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# What Can We Expect from Myeloid Growth Factors?

THE USE of myeloid growth factors in cancer patients has two important aims: (a) by reducing the period of neutropenia, these factors can significantly decrease the morbidity associated with conventional chemotherapy (e.g. by decreasing the number of severe infections and the frequency and severity of mucositis); and (b) by allowing more intensive chemotherapy regimens, these factors might improve response rates and survival [1].

Granulocyte–macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) are the two main myeloid growth factors. In the past few years, the availability of recombinant human (rh) versions of these agents has allowed animal and clinical testing. Despite their similar names, an historical consequence of the same *in vitro* colony assays being used for initial identification, the factors differ biologically and clinically. They have different molecular structure, cell membrane receptors, and target cells—G-CSF more selectively stimulates granulocyte and, to a lesser extent, monocyte precursors, while GM-CSF also affects eosinophils, macrophages and, at least *in vitro*, platelets. Moreover, the genes for these factors are located on different chromosomes (chromosome 5 for GM-CSF and chromosome 17 for G-CSF). Finally, GM-CSF and G-CSF have different effects on neutrophil kinetics [2]. Several phase I/II studies have now been reported. Both agents increase leucocyte numbers in patients before and after chemotherapy [3]. Non-randomised studies suggest a clinical benefit in terms of a reduction of the often severe neutropenia that follows cytotoxic chemotherapy. GM-CSF can cause mild fatigue, weakness, fever, anorexia and transient dyspnoea; at higher but clinically unnecessary doses it can also cause more severe side-effects such as thrombosis, effusions, hypotension and respiratory distress. G-CSF appears to be less toxic, and no maximum tolerated dose has been clearly identified, although rhG-CSF can cause, like GM-CSF, musculoskeletal pains in a small proportion of patients.

GM-CSF appears to act mainly locally, in a "paracrine" fashion, leading to local activation of granulocyte and macrophage function, including stimulation of antitumoral cytotoxicity. G-CSF, on the other hand, can also be detected in the circulation, and serum levels increase following endotoxin stimulation or infection and inflammation, thus behaving more like a "granulopoietin".

Dr Biesma and colleagues (p. 932) report the first double-blind placebo-controlled trial of rhGM-CSF in the treatment, rather than prophylaxis, of chemotherapy-related leukopenia and fever without bone marrow transplantation. Disappointingly, GM-CSF did not shorten the period of fever or antibiotic administration. More placebo-controlled studies of this kind are needed to confirm this negative result, perhaps with a higher dose and earlier administration of rhGM-CSF. It is also possible that at higher doses the toxicity of GM-CSF, which was negligible in this study, will become more important. No similar study has yet been reported for rhG-CSF, but it is clear from phase II and randomised phase III studies (in patients treated with conventional-dose chemotherapy) that G-CSF administered prophylactically significantly reduces the frequency of febrile neutropenia and allows chemotherapy to be administered on schedule [4]. Furthermore, in a preliminary analysis of a study by Morstyn *et al.* [5] in the treatment, rather than prophylaxis,

of febrile neutropenia, G-CSF signficantly reduced the duration of the febrile neutropenic episodes following chemotherapy compared with that in a matched group of historical controls.

The second major goal of myeloid growth factors in cancer therapy (to enhance response rates by increasing the dose intensity of chemotherapy) is more ambitious and may prove successful only for those malignancies that are inherently sensitive to chemotherapy, such as high-grade lymphomas, germ cell tumours, Hodgkin's disease, neuroblastoma and, perhaps, small cell lung cancer. Patients with Wilms' tumour, Ewing's tumour, osteosarcoma, embryonic rhabdomyosarcoma and choriocarcinomas (for whom chemotherapy can result in a 20% or greater improvement in long-term survival) might also benefit from a more intensive approach. However, all these cancers are uncommon.

In experimental models, as originally shown by Skipper more than 20 years ago in experimental leukaemias and in Ridgway osteogenic sarcomas, the dose-response curve to chemotherapy is usually sigmoidal and steep in the linear part of the curve. Dose escalation is often limited by myelosuppression, and dose reductions result in a decreased cure rate before a significant reduction in the complete remission rate. However, no cure is seen unless complete remission is first reached. In patients, it is still difficult to compare the impact of different dosing practices on response rates, and this is particularly true for complicated combination chemotherapies in which more than three or four cytotoxic agents are used. Hryniuk can be credited for popularising the concept of dose-intensity and for developing some of the initial methods to measure dose intensity [6]. Dose intensity can be defined as the amount of drug delivered per unit time, expressed, for example, as mg/m$^2$ per week, regardless of the schedule or route of administration. Other useful concepts are planned dose intensity, as described in the treatment protocol, received dose intensity, which reflects dose reductions and necessary treatment delays, and relative dose intensity, defined as the amount of drug delivered per unit time relative to a chosen standard single drug or, for combination chemotherapy, the average of the decimal fractions of the ratio of the test regimen to the standard regimen. With such analysis, good correlations between dose intensity and response rate have been retrospectively shown for various lymphomas and also for some of the common solid tumours (ovarian, breast and colon cancer). More significantly, for adjuvant therapy in breast cancer, the correlation between dose intensity and outcome is particularly encouraging because almost all the drugs in the programmes analysed were used at the low end of the dose-response curve.

Dr Ardizzoni and colleagues (p.937) attempted to accelerate chemotherapy for small cell lung cancer by planning to give conventional three-weekly chemotherapy on a weekly basis. A randomised design and the inclusion of more patients would have helped to meet the objectives of this study. Nevertheless, the intervals between the cycles of chemotherapy could be shortened, with or without GM-CSF. There was a marginal (and probably not significant) benefit for the GM-CSF treated group.

Accepting the negative value of this approach with GM-CSF, the next step might be to keep the conventional intervals between the cycles of chemotherapy (e.g. 3 weeks), but to enhance dose intensity by attempting to increase doses. For some malignancies, e.g. lymphomas, a modest increase in dose intensity (say 30–50%) may result in a significant increase in response rates. But, for most tumour types, only a substantial increase (e.g. 2–fold or more) is likely to have an impact on response and survival. To date, only rhG-CSF, which reduces both the maturation and release times of bone marrow neutrophils to 1–2 days, rather than the normal 4–5 days [2], has been shown to allow an increase in dose intensity of chemotherapy by increasing the dose (of single-agent doxorubicin) and, at the same time, to decrease the interval between doses from 3 to 2 weeks [7]. This approach in patients with advanced metastatic breast cancer resulted rapidly in high reponse rates of short duration, and led to severe epithelial side-effects as the main dose-limiting toxicities. Prophylactic platelet transfusions and intravenous antibiotic therapy were also required at the higher dose intensities in some patients. To reduce even further the period of myelosuppression, peripheral blood stem cells could be collected and cryopreserved following the first course of chemotherapy, and re-infused in subsequent cycles together with a myeloid growth factor.

The use of recombinant myeloid growth factors should allow us to test the "dose-intensity hypothesis" in well-controlled prospective studies by allowing a faster recovery from neutropenia. The design of these studies is not going to be easy, considering the number of variables potentially involved (e.g. dose, intervals, single-agent chemotherapy vs. combination regimens, patient population, total dose of cytotoxics, pharmacokinetics at the high doses, adjuvant situations or advanced disease). In the absence of better cytotoxic drugs or of mechanisms to overcome drug resistance, the dose-intensity approach must be extensively and carefully studied to achieve the main goal of clinical oncologists—i.e. to increase the survival of cancer patients. However, I predict at least two major obstacles: firstly the non-haematological toxicities of cytotoxic drugs, which may become dose-limiting after an increase in dose by only 2 or 3 fold for some drugs; and secondly, the biology of the tumour itself, including its propensity to "drug resistance", its cellular kinetics and its ability to elicit some form of immune control by the host on any remaining subclinical population of tumour cells.

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