Pergamon

European Journal of Cancer Vol. 31A, No. 9, pp. 1476–1478, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(95)00275-8

Review

Haemopoietic Growth Factors and Childhood Cancer

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IN THE last decade, we have witnessed an explosion in the number of haemopoietic growth factors identified and manufactured. As a consequence, a mass of indigestible publications on the subject have appeared and, in turn, have led to a variety of reviews that seek to guide clinicians through the morass of available information [1–4]. Unfortunately, the upshot of all of this activity is that we are left with an armamentarium of drugs which we do not known how best to use. The only justification for another review, such as this, is to attempt to distil all of the guidelines into a usable form and to see whether any of the very recent publications add to our knowledge. Afficionados who require details of the sites of the genes involved in growth factor production and their alleged target cells are referred to several reviews of these topics [1–4]. My intention, in this article, is to attempt to put matters into a clinical perspective and make suggestions for future studies.

NEUTROPENIA FOLLOWING CHEMOTHERAPY

The gold standard for studies in this field is the randomised placebo-controlled clinical trial. Unfortunately, the literature is littered with anecdotal non-randomised studies of small numbers of patients with a variety of underlying diseases. We are thus not yet in a position to decide whether or not growth factors are of benefit in this situation. Despite this, granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are already being used on what is usually termed a "compassionate" basis. Cynics might wonder whether this compassion is directed towards the patients or the pharmaceutical companies. With regard to acute myeloid leukaemia (AML), there is a possible risk of accelerating the disease because some leukaemic cells express receptors for the myeloid growth factors. This characteristic might be turned to the patient's advantage by using G-CSF or GM-CSF to recruit leukaemia cells into cycle prior to anti-leukaemic drugs [5] but the value of this approach is still speculative. There are early indications, in a randomised placebo-controlled trial, that they may in fact be safe to use in adults with AML [6] but follow-up is too short and numbers too small to justify their use, other than *in extremis*, in children with leukaemia.

The evidence with regard to other childhood malignancies is frustratingly limited and usually restricted to anecdotal or retrospective studies. One example of a retrospective case–control study in neuroblastoma suggested that the administration of G-CSF resulted in fewer days of neutropenia but no reduction in episodes of fever, rate of hospitalisation, duration of hospitalisation or duration of antibiotic therapy [7]. The authors wisely cautioned that the clinical benefit remained uncertain and suggested further investigation in a large prospective multicentre trial. Thankfully, such studies are now under way and are particularly important because high dosage intensity is a burning question, particularly in the therapy of advanced neuroblastoma.

GM-CSF has recently been studied in randomised placebo-controlled trials in adults with acute myeloid leukaemia and germ cell tumours [6, 8]. In AML the incidence and severity of infections and of non-haematological toxicities were similar. GM-CSF did not shorten the period of neutropenia and actually prolonged the duration of thrombocytopenia [6]. As stated above, the only 'plus' mark for GM-CSF was that, in these trials, overall survival was not adversely affected at an early stage of analysis. In the germ-cell tumour study [8] there was a reduction in incidence of infection in the first chemotherapy cycle but not thereafter. There was a high incidence of GM-CSF-related toxicity (mainly fatigue, dizziness, pruritus and skin rash) and the drug had to be discontinued in 14% of cycles. The message is clearly that these are new drugs which deserve to be tested out in the same way as any others and that unexpected toxicities such as thrombocytopenia, possibly related to marrow progenitor cells being 'urged' to mature down one cell line at the expense of another, can only be determined by randomised trial. Initial indications are that G-CSF is less toxic than GM-CSF [9] but the latter may have other benefits, for instance in therapy of systemic fungal infections, and it is to be hoped that trials comparing the two agents will be carried out in future.

G-CSF and GM-CSF are often prescribed in circumstances similar to those in which, in the past, granulocyte transfusions were used. In other words, the clinician faced with a severely neutropenic child who remains febrile despite broad spectrum antimicrobial therapy and including amphotericin feels an almost irresistble urge to reach for the cytokine. There is almost

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Received 8 Mar. 1995; accepted 10 Mar. 1995.

no evidence that this approach is justified in any age group and least of all in children. Studies carried out in children [10–12] have been performed in a prospective/preventative fashion and have not been randomised or associated with an analysis of morbidity or cost. Some trials [10–12] have demonstrated that G-CSF or GM-CSF may reduce the period of neutropenia and, sometimes, the length of time on antibiotics. However, the evidence is simply not strong enough to encourage the adoption of any growth factor for these patients except in the context of a clinical trial. The one possible exception, until such time as the results of appropriate trials are concluded, is in the empirical therapy of the febrile and neutropenic child who is deteriorating despite a full course of antimicrobial therapy.

MYELODYSPLASTIC SYNDROMES

Children with myelodysplastic syndromes have a poor prognosis unless they fall into the rare category of refractory anaemia [13]. There is a strong propensity to leukaemic transformation or infection and bleeding related to marrow failure and at present the only curative procedure is an allogeneic transplant from a matched sibling or unrelated donor [13]. Growth factors have been used, particularly in adults [14, 15], in an attempt to tide patients over infective and bleeding episodes. The outcome has been a rise in neutrophil counts in some patients and, infrequently, a rise in platelets. G-CSF and GM-CSF have each been used and interleukin-3 (IL-3) has also shown some promise but can cause fever, backache, local erythema and bone pain [16]. Once again, the use of these growth factors has been limited by their failure to increase platelet production. There is also real concern that malignant clones may be stimulated by the use of growth factors [15].

BONE MARROW TRANSPLANTATION

Both G-CSF and GM-CSF have been used to treat more than 100 adult patients who failed to engraft or lost a graft after bone marrow transplant [17]. The outcome has been a doubling of survival rates compared with patients treated on a variety of immunomodulatory regimens and/or regrafting. The effect on long term marrow recovery in these circumstances is still uncertain.

315 adults and children undergoing bone marrow transplant for non-myeloid malignancy were entered on a randomised placebo-controlled trial of G-CSF given at a dose of 5 μg/kg/day from the time of transplant. A variety of allogeneic transplant or autologous marrow recipients were studied after myeloablative therapy for leukaemia or solid tumours [18] The trial, which is so far the only one of its type, demonstrated a significant reduction in the number of days of antibiotics, total parenteral nutrition and days in hospital. As with most other similar studies of its type, G-CSF did not alter the day of occurrence of the nadir of counts nor its profound nature. Subsequent non-randomised studies [19, 20] have shown that a similar effect on neutrophil recovery can be achieved by starting the cytokine treatment at about one week after marrow infusion, which might be a more cost-effective approach. The randomised trial showed more rapid recovery of neutrophils in the G-CSF treated patients. Because the neutrophil nadir was unaffected, the incidence of infection was not affected but the duration of fever was reduced, presumably because of the rapid count recovery. Platelet count recovery was unaffected. Although a formal cost-benefit analysis was not carried out it seems reasonable to assume that the reduction in duration of neutropenia ($<0.5 \times 10^9/l$) of around 1 week is of value for this subgroup of patients.

Preliminary studies of other growth factors have been carried out in bone marrow transplant patients. A randomised placebo-controlled trial of recombinant human erythropoietin (epo) [21] enrolled 329 patients, 163 of whom received epo and 166 placebo. The majority of patients had acute or chronic leukaemias and all received high dose therapy with either autologous marrow rescue ($n = 114$) or allogeneic bone marrow transplant ($n = 215$). There were no major differences in side effects between the epo and placebo groups and there was no demonstrable benefit for epo in the patients receiving autologous marrow, but epo did accelerate erythrocyte recovery in the allogeneic group and reduced the need for transfusions after day 20. One could thus consider the use of epo in allogeneic bone marrow transplant patients but the cost-benefit of a reduction in the mean number of transfusions from approximately 13 to 10 seems marginal.

Another approach has been to give IL-3 and GM-CSF sequentially after marrow ablative therapy and autologous marrow reinfusion [22]. An early report in a small number of adults being treated for lymphoma has suggested that this approach may be safe and reasonably well tolerated. The approach is based on the fact that IL-3 expands early haemopoietic progenitor cell population, enabling more effective differentiation into mature cells with GM-CSF, which acts upon more "committed" progenitors. Preliminary indications from this study are that multilineage haemopoietic recovery may be enhanced. Future clinical trials should address this issue in large randomised studies which will hopefully also include the use of thrombopoietin and possibly other factors such as c-kit ligand.

PERIPHERAL BLOOD STEM CELLS

The use of stem cells harvested from peripheral blood (PBSC) by the use of cell separators might negate the need for bone marrow harvesting and avoid general anaesthesia. The technical problems of such procedures in children are considerable but have now largely been overcome. The yield can be improved by carrying out the harvest after chemotherapy and/or stimulation with G-CSF or GM-CSF [23] but optimal regimens have not yet been identified. It should never be forgotten that a faster blood count recovery will not abrogate all the problems of mucositis and will have no effect at all on toxicities such as veno-occlusive disease. We also have no real idea of the cost-benefits and impact of such procedures upon survival. It is thus to be hoped that in the near futue there will be randomised trials, in which potential risks, including the stimulation of circulating malignant cells, can be properly assessed.

TOXICITY

The potential immediate problems of the use of growth factors have already been discussed but the importance of long-term follow-up must be emphasised. As yet, very few studies have been in progress for long enough to have any chance of detecting a potentially detrimental impact, such as the risk of increasing the incidence of recurrence of acute myeloid leukaemia. The only group of children examined over prolonged periods—of several years—are those treated for severe aplastic anaemia and congenital neutropenia [23, 24]. In the patients with severe congenital neutropenia there is a 28% incidence of osteopenia, 22% of splenomegaly, and an 11% incidence of a syndrome including vasculitis, glomerulonephritis, marrow fibrosis and hepatosplenomegaly. Some of these features, however, may not be related to the growth factors. More worryingly, these studies have shown a 7% incidence of myelodysplasia (MDS) or leu-

Table 1. Some crucial questions about growth factors that need to be answered

What is the long-term toxicity? Will there be an increased incidence of haemopoietic disorders; including clonal disorders, e.g. monosomy 7?
Is it safe to use myeloid growth factors in myeloid malignancies, or will survival be compromised?
Will the myeloid growth factors reduce the toxicity of chemotherapy?
Will cocktails of growth factors (e.g. with thrombopoietin and c-kit ligand) encourage more rapid recovery of other cell lines, especially platelets, after marrow-ablative therapy?
Should myeloid growth factors become an integral part of planned progressive antimicrobial therapy in infected and/or bleeding patients?
Will the addition of GM-CSF or M-CSF improve the outcome of amphotericin therapy for systemic fungal disease?
Can CSFs facilitate trials of high dose-intensity chemotherapy and will this have an impact on survival from childhood malignancy e.g. neuroblastoma and osteosarcoma?
Will the adjunctive use of growth factors and haemopoietic stem cell harvesting improve the outcome of therapy for malignancy?

kaemia often associated with monosomy of chromosome 7 in the bone marrow. In one series of 87 children, 3 of 67 with severe aplastic anaemia and one of 20 with severe congenital neutropenia have developed myelodysplasia or acute myeloid leukaemia [25]. 3 of these 4 children had monosomy 7 and a fourth showed trisomy 21 in the marrow blasts. All had been treated with G-CSF. It is well known that patients with both severe aplastic anaemia and severe congenital neutropenia can develop clonal haemopoietic disorders and it must also be understood that prolonged courses of growth factors, such as these patients have received, may have a greater chance of promoting the growth of malignant clones. Future studies will concentrate on defining the precise risk and possibly in identifying patients, such as those with specific G-CSF growth factor receptor gene defects [25] at increased risk of these complications.

CONCLUSIONS AND FUTURE PROSPECTS

The story so far is of some promise and some shattered dreams. There are many more questions than answers and some of the more important ones are listed in Table 1. We should now set out to test new growth factors such as thrombopoietin [26], the gene for which was cloned in 1994 [27], and the older agents singly and in combination and in conjunction with other approaches such as peripheral stem cell harvesting. Haemopoietic growth factors deserve to be treated just like other drugs. This exciting era must not be marred by submission to the temptation to bypass the need for trials which will allow us to establish their proper role.

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Acknowledgements—I thank Judith Mott and the REACH Fund for secretarial support.