Current Status of Intraperitoneal Antineoplastic Drug Delivery

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Intraperitoneal Chemotherapy: Historical Perspective

Following the initial introduction of cytotoxic pharmaceutical agents into the armamentarium of physicians caring for patients with malignant disease, attempts were made to treat cancers involving the abdominal cavity (e.g., advanced cancers of the ovary, stomach, and colon) by instilling the drugs directly into this body compartment [1]. While these early efforts revealed malignant ascites formation could be reduced by this approach, there was little (if any) evidence for “shrinkage” of tumour masses, and with the drugs employed in these early years considerable local toxicity (abdominal pain) was observed.

With the further observation that systemic drug administration was at least as effective, less cumbersome and resulted in less side effects, the use of intraperitoneal (IP) anti-neoplastic therapy became relegated to those situations where it was hoped malignant fluid accumulation could be controlled to provide meaningful short-term palliation of distressing symptoms [2].

The “Dedrick Model” and Pre-clinical Evaluation of Intraperitoneal Chemotherapy

Then, in 1978, Robert Dedrick and his colleagues at the National Cancer Institute published a landmark paper that provided a compelling, but entirely theoretical, rationale to re-explore the administration of antineoplastic agents as therapy of ovarian cancer [3,4]. Based on existing data regarding the natural history of this malignancy, the pharmacology of cytotoxic agents available at that time, and the known physiology of drug transport into, and out of, the body compartment (e.g., uptake from the peritoneal cavity principally via the portal circulation), the “Dedrick model” suggested it should be possible to expose tumour present within the cavity to substantially higher concentrations (> 100-fold) of specific cytotoxic agents than with systemic delivery.
A number of subsequently conducted pre-clinical evaluations revealed the potential for greater tumour cell kill associated with the concentrations of antineoplastic drugs possibly achievable within the peritoneal cavity following regional drug delivery [5], as well as the fact certain drugs administered by the IP route could result in considerable local toxic effects (e.g. doxorubicin) [6].

Both theoretical considerations, and rather extensive experimental observations, permit the development of a general outline for what might be described as the “ideal antineoplastic drug” for IP administration:

- Active antineoplastic agent against the tumour type being treated
- Clinical, or pre-clinical, data exist for the agent supporting the favorable impact of increasing the dose or duration-of-exposure (AUC) on its cytotoxic potential
- Agent is not a vesicant
- Agent demonstrates slow clearance from the peritoneal cavity and rapid clearance from the systemic circulation
- Agent undergoes extensive metabolism to a non-toxic metabolite during its first passage through the liver
- Agent does not require activation in the liver to become an “active” cytotoxic drug

Penetration of Cytotoxic Antineoplastic Agents into Tumour Tissue

Perhaps the most important observation in these experimental studies, which substantially impacts the potential clinical relevance of IP antineoplastic drug delivery, was the consistent finding that following regional delivery there is very limited direct penetration of the agent into tumour tissue [7-10]. Depending on the investigational model employed, the depth of penetration varied from several cell layers to a maximum of a few millimeters from the surface of cancerous or normal tissue.

These data strongly argue that the patient population which potentially may benefit from IP drug delivery, and the group which prospectively should be examined in clinical trials, would be those individuals with very small volume cancer present within this body compartment when the regional treatment strategy is initiated.

Clearly, from the perspective of these experimental considerations, patients with microscopic residual disease (following surgical resection of the primary lesion and metastatic implants) would be the best group to employ regional treatment. However, patients with small volume residual macroscopic cancer may also benefit, particularly as it must be recognized that “standard anti-cancer” therapy includes a number of individual drug administrations (e.g., 4-6 courses), rather than a single therapeutic cycle [11].