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Biological Response Modifiers

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COMPARED to cytotoxic agents, a variety of differences exists not only in the principles of preclinical investigation, but also in the *in vivo* application of biological response modifiers (BRMs). Our *in vivo* experience until now has been based on clinical trials with interferons, interleukin-2 and haemopoietic growth factors. Currently, several phase I and early phase II trials are underway with various other cytokines.

Treatment with biologicals generally means modulating a cascade of events, and these broad regulatory effects must be carefully studied for unexpected results. As BRMs do not act independently but within a complex network, we are only beginning to understand side effects or that the whole range of positive effects cannot be foreseen from experimental animal studies. Furthermore, induction of secondary effects may be related to dosage and timing of cytokine application.

It will require the presence of the complete immune system and long-term clinical studies to translate the impact of immunomodulatory *in vitro* effects to *in vivo* implications.

A further difficulty in BRM therapy is the problem of dosage. We may have been partially blinded by our experience with cytotoxic agents and by the fact that certain tumours, such as renal cell cancer, can be successfully treated with cytokines, like interferons, at dose levels where they act more by direct cytotoxic mechanisms than by immuno-modulation. In biological therapy, we must administer the optimal immunomodulatory dose (OID) rather than maximally tolerated dosages (MTD) which, from our experience with cytotoxic agents, we are accustomed to using to eradicate a tumour.

An example of the possible pitfalls of dosage is represented by IFNγ, where a bell-shaped curve of activity has been shown *in vitro* [1] and confirmed *in vivo* [2], suggesting that too high a dosage may suppress a desired response and too low a dosage may fail to invoke it. From this example, it can be seen that a cytokine dose might be independent of the MTD, and also that *in vivo*, more is not necessarily better, as was reported for recombinant interferon-alpha (IFNα), for instance in patients with metastatic carcinoid tumours [3].

We expect too much from immunomodulatory agents when we aim to treat or even cure a high tumour burden. The possible value of biological agents in cancer therapy definitely lies more in the prolongation of complete or partial remissions achieved after surgery, chemotherapy or radiotherapy, when the tumour load had been reduced to a level where the body has a chance of destroying minimal residual disease through its own immunosurveillance. As inevitable alteration of the immune system by chemotherapy hampers this physiological fight against malignant disease, clinical trials with cytokines given after cytoreductive treatment are necessary aiming to prolong remission or reduce the relapse rate.

Furthermore, immunomodulation rather implies that long-term effects might be achieved only after some months of treatment. Stable disease may occur instead of regression which is essential in an adjuvant setting, provided life quality is maintained. Target cells for immuno-modulation can belong to the lymphatic system, but the monocyte/macrophage system also plays an important role in tumour surveillance. Cytokines such as GM-CSF [4], M-CSF [5] or IL-3 [4] have been shown *in vitro* to stimulate antitumour cytotoxicity of macrophages, suggesting a possible clinical application of these factors, for instance in an adjuvant setting. G-CSF [6] and interleukin-8 [7] are able to stimulate neutrophil function in disorders like myelodysplastic syndromes (MDS), where deficient neutrophil function increases the risk of lethal infection.

INTERFERONS

Interferons have many cell regulatory activities and IFNα has demonstrated activity in a broad range of malignant disorders [8]. There are now numerous data on its effects in animals and in man, but no clear conclusions can be reached concerning the way(s) it inhibits cancer. Although IFNγ has been shown to have dose-dependent antitumour activities *in vitro*, it is active at low dosage for hairy cell leukaemia [9] or APUDoma [3].

Thus, despite more than one decade of clinical studies, the development of IFNα is still in its early developmental stages as such basic parameters as optimal dose and therapeutic schedule remain to be determined. We only recently learned the value of maintenance treatment with IFNα in patients with multiple myeloma in partial or complete remission [10].

A further therapeutic approach for IFNα and perhaps other cytokines might be the biomodulation of cytotoxic agents [11].

INTERLEUKIN-2 (IL-2)

IL-2 has been introduced into clinical trials because of its ability to generate lymphokine-activated killer (LAK) cells which show a greater range of target cell killing than NK or cytotoxic T cells [12]. Therapeutic studies with IL-2 have aimed to induce the antitumour effects of lymphocytes with or without the *in vitro* generation of LAK cells. Overall, however, IL-2 therapy has not fulfilled the high expectations made of it to date. Clinical trials aiming to apply IL-2 in minimal residual disease are currently being initiated.

The relation of IL-2 to the soluble form of its receptor warrants further *in vivo* investigation as it may improve our understanding of the immune system. Production of IL-2 is mainly restricted to activated mature T lymphocytes and regulates growth of T cells at an autocrine level [13]. Only when antigens bind to the

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T cell receptor in the presence of macrophages or cytokines are T cells triggered to secrete IL-2, enter to S phase and temporarily express IL-2R, which can be released into the serum as a soluble IL-2 receptor (sIL-2R) [14].

An increase in serum sIL-2R expression has been reported in patients with various malignant disorders. In some of them, the sIL-2R serum level appears to be closely correlated with progression and response to therapy [15]. In this régard, sIL-2R has been suggested as a "blocking factor" produced by the malignant cells to inhibit the host's immune response to the tumour. Thus, it is tempting to speculate that exogenous application of IL-2 might help overcome this dysregulation of the immune system.

A dilemma is the lack of appropriate preclinical models. New research approaches must therefore be defined, and close cooperation among preclinical and clinical scientists must be promoted.

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Combined Modality Treatment in Small Cell Lung Cancer (SCLC)

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DESPITE THE accepted use of chemotherapy as primary treatment in SCLC, with increasing intensity and sophistication of drug treatment protocols, more than 90% of patients relapse and die from recurrence of chemoresistant tumour. One of the many strategies used to prolong remission and increase long term survival was the introduction of irradiation to bulky sites of primary and metastatic disease and other common sites of failure, including prophylactic cranial irradiation (PCI). Moderate radiation doses can reduce by half the expected lifetime risk of recurrences both at primary site (60 versus 30%) and in the brain (30 versus 10%), but numerous randomised trials have failed to translate this "local control" advantage into survival benefit. There could be a number of reasons for this, related to the population of patients studied, to the technical aspects of radiation delivered or to increased toxicity resulting from the use of combined modality therapy. The most likely, however, is the methodological problem of sample size needed to show small differences. This has been addressed finally by a meta-analysis combining results of 13 randomised trials and 2001 limited stage SCLC patients. In this large group, the relative risk of death for patients receiving combined modality therapy was 0.86 (95% CI

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