Pharmacodynamic Aspects of Intraperitoneal Cytotoxic Therapy

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Introduction

The pharmacokinetic (PK) properties of cytotoxic drugs, described by parameters such as plasma half live and distribution volume, are generally well studied and have implications for toxicity and development of dosage regimens. The PK rationale for intraperitoneal (ip) cytotoxic drug therapy is discussed in chapter 8.

In order to exert their anticancer effects, drugs have to gain access to tumour cells by penetrating into tissue. The available data on tumour tissue distribution of cytotoxic drugs and their relation with antitumour efficacy are limited, and mainly stem from in vitro multicellular models such as tumour spheroids (spherical tumour aggregates; diameter approximately 1 mm) and multilayered cell cultures [1]. Tissue penetration in these models is studied following incubation in a medium containing anticancer drugs, and generally the results show a very limited cytotoxic drug penetration. Since abstraction is made of vascular drug supply and the geometry of drug penetration is from the periphery towards the centre, the results of these models apply even more to ip chemotherapy than to intravenous administration. On the other hand, the renewed interested in ip chemotherapy in the management of peritoneal surface malignancy generated data relating specifically to tissue penetration of ip administered cytotoxic drugs, combined or not with locoregional hyperthermia.

This chapter provides a summary of the available data concerning the pharmacodynamics of cytotoxic drug administration with an emphasis on drugs used clinically during hyperthermic intraperitoneal chemoperfusion (HIPEC).

General Pharmacodynamic Aspects of Intraoperative Intraperitoneal Chemotherapy

Results from experiments with multicellular models have shown that direct tissue penetration of most cytotoxic agents is very limited in space (usually less than 1
Intraperitoneal chemotherapy effectiveness will therefore be limited to tumour nodules of a very small dimension or to loose cancer cells. The presence of small tumour nodules will result in an additional advantage related to the population kinetics of tumour growth. Indeed, human cancers are known to obey Gompertzian growth kinetics, implying that instead of a continuous exponential growth, a plateau is reached when nutrient and oxygen supply no longer meet demands resulting in a decline in growth when the tumour size increases. Small residual tumour will have the largest growth fraction and therefore the fractional kill by chemotherapy will be much higher than later in the course of the disease.

The penetration of cytotoxic drugs into peritoneal tumour nodules is a complex, multi-step process summarized in Fig. 1.

**Figure 1.** Schematic representation of drug penetration into peritoneal metastatic tumours. Drug supply is a function of pharmacokinetic parameters such as dose, concentration, and exposure time. The periphery of the tumour is entered by diffusion and convection. The extent of penetration will depend on drug properties and properties related to the tumour. Once intracellular, drug will accumulate into tumour cells by binding to target structures, non-specific binding, and sequestration in cellular organelles. A fraction of the drug will be altered by metabolic pathways. Tumour in the immediate vicinity of blood vessels (ovals) will also be reached by absorbed drug present in the microcirculation. Systemic drug absorption occurs both in submesothelial tissue and in tumour tissue. T, tumour nodule; M, mesothelium; PK, pharmacokinetics; IFP, interstitial tissue pressure; ECM, extracellular matrix; MW, molecular weight.