of antagonists to these growth factors and finally disruption of the signal pathway involved once these growth factors are internalised within the cell. As it is likely that many growth factors are involved in lung cancer, this latter approach may prove to be the most important in therapeutic studies of patients with this disease.

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Eur J Cancer, Vol. 27, No. 3, pp. 369–372, 1991.
Printed in Great Britain

0277-5379/91 $3.00 + 0.00

Haemopoietic Growth Factors: Unravelling the Secrets of Blood Formation

M. H. Bronchud

INTRODUCTION

EVEN BEFORE the Old Testament book of Leviticus was written, mankind had a particular fascination for blood ("for it is the life of all flesh", Leviticus). Most cellular elements of this liquid organ derive from the bone marrow by a process called "haematopoiesis", often abbreviated to "haemopoiesis". The production of blood is the best understood of all the many processes of cellular proliferation and differentiation in the living organism, both in terms of its molecular and its cellular mechanisms. The reasons for the clearer understanding of this fundamental process, when compared to other body tissues, are mainly technical: easy sampling of mature cells from peripheral blood and of progenitor cells from the bone marrow; the production of highly differentiated products by mature blood cells; good morphological markers; and the development over the last three decades of functional assays to measure the number and quality

of progenitor cells, and also the activity of mature cells. To these advantages, we can now add the discovery and production by molecular techniques of a number of important protein, or glycoprotein, regulators of the proliferation, differentiation and functional activation of most blood cell types. The existence of some of these substances, for example erythropoietin, had been suspected for a long time on the grounds of classic physiological experiments in anaemic experimental animals; others were inferred from the seminal observations in the 1960s that mature macrophages and neutrophils developed from bone marrow cells exposed in semi-solid culture conditions *in vitro* to media "conditioned" by the growth of non-haemopoietic cells and were, therefore, named colony-stimulating factors (CSFs). Others still, have been more recently purified from activated lymphocytes and inflammatory cells, and because they are also involved in the modulation of these cells, they have been called "interleukins" [1, 2].

IN VITRO FINDINGS

Thus CSFs are a class of "growth factors", in that they are necessary for the *in vitro* survival, proliferation and maturation of blood cells without being nutrients. Growth factors differ from conventional hormones in that the latter are synthesised by specialised glands and carried by the blood to their target cells, perhaps far away from their site of origin. Most growth factors identified so far instead appear to be made systemically and the approach of conventional endocrinology, i.e. ablation of the secreting source to monitor the subsequent metabolic changes, cannot be applied.

Although growth factors usually have a fairly restricted range of target cells, they exert a multiplicity of actions on such cells. Some colony-stimulating factors are more restrictive in their activities than others. Macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF) and, of course, erythropoietin (EPO) are fairly "lineage-specific", stimulating mainly macrophages, neutrophil granulocytes and red blood cell progenitors, respectively.

Granulocyte–macrophage colony-stimulating factor (GM-CSF) and interleukin-3 (IL-3), also known as "multi-colony stimulating factor", on the other hand, exhibit *in vitro* stimulatory activities on more than one cellular lineage.

There are still large gaps in our knowledge about the role of these regulators in the very early stages of haemopoiesis, but the tridimensional structure of the marrow and the interactions of cells relative to their spatial arrangement *in vivo* are suspected by many to hold the key to many of the secrets of the regulation of pluripotent stem cells [3, 5]. Perhaps cell-contact regulatory processes between stem cells and the surrounding stroma, less well understood at the molecular level, are partly mediated by similar molecules displayed on cell membranes or attached to glycoproteins in the extracellular matrix [6]. It is also becoming apparent that a rather heterogenous group of negative haemopoietic regulators, or growth inhibitory proteins or peptides, exist [7]. They operate at picomolar to nanomolar concentrations through high-affinity receptors, as CSFs do, and act within minutes to hours in a fairly specific manner on stem cells and progenitor cells, to arrest DNA synthesis during S-phase or to prevent entry into DNA synthesis during G1. Although several laboratories worldwide have isolated putative inhibitors of this kind, they are proving difficult to fully characterise and molecularly clone. An entirely new and unexpected type of growth factor inhibitor, an endogenous interleukin-1 (IL-1) receptor antagonist protein, has been recently purified and molecularly cloned, exhibiting a potent inhibition of some IL-1 induced effects *in vitro*, and potentially leading to new types of treatment for certain human inflammatory diseases [8].

The intracellular mechanisms triggered by the binding of CSFs to their receptors are poorly understood, but, in spite of their molecular differences several CSFs stimulate a number of consensus biochemical events that include stimulation of tyrosine and serine-threonine substrate phosphorylations, and the activation of many of the same genes (proto-oncogenes c-*fos* and c-*myc*, ornithine decarboxylase and members of the stress response genes family). An important common pathway of this complicated "signal-transduction cascade" involves the tyrosine-kinase activity associated with several growth factor receptors, notably the epidermal growth factor (EGF) "receptor family". Recent data suggest that tyrosine phosphorylation is also important for GM-CSF and IL-3 receptor mediated signal transduction, and that a fine balance between CSF-induced protein-tyrosine kinase activity and protein-tyrosine phosphatase activity strongly influences the proliferative behaviour of target cells [9].

The intercellular interaction between different CSFs and interleukins is also of considerable complexity. Multicellular organisms have evolved several sophisticated defence mechanisms against pathogenic agents. These include humoral and cellular responses which must be finely coordinated to defeat successfully the invading agent without harming the host. Several interleukins and CSFs are part of this "cytokine cascade". They can interact locally within the tissue, in a "paracrine fashion", or can circulate in the blood stream to reach distant sites. The *in vivo* activity of a particular interleukin or CSF is often dependent on the presence or absence of other cytokines, either because they change the number or type of membrane receptors, because they stimulate or suppress the production of other cytokines, or because of intracellular mechanisms that lead to different patterns of gene expression by a particular cell. Thus, IL-1 stimulates release of G-CSF and GM-CSF by endothelial cells [10]; GM-CSF leads to the release of IL-1 and tumour necrosis factor (TNF) by monocytes [11]; and relatively high *in vitro* concentrations of G-CSF can lead to interferon-alpha production by granulocytes [12]. Moreover, at moderate concentrations, IL-3 down-modulates GM and M-CSF receptors and at higher concentrations IL-3 and GM-CSF also down-modulate G-CSF receptor numbers on mouse bone marrow cells [13].

IN VIVO AND CLINICAL RESULTS

The recent availability of large quantities of purified recombinant CSFs and interleukins has led to a number of phase I and II studies, and extensive clinical data has been collected for G-CSF, GM-CSF and EPO. EPO is already available commercially, mainly as a treatment for end-stage renal failure, though it has also shown promise in the anaemia associated with multiple myeloma and malignant disease, and G-CSF and GM-CSF are likely to follow suit in the next few months and become widely available for clinical use. Some phase I trials with IL-3 and IL-1 have already been completed, and others are in progress with other cytokines with haematopoietic activity, such as IL-6.

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Received 19 Nov. 1990; accepted 28 Nov. 1990.
Presented in part at the Second European Winter Oncology Conference (EWOC-2), Méribel, France, January 1991.

The most attractive clinical application of myeloid growth factors in cancer patients is the likely reduction in the toxicity of myelosuppressive treatments and the potential to intensify chemotherapy regimens, which could lead to better therapeutic results. Extensive literature on these therapeutic aspects is already available for G-CSF and GM-CSF, and has been recently reviewed [14–16]. Treatment with both agents results in increased circulating leucocyte and peripheral stem cell counts, and an increased marrow cellularity, mainly as a consequence of amplification in the maturation compartment of the myeloid series. No evidence has been found for the recruiting by these CSFs of more primitive haemopoietic stem cells to undergo differentiation, which could have led to stem cell exhaustion and pancytopenia.

The theoretical concern that they might stimulate tumour growth has not been evident clinically in any of the tumour types studied, but they should be used with caution; or not used, in some myelodysplastic syndromes and in myeloid leukemias, at least until more clinical data have been produced regarding their safety in these indications [17].

Although G-CSF appears to be less toxic, and to lead to a more rapid and specific release of new mature neutrophils, no comparative studies comparing the two CSFs have been done, but prospective randomised studies will be needed to determine the relative uses of these two growth factors in different clinical situations.

With time, and if the use of these agents in conjunction with intensive chemotherapies translates into a better quality of life or an improved survival for cancer patients, they will perhaps add their initials to well known combinations of cytotoxic agents (for example high dose CHOP-G or CHOP-GM; CAF-G or CAF-GM; CAE-G or CAE-GM).

A recent phase I/II study of IL-3 has shown encouraging increases in platelet counts and reticulocyte counts in patients with advanced tumours but normal haemopoiesis, and more modest increases in neutrophil counts than those reported for G-CSF and GM-CSF. Better improvements in platelet counts were experienced by some patients with bone marrow failure and prolonged cytopenias [18]. Toxicity was mild: mainly headache, fever and flushing, perhaps related to histamine release. Some eosinophilia and basophilia were also observed. It might be of therapeutic interest that platelet transfusions were discontinued in some transfusion-dependent patients. The increase in platelet and other cell counts, however, occurred after some two weeks of treatment with IL-3, in contrast to the much faster action on leucocyte numbers of G-CSF and GM-CSF.

More worryingly, the increase in counts was sustained even after the end of IL-3 treatment, with marked increases in cellularity and a persistent shift to the left of haemopoiesis in the bone marrow, confirming an effect at an early stem progenitor cell level and suggesting that if chemotherapy is administered shortly after the end of growth factor treatment, there might still be stimulated progenitor cells cycling in the marrow. This is of some concern because, under these circumstances, cytotoxic agents might theoretically result in more myelosuppression, and because harm could be produced to cycling stem cells with a potential increase in the risk of treatment-related leukemia, as an undesirable long-term consequence of cytotoxic therapy [19].

In the absence of a much sought after, but still elusive, specific "megakaryocyte growth factor", another potential candidate to stimulate platelet production in patients is IL-1. A recent preliminary report on the clinical use of recombinant IL-1-beta suggests that this growth factor might result in significant leukocytosis, and a 50% increase in platelet counts at 10 ng/kg doses, with a not negligible toxicity consisting mainly of fever, headaches, chills, hypertension and supraventricular cardiac arrhythmias [20].

Further reductions in chemotherapy-related myelosuppression might theoretically be obtained by suitable combinations of synergistic growth factors, or by infusions of peripheral blood stem cells in conjunction with CSFs. IL-1 and G-CSF were shown by Moore and Warren to act synergistically in myelosuppressed mice [21]. Donahue *et al.* have recently reported that the combination of IL-3 and GM-CSF induced a synergistic peripheral neutrophilia in primates [22], but the experimental design included several days of pretreatment with IL-3, which may not be of clinical value since G-CSF or GM-CSF alone can produce an immediate increase in circulating neutrophils. The concurrent administration of IL-3 and G-CSF to rats resulted in only a slight additive effect on the increase of circulating neutrophils induced by both agents independently, that was often statistically insignificant as compared with the neutrophilia induced by G-CSF alone [23]. Some clinical studies on combinations of growth factors are underway, and should ideally lead to randomised comparisons with G-CSF or GM-CSF alone.

Although the clinical use of CSFs can significantly ameliorate neutropenias, it will probably never completely abrogate chemotherapy-induced neutropenia, because, unless some specific "chemo-protector" of the bone marrow microenvironment is discovered, cycling progenitor and pluripotent stem cells will continue to fall victims of cytotoxic agents. Nevertheless, collection and subsequent re-infusion of peripheral blood stem cells (obtained by leucophoresis following chemotherapy and during CSF infusion) has been shown to be of clinical use even after high-dose chemotherapy or in patients with a history of prior pelvic irradiation [24, 25]. This technique is certainly highly promising, but because it is also labourious and expensive it should also be sufficiently validated by randomised studies (for example compared to bone marrow with CSFs or CSFs alone, before its universal application [26].

CONCLUSION

Even if the discovery and production by molecular techniques of haemopoietic growth factors have certainly not unravelled all of the secrets of blood formation, they have contributed to a better understanding of this complex process, and to an improved knowledge on the coordination of some inflammatory responses. Their value as drugs worthy of clinical use, in some congenital and acquired disorders of bone marrow function, and in several neoplastic and infectious diseases, is no longer questioned, but more work needs to be done to better define their indications and implications.

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Eur J Cancer, Vol. 27, No. 3, pp. 372–376, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Neurotoxic Side-effects of Cisplatin

F.P.T. Hamers, W.H. Gispen and J.P. Neijt

INTRODUCTION

IN THE last decade an increasing number of papers has been published on the neurotoxicity of anticancer agents. With the improvement of supportive care the administration of higher cumulative dosages is now a reality and as a conseqeunce neurotoxic side effects are encountered more frequently. In this review iatrogenic neurotoxiciy in cancer patients is discussed, with emphasis on cisplatin induced neurotoxicity.

A wide variety of neurological signs and symptoms can be diagnosed in patients treated for cancer [1]. In the differential diagnosis, neurological symptoms due to treatment, the neurological symptoms directly related to the tumour and metastases must be taken into consideration. For instance, a peripheral neuropathy may be related to treatment but can also occur as a paraneoplastic phenomenon. In these cases the peripheral neuropathy is already present before treatment is instituted. The duration of this type of neuropathy may vary between 2 and 11 months before the presence of a malignant tumour is confirmed. Treatment of the malignancy can improve the neurological symptoms. Weissman *et al.* reported on a 61-year-old man who was found to have small cell lung cancer following a one year history of a progressive peripheral sensorimotor neuropathy [2]. The neuropathy initially improved following chemotherapy, but subsequently progressed to the point of respiratory failure. Treatment with plasma exchange, additional chemotherapy, and radiotherapy resulted in a sustained complete tumour remission and neurological recovery. This example illustrates the importance to recognise a sensorimotor neuropathy as related to the tumour and not related to the antineoplastic treatment.

NEUROTOXICITY DUE TO CISPLATIN

A number of severe side-effects accompany the use of cisplatin. Short-term phenomena like nausea and vomiting are seen in nearly all treated patients. More threatening are the effects of cisplatin that appear at higher cumulative doses. A loss of hearing, first affecting the higher frequency ranges, can lead to clinical deafness, especially after regimens with high single doses of cisplatin. Renal toxicity causing a marked reduction in the glomerular filtration rate can be reduced by forced hydration, diuretics and a slow rate of infusion of the drug. The use of more aggressive single-dose treatment has put emphasis on cisplatin induced neurotoxicity, now regarded as the major dose-limiting side-effect. Neurological toxicity occurring in patients treated with cisplatin is limited in most cases to peripheral

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Received 14 Nov. 1990; accepted 23 Nov. 1990.
Presented in part at the Second European Winter Oncology Conference (EWOC-2), Méribel, France, January 1991.