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Perspectives and Commentaries

Intraperitoneal Chemotherapy: Belly-Bath or Pain-in-the-side?

HOWARD S. HOCHSTER†* and MARTINE PICCART†

Service de Médecine Interne, Institut Jules Bordet, rue Héger-Bordet, 1000 *Brussels, Belgium and* †*The Stanley and Rita H. Kaplan Cancer Center, Division of Medical Oncology, New York University Medical Center,* 550 *First Avenue, New York, NY* 10023, *U.S.A.*

(A COMMENT ON: Canal P, Bugat R, Rokoszak B, Berg D, Soula G, Roche H. Pharmacokinetics and efficacy of i.v. and i.p. VM26 chemotherapy in mice bearing Krebs II ascitic tumors. *Eur J Cancer Clin Oncol* 1986, **22**, 765–771.)

THE ARTICLE published by Canal *et al.* in the *European Journal of Cancer and Clinical Oncology* demonstrates the pharmacologic and clinical utility of administering the epipodophyllotoxin, VM-26, in the peritoneal cavity [1]. When given to mice bearing the Krebs II ascitic tumor, the pharmacologic advantage for this drug is 15–30 compared to intravenous (i.v.) administration. Furthermore, at the higher dose levels mice could be cured of their intraperitoneal tumors when given the drug by the intraperitoneal (i.p.), but not the i.v. route. If this experience is verified in humans, it will be possible to add VM-26 to the growing list of chemotherapy drugs which can safely be administered by the i.p. route.

Interest i.p. drug administration has been renewed since the late 1970s when it became evident that combination chemotherapy could frequently cause clinical complete remissions in ovarian cancer, but at "second-look" laparotomy many of these patients had residual microscopic disease. Previously, chemotherapy had been administered in the peritoneal cavity to patients with ascites in an attempt to cause sclerosis. In the 1970s, with advances in peritoneal dialysis for renal failure, better understanding of membrane-dialysis physiology, and development of indwelling peritoneal catheters, interest turned to i.p. drug administration as a kind of "reverse" dialysis. Dedrick and co-workers at the American National Cancer Institute proposed a model of i.p. drug administration in large volumes to ensure homogeneous drug distribution. They outlined the properties desirable for drugs to be administered by this route and the pharmacologic advantages expected [2]. Reports quickly followed on the ability to give chemotherapy intraperitoneally with the predicted pharmacologic advantage, including 5-FU [3], methotrexate [4, 5], doxorubicin [6], and cisplatin [7, 8, 9]. More recent investigations have included other chemotherapy drugs, combination chemotherapy [10], and biologic response modifiers [11].

Experience with clinical trials involving several hundred patients have now been reported at meetings sponsored by the Gastrointestinal Study Group and, more recently, by the EORTC in Amsterdam. Some issues, including the following, have been adequately addressed to date, yet many others remain to be answered.

1. *Feasibility*

A large number of patients have been treated in quite a few centers using either the Tenckhoff catheter or the subcutaneously implanted Port-a-Cath. A few centers have chosen repeat blind punctures with temporary catheters. Patient acceptance in all cases appears high, though these studies usually consist of highly-motivated patients. Pharmacologic studies have shown that predicted regional advantage exists for all drugs studied.

2. *Safety*

Both permanent catheter systems have proven to be safe with approx. 3% complication of bowel perforation and 10% bleeding requiring trans-

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*Fellow of the F.O.C.A. Foundation, Brussels, Belgium.

fusions [12]. About another 10% may experience leakage of fluid around the catheter. Infections of the catheter site or peritonitis has been reported in 8% of the cases, despite the high degree of patient self-care required in the Tenckhoff system. More minor complications of catheter outflow obstruction may been seen in up to half the patients.

3. *Toxicity*

Many conventional chemotherapy agents have been found to be unacceptable for i.p. administration due to significant local, dose-limiting toxicity including doxorubicin, methotrexate, 5-FU, and mitomycin C. Other drugs such as cisplatin, cytosine arabanoside, and melphalan can be given in doses equal to or greater than with systemic administration due to reduced myelosuppression. Intraperitoneal administration also allows simultaneous administration of a neutralizing agent such as leukovorin with methotrexate [6] or thiosulfate with cisplatin [8, 13]. In the latter case thiosulfate is concentrated in the kidneys where it complexes with platinum species allowing up to 2.5 times the maximum systemic dose to be administered without renal toxicity.

4. *Efficacy*

While some investigators have reported results in terms of disappearance of ascites or conversion of cytology from positive to negative, it is difficult to evaluate the clinical utility of these end-points. The results of i.p. cisplatin trials at the Netherlands Cancer Institute are more encouraging [14]. These show that one-third of ovarian cancer patients having microscopic residual disease at second-look surgery after combination chemotherapy will have negative third-looks after 4 to 8 courses of i.p. cisplatin. Only one randomized study has been performed to date involving i.p. chemotherapy. Patients with colon cancer at high risk for recurrence were treated with i.p. or i.v. 5-FU. No difference in disease-free or overall survival was noted and i.p. 5-FU gave more abdominal discomfort but less myelosuppression. Nonetheless, use of i.p. 5-FU changed the distribution of recurrences, significantly reducing the incidence of recurrence at the peritoneal surface [15]. At present the Southwest Oncology Group is carrying out a prospective, randomized study of i.v. cyclophosphamide plus i.p. vs. i.v. cisplatin in advanced ovarian cancer. This study may yield important data concerning the relative efficacy and tolerance of the same cisplatin dose when given by the i.p. or i.v. route.

While these small studies have clearly demonstrated the feasibility of i.p. chemotherapy drug administration, there are numerous, critical theoretical and practical questions yet to be answered regarding the appropriate use of this technology.

Theoretical questions include the following. What exactly does the administration of i.p. chemotherapy do to tumor nodules? It appears that the drugs may penetrate some 5–6 cell layers from the peritoneal fluid. In that case, is there any reason to use this technique if there is macroscopic disease present? Perhaps multiple courses will strip off successive layers of cells, like peeling an onion. Would it, in fact, be desirable to therefore utilize the ideal i.p. drug if it existed (that is, one which gave no systemic exposure)? Perhaps the situation exemplified by cisplatin is more desirable, where one may escalate the i.p. dose and still achieve maximally-tolerated systemic exposure. In that case one attacks the tumor on two fronts, from both the peritoneal side and through its blood supply. Does the *in vitro* situation of dose–response really hold in the human, and if so, does the pharmacologic advantage gained by i.p. administration really amount to significantly more cell kill/cures? Perhaps the dose–response curves in the patient for the current drugs are so flat that no practical advantage is gained with this technique. Will this be a useful way to give biologic response modifiers such as interferon or monoclonal antibody conjugates? Are there other strategies for rendering intraperitoneal cells more sensitive to the drugs given by i.p. route or to neutralize their systemic effects?

Clinical questions include the following. 5-FU kinetic studies suggest most of the peritoneal drug supply passes into the portal system and then through the liver. Might this technique substitute for hepatic artery infusions? As noted above, is this technique clinically useful, despite pharmacologic advantage of 30–500 times for the peritoneal cavity? Is it sufficiently effective that it is worth the additional expense, trouble, and local discomfort to the patient? There is no evidence today that i.p. chemotherapy is more effective than i.v. administration. As noted above, the single randomized trial of i.v. vs. i.p. therapy (adjuvant 5-FU in colon cancer) showed no difference in disease-free, or overall, survival. What is the appropriate place for the use of i.p. drug administration? Will it be useful in stage IIc or microscopic stage III ovarian cancer? Should it be used as first line therapy in the case of ruptured cystic ovarian tumors? Will it be an effective salvage in maximally debulked (chemotherapeutically and surgically) ovarian cancer?

These questions remain to be explored in well-designed investigations. Both small, theoretically-oriented studies and large, randomized clinical trials of i.v. vs. i.p. chemotherapy are desperately

needed. Though the technology is readily available universally, we must bear in mind that the efficacy of this technique has not been adequately proven and that no trial to date shows that the technique is preferable to i.v. chemotherapy. Hopefully, the next generation of randomized studies will show that this is not only a novel way to give chemotherapy, but that in certain contexts it is the preferred route.

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