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Tumour Necrosis Factor as an Anticancer Agent

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WHEN the human gene encoding tumour necrosis factor (TNF) was cloned in 1984 [1], there was excitement at the prospect of large amounts of purified recombinant material for clinical cancer trials. This factor was potentially an important advance in cancer treatment. The historical background [2] and preclinical studies with partially purified material [3] gave grounds for cautious optimism. Manda *et al.* [4] reported on the antitumour effect of TNF and 5-fluorouracil in the murine Meth A sarcoma model, and highlighted the importance of tumour blood supply to the antitumour effect of TNF. This adds to the large body of data now available in animal models on the antitumour efficacy of TNF as a single agent, or in combination with other cytokines and cytotoxic drugs. However, the promising results in animal models have not, as yet, been reflected in clinical trial data. Six years after the TNF gene was cloned there is little evidence for antitumour activity of this agent in man, although most of the completed studies are phase I trials [5]. An understanding of the history of TNF and the advances made since the gene was cloned provides some explanation for the disappointing results obtained in clinical cancer trials. Such information may indicate ways in which the undoubted power of this cytokine could be effectively used singly or in combination with other antitumour agents. In addition, there is now evidence that endogenous TNF production may be inextricably bound with growth and metastasis of some tumours, and that neutralization of TNF activity may be of potential therapeutic benefit.

HISTORY

The history of TNF begins with anecdotal observations over several centuries, of tumour regression and even cure, in advanced cancer patients suffering concomitant bacterial infections. A case history of a patient cured of a recurrent lymphosarcoma after two attacks of erisipelas led a New York surgeon, W.E. Coley, to treat his patients with filtered medium from bacterial cultures. Over 1200 advanced cancer patients were treated with 'Coley's mixed toxins' and the results make interesting reading [2]. Injection of toxins, generally in or near the tumour site, caused high fever, chills and rigors—side-effects reminiscent of cytokine therapy. In some patients leucocytosis, anorexia, nausea and vomiting were seen. The complete response rate was 22% (270 of 1200 patients). In 30 case histories [2], patients with advanced and metastatic tumours such as sarcoma, melanoma, ovarian and cervical carcinoma were reported to be cured of their disease. This form of cancer therapy was discontinued primarily because of the inability to obtain standard preparations, the variable results obtained and the advent of chemotherapy and radiotherapy.

Experimental animal studies continued with bacterial extracts and led to the discovery that bacterial endotoxin would cause necrosis of murine tumours, particularly the experimental murine Meth A sarcoma. In 1975, the observation was made that bacterial endotoxin *per se* did not cause tumour regression, but that this was due to an induced host factor, 'tumour necrosis factor' [6]. In the intervening 10 years before the TNF gene was cloned and large quantities of pure protein became available, experimental studies showed that TNF was produced by macrophages and that this factor killed some tumour but not normal cells. Moreover 'tumour necrosis serum' obtained from endotoxin treated animals caused regression of murine tumours and human tumours in nude mice, sometimes with just one administration [3].

TNF AS A CYTOKINE

Studies with purified recombinant TNF have revealed numerous cell regulatory activities, indicative of its being an important mediator of inflammation and immunity, and a key member of the cytokine network. TNF is able to induce cytokines such as interferon (IFN) beta, interleukin-1 (IL-1), IL-6, granulocyte–macrophage, granulocyte, and macrophage colony-stimulating factors, and other mediators such as platelet activating factor, and prostaglandins [7]. TNF has a wide range of actions on different normal cell populations *in vitro*, e.g. endothelial cells, fibroblasts, adipocytes, keratinocytes, osteoclasts, B and T cells, neutrophils, eosinophils, and macrophages. It is not surprising that TNF probably plays a crucial role in many processes of infection, inflammation, autoimmune disease, and tissue remodelling [8]. TNF is cytotoxic/cytostatic for a variety of tumour cell lines *in vitro* [9]. However, TNF can be cytotoxic for normal cell populations such as endothelial cells under certain *in vitro* conditions [10]. Moreover, the majority of tumour cell lines (approximately 70%), are not growth inhibited by TNF. The precise mechanism of TNF cytotoxicity is not known, and several factors such as activation of phospholipase A2, serine proteases, superoxide generation, and activation of lysosomes may be involved [11–14]. With the cytotoxic effect, TNF can also induce mechanisms that protect cells against its own cytotoxic effect, e.g. the induction of manganese dependent superoxide mutase [15].

EXPERIMENTAL MURINE TUMOURS

Treatment of murine tumours with recombinant human or mouse TNF confirmed that the pure recombinant product would induce necrosis of the Meth A sarcoma [16]. Much of the evidence suggested that in this, and other syngeneic models, the action of TNF was indirect. The tumour cells themselves were not killed by TNF *in vitro*, and tumour necrosis was only seen when the tumour was adequately vascularized. TNF was reported to induce a rapid extravasation of red cells into the tumours, and lead to intravascular deposition of fibrin [17, 18]. In some of the highly immunogenic murine tumours, the action of TNF was, at least partly, T cell dependent, and cured mice were resistant to rechallenge by the same tumour cells [16]. Thus the antitumour action of TNF in murine cancer may be two-fold, i.e. via effects on tumour vasculature, and stimulation of a specific host immune antitumour response. It is not clear how such mechanisms relate to poorly immunogenic human tumours.

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NUDE MOUSE MODELS

Recombinant TNF has been shown to induce regression of some human tumour xenografts in T cell deficient nude mice, particularly if given intratumourally [19]. Systemic administration was rarely effective. When TNF was given intraperitoneally to treat intraperitoneal human ovarian cancer xenografts, a 2–3-fold increase in lifespan was seen [20]. However, further studies revealed that although TNF therapy induced some necrosis of free floating tumour clumps, other tumour cells in TNF treated mice adhered to the peritoneal surface and formed multiple intraperitoneal deposits [21]. Tumours in control mice did not behave in this way, suggesting that TNF had stimulated tumour adherence and implantation. Further evidence of this 'undesirable' effect of TNF came from more recent studies with Chinese hamster ovary cells transfected with the TNF gene and producing large quantities of its protein product. Transfection of the TNF gene into cells enhanced their ability to invade the peritoneal and liver surfaces and metastasize to the lungs of nude mice and injection of antibodies to TNF prevented this (Malik *et al.* submitted). Other investigators have also hinted that TNF can enhance the metastasis of murine tumours [22], and that tumour implantation can be enhanced by preincubating tumour cells with macrophages, a major source of TNF *in vivo* [23]. Several factors could contribute to TNF induced tumour progression. Thus, TNF can induce enzymes that may enhance tumour spread, e.g. collagenases, stimulate angiogenesis *in vivo*, stimulate bone resorption, and increase the adherence of tumour cells to endothelium [24–27].

ENDOGENOUS TNF IN HUMAN CANCER

The role of endogenous TNF in the pathophysiology of human cancer is an issue of some interest. It is possible that endogenous TNF production could contribute to cancer cachexia, anaemia, and hypercalcaemia, as shown by animal studies [28, 29]. There is conflicting evidence concerning the presence of TNF in serum from cancer patients [30, 31].

Since cytokines generally act in a paracrine or autocrine manner it may be more appropriate to search for evidence of TNF production in tumours. Our first studies showed that low levels of TNF messenger RNA were found in human colorectal tumours [30], and *in situ* hybridization studies revealed that this was produced by a small minority (<0.1%) of stromal cells [31]. However, more recent studies in our laboratory have shown that a higher proportion (up to 8% of epithelial cells in an individual field) of cells express TNF messenger RNA in eight of 14 cases of human ovarian cancer. The cells expressing TNF are found in epithelial areas and have the surface phenotype and morphology of tumour cells [31]. An example of our results is shown in Fig. 1. Preliminary immunoperoxidase studies have demonstrated TNF protein in the tumour cells. Production of TNF by some cells in a tumour may not only contribute to the cachectic state, but our xenograft studies suggest that TNF producing cells may show an enhanced capacity to invade. In addition, TNF production may stimulate lysis of bone and cartilage and promote angiogenesis. TNF producing tumours may show an altered response to cytotoxic drugs or other cytokines, and would be unlikely to respond to exogenous TNF.

CLINICAL TRIALS

Thus, the results of 6 years of preclinical studies with recombinant TNF are not entirely encouraging for its prospects as an anticancer agent. In clinical trials TNF has been given by

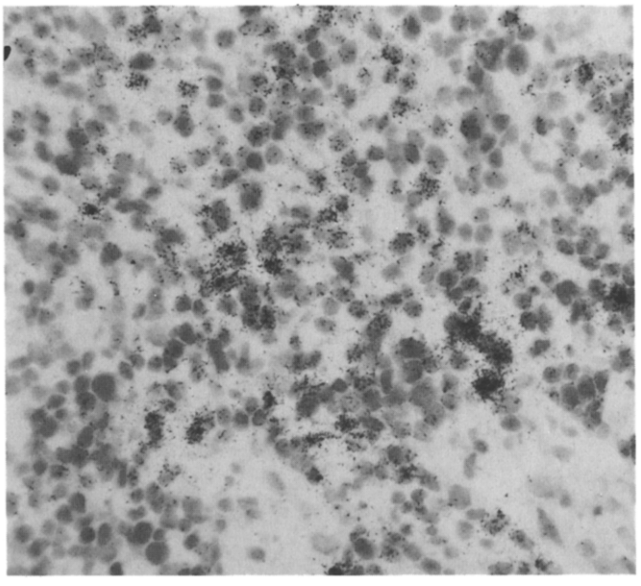

Fig. 1. The presence of mRNA to TNF in a human ovarian cancer specimen detected by *in situ* hybridization with a TNF antisense riboprobe. TNF-positive cells shown by areas of silver grain deposition. (× 64.)

parenteral, intratumoral, and intracavitary routes [5, 33]. Most studies have used short infusions or bolus administration, although two groups gave continuous infusions. The maximum tolerated dose of TNF is about 200 $\mu g/m^2$ per day for bolus administration, and 500 $\mu g/m^2$ per day for continuous infusion with hypotension being the major dose-limiting side-effect. Other common acute side-effects include fever, rigors, headache and fatigue—side-effects similar to those seen with the administration of other cytokines such as IFN-α and IL-2. The overall response rate in all reported studies with systemic therapy is less than 1%. Some partial responses have been seen in both haematological and solid tumours but these were short-lived. Local administration has been claimed to be more effective in one study, and ineffective in another, but has limited clinical application [34, 35].

How do we reconcile the early toxin studies, which probably induced endogenous TNF, with the apparent inactivity of recombinant human TNF in clinical trials? There are many possible reasons. For instance, the hyperthermia the toxins induced may have contributed to the effects, and patients treated with Coley's toxins were generally treated for months, and often for up to 2 years, whereas clinical trials of TNF have rarely lasted more than a few weeks. In addition, the levels of TNF achieved in toxin treated patients may have been higher than those in patients given exogenous TNF. But, most important, Coley's toxins probably induced a 'cocktail' of cytokines in the patients, not just TNF. Likewise, animals receiving tumour necrosis serum were probably exposed to a similar cocktail of cytokines.

THE FUTURE

As the functional relationships between cytokines become better understood, the use of cytokine combinations in cancer therapy becomes a possibility. The inclusion of TNF may bring the cytokine cocktail closer to that achieved in animals or human patients given bacterial products to induce tumour regression. There are several preclinical studies suggesting that TNF may

be a useful component of cytokine combinations. IFN-γ enhances the ability of TNF to lyse many tumour cell lines, and can render some TNF resistant cells sensitive [35]. The antitumour activity of TNF in experimental animals was also increased by IFN-γ but in some models toxicity was increased as well [37]. Two animal studies have shown synergistic activity between TNF and IL-2 against subcutaneous tumours or single large visceral masses [38], and other studies have shown synergy between IFN-α and IL-2 [39]. Greater anti-cancer activity in murine models has recently been achieved by the combination of TNF, IL-2 and IFN-α, with a single i.v. dose of TNF followed by concurrent IL-2/IFN-α therapy [40]. Extent of tumour regression, increase in lifespan, and cure rate were superior when all three cytokines were combined than with any cytokine alone or any combination of two cytokines. These results are as good as, if not better than, those reported with IL-2/LAK (LAK = lymphokine activated killer cells) therapy in similar models.

Similarly, several studies in experimental models have shown that TNF in combination with cytotoxic drugs, particularly but not exclusively, inhibitors of DNA topoisomerase II [41], has a synergistic antitumour effect. It is apparent that *in vitro*, TNF can be toxic for drug resistant lines and may therefore be of some use in combination trials in man. Such approaches in patients are currently being assessed. In addition, in all future clinical trials of TNF, we believe that it will be important to first investigate the involvement of this cytokine, or other members of the network, in the growth and spread of the tumour.

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News

EWOC2

Medical conferences in the middle of winter are common in many specialties, including now in oncology. The second European Winter Oncology Conference (EWOC2) will be held from 19 to 25 January 1991, in Méribel, a French alpine resort. This initiative, held under the auspices of FECS, EORTC and ESO, is encouraged by the success of the first session in January 1989, in Crans-Montana, Switzerland. More than one hundred participants discussed in detail many aspects of oncology with a distinguished European faculty. The informal atmosphere provided a unique opportunity for exchange of information and all participants were enthusiastic about the format of the conference, which also gave enough time for other activities. The 1991 event has lectures scheduled in urology, lymphoma, lung and head and neck cancer, antiemetics, growth factors, neurotoxicity, AIDS, drug development, breast cancer, radiation biology and new routes of drug delivery, with the possibility for oral presentations and poster sessions. The conference is intended to provide surgeons, radiotherapists, medical oncologists and all allied professionals with the opportunity to have maximum contact with the faculty to bring the most recent data in a critical format to all those treating cancer patients. The faculty çomprises: V. Diehl, N. Nissen, T. Philip, M. Brada, A. Horwich, F. Debruyne, A. van Oosterom, L. Denis, H. Hansen, A. Gregor, D. Carney, M. Clavel, J.P. Armand, M. Aapro, G. Blackledge, J. Neijt, S. Monfardini, S. Kaye, A. Goldhirsch, J.C. Horiot and A. Aigner. Information can be obtained from the conference secretariat, Imedex, PO Box 3283, 5203 DG Hertogenbosch, The Netherlands (fax 73 414766).

Secretaries in Oncology

The European School of Oncology held the first seminar for secretaries in oncology in April 1990, in Venice. This was an international gathering with representatives from 11 countries. The meeting, held on the island of San Servolo, provided a forum for comparison of educational background and discussion of practical methods and techniques, as well as an opportunity to discuss pertinent topics such as breast cancer and medical ethics. The next course will be held in June 1991, and further details may be obtained from the European School of Oncology, Via Venezian 1, 20133 Milan, Italy (tel 235923, fax 2664662).

Neoplasia in the Elderly

The first NCI–EORTC meeting on neoplasia in the elderly will be held at the European School of Oncology in Venice on 15–16 October 1990. The meeting will be chaired by Dr Silvio Monfardini (CRO, Aviano) and Dr Bruce Chabner (NCI, Bethesda). Further information may be obtained from Dr Umberto Tirelli, Centro di Riferimento Oncologico (CRO), Via Pedemontana Occidentale, 33081 Aviano (PN), Italy (tel 434 659282, fax 434 652997).

Ovarian Cancer

The Italian Branch of the European Familial Ovarian Cancer Registry has been established at the Università Cattolica del Sacro Cuore in association with the EORTC Gynaecological Cancer Cooperative Group. The group is chaired by Professor Salvatore Mancuso, in collaboration with the US Familial Ovarian Cancer Registry.

The group aims to obtain detailed information about the incidence of familial ovarian cancer, to study patterns of genetic transmission and to identify and register high-risk subsets of ovarian cancer with breast, endometrium and colon cancer.

For further information contact the study coordinator, Dr Stefano Greggi, Istituto di Clinica, Università Cattolica del Sacro Cuore, Largo Agostino Gemelli 8, 00168 Rome, Italy (tel 33051, fax 338066).

ECCO 6

The sixth European Conference on Clinical Oncology and Cancer Nursing (ECCO 6) will be held in Florence from 27 to 31 October 1991. ECCO 6 is organized under the auspices of the Federation of European Cancer Societies and aims to provide a common forum for clinicians and basic scientists involved in oncology to discuss recent achievements and highlight areas of future interest. To receive further information, please contact Dr Natale Cascinelli, Secretary General ECCO 6, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via Venezian 1, 20133 Milan, Italy (tel 2663992, fax 26680636).

Joint ESPO-IPOS Conference

The European Society for Psychosocial Oncology and International Psychosocial Oncology Society (ESPO-IPOS) Joint Conference, during the UICC Conference in Hamburg, will now be held on Monday, August 20th, 1990. Otherwise the conference is as planned. Further details from Professor M.V. Kerekjarto, Department of Medical Psychology, University Hospital Hamburg, Martinistr. 52, 2000 Hamburg 20, FRG (tel 4682363, fax 4634965).