additional trials demonstrating clinical significance have yet to be undertaken. The use of CSFs may allow dose optimisation and a limited degree of dose escalation in solid tumours. However, whether the increase in dose achieved, before non-haematological toxicity comes into effect, will be sufficient to improve response and survival is as yet unknown.

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Cytokines in Clinical Cancer Treatment Trials: Methodological Aspects

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INTRODUCTION

SEVERAL CYTOKINES have been incorporated into modern clinical cancer treatment. Their inclusion is based on direct and indirect anti-tumour effects, or on a supportive role with cytotoxic drug therapy. Clinical evaluation of these agents differs from that for chemotherapeutic compounds because dose–response relationships are not as clearly defined as for cytotoxic drugs, where a general premise still maintains that a higher dose corresponds to a more dramatic clinical response [1–3]. The optimal dose of cytokines may be unrelated to the maximum tolerated dose (MTD) as a network of interacting variables *in vivo*, controlled by different feedback systems, determines biological responses and therapeutic effects. Thus, phenomena of tolerance and priming may well be observed in this setting.

CYTOKINES AS ANTI-TUMOUR AGENTS

As with other drugs, it is essential to determine toxicity, optimal dose and schedule, as well as suitable routes of administration for cytokines with anti-tumour potential. With respect to safe handling in the clinical setting, it is also recommended to define the MTD. As the final pathway of cytokine-mediated anti-tumour effects will be completely different from one com-

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pound to another, a thorough evaluation of biological responses and their involvement in anti-tumour effects is circumstantial. This is a prerequisite to defining the optimal biological dose (OBD) [4], generally explored in phase Ib studies [5] (Table 1). However, it is a major problem insofar as *in vivo* parameters of host defense and immune responses do not correlate regularly with anti-tumour responses. Neither do they have sufficient prognostic capacity.

The interleukin (IL)-2 experience demonstrates that high dose regimens, approaching the MTD, may be more effective in renal cell carcinoma than low dose regimens [6, 7]. However, stimulatory effects on memory T-cell responses are more readily achieved at lower doses, unfortunately without concomitant effects on clinical responses. The same applied to variations in scheduling, found to be of major importance for induction of either activated natural killer or T-cells [8]. With respect to interferon-α, doses well below the MTD have been shown to be optimal in the treatment of hairy cell leukaemia [9].

There is some concern that the majority of clinical trials with immunomodulating agents have been performed in patients with advanced, widespread disease. Though providing useful information on toxicities, data on anti-tumour effects may be obscured, since immune response may be altered in patients with late stage cancer [10].

CYTOKINES AS SUPPORTIVE AGENTS IN CANCER THERAPY

The availability of haematopoietic growth factors (HGF) has provided an additional application for cytokines in supportive care. They are designed to reverse or ameliorate bone marrow and immunological toxicity of cytotoxic drugs, to support high dose chemotherapy, with or without peripheral blood stem cell (PBSC) transplantation, or to mobilise PBSCs.

Table 1. Sequence of clinical trials for the development of biological response modifiers from Creekmore and colleagues [5]

Phase Ia	Dose-finding study to determine toxicity, MTD and recommended dose(s) for further trials. Pharmacokinetics and biodistribution. Imaging studies for antibodies. Typically 3 to 6 patients per dose level. Single institution trials with rare exceptions.
Phase Ib	Dose-finding study to determine the optimal dose for the desired biological effect(s). Correlations sought between observed clinical anti-tumour responses and biological endpoints. Single institution trials with rare exceptions, usually in centres with highly specialised expertise in immunological monitoring or other required laboratory techniques.
Phase II	Study to determine clinical anti-tumour response rates. Typically 30 patients at a fixed dose, depending on degree of accuracy desired. May be performed in multiple institutions, depending on degree of accuracy desired. May be performed in multiple institutions, depending on complexity. Trials should be performed at the MTD to examine direct effects and the OBD to examine indirect anti-tumour effects.
Phase III	Comparison of therapeutic efficacy with standard therapy control group. Often large trials with several hundred patients per arm, performed in cooperative groups.

MTD, Maximum tolerated dose; OBD, Optimal biological dose.

Clinical trials designed to evaluate the supportive application of HGFs in established anticancer regimens should address specific indications, which include:

- chemotherapy-induced cytopenia
- chemotherapy dose intensification
- recruitment of progenitor cells
- bone marrow and PBSC transplantation

Future prospective clinical trials should evaluate the role of colony-stimulating factors (CSFs) in these indications, in a randomised placebo-controlled fashion. Optimal dose, schedule and combination of different CSFs are issues of similar importance.

Task Force discussion addressed a number of endpoints which should be considered when assessing the clinical use of CSFs in cancer therapy.

(1) survival: in all clinical studies evaluating new cancer therapies, survival must be the primary endpoint for analysis. The response rate and duration of response have long-term clinical significance only when correlated with survival. It is still inconclusive whether treatment with CSFs, following cytotoxic chemotherapy, results in an increased survival benefit for patients.

(2) Safety: as CSFs are used as supportive treatment, toxicity must be maintained within tolerable limits, i.e. WHO grade 2–3. Safety also relates to the overall toxicity, such as a neutropenic period following chemotherapy or a bone marrow or PBSC transplantation. Time to neutrophil recovery has, in the past, been used as an endpoint. However, studies have shown that this does not necessarily translate into fewer infections, decreased antibiotic use or improved survival. Therefore, neutrophil recovery should be documented but remain of secondary interest.

(3) Quality of life: this is an important aspect, however, standardisation of patient questionnaires and overall assessment of quality of life is still unresolved. The Food and Drugs Administration, USA (FDA) continues to encourage its inclusion in protocols.

(4) Cost: absolute costs for therapy will differ by country, region and even by individual hospital within a region. In order to effectively compare the cost of treatment with or without CSFs, the cost implications of patient care in the different treatment arms must be determined. The main components are likely to be the number of transfusions required, days in hospital, days of parenteral nutrition, the prophylactic and therapeutic use of antibiotics and nurse hours. Protocols should clearly define the indications for each intervention.

PROSPECTS

The CSFs have a high cost and it is necessary to identify the most efficient use of these compounds, alone or in combination with other cytokines. This should be done in controlled randomised trials with well defined endpoints as discussed. This may be especially relevant for dose intensification of cytotoxic drugs made possible by the use of CSFs with or without autologous bone marrow transplantation or PBSC transplantation. Expansion of stem cells or certain haematopoietic cell lineages by CSFs *in vitro* constitutes another field of clinical use that points to the role of cytokines in somatic cell therapy.

With respect to the anti-tumour application of cytokines, a more rational approach is mandatory. However, it is strictly dependent on a deeper knowledge of host physiology, e.g. defense mechanisms and tumour immunology. While the mode

of action of chemotherapeutic agents can well be studied *in vitro* due to direct cell toxicity, the evaluation of cytokines requires the complex machinery of host responses—a fact that underlines the central role of *in vivo* studies in this setting. This seems to be even more important with respect to the paracrine mode of action of cytokines like IL-2 or granulocyte–macrophage colony-stimulating factor in induction of tumour antigen-specific T-cell responses being worked out in models of tumour vaccination with cytokine gene transfected tumour cells.

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News

International Microscopy and Image Analysis Conference

The Royal Microscopical Society is organising a conference which will include tutorials, reviews and technical lectures, and posters from experts in the field of instrumentation, analytical methodology in life sciences, cytometry, cytochemistry, cytology and image analysis. An exhibition of the latest microscopes, instrumentation and technology will run concurrently. MICRO 94 will be held on 12–15 September 1994 at the Earls Court Park Inn, Lillie Road, London, U.K. Further details are available from the Royal Microscopical Society, 37/38 St Clements, Oxford OX4 1AJ, U.K. Tel: 0865 248768; Fax: 0865 791237.

Clinical Hyperthermia

The 17th International Symposium on Clinical Hyperthermia will be held in Pavia, Italy between 1–5 May 1994. For further information, please contact either: Secretariat Clinica Citta Di Pavia, Via Parco Vecchio 27, 27100 Pavia, Italy. Tel. 382 463201; Fax 382 576821 or Dr Homayoon Shidnia, Indiana University Medical Centre, 535 Barnhill Drive, Indianapolis, Indiana 46202-5289, U.S.A. Tel. 317 274-8809; Fax 317 274 2486.

Hellenic Biomedical Diaspora

The Third World Conference of the Hellenic Biomedical Diaspora, organised by the Hellenic Medical Society of Great Britain, the Athens Medical Society and the Association Medicale Hellenique de Belgique, will be held in Athens, Greece, between 21–23 October 1994. For further information, please contact: Conference Secretariat, 84 Hippocratous Street, 10680 Athens, Greece. Tel. and Fax 30 1 3626972.

British Oncological Association

The Ninth Annual Meeting of the British Oncological Association will be held at the University of Surrey, Guildford, U.K., between 10–12 July 1994. For further details, please contact the Meetings Secretariat, BOA 1994, Congress House, 55 New Cavendish Street, London W1M 7RE, U.K. Tel. 071 486 0531; Fax 071-935 7559.

Bone Marrow Transplantation

Sutter Cancer Center presents the 1994 International Symposium on Bone Marrow Transplantation on 17–19 September 1994 at the Fairmont Hotel in San Francisco, California, U.S.A. Designed for physicians and nurses, the program will include topics such as autologous transplantation, allogeneic transplantation, matched unrelated transplantation, peripheral blood stem cells, and the economics of bone marrow transplantation. For more information, contact Sutter Community Hospitals CME Department at 1-800-777-0231.