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Feature Articles

Immunomodulatory Agents: the Cytokines

R.C. Stein and A.G. Dalgleish

THE ACTION of several cytokines against tumour cell lines *in vitro* or certain animals *in vivo* is impressive enough to expect them to exhibit significant anti-cancer activity in man. Dramatic responses and rejection of some animal tumours to schedules involving interferon, interleukin (IL)-2 and tumour necrosis factor lead to high hopes that they might prove to be the elusive panaceas for cancer, a hope that was widely publicised by the media with both interferon and interleukin-2 appearing as 'cancer cure' cover stories in *TIME* magazine. The failure to fulfil the preclinical promise has mimicked the course of many conventional 'wonder' drugs, where early (unrealistic) expectations were soon disappointed, leading to a backlash ("it's far too toxic, I wouldn't give it to my dog") which over the months and years may lead to the drug finding a niche in the treatment of a particular disease condition for which it is well suited. (This scenario will be familiar to all those who have read Lawrence's "Clinical Pharmacology.") It should, therefore, not be surprising that the first anti-cancer cytokines are following a similar course. In the case of interferon-α, the initial hopes have been dashed, the toxicity has virtually prevented any further high dose trials, yet a number of 'niche' uses in the treatment of hairy cell leukaemia, chronic myeloid leukaemia, Kaposi's sarcoma and maintenance treatment for multiple myeloma has led to widespread acceptance that it has a role to play in treating cancer[1]. The learning curve has also led to the realisation that cytokines are not drugs and are not necessarily associated with a direct dose-effect which is the case for many conventional drugs. Indeed, the use of low dose interferon-α is not only much less toxic (and cheaper) but also more practical [as it may be given subcutaneously (s.c.) at home] and in many conditions is as effective. In addition, even though partial responses might not be achieved, prolonged periods of static disease with improved Karnofsky or ECOG scores may be of considerable clinical benefit. The low dose, low toxicity regimens have now led to a number of studies looking at the role of interferon-α in combination with chemotherapy and other cytokines. There are three main types of interferon: α, β and γ. The studies referred to so far involve interferon-α. Perhaps, surprisingly, β and γ have not been as effective as interferon-α and have even been detrimental in some conditions (e.g. β in Kaposi's sarcoma and γ in renal cell carcinoma). Nevertheless, it still remains possible that combinations of α and γ may be better than α alone.

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IL-2

IL-2, initially known as T-cell growth factor, was first used in the clinics in conjunction with lymphokine-activated killer

(LAK) cells, which are autologous lymphocytes activated and expanded *in vitro* and re-infused with additional IL-2 [2]. The history of IL-2 once more follows the swinging graph of high hopes, dashed optimism and cynical criticism (especially of its toxicity), although it has yet to find a niche condition in the same manner as interferon-α. The occasional response of patients with metastatic melanoma (MM) and renal cell carcinoma to high dose LAK cells and bolus IL-2 has led to detailed investigations of this approach. A number of important questions have now been addressed that can be summarised as follows:

1. The addition of LAK cells (which is expensive in terms of time, equipment and consumables) does not improve the response rate to IL-2, although there is a trend for more long-term survivors (as opposed to responders) who have received LAK cells [3, 4].
2. Bolus intravenous (i.v.) IL-2 is more toxic than continuously administered IL-2 which can then be titrated against side-effects. There appears to be no difference in efficacy between the two modalities [5].
3. High dose IL-2 may not be necessary in order to induce a response as lower doses administered in a very practical s.c. schedule have also been associated with response, especially when combined with interferon-α, also given s.c. in low doses [6–8].

Initially, IL-2 was thought to induce immune responses against tumour cells by inducing LAK cells. However, there is no evidence that LAK activity correlates with tumour responses (which could probably explain some of the above observations!) [9]. Other possible mechanisms include the induction of NK cells and tumour-specific cytotoxic T-cells (CTL) which are referred to as tumour-infiltrating lymphocytes or TIL cells. TIL cells are 50–100 times more effective than LAK cells in tumour killing in an animal model, and they have, therefore, been harvested and expanded *in vitro* with IL-2 prior to re-infusion, with better results than LAK cell infusion. However, they can only be rescued from a fraction of melanoma patients' tumours and many tumour sites make this an impractical approach [10].

Tumour necrosis factor (TNF-α)

The dramatic ability of TNF to induce haemorrhagic necrosis in certain tumours of experimental animals has not been extrapolated to clinical studies in man where not only does it appear to be devoid of significant anti-tumour activity, but it is also very toxic, having potent effects on the vascular endothelium, resulting in localised coagulation and thrombosis, hypotension and shock [11]. Any future use of TNF-α will be limited to low dose schedules involving the co-administration of other cytokines such as IL-2. TNF-α is similar to IL-1 which is currently being investigated for its potential anti-tumour activity.

IL-1

Two distinct IL-1 genes, and their corresponding proteins, α and β, which have only approximately 25% homology, have been identified. However, both IL-1 species act through the same receptors and appear to have similar biological properties [12]. Amongst the protein actions of IL-1 and B-, T- and natural killer (NK) cell activation and the induction of many elements of the inflammatory response, including neutrophilia. The extent to which these effects are directly mediated is unclear, as IL-1 is able to induce many other cytokines, including TNF, IL-2, IL-4 and IL-6.

Although IL-1 has direct anti-proliferative effects against a number of cultured human tumour cell lines (including melanoma [13] and ovarian [14] lines), direct tumour cell inhibition is likely to be the exception rather than the rule [15]. A number of murine tumours regress *in vivo* in response to IL-1 [16, 17] but this probably occurs through the mediation of other immune effectors. At high doses, IL-1 is able to induce haemorrhagic necrosis of some murine tumours in a TNF-independent manner [18]. The relevance of this observation to the treatment of human cancer is uncertain as it is unlikely that such high doses would be tolerated. Synergy occurs between IL-1 and various cytotoxic drugs in murine models [19], but similar synergy observed between IL-2 and cytotoxic drugs in murine tumour models has not yet been shown to be applicable to human cancer.

In addition to its effects on tumours, IL-1 is able to protect mice against the lethal effects of radiation injury and some cytoxic drugs [20, 21]. The mechanisms are complex and apparently include protection of the stem cell compartment from lethal injury. These protective actions are likely to involve an interaction with other cytokines, particularly IL-6, which may be able to act as a substitute for IL-1.

Phase 1 trials of both IL-1α (Dainippon Pharmaceutical Co. [22] and IL-1β (Immunex) [23] in patients with advanced cancer have been reported. In both studies, IL-1 was administered by short i.v. infusion, once daily, for either 7 (IL-α) or 2 (IL-β) consecutive days. The maximum tolerated doses were 0.3 μg/kg for IL-1 and 0.1 μg/kg for IL-1β. The dose-limiting toxicities were similar to those reported for TNFα and IL-2, i.e. prominent hyptotension and evidence of vascular leak syndrome with fevers, chills, emesis and malaise. IL-1 and TNF induce the synthesis of nitric oxide, a potent physiological vasodilator, by direct action on vascular smooth muscle [24, 25]. This mechanism may represent a common pathway for the hyptotension associated with both exogenous and endogenous cytokines. The hypotensive effect of IL-1 in anaethetised dogs can be rapidly reversed by the administration of nitric oxide synthesis inhibitors, which has obvious therapeutic implications.

The principal haematological effects of IL-1 are a rise in neutrophil count and a late rise in platelet count [22, 23, 26, 27]. Two studies suggest that IL-1 may ameliorate cytotoxic-induced myelosuppression, particularly thrombocytopenia [23, 27]. However, in a further small study, no beneficial effects were noted on haematological indices in 4 patients with refractory aplastic anaemia [10, 28]. In a limited study in patients with advanced urological malignancies, IL-2-induced *in vitro* LAK cell generation was enhanced following daily s.c. injection of IL-1β suggesting a possible role for combination therapy with these agents [29]. Phase II trials of IL-1 in cancer are in progress.

IL-4

IL-4 has a wide range of actions on immune and haemopoietic cells [30]. It appears to be secreted by activated T-cells and by mast cells [31], suggesting that it acts locally as part of the immune response. The actions of IL-4 on B- and T-cells are variable and appear to depend on co-stimuli; there may also be species differences. IL-4 is able to promote T-cell proliferation, induce LAK activity in peripheral blood mononuclear cells (PBMC) prestimulated by IL-2 (although it inhibits the generation of LAK cells by IL-2) and induce antigen-specific cytotoxic T-cells. Recent studies in cultured human renal and gastric carcinoma cells indicate that IL-4 may inhibit growth through tumour expression of the IL-4 receptor [32, 33], but the relevance of these observations to the situation *in vivo* is unclear.

IL-4 also has a direct anti-proliferative action on B-cell chronic lymphocytic leukaemic cells *in vitro*[34], and, interestingly, also protects against apoptosis [35].

Although the properties of IL-4 suggest a role in tumour immunotherapy, relatively few studies have been carried out *in vivo*. In murine tumour models, IL-4 injected around tumour-draining lymph nodes causes tumour regression and induces a persisting immune response against further tumour challenges [36, 37]. Recent evidence suggests that the mechanism of tumour regression is eosinophil-dependent [38].

Recombinant human IL-4 is available in both a glycosylated (Sterling, U.K.) and a non-glycosylated (Schering-Plough, Bury St Edmunds, U.K.) form. Phase I trials of both i.v. and s.c. administration have been reported [39–42]. The major adverse effects reported are fatigue, headache, emesis, diarrhoea and nasal congestion. Gastrointestinal ulceration, predominantly of the gastric antrum, has been reported in 9 out of 44 patients in one series, most of whom were treated with 30 or 60 μg/kg/day i.v. IL-4 [42]. Hypotension, fever and oedema (with features of the capillary leak syndrome) although recorded, were not prominent in these studies. In this respect, it is interesting that circulating levels of TNFα and IL-1β do not increase in patients treated with IL-4 (in contrast to those receiving IL-2). Patients receiving once daily s.c. non-glycosylated IL-4 [40] have a similar spectrum of toxicities to those receiving the higher dose i.v. therapy (although nasal stuffiness was not recorded).

Several of the phase I studies indicate encouraging signs of clinical activity, but only one convincing response (in a case of Hodgkin's disease) has been reported [42]. Phase II studies are in progress with IL-4 being administered both alone and in combination with IL-2. Synergy between IL-4 and IL-2 in a clinical setting have not yet been supported by formal publication of results.

IL-6

IL-6 is best known for its ability to stimulate the production of acute phase proteins. It is also able to promote the growth of B- and T-cells, to act as a differentiation factor for cytotoxic lymphocytes and to enhance NK cell, LAK cell and TIL activity [44]. Its actions overlap considerably with those of IL-1 and TNFα, both of which are stimulators of IL-6 production *in vivo*. IL-6 is able to induce regression of early tumours in a weakly immunogenic murine transplantable tumour model, but it is ineffective against more advanced tumours and in a non-immunogenic tumour model [45]. A phase I trial of once daily s.c. IL-6 for 7 days has recently been reported from the NCI. All patients experienced fever, chills and fatigue. A number of immunological effects, including rises in C-reactive protein levels, a rise in platelet count and increased expression of the IL-2 receptor on lymphocytes, were observed at a dose of 10 μg/kg/day. At a dose of 30 μg/kg, hepatoxicity and cardiac dysrhythmias were observed [46]. Very little toxicity has been observed in mice, even with extremely high doses [47]. Phase I clinical trials of IL-6 are currently in progress at the NCI although its therapeutic potential seems to be rather limited. In some haematological malignancies (particularly myeloma) and Kaposi's sarcoma, IL-6 has been implicated as a major growth factor.

IL-7, IL-10 and IL-12

IL-7, IL-10 and IL-12 act as T-cell growth factors and are available as recombinant proteins. As yet, none have reached clinical trials, but pre-clinical tests indicate a potential role for IL-7 in immunotherapy whilst both IL-10 and IL-12 have the ability to promote *in vitro* cytotoxicity against tumour cells.

IL-7 was originally isolated from bone marrow and thymic stromal cells. It acts as a growth factor for immature B- and T-cells and for mature T-cells, both *in vitro* [48] and *in vivo* [49]. IL-7 induces LAK activity in PBMC [50] and generates tumour-specific CTLs from both murine tumour-draining lymph node lymphocytes [51] and human TIL [52]. The actions of IL-7 on human cells show synergism with IL-2. Murine IL-7-generated anti-tumour CTLs are effective in adoptive immunotherapy [53]. Murine glioma and fibrosarcoma cell lines transfected with the IL-7 gene have reduced tumorgeneity in immunocompetent syngeneic mice [54, 55]. Phase I trials of IL-7 are planned.

IL-10 was first identified as a product of murine T helper cells. Its human counterpart inhibits the secretion of interferons, colony stimulating factors and TNFα, IL-1α, IL-1β and IL-6 by PBMC. It is also able to reduce the antigen presenting capabilities of monocytes by downregulation of class II major histocompatability complex (MHC) [56]. In addition to these immunosuppressive actions, IL-10 has been shown to have a number of immunosuppressive actions, IL-10 has been shown to have a number of immunostimulant properties *in vitro*. These include augmentation of the proliferative actions of IL-2 and IL-4 on T-cells, and enhancement of IL-2 stimulated cytotoxic T-cell development [57, 58]. It remains to be established which of these apparently contradictory sets of actions predominate *in vivo*. IL-10 is also thought to have a regulatory effect on Th-1- and Th2-like responses, promoting a switch from Th1 (cell mediated immunity) to Th2 (humoral mediated immunity) [59].

IL-12, which was first cloned in 1991 [60], is a heterodimeric cytokine, originally named cytotoxic T-cell or NK cell stimulatory factor (NKSF). It is doubtful whether all the *in vitro* properties of IL-12 have been identified, but it is known to be a growth factor for activated T lymphocytes and NK cells. Studies of its ability to generate LAK activity from purified NK cells and to facilitate CTL responses against allogeneic tumour cells suggest evidence for a complex interaction between cytokines including IL-2 and TNF [61, 62]. The ability of IL-12 to promote a Th1-like response and to enhance NK activity suggests that IL-12 may be useful in cancer therapy, especially as an adjuvant therapy to classical bulk reduction modalities for humans with a high incidence of relapse.

CONCLUSION

This review, although far from exhaustive, reflects the huge potential for cytokines to alter the immune response against tumours. Although direct administration of cytokines either alone or in combination, has hitherto been disappointing, the marked inhibitory effects on tumour cell lines following direct transfection suggest that we have much to learn with regards delivery and packaging, and that a thorough understanding of cytokines may yet lead to a really useful role in cancer management.

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Systemic Treatment of Colorectal Cancer

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INTRODUCTION

COLORECTAL CANCER (CRC) is among the most common cancer types, second to breast cancer in women and third to lung cancer and prostate cancer in men. The prognosis depends largely on the extent of disease at the time of diagnosis, i.e. stage according to Dukes or the TNM system, although several other factors have been found to independently influence prognosis [1]. At present, less than 50% of all CRC patients are cured of this disease. Despite long-standing efforts for early diagnosis in order to improve the cure rate, there is still no established screening procedure which is widely practised.

This paper deals with the systemic treatment of CRC both in metastatic disease and in the adjuvant setting. Since locoregional treatment to the liver via the hepatic artery is not strictly systemic treatment, the reader is referred to two recent reviews of the subject, one arguing in favour and one against an established benefit [2, 3].

Metastatic disease

Almost by definition, metastatic CRC is incurable. There are, however, a few exceptions to this. Long-term disease-free survival (or cure) can be achieved in patients undergoing surgical resection of lung or liver metastases, provided this is the only metastatic site. There are rare reports of apparent cures by chemotherapy which may be overlooked in large studies by early reporting of results [4]. However, the use of chemotherapy in CRC is aimed at palliation and prolongation of survival. Endpoints for studies have been response, survival time, improvement of symptoms and symptom-free survival time.

The characteristics of patients treated in a specific study is very important. Their influence on survival is higher than any treatment. Selecting patients with good prognostic factors is likely to achieve longer survival times even without any treatment. Prognostic factors for survival are shown in Table 1 [5, 6]. Likewise, response to chemotherapy depends on the patients condition and other variables, though the predictibility is not that good. Factors reported to influence chemotherapy response are shown in Table 2 [6, 7].

5-Fluorouracil single agent treatment

5-Fluorouracil (5-FU) has been the most widely used and studied drug in CRC. Early on in its use in CRC, it was found to be effective. However, the methods then used to document efficacy and measure disease parameters were not as well

Table 1. *Metastatic colorectal cancer: prognostic factors for survival* [5, 6]

Performance status
Grade of anaplasia
Measurable disease*
Symptoms*
Elevated LDH and/or CEA and/or WBC
Lung versus liver metastases

* Presence indicates poor prognosis. LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; WBC, white blood cells.

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