Recombinant Granulocyte-Macrophage Colony-Stimulating Factor (rGM-CSF)
A Review of its Pharmacological Properties and Prospective Role in the Management of Myelosuppression

Susan M. Grant and Rennie C. Heel
Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by: J.H. Antin, Hematology Division, Brigham and Women's Hospital, Boston, Massachusetts, USA; H.E. Broxmeyer, School of Medicine, Indiana University, Indianapolis, Indiana, USA; S.W. Edwards, Department of Biochemistry, The University of Liverpool, Liverpool, England; A. Ganser, Department of Hematology, University of Frankfurt, Frankfurt, Federal Republic of Germany; A.M. Gianni, Divisione di Oncologia Medica, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy; A.D. Ho, Faculty of Medicine, University of Ottawa, Ontario, Canada; A.V. Hoffbrand, Department of Haematology, The Royal Free Hampstead NHS Trust, London, England; D. Linch, Department of Haematology, University College and Middlesex School of Medicine, London, England; D. Metcalf, Cancer Research Unit, The Walter and Eliza Hall Institute of Medical Research, Melbourne, Victoria, Australia; J.J. Nemunaitis, Hematopoiesis Program, Western Pennsylvania Cancer Institute, Pittsburgh, Pennsylvania, USA; S. Okamura, Cancer Center, Kyushu University Hospital, Fukuoka, Japan; W.P. Steward, Beatson Oncology Centre, Western Infirmary, Glasgow, Scotland; S. Vadhan-Raj, Department of Clinical Immunology and Biological Therapy, MD Anderson Cancer Center, The University of Texas, Houston, Texas, USA.

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Summary
Synopsis

Recombinant granulocyte-macrophage colony-stimulating factor (rGM-CSF) is a polypeptide hormone produced through recombinant DNA technologies in glycosylated (yeast or mammalian expression systems) or nonglycosylated (Escherichia coli expression system) form. It is a multi-lineage haematopoietin which stimulates proliferation and differentiation of bone marrow myeloid progenitors and increases peripheral white blood cell counts when administered systemically. Treatment is generally well tolerated, although mild to moderate flu-like symptoms are common and rGM-CSF-induced fever and fluid retention may be problematic in occasional patients.

rGM-CSF accelerates recovery of peripheral neutrophil counts after bone marrow transplantation, and results of a placebo-controlled randomised trial correlate this with reduced infectious episodes and shortened length of hospitalisation in patients with lymphoid malignancies. A substantial number of patients with graft failure after bone marrow transplantation also respond to rGM-CSF. The duration of myelosuppression secondary to cancer chemotherapy can be significantly reduced by rGM-CSF which has permitted investigation of antineoplastic dose-intensity escalation.

In some haematopoietic disorders (e.g. aplastic anaemia, myelodysplasia and neutropenia secondary to HIV infection and antiviral therapy), rGM-CSF produces clinically useful increases in peripheral blood granulocyte counts, although the effect is generally not sustained after drug withdrawal. The potential for rGM-CSF to stimulate proliferation of the abnormal clone in myelodysplasia and in acute myelogenous leukaemia following induction therapy is of concern. Available data suggest, however, that with appropriate monitoring and exclusion of high-risk patients this serious potential risk can be avoided, and that myelopoiesis is enhanced in such patients by rGM-CSF treatment.

Recombinant colony-stimulating factors are a new therapeutic modality; hence many aspects of their use remain to be clarified. Nonetheless, as one of a small group of novel agents rGM-CSF has major potential in the management of myelosuppression secondary to cytoreductive therapy with or without bone marrow transplantation, and in amelioration of disturbed myelopoiesis. It represents an important application of biotechnology to a difficult area of therapeutics.

Pharmacological Properties

Endogenous GM-CSF is produced by T-lymphocytes, macrophages, fibroblasts and endothelial cells, and participates both in the complex regulation of blood cell formation and in activation of mature leucocytes. It is a polypeptide which is variably glycosylated in its native state although the carbohydrate content is not essential for its biological effects, and the 3 available recombinant forms (which differ in extent of glycosylation) are similarly active in vivo. Proliferative activity and priming of mature cells are manifest at similar picomolar concentrations of GM-CSF, and it is the programming of the cell which appears to determine the response to binding of GM-CSF to its cell surface receptor.

In concert with other colony-stimulating factors, GM-CSF facilitates lineage commitment and subsequently supports or amplifies the clonogenic activity of lineage-restricted factors, with the strongest effect seen on the granulocyte-macrophage lineage.