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Commentary

New Immunotherapeutic Approaches: The Use of Cytokines to Stimulate the Immune System or to Control the Growth of Malignant Lymphoid Cells

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(A COMMENT ON: Stahel RA, Sculier JP, Jost LM *et al.* Tolerance and effectiveness of recombinant interleukin-2 [r-met Hu IL-2 (ala-125)] and lymphokine-activated killer cells in patients with metastatic solid tumors. *Eur J Cancer Clin Oncol* 1989, **25**, 965–972.)

IMMUNOTHERAPEUTIC approaches to cancer are based on the assumption that malignant cells express molecules (antigens) which are different from those expressed in their normal counterparts. Historically, two fundamentally different approaches have been used: the first consists of immunizing animals with tumor cells and then injecting the antibodies—in their modern version, monoclonal antibodies—into the patients. This passive immunotherapy assumes that tumor-associated antigens may immunize heterologous animals, even if they are not immunogenic in the cancer-bearing host. It can even be used in the absence of tumor specific antigens, if injected antibodies recognize the tumor better than normal cells. Presently, passive immunotherapy trials are conducted with monoclonal antibodies linked to toxins, drugs or isotopes (reviewed in [1]). The second immunotherapeutic approach is based on the hypothesis that tumor-specific antigens may be immunogenic for the cancer-bearing host. Therefore, the stimulation of the host's immune system, either specifically by tumor cells (antigens) or non-specifically with immunostimulants, might have anti-tumour effects.

Although positive results using both approaches have been reported from time to time [1, 2], the analysis of the overall data is rather disappointing. This lack of promise is perhaps due to either a lack of tumour-specific antigens or an insufficient level of stimulation of the immune system. In the first case, immunotherapy would have no future; in the second new ways to stimulate immune effector functions may improve anti-tumor responses. Today the availability of cytokines to effectively stimulate the immune system leads to the further investigation of non-antigen-specific immunostimulation.

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ACTIVATION OF EFFECTOR FUNCTIONS OF THE IMMUNE SYSTEM WITH CYTOKINES

One of the major steps in understanding of the immune system has been the identification, during the last decade, of the molecules which mediate the interaction between immunocompetent cells and/or are responsible for effector activities. Among them some have received special attention for their use in the treatment of cancer. Interferons (IFNs), which are endowed with both direct anti-tumor activities and immunoregulatory functions, were the first cytokines that were extensively tested in clinical trials and that have shown therapeutic efficacy in several hematological malignancies and a few solid tumors [1]. Interleukin 3 (IL3), as well as the other colony stimulating factors (CSF), can be used after high-dose chemotherapy followed or not by autologous bone-marrow transplantation [1]. The pioneering work of Rosenberg and his colleagues, in animals [3] and in humans [4] has initiated therapeutic trials using interleukin 2 (IL2) in various protocols throughout the world. IL2 is a potent inducer of cells which become capable of lyzing tumor cells. These lymphokine activated killer (LAK) cells may be derived from NK or T lymphocytes. Originally,

it was thought that IL2 activates mainly NK cells in peripheral blood, lymphocytes and cytotoxic T cells when lymphocyte-infiltrated tumors are treated *in vivo*. This assumption may have to be reconsidered in the light of data from the ongoing clinical trials. Therapeutic effects have been obtained in animal models as well as in the treatment of several metastatic human tumors, especially melanoma, renal cell cancer and lymphoma [1, 5–7]. Regardless of the antigen recognized, these results demonstrate that an effective stimulation of the immune system may result in anti-tumor activity.

The therapeutic effect of IL2 seems to be a direct consequence of the activation of immune effector cells since high doses of IL2 are more efficient than low doses and association with activated lymphocytes or interferon α is more effective than IL2 alone [3–7]. While this scheme oversimplifies the results—and various exceptions can be found—it basically reflects what can be concluded from the various, though not random, trials that can be analyzed. In any case, the relationship between therapeutic effect and immune activation is clearly established and for the first time, unequivoqually.

The secondary toxic effects of IL2, and infused cells, are important and cover a wide spectrum from fever, chills, nausea, diarrhea, erythrodermia to mental confusion, cardiac toxicity and strong capillary leak syndrome [4, 8]. Until now, therapeutic success could not be dissociated from the secondary effects that are a direct result of the pleiotropic activities of the cytokine.

Although not all trials have generated definitive conclusions, it is clear that the therapeutic results reported in melanoma with [5, 6] or without [5, 7, 8] activated cells, in renal cell carcinoma [5, 8] and in a few other tumors [5, 7] have brought us to the threshold of a new era in cancer treatment. They have established the use of cytokines as a fourth modality to treat cancer patients [9]. However, major problems remain to be solved before this approach can be generalized.

The first problem to consider is toxicity. A heated debate has arisen between proponents of immunotherapy and those who disagree with them. The latter group argues that even if IL2 is beneficial in the treatment of metastatic tumors which are resistant to other therapy, due to its toxicity, it will never become a major treatment for cancer. Indeed, the fact that the success of IL2 therapy seems to be related to the amount of the cytokine given to the patients may support this position. However, with the development of the clinical trials, it appears that the toxic effects, particularly capillary leak syndrome, can be monitored by controlling the liquid supply to the patients. Moreover, toxicity is, for most symptoms, reversible during the hours following the infusion of IL2 [8]. Special care must be taken with the amounts and kinetics of administration when cells are infused with IL2, but with the proper conditions the adverse effects can also be controlled. With the experience that we have gained after 1 year of different therapeutic trials using IL2, I feel that treatments at the maximal tolerated doses are useful and can be managed in intensive care units. They, of course, require that patients are in good general condition (Karnovsky index >60), which therefore alters the interpretation of the overall therapeutic effects especially when considering patients survival compared to other treatments. They also require a permanent follow-up of the patients during treatment to decide when, if necessary, to interrupt IL2 infusion, in order to maintain an equilibrium between the dose-related beneficial and harmful effects.

A second fundamental question about IL2 therapy concerns the small number of responding tumors—why are melanoma and renal carcinoma sensitive and not breast or lung carcinomas, responsive, for example? Two theoretical answers to this question are possible: first, most tumors do not express tumor-specific antigens and will therefore not be sensitive to immunotherapy; alternatively, the proper way to provoke the immune effector reactions in these tumors has not yet been found. It is not possible to discriminate between these two possibilities today but the answer to this question will make immunotherapy a major or a minor treatment of cancer. In the coming years, it is therefore essential to pursue therapeutic studies in various types of cancers with IL2 alone, but also with IL2 associated to other cytokines [IFNs, tumor necrosis factor (TNF), IL4 etc.] or to cells [LAK, tumor infiltrating lymphocytes (TIL)]. In this respect, the field opened by the use of TIL not only as effector cells but as vectors of genes, opens a new realm of possibilities for investigation. If most tumor cells do not express specific antigens but have an antigenic distribution such that tumor-infiltrating lymphocytes are concentrated at the tumor site, the latter, transfected *ex vivo* with genes coding for IFN, TNF, etc. could be used as novel forms of 'cellular immunotoxins'. Finally, it is possible that administration of a combination of different cytokines and effector cells may increase the potency of the therapeutic effects. It is conceivable that in a heterogeneous tumor, some cells are sensitive to LAK, others to TIL, with sensitivity being increased by IFNα or decreased by IFNγ. Now that the first therapeutic trials with IL2 have advanced beyond a point of turning back, basic research in experimental models and in humans are much needed to move forward in establishing immunotherapy as a major tool in the treatment of cancer.

THE CYTOKINE APPROACH FOR THE TREATMENT OF LYMPHOID MALIGNANCIES

The cytokines involved in the control of growth and differentiation of normal lymphocytes sometimes also play a role in the development of malignant lymphoid cells. IL2 and IL2 receptors have been implicated in the growth of T cell lymphomas, especially those induced by HTLV I. It has been suggested that the low affinity receptor for IgE (FcεR), also known as CD23, and its soluble cleavage product, IgE-binding factor (IgE-BF), act in an autocrine loop in Epstein–Barr virus-transformed (EBV-transformed) B cell proliferation [10]. Interleukin 6 (IL6) is produced by myeloma cells—or cells in their vicinity in the bone marrow—and may be the major growth factor for the development of myeloma and plasmacytoma [11]. A low molecular weight B cell growth factor (BCGF) has been implicated in the pathogeny of hairy cell leukemia [12]. The number of normal growth factors and receptors which play a role in malignancy is steadily increasing and the therapeutic approaches based on inhibition of their activity is under way. Since, in the cytokine cascade, some factors induce while some inhibit the action of other cytokines, it is tempting to use cytokines to control growth factor activities. Here, we summarize two such approaches.

IFNα treatment of hairy cell leukemia

IFNα, though not IFNγ, has proven efficient in the treatment of hairy cell leukemia. The mechanism of its effect has recently been analyzed. Hairy cells are malignant cells of the B cell lineage whose growth depends on the presence of BCGF [12]. Treatment *in vitro* with IFNα, but not with IFNγ, induces their resistance to the stimulatory signal of BCGF by interfering with the intracellular transduction of this signal [12]. B lymphocytes from patients receiving IFNα therapy are also insensitive to BCGF stimulation suggesting that the therapeutic effect of IFNα is indeed due to the inhibition of an autocrine growth factor loop [12].

Fc receptors (FcR), immunoglobulin-binding factors (IBF) and B cell malignancies

Receptors for the portion of immunoglobulins (FcR) and their soluble cleavage products, IBF, are involved in the control of B cell proliferation and differentiation to antibody producing cells [13]. Among them, FcεR, IgE-BF, FcγR, and IgG-BF have been shown to act on malignant B cells. It has been suggested that FcεR is a receptor for B cell-specific growth factors [10], with IgE-BF itself exerting growth factor activity [10]. In this respect, it is of interest to note a Rai-stage-related increase of serum levels of IgE-BF in patients with B-chronic lymphocytic leukemia [14]. In murine *in vitro* experiments, it has been shown that FcγR-positive, IgG-BF-producing T cells are capable of inhibiting the growth and differentiation of hybridoma B cells [15]. In addition, myeloma-bearing mice have elevated numbers of FcR-positive T cells as well as elevated levels of IgG-BF in their serum [16], suggesting a correlation between B cell malignancies and the production of FcR and IBF. In humans, the genes coding for the various FcγR have been cloned and their circulating forms (IgG-BF) are being tested in various diseases. This work may eventually form the foundations for the therapeutic use of these factors, for instance, to inhibit an IL6-dependent autocrine loop.

CONCLUDING REMARKS

I have briefly summarized two new immunotherapeutic approaches for the treatment of cancer. The first, based on the hyperactivation of the immune system, is in principle applicable to most tumors, while the second may represent an 'à la carte' treatment of a restricted number of malignancies. The use of these treatments is limited by their toxicity and their cost. The rationales for the various therapeutic approaches as functions of the pathologies need to be more thoroughly discussed, and statistically exploitable trials are also necessary. However, immunotherapy has already established itself as a viable treatment of cancer, still in its primary stages, promising an interesting development.

Finally, if cytokines are to be used in treating a large spectrum of tumors, their cost becomes a pertinent issue, especially if cells cultured *in vitro* are necessary. This problem is not unique to cancer treatment and clinicians and scientists are far from being the only individuals concerned. It is clear that the economic issues involved in implementing these new therapeutic approaches will strongly govern their actual use.

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