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Intraperitoneal Immunotherapy for Ovarian Cancer with Alpha Interferon

INTRAPERITONEAL IMMUNOTHERAPY has been studied recently in a variety of solid tumours that otherwise might be incurable [1, 2]. Using the intraperitoneal administration of a cytokine, such as the interferons and the interleukins, some complete regressions of tumours have been documented [1–6]. The lack of effective therapies for many malignancies coupled with these intriguing albeit uncommon responses has led investigators to seek more efficient or more innovative technical approaches to the administration of these immunotherapies.

The concept of the regional administration of drugs is appealing in patients whose tumours are confined to, and have not yet metastasised beyond a definable body cavity. Malignant lesions that are isolated to the peritoneal cavity, such as residual ovarian cancer, have been treated in many clinical trials with intraperitoneal drugs, most frequently with cytotoxic chemotherapy such as cisplatin alone or in combination with other agents [7, 8]. The rationale for this approach is based on the straight-forward premise that a higher concentration of the drug can be brought into direct contact with the residual tumour cells and that this might provoke a response in malignancies that otherwise might be resistant. Coupled with the use of drugs that have a pharmacokinetic advantage when placed directly into the peritoneal cavity (i.e. the agent has a high peritoneal to plasma ratio based largely on its molecular weight and lipid solubility), some agents have a steep dose–response curve in the range that can be used for intraperitoneal therapy. This approach has been promising as a "salvage" treatment for minimal residual ovarian cancer with complete responses of 20–30% when small disease persists after systemically administered induction chemotherapy with a cisplatin combination [7, 8].

The intraperitoneal use of a biological response modifier (BRM) or immunotherapy has been used for similar reasons, but also because it has been postulated that one might obtain the activation of regional effector mechanisms in the peritoneal cavity [9–14]. Thus, "regional" immunotherapy, if delivered efficiently and made tolerable, could provide a means by which a biological therapy might be rendered effective, even when it has been found to be ineffective when administered intravenously. This might be particularly true for cytokines and white cells which appear to require direct contact with the malignant cells in order to kill them [1–6, 9–13].

Prior clinical trials of intraperitoneal BRMs have used either non-specific immunomodulators, such as *Corynebacterium parvum* [9, 11], or cytokines, such as recombinant alpha interferon (rIFNα) [6, 12]. These trials have produced a similar rate of surgically documented complete responses in patients whose residual ovarian cancer has been minimal, i.e. less than 5 mm maximum residual disease, and confined to the peritoneal cavity. *C. parvum*, as expected, induces a rather profound local reaction and its toxicity precludes more widespread testing. On the other hand, intraperitoneal rIFNα is well-tolerated locally but has significant systemic side-effects. As might be expected, *C. parvum* produced an appreciable amount of peritoneal fibrosis, presumably because it induces cells that promote the deposition of collagen. However, the attraction of these cells and the release of vasoactive molecules also might be responsible for the rejection of tumour cells via non-specific killing, i.e. the malignant cells are overwhelmed by the intense and massive outpouring of chemoattracted white cells and their products into the body cavity. In fact, the mechanism of tumour cell killing in these circumstances is not known, although regional effector mechanisms, such as antibody-dependent cell-mediated cytotoxicty (ADCC) are augmented after the administration of intraperitoneal *C. parvum* [12].

Interferon is a cytokine capable of the generation of cytotoxicity when autologous peripheral blood lymphocytes are incubated with human ovarian carcinoma cells [13, 14]. With intraperitoneal recombinant alpha interferon (rIFNα), natural killer (NK) cytotoxicity is augmented and this phenomenon is associated with tumour rejection [10–12]. However, stimulation of NK is not invariably associated with clinical response. *In vitro* data suggest that the dominant mechanism responsible for killing tumour cells in the peritoneal cavity involves the direct effects of IFN on the cancer cells, similar to the cytotoxic chemotherapeutic agents [10]. The interferon molecule might disrupt the tumour cells such that they become more vulnerable to the subsequent effects of cytotoxic drugs, such as cisplatin.

The use of alpha interferon has received considerable attention in the treatment of malignancies. In phase II trials, systemically administered alpha interferon has produced responses in up to 18% of patients with advanced ovarian cancer [15, 16]. Recombinant human (rh) alpha interferon administered by the intraperitoneal route also has demonstrated activity in ovarian cancer patients with very small volume, i.e. minimal residual disease (MRD) (microscopic disease or tumour nodules <5 mm), that is persistent after first-line chemotherapy [6, 17]. The toxicity of intraperitoneal alpha interferon as a single agent also has been defined in these studies [6]. Administration of the drug in the range of 25–50 × 10^6 U three times a week was not tolerated because of persistent general malaise, fever and gastrointestinal toxicity. However, in those patients treated with the same dose once a week, the treatment was tolerated for 8–16 consecutive weeks. Notably, there was an absence of significant neurotoxicity and renal toxicity. While most of the side-effects of single-agent alpha interferon appears to be complementary with cisplatin, the general malaise and gastrointestinal toxicity produced by each one could potentially be additive when the agents are combined. Willemse *et al.* [17] reported similar results in another trial of intraperitoneal alpha interferon in 20 patients with ovarian cancer, and of 17 who had a reassessment laparotomy, 5 (29%) had complete responses and 4 (24%) had partial responses. Responses in both studies were confined to patients whose disease was minimal residual (MRD) <5 mm. The toxicity encountered in this trial was similar to that seen in the GOG (Gynecologic Oncology Group) phase III trial [6]. Thus,

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overall, 28 surgically evaluated patients have been treated in these two trials and 14 (50%) responded, with 9 (32%) complete responses. All of the responding patients had microscopic or small (<5 mm) largest residual disease. The combined surgically defined complete response rate in patients with MRD was thus 50% (9 of 18 patients). These data suggest that the use of high-dose intraperitoneal interferon given frequently can produce the regional control of very small volume disease confined to the peritoneal cavity. However, survival data are not available on these patients, and as such, it is unclear if this approach can produce prolonged progression-free intervals.

There has been substantial evidence to suggest synergy between various interferons and standard cytotoxic agents [18–25]. Synergy has been noted *in vitro* with anthracyclines [18, 19], actinomycin-D [20], vinca alkaloids [21], 5-fluorouracil [22], and mitomycin [23]. Interferon also has been shown *in vitro* to act in concert with cisplatin to synergistically kill ovarian cancer cells [20, 24], and the current clinical trial tests this combination. In several reports, the synergy is seen only when the cells are exposed to the interferon prior to the cytotoxic agent [18–20, 22], presumably because the cytokine stimulates the proliferation of the cells making them potentially more susceptible to the cytotoxic effects of the drug. *In vivo* studies also have shown interferon to potentiate the cytotoxicity of cyclophosphamide and cisplatin in non-small cell lung cancer xenografts [24]. The preclinical data suggests that enhancement of the cytotoxic effect can be achieved when the cancer cells are exposed to the antiproliferative effects of interferon prior to the administration of the cytotoxic agent [20–22, 25]. The results reported by Bezwoda *et al.* [26] confirm these prior observations in that the *in vitro* synergy observed between cisplatin and interferon and the antitumour effect of interferon is most likely related to the direct inhibitory effect of the molecule and not to immune modulation.

Because of the significant *in vitro* synergy between cisplatin and other agents, a search for clinically tolerable and effective combinations is being undertaken. The demonstration that there is synergy *in vitro* between cisplatin and alpha interferon provided the impetus for several phase I–II trials [27–29]. Nardi *et al.* [27] reported 14 evaluable patients who were treated with weekly doses that alternated with 50×10^6 U of intraperitoneal alpha interferon and 90 mg/m^2 of cisplatin. In this trial, the surgically-documented complete response rate was 50% (7 of 14 patients), and all of these responses were confined to those patients who started their treatment with microscopic or <5 mm residual disease (MRD). The toxicity was similar to that seen in the phase I–II trials of alpha interferon alone, although the authors reported somewhat fewer symptoms of general malaise and gastrointestinal toxicity. Therefore, the combination of intraperitoneal cisplatin and interferon appeared to be tolerated in these patients, and had an appreciable response rate. The survivals of those patients who had a complete response was generally longer than that of patients who were non-responsive. However, since response rates are similar to those reported in other series of single-agent intraperitoneal cisplatin, it was unclear whether the addition of the interferon to the cisplatin had any additive affect on the response rate. Another clinical phase I study [28] conducted at two institutions demonstrated that combined intraperitoneal therapy with cisplatin and alpha interferon given within several hours of one another every cycle can be administered safely to patients with residual ovarian carcinoma after systemic chemotherapy. The maximum tolerated doses (MTD) of the combination of alpha interferon and cisplatin as determined by the phase I trial, are 25×10^6 U alpha interferon and 60 mg/m^2 cisplatin. The therapy was best tolerated given as one cycle every 3 weeks, and of the 8 patients who were treated with this precise dose, the median number of treatment cycles was six courses. The complete responses were noted in 2 patients after five and six treatment cycles, respectively, and partial responses were seen in patients treated with four and eight cycles, respectively.

However, when the two-institution trial schedule that combined intraperitoneal alpha interferon and cisplatin was applied to the cooperative group setting, the Gynaecologic Oncology Group (GOG), a very low response rate was seen—only one (7%) partial response was seen [29]. This poor outcome can be compared with the other phase I–II trials of cisplatin-based or alpha interferon intraperitoneal therapy in patients with persistent small-volume residual ovarian cancer (where response rates of 20–40% have been noted) [6–8]. The difference probably can be accounted for by the fact that, in this series, most (15 of 18) evaluable patients had extensive carcinomatosis that was cisplatin-resistant and the maximum tumours were larger, i.e. >5 mm.

In the trial by Bezwoda and colleagues [26], 35 patients with advanced ovarian cancer and ascites confined to the peritoneal cavity were treated with intraperitoneal therapy with recombinant alpha interferon, some in combination with cisplatin. The finding of 7 responses in 19 (36%) patients treated in a phase I trial of intraperitoneal alpha interferon only is intriguing and provides additional information that this mode of immunotherapy is appropriate in some patients with solid tumours, especially applicable to those whose tumours are localised to the peritoneal cavity, e.g. primary carcinomas of the ovary. In the phase II portion of the study, 16 patients were treated randomly with cisplatin with or without interferon. The combination of interferon and cisplatin produced a somewhat higher response rate than with interferon alone—5 of the 7 patients (77%) of the patients treated with the combination responded, while 2 of 9 (22%) treated with cisplatin only responded. Furthermore, the responses correlated with the *in vitro* data in which the two agents produced synergy in the antitumour effect. The authors have concluded, similarly to previously published work, that the direct antitumour effect of cisplatin can be augmented by the concomitant exposure of the cancer cells to alpha interferon.

The potential of this particular cytokine to agument the antitumour effect of a typical cytotoxic chemotherapeutic agent, i.e. cisplatin, offers a potential strategy for biological therapy. There is evidence that even very low doses of a cytokine, e.g. tumour necrosis factor, can significantly augment the antitumour properties of drugs like cisplatin, doxorubicin and cyclophosphamide [30]. If this is the case, then the use of prolonged exposure, low-dose cytokine therapy, administered in conjunction with cytotoxic chemotherapy, could offer an advantage and minimise the toxicity of cytokine biotherapy. The intraperitoneal route offers a means by which continuous exposure can be made practical. Because the cytokine does not, as a single agent, produce a high number of complete responses, especially in patients with bulky disease, its place in the treatment of the disease remains to be defined.

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