Pharmacology of Perioperative Intraperitoneal and Intravenous Chemotherapy in Patients with Peritoneal Surface Malignancy

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KEYWORDS

• Peritoneal metastases • Pharmacology • Intraperitoneal chemotherapy
• Intravenous chemotherapy

KEY POINTS

The main teaching points of this article are:

- To understand the pharmacologic principle of dose intensification, the main rationale for providing locoregional cancer chemotherapy.
- To provide an update on the pharmacologic data available concerning the cancer chemotherapy drugs used in locoregional cancer chemotherapy protocols.
- To identify current controversies regarding the use of intraperitoneal and intravenous cancer chemotherapy in patients with peritoneal carcinomatosis.

INTRODUCTION

Peritoneal surface malignancy (PSM) is a common secondary manifestation of digestive and gynecologic malignancies alike.[1–3] Less frequently, PSM originates from a primary peritoneal cancer such as mesothelioma.[4] Despite continuing advances in systemic chemotherapy, no long-term survival is reported in PSM patients with this treatment modality alone. By contrast, cytoreductive surgery (CRS) combined with perioperative intraperitoneal (IP) and intravenous (IV) chemotherapy has resulted in encouraging clinical results in both phase II and phase III trials.[5–13] Now that the proof of principle for these new treatment modalities has been demonstrated, the question

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remains as to where further improvement is to be sought. Although further clinical trials are needed, an equally important role exists for pharmacologic research in this setting. A disturbing variety of perioperative chemotherapy protocols is used in PSM patients, based on often scant pharmacologic data. This article reviews the current pharmacologic data and offers guidance toward further improvement and standardization of these cancer chemotherapy regimens.

DOSE INTENSIFICATION

One of the main limiting factors governing dosimetry in systemic chemotherapy is hematological toxicity. In other words, the actual dose given IV is not so much the dose one wants to give based on cytotoxicity studies, but rather the dose tolerated by the patient's hematological reserve. By contrast, the dose intensification offered by the peritoneal membrane after IP administration gives a unique opportunity to expose the residual microscopic intraperitoneal tumor cells in PSM patients after CRS to very high doses of the cancer chemotherapy drug. This concept of dose intensification was first explored by Dedrick and colleagues.[14–18] In his landmark article of 1978 Dedrick concluded that the peritoneal permeability of several hydrophilic anticancer drugs may be considerably less than the plasma clearance of that same drug.[14] **Fig. 1** demonstrates his 2-compartment model. The transport over the membrane is modeled according to the equation:

$$\text{Rate of mass transfer} = PA\,(C_P - C_B)$$

where PA is permeability area (PA = effective contact area × permeability), C_P is concentration in peritoneal cavity, and C_B is concentration in the blood. Although the equation permits calculation of the pharmacokinetic advantage, the model does not tell anything about the specific penetration of the cancer chemotherapy drug

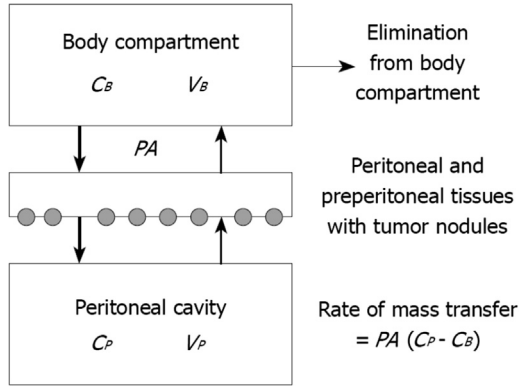

Fig. 1. Traditional 2-compartment model of peritoneal transport in which transfer of a drug from the peritoneal cavity to the blood occurs across the "peritoneal membrane." The permeability-area product (PA) governs this transfer, and can be calculated by measuring the rate of drug disappearance from the cavity and dividing by the overall concentration difference between the peritoneal cavity and the blood (or plasma). C_B = the free drug concentration in the blood (or plasma); V_B = volume of distribution of the drug in the body; C_p = the free drug concentration in the peritoneal fluid; V_p = volume of the peritoneal cavity. (*Modified from* Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: Tissue penetration and surface exposure. J Natl Cancer Inst 1997; 89(7):483; with permission.)