Hyperthermic intracavitary chemotherapy in abdomen and chest
van Ruth, S.

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CHAPTER ONE

Introduction and outline of the thesis
Hyperthermic intracavitary chemotherapy has gained more attention recent years as therapeutic approach for loco-regional disseminated cancers. Spratt et al. was the first who described this technique for a patient with pseudomyxoma peritonei. Nowadays, this multimodality treatment is used in more than 30 centres worldwide. Hyperthermic intraperitoneal chemotherapy perfusion has been studied in patients with malignant mesothelioma, peritoneal sarcomatosis and peritoneal carcinomatosis of gastric origin, but most efforts have been put on patients with pseudomyxoma peritonei and peritoneal carcinomatosis of colorectal origin.

Intracavitary administration of chemotherapy has the potential to reach a high local dose with limited systemic side effects. Hyperthermia itself has a direct cytotoxic effect at a level exceeding 42°C and is known to enhance the cytotoxicity of several cytostatic drugs, starting at a temperature of 39°C. Furthermore, the penetration depth of most cytostatic drugs is improved by hyperthermia. However, cytoreductive surgery is mandatory in order to leave as little residual tumour as possible because the penetration depth of cytostatic drugs is limited to at most a few millimetres. Intra-operative chemotherapy allows distribution of drug and heat uniformly to all surfaces of the abdomen. For this reason, an operative setting under general anaesthesia is preferable over simple instillation of chemotherapeutics in addition to the fact that hyperthermia is not tolerated in awake patients.

Since 1996, The Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital has gained ample experience with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Both patients with pseudomyxoma peritonei and peritoneal carcinomatosis of colorectal origin have been treated. The cytostatic drug in our treatment regimen has been Mitomycin C (MMC) because of its known activity in colorectal cancer, its direct cytotoxic effect and its thermal enhancement.

Cytoreductive surgery and hyperthermic intracavitary chemotherapy perfusion in the thoracic cavity was performed in our institute in 1998. This technique has been named Hyperthermic Intrathoracic Chemotherapy (HITHOC) perfusion. Both patients with limited malignant pleural mesothelioma and pleural thymoma were studied because these diseases can be seen as loco-regional disseminated cancers that might benefit from a loco-regional intensified therapeutic approach. Only minor experience with this multi-modality treatment exists worldwide; only case reports or small series of patients have been published. The intrathoracic cytostatic agents that have been used, cisplatin and doxorubicin, are well known cytostatic drugs assessed as systemic therapy in both mesothelioma and thymoma patients. Witkamp has reported the initial data on cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy in his thesis from our institute. The present thesis deals with several aspects of both HIPEC and HITHOC procedures.

Chapter two gives a review on the surgical management so far of malignant pleural mesothelioma (MPM). Surgery has been considered the mainstay of treatment of MPM, unless the fact that surgery alone is never curative. Therefore, the emphasis has been on surgery combined with adjuvant therapies in recent years, but this approach did not lead to a clear survival benefit for MPM patients so far. Based on our favourable results with cytoreduction and
HIPEC in peritoneal disseminated colorectal cancer, we developed a feasibility study with cytoreduction and HITHOC for MPM and pleural thymoma patients. The initial results are described in chapter three. A larger series of patients with MPM treated by this multimodality treatment with more extensive follow-up is given in chapter four. Part of succeeding this treatment is optimisation of the dosage of the cytostatic drugs that were used. Therefore pharmacokinetics of cisplatin and doxorubicin were studied. Chapter five describes the possibility to achieve a high local dose in the thoracic cavity with limited systemic uptake. It is important to know whether the chemotherapy has the potential to kill residual tumour after cytoreduction. For this reason, the penetration characteristics of doxorubicin were analysed and reported in this chapter as well.

In his thesis, Witkamp reported on some of the pharmacokinetics of MMC during HIPEC procedures. Chapter six gives a review of the pharmacokinetics of MMC after intra-operative intraperitoneal administration as reported in literature so far. Several aspects such as dose method, accompanied hematotoxicity and uptake with regard to the peritoneal-plasma barrier provide more insight into this complex matter. To gain better insight into the pharmacokinetics of MMC, like distribution volume and elimination kinetics, we developed a population pharmacokinetic and pharmacodynamic model (chapter seven) based on a large series of pharmacokinetic data. Knowledge of the relationships between pharmacokinetics and pharmacodynamics can contribute to rationalise the dosing and may lead to a more accurate dose advice. An estimated ideal dose of MMC is provided at the end of this chapter. Another important part of HIPEC is the application of hyperthermia. The effect of hyperthermia used during HIPEC was further investigated and the results are reported in chapter eight. Special attention was given to the possible relation between core temperature and temperature gradient because it was anticipated that core temperature could influence the heat penetration. The earlier thesis on HIPEC from our institute showed that cytoreductive surgery and HIPEC seems an attractive approach not only for patients with colorectal cancer but also for patients with pseudomyxoma peritonei (PMP). The diverse problem clinical appearance of PMP and its variable clinical course after cytoreduction and HIPEC was a challenging feature we were confronted with. Based on studies of Ronnett et al\textsuperscript{21,22}, a better classification of PMP in three pathologic entities could be made. We also studied the pathology of PMP in order to come to a better selection of candidates for our therapeutic approach (chapter nine). Until now, no general accepted protocol for follow-up of PMP patients after cytoreduction and HIPEC has been described. Physical examination and Computed Tomography are mostly used. Tumour marker studies in PMP patients are scarce. Chapter ten provides new data on the tumour marker Carbohydrate Antigen 19.9 (CA19.9) in PMP patients, treated by cytoreduction and HIPEC. The usefulness of this marker during follow-up as an alternative for performing routine CT scans is shown. In chapter eleven a general discussion and conclusions of the presented data are given.
Introduction and outline of the thesis

References


21 Ronnett BM, Yan H, Kurman RJ, Shmookler BM, Wu L, Sugarbaker PH. Patients with pseudomyxomma peritonei associated with disseminated peritoneal adenomucinosis have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. Cancer 2001; 92:85-91.