem cell factor (SCF), IL-1 or IL-3 as early acting factors with megakaryocyte colony-stimulating activities, should be combined with IL-6 or IL-11 as factors acting on later stages of megakaryopoieses, offering another important area for further intensive research.

SCF, M-CSF, IL-1, IL-4 and IL-6

The following factors have recently entered clinical trials, or will be doing so in the near future: SCF, M-CSF, IL-1 and IL-6. SCF has been known to affect haematopoiesis, gametogenesis and melanogenesis when absent, as in the Steel and W mouse mutations. *In vitro* results show a dramatic synergy with other CSFs in stimulating progenitor survival, proliferation and differentiation. Animal studies so far have not revealed particular advantages over other CSFs when SCF was administered alone. However, all *in vitro* data point to a therapeutic potential of SCF when used in conjunction with, for example, G-CSF.

Studies with M-CSF are directed at exploration of possible fungicidal or other antimicrobial activity of this compound. Unexpectedly, a decrease in serum triglycerides and cholesterol may be accompanied by M-CSF adminstration.

IL-4 has shown anti-tumour activity in a murine model of renal carcinoma. No therapeutically significant effect on bone marrow stem cells has been demonstrated so far. IL-1 has been called haematopoietin-1 because of its synergistic effect on CSF-induced progenitor proliferation *in vitro*, as well as its radioprotective activity *in vivo*. Its therapeutic potential may include thrombopoietic activity, as well as effects on various populations of stem and progentior cells when used in combination with other CSFs. IL-6 has shown thrombopoietic activity in animal models and phase I clinical trials. Data on the possible therapeutic potential of IL-6 will emerge shortly.

OTHER NEW HGF

Promising cytokines undergoing preclinical development at this time are IL-11 (possible thrombopoietic activity), IL-9, macrophage inflammatory protein (MIP)-1 alpha (possible stem cell protection during chemotherapy) and a GM-CSF/IL-3 fusion protein (possibly combining or potentiating the effects of GM-CSF and IL-3 when given alone).

POSSIBLE RISKS IN THE USE OF HGF

In vitro studies have demonstrated the presence of functional receptors for HGFs and other cytokines on haematopoietic tumour cells and on a variety of solid tumour cells. Although stimulation of tumour growth has not been observed during HGF application, this possibility will have to be carefully investigated with all new cytokines entering clinical trials.

Leukaemic tranformation was considered as another serious possible side-effect before CSFs were evaluated in larger numbers of patients with acute leukaemia. Although the clinical situation of patients with leukaemia was, in general, not worsened by CSF administration, it was noted that the growth of leukaemic cells could be stimulated *in vivo* in patients with acute leukaemia [10]. This has led to a new concept of possibly rendering more leukaemic cells sensitive to the action of S-phase specific drugs, such as cytosine arabinoside, by driving leukaemic cells into cycle by CSF application prior to chemotherapy.

PERSPECTIVES

New indications for a wider, but also more disease-specific use of HGFs, will certainly develop with the increasing general accessability of these factors in clinical medicine. Single factor regimens may develop as an ideal treatment option for cytopenias, whereas for other indications the search for better therapies will go on using combinations of factors, or the discovery and development of new substances. In the transplantation setting, peripheral blood stem cells mobilised by CSFs may also evolve as an important source for haematopoietic stem cell allografts. There may be a growing role for HGFs in cultivation of haematopoietic stem cells *in vitro*. For example, for reinfusion after *ex vivo* expansion to achieve even faster and more reliable regeneration during myelosuppression, or to enable and possibly enhance gene transfer into haematopoietic stem cells for therapeutic purposes.

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