Pergamon

European Journal of Cancer, Vol. 35, Suppl. 3, p. S1, 1999
© 1999 Elsevier Science Ltd. All rights reserved.
Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00079-9

Introduction

H. Zwierzina

Universität für Innere Medizin, Anichstrasse 35, 6020 Innsbruck, Austria

THE BIOLOGICAL Therapeutics Development Group (BTDG) of the European Organization for Research and Treatment of Cancer (EORTC) holds regular expert meetings on current developments in biological therapy. This supplement reports the proceedings of a workshop which was originally set up to deal with the design of clinical trials that investigate monoclonal antibodies (MAbs) and anticancer vaccines using granulocyte-macrophage colony-stimulating factor (GM-CSF) as an adjuvant. During the planning phase, however, it was felt that we should also include further new developments in the field and update current knowledge on GM-CSF used as a haematopoietic growth factor and its potential clinical role in the treatment of mucositis after chemotherapy and/or radiotherapy.

Until recently, GM-CSF has been regarded exclusively as a haematopoietic growth factor involved in the regulation of proliferation and differentiation of haematopoietic progenitor cells with some additional effects on the monocyte/macrophage system. But it has become apparent that GM-CSF also has multiple pleiotropic activities (Table 1) which seem to be clinically relevant: it plays an important role in inflammatory processes, contributes to the regulation of the immune response through effector cells such as granulocytes, macrophages or lymphocytes, represents an essential growth factor for dendritic cells and is involved in wound healing. Based on these data, GM-CSF is no longer being investigated as a haematopoietic growth factor only.

Genetic engineering has made it possible to produce 'humanised' antibodies which correspond with human antibody molecules and have the advantage of remaining in the body for longer periods of time. Because of their specific antigen-binding, MAbs represent a potentially extremely effective form of cancer treatment by acting on tumour-associated surface structures. Binding of the antibody to the cell surface recruits cytotoxic effector cells such as lymphocytes and macrophages while also activating the complement system. Antibody-dependent cellular cytotoxicity (ADCC) is considered to be one of the major effector functions of non-conjugated MAbs in tumour therapy. Their antitumour activity might, therefore, be augmented if the cytotoxic capability of the effector cells can be increased. Based on this assumption the efficacy of therapeutic MAbs could be further stimulated by GM-CSF which has been shown to enhance ADCC of both granulocytes and monocytes.

Another approach for using the immunostimulating activities of GM-CSF is the combination with anticancer vaccines. The identification of a variety of tumour-associated antigens represents a unique opportunity to induce immunological antitumour responses *in vivo*. Therefore, numerous clinical trials have been initiated, which are devoted to investigating cancer vaccines. This strategy is based on recent developments in cancer immunology which demonstrate the critical role of T cells in anticancer responses and the antitumour activity of cancer vaccines both in animal models and in patients. Antigens recognised by T cells are peptide fragments of intracellular proteins that are bound to the MHC molecules and then expressed on the cell surface. When administered with antigenic peptides, GM-CSF is able to elicit both a specific antibody and a cellular immune response, thus representing a potent adjuvant for the generation of immune responses to foreign proteins as well as peptides derived from a self-tumour antigen. The importance of using GM-CSF as an adjuvant in this setting is further emphasised by the fact that peptides given alone may not be immunogenic, whereas in combination with GM-CSF a strong delayed-type hypersensitivity reaction (DTH) response can be detected.

Dendritic cells (DCs) are highly specialised to initiate primary immune responses by presenting antigens to lymphocytes and have the ability to stimulate even very rare antigen-specific T cell clones. Consequently the DC network plays a central role in the induction of T cell as well as B cell immunity *in vivo* and may, therefore, serve as a natural adjuvant in future strategies for specific immunotherapy with tumour antigens. Recent advances in our understanding of DC biology have been greatly supported by the ability to grow large amounts of DC *in vitro*. GM-CSF in combination with IL-4 is the most important cytokine for the development of functional DC and acts in concert with a varying mixture of other cytokines such as IL-1 and TNF-alpha to direct the development of individual DC subpopulations.

It can be concluded that the therapeutic potential of GM-CSF by far exceeds its known role as a haematopoietic growth factor because of the factor's essential effects within the immune system.

Table 1. *Effects of GM-CSF on the immune system*

• Recruitment of effector cells such as granulocytes, monocytes/macrophages.
• Stimulation of effector cell function.
• Induction of MHC class II antigen expression.
• Upregulation of costimulatory molecules (CD80, CD86) and adhesion molecules.
• Support of naïve T cell growth.
• Enhancement of dendritic cell growth and function.