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Haemopoietic Growth Factors: Uses and Misuses

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THE CLINICAL development of recombinant human myeloid growth factors must be regarded as one of the fastest in pharmaceutical history: it took just over five years from the publication of the first report on their clinical use in cancer patients treated with chemotherapy [1], to their approval as drugs worthy of clinical use. Recombinant granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) entered the oncological and haematological arena with great impetus, at a time when pessimism was beginning to prevail because of the relative lack of major therapeutic breakthroughs.

Since then, both G-CSF and GM-CSF have been widely used across the world to reduce the incidence of febrile neutropenia [2], to allow the administration of planned chemotherapy on time (without dose reductions or dose delays due to neutropenia) [3, 4], to speed up haematological recovery following bone marrow transplantation (autologous or allogeneic) [5, 6], and to mobilise peripheral blood progenitor cells (PBPC) [7–9]. Both these growth factors are available in their recombinant forms as glycosylated and non-glycosylated molecules, but glycosylation does not appear to be important for biological efficacy *in vivo*.

The fact that they are usually very well tolerated at the recommended doses (G-CSF being, in general, better tolerated than GM-CSF), is somewhat counter-balanced by the fact that they are largely perceived as being expensive drugs; at times, doubling the total costs of a conventional chemotherapy regimen. As with most things in life, there is no universal agreement on their precise indications, particularly with regards to their cost-effectiveness. At one end, there are some cytokine-enthusiasts who would favour a widespread use of these substances, including, some say, "a general agreement that, given the track record of the administrative chairs of many of the cancer cooperative groups, they may in fact also be open to taking G- or GM-CSF. . .". At the other end of the spectrum, there are still a few remaining "biotech-negativists" who view the subject with great scepticism. A more balanced view is that whenever it seems important to at least maintain or increase the dose intensity of a given chemotherapy treatment, or to protect patients from a reasonable chance of developing a potentially life-threatening neutropenic febrile episode, there is no good justification for not using recombinant haemopoietic growth factors.

Chemotherapy fails either because chemosensitive tumour cells remain after inadequate treatment, or resistant malignant clones predominate despite therapy. Drug-related toxicity, which compromises the ability to give adequate treatment, and multi-drug resistance, which renders chemotherapy ineffective, are major obstacles to improving the success of cytotoxic cancer chemotherapy. Adequate management of drug-related toxicity should ensure that chemotherapy regimens are given at an effective dose. Avoiding or defeating drug resistance is a more difficult proposition. Long-term continuous infusion of some cytotoxic drugs is being investigated and might help to circumvent kinetic drug resistance, by killing (at least in theory) slowly cycling tumour stem cells. New inhibitors of multi-drug resistance proteins are also receiving increasing attention. However, the advent of new technologies, such as the use of recombinant human colony-stimulating factors and PBPC, has inevitably given impetus to more aggressive experimental chemotherapies for chemosensitive malignant diseases. Undoubtedly, these new technologies for bone marrow rescue have greatly reduced the risks for patients, and treatment related deaths are now infrequent: less than 5% instead of 10–20% seen only a few years ago.

At the same time, a number of related molecules (or "cytokines") have also been identified and molecularly cloned. These are intimately involved in the triggering and fine tuning of the inflammatory and immunological responses. These molecules include some sixteen "interleukins", of which at least thirteen have entered clinical development. Often, their true physiological role is not known or fully understood, and yet attempts are being made to find them a suitable pharmacological role. Some are fairly selective in their actions for some differentiated cell types (e.g. erythropoietin or G-CSF), others are more pluripotent (e.g. IL-3 or Stem Cell Factor); and a number will be truly pleiotropic (e.g. IL-1 or TGF-β). Moreover, there is a growing conviction that all these regulators exhibit a high degree of redundancy: there appear to be more regulators with similar or overlapping actions than would seem to be really necessary to achieve the required cell proliferation [10].

Recently, negative regulators of haemopoiesis (e.g. MIP-1α) have also been molecularly cloned and are entering clinical development. It is hoped that these inhibitors will make normal haemopoietic stem cells and progenitor cells less sensitive to the toxic effects of chemotherapy, thereby reducing myelosuppression. It remains to be seen whether the inhibitory effects of these new substances are truly selective, or whether they also involve other normal proliferating cellular compartments. A new humoral regulator of megakaryocytopoiesis, known as Mpl-ligand, has also been described and has the expected characteristics of a thrombopoietin [11].

Naturally, there is concern, in these days of tight budgets and financial constraints, that the proliferation of these "high-tech" treatments and the introduction of more and more recombinant products will lead to, or accelerate, the bankruptcy of public health systems. Clinical, financial and ethical aspects should

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be discussed when drafting institutional protocols, and when considering individual candidates for high-dose chemotherapy treatments, recombinant growth factors or cytokines, and, perhaps, the new-coming recombinant tumour vaccines or gene therapies. Although the aim of intensive chemotherapy (with bone marrow and/or PBPC rescue) is to return the patient to a normal productive life, the fact that this is not accomplished in all patients should not preclude attempting this type of therapy.

There is now good evidence to justify high-dose chemotherapy in acute myeloid leukaemias (in first or second remission) and mounting evidence for its application in acute lymphoblastic leukaemias with poor prognostic features (as consolidation of first or second remission), and in relapsed chemosensitive Hodgkin's disease and non-Hodgkin's lymphomas. On-going prospective studies are in progress to assess the impact of these therapies up-front as consolidation of first remission in poor prognosis non-Hodgkin's lymphomas; in germ cell cancer refractory to cisplatin (or even up-front in poor-prognosis groups); in advanced epithelial ovarian cancer (in young patients with poorly or moderately differentiated tumours); in breast cancer, as adjunct to primary therapy in patients with metastatic disease in more than ten (or more than four) axillary lymph nodes; and in several other, more speculative, clinical situations. However, the design and implementation of these studies is fraught with difficulties, due to the large number of variables involved, the considerable costs and the need for multicentre studies [12]. Even relatively simple questions, such as whether to use growth factors or not to use them, following re-infusion of PBPC, have not been unequivocally answered [13].

Outside high-dose protocols, the routine prophylactic use of recombinant haemopoietic growth factors is more controversial. There is retrospective, and some prospective, evidence that some chemosensitive tumours require a minimum (or "threshold") dose intensity of chemotherapy to be controlled or eradicated; while for others, total dose of a given cytotoxic (e.g. cisplatin) may be more important than dose intensity *per se* [14]. Most will agree that in patients with chemosensitive malignancies undergoing their first chemotherapy treatment, dose intensity should not be reduced for trivial reasons.

The use of recombinant CSFs in the treatment, rather than prophylaxis, of febrile neutropenia has not been thoroughly investigated and therefore, no firm recommendations can be made on the subject.

Current cost-effectiveness analysis, performed both in Europe and in the U.S.A., suggest that prophylactic therapy with recombinant CSFs cannot be justified if the expected risk of neutropenic fever is below 20%, but can be justified if it is above 40% [15]. One of the problems is that these risks are often poorly recorded in the literature and are rather difficult to assess on an individual basis. Thus, some chemotherapy regimens commonly employed for, for example, small cell lung cancer are associated with a sufficient risk of febrile neutropenia to warrant the use of prophylactic growth factors [2, 3], but many equally effective other regimens are less toxic [16]. Careful analysis of the incidence of infectious complications, rather than merely granulocyte nadirs and duration, should be performed. Alternatively, older patients, patients with impaired bone marrow reserve (due to previous chemo- or radiotherapy, or heavy involvement by tumour), or patients with significant immunodepression (e.g. AIDS patients) should also be considered as candidates [17].

In summary, there are still more questions than answers regarding the optimal use of recombinant human haemopoietic growth factors, but their introduction into the clinic has given new life and new hope to the way we approach cancer therapy.

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