Biological therapy

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This is the seventh in a series of articles examining recent developments in cancer

Biological therapy for cancer may be defined as a treatment that uses biological materials, usually cells or cell products, which either have direct effects on tumour cell proliferation or differentiation or modify the host biological response to the malignant disease.¹ The subject has a long history, extending back to the last century when patients were treated with extracts of infectious organisms or tumours, with occasional success claimed. In the 1970s immunotherapy with BCG and allogeneic or autologous tumour cells was widely investigated, but carefully performed clinical studies failed to show consistent success. However, in the past few years there has been increasing interest in biological therapy for cancer and considerable research activity. In this article we will try to explain the reasons for the increasing current interest and try to discern whether there is really promise of progress.

Potential of biological therapy

The rekindling of interest in biological therapy for cancer followed inevitably from the developments in biology in the 1970s and 1980s. In particular, the techniques and knowledge generated by molecular biologists transformed our understanding of cell proliferation and differentiation and cell to cell interaction in the immune system and elsewhere. The identification of the molecular basis of many biological processes has presented new ideas for biological treatment. Perhaps the best example of this lies in the characterisation of the T cell growth factor interleukin 2, which promotes the proliferation of T lymphocytes as well as stimulates other cytotoxic cell populations and macrophages. The biology of interleukin 2 led to experimental cancer therapy, and Rosenberg *et al* introduced it into the clinic to enhance immune responses against tumours with limited but definite success.² In addition, DNA recombinant technology has allowed the expression of the genes for many potent biological materials in prokaryotic or eukaryotic systems, resulting in the production of large quantities that can be readily purified for clinical use. Molecular biology has not only presented the ideas for biological therapies but has also presented us with the means of carrying out those ideas by using recombinant proteins.

Some of the agents now available have direct anticancer effects: interferons have antiproliferative effects; tumour necrosis factors have a direct cytotoxic effect. However, others such as interleukin 2 or interleukin 6 may act by enhancing naturally occurring responses to cancers.³ Other biological factors may be useful in reducing the toxicity of conventional chemotherapeutic drugs—for example, haemopoietic growth factors ameliorate the bone marrow toxicity of some cytotoxic drugs. The interaction of biological treatments with chemotherapy or radiotherapy offers valuable combined approaches which already have shown some promise.⁴

Although current interest has concentrated on recombinant proteins, other biological approaches including monoclonal antibodies, active immunisation, and adoptive cellular therapy are being studied. Monoclonal antibodies directed against tumour associated antigens have been used as anticancer agents in many

centres and tumour regression has been described, although it is uncommon and short lived so far. Antibodies to idiotypic immunoglobulin determinants on B lymphomas are a theoretically attractive treatment because each idio type is tumour specific, but results are still disappointing, as are those for monoclonal antibodies to antigens associated with melanoma and epithelial cancers. Improvements may come from clearer understanding of basic immunology, genetically engineered antibodies, or the use of monoclonal antibodies in combination treatments.^{5,6} Active immunisation with melanoma tumour antigens can apparently produce tumour regression⁷ and needs further research. Adoptive transfer of cells achieved popularity after the work of Rosenberg *et al*² but has not been proved to add to the effects of interleukin 2.⁸

Cytokines

The recombinant proteins of greatest current interest are cytokines. Cytokines are low molecular weight polypeptides (usually less than 80 kDa) produced by a wide range of cell types. They usually act locally in a paracrine or autocrine fashion but may remain bound to the cell surface in some circumstances. They are produced in response to inducing signals, have a short half life and high biological potency, bind to high affinity specific cell surface receptors, and affect cellular growth (stimulation or inhibition) or cellular differentiation, or both.^{1,9} Cytokines have usually been discovered as the result of the identification of a particular action such as the antiviral effect of interferons or the T cell growth effects of interleukin 2. They almost all have multiple actions, and the first activity described may not be the most important to the oncologist. The table lists the cytokines which are being clinically evaluated or are nearing clinical trials, together with known actions and therapeutic potential. The list is impressive, the biology complex, and the therapeutic potential considerable. There are a few common themes about our present state of evaluation of cytokine therapy.

Firstly, several cytokines have definite anticancer activity in humans. Interferon alfa, interferon gamma, and interleukin 2 have a small but consistent effect against haemopoietic cancers, renal cancer, and melanoma and less consistent effects against other cancers.⁵ The activity of tumour necrosis factor is much less, and the value of interleukin 4, interleukin 6, and the growth factors or their antagonists is much less clear. Secondly, so far (with the exception of interferon against hairy cell leukaemia) the effects are small and benefits are found in a minority of patients.

Thirdly, we still do not know how to use any cytokine properly. The ideal dose and schedule of interferon alfa has not been established precisely despite 15 years of clinical research, and the optimal dose, schedule, and route of administration for interleukin 2 are still unknown. Most studies have aimed at finding a use for cytokines in treating established, advanced, and poor prognosis cancers. There is some evidence suggesting that their most useful role is as a maintenance treatment given after initial induction of remission by chemotherapy, surgery, or radiotherapy.

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Lastly, cytokines have so far been quite toxic.^{1-3,9} The pleiotrophic effects on cells and organisms seen in the laboratory are manifest as adverse reactions when cytokines are used in the clinic. Febrile reactions, endothelial toxicity, hypotension, and renal toxicity have all been seen. The toxicities are different from those associated with conventional cytotoxic chemotherapy but are not less severe. The reagents have to be handled with the greatest care in the clinic.

Clinical activity of cytokines

INTERFERONS

Interferon alfa, for which there are at least 20 genes on chromosome 9, is in many ways the prototype cytokine. Interferons beta and gamma are encoded by single genes on chromosomes 9 and 12 and a distinct role for them has not yet been determined despite some biological differences from interferon alfa.¹⁰

Interferon extracted from leucocytes was introduced into clinical practice in the 1970s and the initial effects were promising, particularly in the treatment of multiple myeloma and osteosarcoma. Unfortunately, this promise was not sustained when larger numbers of patients were treated and interferon fell largely into disrepute. This situation has been altered as a result of five observations:

- A large and consistent benefit for patients with hairy cell leukaemia, a rare form of leukaemia mainly in middle aged men, was observed.¹¹ Although not curative, giving interferon alfa transformed the prognosis of patients with this disease with clinical remissions and excellent quality of life after the introduction of treatment.
- Responses to interferon with reduction in tumour volume were seen with several relatively common solid cancers such as renal cancer, melanoma, and neuroendocrine tumours. These effects occurred in a substantial minority of patients but were not usually longlasting and probably never curative.³
- Interferon alfa is capable of maintaining remissions induced by chemotherapy, especially in multiple myeloma and non-Hodgkin's lymphoma, despite its rather poor performance in treating patients who have active or advanced diseases.¹² Very few other anticancer treatments can maintain remissions. Even diseases like Hodgkin's disease or testicular cancer which are very sensitive to cytotoxic chemotherapy do not benefit from prolonged maintenance chemotherapy. The discovery of any treatment that can maintain remissions, particularly when these remissions are relatively frequent, as in the haemopoietic cancers, must be welcomed and explored further.

Interferon alfa may be particularly important in epithelial cancers such as breast and ovarian cancer in which responses to chemotherapy occur in most patients with advanced disease but most die as a result of relapses within one or two years.

- Interferon alfa combined with cytotoxic chemotherapy seems to increase the response rate significantly, with lengthy remissions extending to one or two years reported in some patients with advanced colorectal cancer.⁴ Although not yet confirmed by a randomised prospective trial, this treatment seems to offer the prospect of useful remissions in this drug resistant disease.
- Prolonged treatment with interferon alfa seems to be capable of producing cytogenetically defined remissions of chronic granulocytic leukaemia.¹³

INTERLEUKIN 2

The scientific basis of treatment with interleukin 2 was among the most exciting topics in oncology in the 1980s. The prospect of an agent that directly amplifies immune responses to tumours was greeted with great enthusiasm. Rosenberg *et al* showed that high doses of interleukin 2 given together with the passive transfer of lymphocytes which had been stimulated by interleukin 2 in vitro were capable of producing remissions in a substantial minority of patients with a wide range of cancers, particularly renal cancer and melanoma.² However, there was high associated toxicity. More recent work using different methods of administration such as continuous intravenous infusion or subcutaneous injections, has confirmed that this approach is capable of producing tumour regressions and that some of these remissions last several years, with some evidence of prolonged survival (M Jones *et al*, unpublished data).

TUMOUR NECROSIS FACTOR

In many ways tumour necrosis factor has been the most disappointing of the cytokines tried as potential cancer treatments.¹⁴ It is the only cytokine whose existence was suspected as the result of the discovery of anticancer activity in the serum of mice primed with BCG and then exposed to endotoxins. It exerts powerful antitumour effects in model systems both directly on cells in vitro and indirectly in vivo, probably through its effects on endothelial cells and the resulting destruction of tumour vasculature. Secondary release of other cytokines may also be important in the effects of tumour necrosis factor. In humans, however, it is toxic and associated with only occasional regressions of cancer,¹⁴ and the concentrations achievable in the blood of patients are much lower than those which are

Action and therapeutic effects of cytokines

Name	Action	Therapeutic effects
Interferon alfa	Antiviral, antiproliferative, immunomodulatory	Remissions in renal cancer, melanoma, hairy cell leukaemia, and chronic leukaemia.
Interferon gamma	Activation of natural killer cells and macrophages	Maintenance in myeloma
Granulocyte colony stimulating factor	Stimulation of haemopoietic progenitor cells in bone marrow to proliferate and differentiate producing colonies of mature end cells.	Some antitumour activity
Macrophage colony stimulating factor	Enhancement of end cell function. Granulocyte and macrophage factors are lineage restricted, granulocyte macrophage factor and interleukin 3 affect all three lineages	Enhancement of bone marrow recovery and end cell function. Increased dose and frequency of chemotherapy. Reduction in incidence of, and faster recovery from, infection
Granulocyte macrophage colony stimulating factor		
Interleukin 3		
Interleukin 2	Expansion and activation of T (and B) lymphocytes	Antitumour agent in renal cancer and melanoma
Interleukin 4	B cell growth factor, increase T cytotoxicity, inhibit lymphokine activated killer cell formation	Early clinical trials
Interleukin 6	B cell growth factor. Modulates haemopoietic progenitor cells to respond to lineage restricted factors	Use of antagonists or antibodies in myeloma and autoimmune disease. Anticancer effect in laboratory
Tumour necrosis factor	Cytotoxicity in vitro and model systems	Occasional antitumour activity. Antibodies to tumour necrosis factor may lessen severity of shock
Epidermal growth factor	Fibroblast growth stimulation	Overproduction of the factors or abnormal expression of their receptors, or both, may stimulate proliferation of malignant cells
Transforming growth factor alfa	Growth inhibition	
Platelet derived growth factor		
Transforming growth factor β	Growth stimulation or inhibition depending on cell concerned and the presence of other factors	Molecular variants of factors or role receptors have putative role as anticancer agents

Scan of patient with metastatic renal carcinoma with pleural and pulmonary disease (top) and hypercalcaemia. Treatment with 20 day intravenous interleukin 2 cleared his disease, except for small area of pleural thickening (bottom). Remission continued at 6 months

necessary to produce regressions of cancers in experimental models.¹⁴ Better understanding of the biology of tumour necrosis factor, its inhibitors, and its interaction with other cytokines and with cytotoxic drugs may yet find it a useful role as an anticancer drug. At present such a use is highly speculative, and in some circumstances tumour necrosis factor can stimulate tumour growth in vitro.

HAEMOPOIETIC GROWTH FACTORS

The evidence that haemopoietic growth factors can stimulate the bone marrow in man and reduce myelosuppression by cytotoxic drugs is now conclusive.¹⁵⁻¹⁷ These agents have an established role in treating patients with life threatening sepsis with neutropenia. The lineage specificity of the available haemopoietic growth factors means that their value is greatest for patients with neutropenia. Whether the marrow stimulation achieved with haemopoietic growth factors will result in a general improvement in prognosis for patients with cancer is unclear. Sepsis is reduced, but most neutropenic sepsis can be handled safely with modern antibiotics. Perhaps the central question is whether haemopoietic growth factors will allow increased doses of cytotoxic drugs and whether this will result in more remissions and perhaps more cures. Although increased tolerance to chemotherapy can be achieved, it is not yet clear that the dose escalation which is possible will result in major benefits in terms of quantity or quality of life for patients.¹⁷

Conclusion

Biological treatments, particularly DNA recombinant cytokines, have an established place in the management of some human cancers. Induction of long term remission in hairy cell leukaemia by interferon, maintenance of remission in multiple myeloma,

and the treatment of renal cancer with interferon or interleukin 2 are now part of established practice in oncology in many centres and are recognised by regulatory authorities in most European countries. The mechanisms of action of cytokines clearly present possibilities different from those of cytotoxic chemotherapy. However, the benefits of biological therapies at present are relatively small and limited to a small proportion of patients.

It is too early to conclude that further research into biological therapy will result in larger benefits for larger numbers of such patients. There are, however, some encouraging signs. In 1992 biological therapy is in a position rather similar to that of chemotherapy in the 1940s. A small number of active reagents exist, only a minority of patients with any particular disease seem to respond, and the responses are usually of short duration with occasional durable remissions or cures. In the three decades after the 1940s chemotherapy developed rapidly, with new drugs, combination chemotherapy, high dose treatments, and adjuvant chemotherapy. These led to impressive advances in treatment of paediatric cancers, haemopoietic cancers, and germ cell tumours, resulting in the cure of many patients with these cancers by the early 1980s. Will the next few decades see similar advances in our understanding and use of biological therapy? Will these advances occur this time in common cancers? The evidence available certainly suggests that research into this application of the new biology to medicine is worth pursuing.

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