Hyperthermic intracavitary chemotherapy in abdomen and chest

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CHAPTER ELEVEN

General discussion and conclusion
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This thesis reflects the efforts on hyperthermic intracavitary chemotherapy research over the past five years in The Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital. Both cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in PMP and carcinomatosis peritonei of colorectal origin\(^1\) and cytoreductive surgery and hyperthermic intra-thoracic chemotherapy (HITHOC) in patients with MPM and pleural thymoma were studied.

Cytoreductive surgery and HITHOC.

**Pharmacokinetics**

A major safety issue in studies using intraperitoneal chemotherapy perfusion is the resulting systemic drug exposure. Knowledge of pharmacokinetics can help the clinician to rationalise the dosing and may lead to a more underpinned dose advice in further studies. The cytostatic drugs during HITHOC were doxorubicin and cisplatin, both cytostatics of which is known that they have some effect after systemic administration in both mesothelioma and thymoma patients.\(^1\)\(^3\) The pharmacokinetics of cisplatin during HITHOC has been described earlier, whereas doxorubicin pharmacokinetics during HITHOC has not yet been reported in literature.\(^7\) Our data on doxorubicin show a favourable area under the curve (AUC) ratio for perfusate/plasma, indicating the high exposure in the thoracic cavity, while maintaining the systemic exposure below toxic limits. The observed doxorubicin plasma AUC after intrathoracic instillation was about 1/10 to 1/15 of the level, when given intravenously. This implies that the maximal tolerable plasma AUC was by far not reached in our series.\(^8\)\(^10\) In further studies, therefore, dose escalation of doxorubicin could be investigated. On the other hand, the possibility of doxorubicin-related local toxicity has to be kept in mind; congestive heart failure after intrapleural administration in rabbits has been reported.\(^11\) Assessment of the ejection fraction and cardiology follow-up is part of our treatment protocol. Initial analysis however, has not shown a significant impact of the dose levels of doxorubicin on the cardiac function. Details will be published in the near future.

The penetration depth of doxorubicin appeared variable and in general it is limited to a few cell layers at most. These results were discouraging, since other used intracavitary drugs, like cisplatin and mitomycin C, have shown a penetration depth in the range of a few millimetres.\(^12\)\(^13\) This finding emphasises the importance of cytoreductive surgery when using doxorubicin. Intra-thoracic chemotherapy can only be expected to be of therapeutic value after complete or near complete cytoreduction.

**Survival figures**

In literature one case report and one series dealing with HITHOC for pleural thymoma have been described.\(^14\)\(^15\) A 5-year survival of 55% was reported (n=15). Also survival of pleural thymoma patients after HITHOC is promising in our series. We therefore, intend to continue entering thymoma patients with pleural metastases in our HITHOC protocol. Larger series
with longer follow-up however, are necessary to elucidate if this multi-modality treatment takes a part in the treatment of this disease. The survival figures of cytoreductive surgery with HITHOC in MPM patients were discouraging with a median survival of 11 months. Yellin et al.\textsuperscript{16} reported a median survival of 15 months in 7 MPM patients after pleural perfusion using cisplatin with 2 patients surviving more than 30 months. In the series of Carry et al.\textsuperscript{17} on intrapleural chemotherapy including 3 patients with MPM, two patients died within one year. The third patient is still alive after 22 months, but with recurrent disease. Due to these discouraging results and to the high morbidity rate, we are of the opinion that HITHOC cannot be recommended as palliation in MPM.

**Reasons why HITHOC failed in mesothelioma patients**

There are two possibilities why multi-modality treatment in the form of surgery combined with HITHOC failed in MPM patients.

First the possibility of inadequate surgery. The growth pattern of mesothelioma is characterised by involvement of the entire pleura and interlobular space.\textsuperscript{18} Anyone engaged in surgery for MPM is impressed by the variation of growth patterns. Sometimes, the tumour has a clear sharp margin and can easily be separated from neighbouring structures. At other times, infiltrative growth with accompanying fibrosis is so dense that any attempt on removal is an illusion. Optimal debulking in our series of stage I MPM patients could be reached in only 75\% of the cases (estimated residual tumour <2.5 mm). Although not fully represented in the present staging system (TNM classification according to IMIG\textsuperscript{19}), various growth characteristics determine to a large extent the completeness of any surgery, being decortication or pleuropneumonectomy. Also the accuracy of CT scanning for preoperative staging varies, but is reported to be as low as 30\%.\textsuperscript{20,21} Positron Emission Tomography (PET) seems to be useful to determine the extent of tumor.\textsuperscript{22} Mediastinoscopy is useful to determine the nodal status. However, 25\% of the MPM patients have nodal involvement confined to areas as the peri-diaphragmatic or the internal mammary region which are not accessible to this procedure.\textsuperscript{23} More accurate staging methods are desirable for better selection of patients. It seems to be clear that only patients with stage I MPM may benefit from aggressive loco-regional therapies and only this subset of patients are candidates to take part in future studies.

The other part of our treatment modality in mesothelioma patients that may be the explanation for failure is the chemotherapy perfusion. The limited penetration depth of doxorubicin implies that this drug may not be the suitable agent for this multi-modality treatment. Notwithstanding the favourable pharmacokinetics of doxorubicin, residual tumour cells have probably not been destroyed. The other intracavitary used drug, cisplatin, has a reported penetration depth of 5 mm. This depth should be enough to eliminate residual tumour since usually tumour deposits of only less than 2.5 mm were left behind.\textsuperscript{24} However, mesothelioma cells are relatively resistant to both doxorubicin and cisplatin as shown in literature. Response rates never exceed 40\% when given intravenously, and these cells may therefore have survived HITHOC.\textsuperscript{24,25} Unless the presumed dose-effect relation, the applied high doses chemotherapy were probably inadequate. Future studies could focus on other treatment
modalities, for example radiotherapy of the hemithorax. Studies of Rusch et al\textsuperscript{26} indicate that surgery combined with this modality prolongs survival.

Cytoreductive surgery and HIPEC.

**Pharmacokinetics**

The pharmacokinetics of MMC used during hyperthermic intraperitoneal chemotherapy have been reported in several studies.\textsuperscript{14,27,34} Several treatment modalities that are world-wide applied, however, do not allow a good comparison of all reported pharmacokinetic data. The tendency in the literature to report only concentrations or an AUC of the perfusate should be opposed. The perfusion characteristics, as applied in The Netherlands Cancer Institute/ Antoni van Leeuwenhoek hospital, include semi-open abdomen, basic perfusate volume of 3 litres, perfusion rate of 1 L/min, abdominal temperature of 40°C, 90 minutes of perfusion and three drug additions (50% at t=0 minutes, 25% at t=30 minutes and 25% at t=60 minutes). The developed pharmacokinetic-pharmacodynamic model can be used to simulate different dosage schemes in order to optimise MMC dosing during HIPEC. Based on our observations, we recommend dosing based on square metre body surface area (BSA) and the mentioned three drug additions. Other institutes with different perfusion techniques should study their own pharmacokinetics to come to the best dose (method) for their perfusion device. The found linear pharmacokinetics of MMC do not allow dose increments when using dosage based on a fixed concentration in perfusate, because incrementing per litres perfusion fluid could result in unacceptable systemic toxicity. When 10\% grade III/IV leucopenia is accepted, this results in a dose recommendation of 25 mg/m\textsuperscript{2}. In our series with 35 mg/m\textsuperscript{2}, 25\% severe leucopenia was encountered, however, without frequent serious consequences. Liberate use of wide spectrum antibiotics during a leucopenic period and an active policy to perform re-interventions before or after the expected nadir (10 days) are necessary. With help of the model further simulation studies with changing variables (like BSA, litres perfusion fluid, extent of resection, renal and liver functions) may lead to a more accurate dose advice.

**Hyperthermia**

Our work on heat penetration applied during HIPEC shows that the depth of penetration is limited to a few millimetres at most. The relation between temperature and depth was analysed using a piecewise linear model with two slopes: one until a depth of 1 mm (the mean distance between intraperitoneal and subperitoneal level) and one beyond that depth. In the transition between the intraperitoneal and subperitoneal level the decline in temperature was sharp, probably due to the characteristics of the peritoneum. The peritoneum is well-vascularised, leading to cooling down of the hyperthermic perfusion fluid in contact with the relatively cool blood flow. This dependence of hyperthermia on blood flow is known as the 'heat sink effect'. It is a valid question whether peritonectomy procedures will influence the heat penetration. We will study this in the near future. It is surprising that no other studies on heat
penetration have been reported in literature, bearing in mind the fact that hyperthermia is widely used during intracavitary chemotherapy perfusions.

**Pseudomyxoma peritonei**

Pseudomyxoma peritonei remains an enigma. The term PMP is often applied to a heterogeneous group of pathologic lesions characterised by the presence of abundant extra-cellular mucous with or without epithelial cells. The appendix is the most frequent site of origin, while involved ovaries are probably secondary tumour deposits. We did similar observations in our series. We now have ample experience with cytoreductive surgery and HIPEC for pseudomyxoma peritonei. So far we treated 80 patients (date of gauging: November 2002), a quite large series for this rare disease. The appearance of PMP can be diverse at surgery; sometimes only mucous fluid is seen, whereas in other patients more firm tumour tissue is found. Also during follow-up diverse clinical courses are seen. To examine if histologic characteristics could be identified in order to predict outcome, the pathology of PMP patients was studied. The degree of atypia and focal proliferation emerged as prognostic factors for survival. In 1995 Ronnett et al the following pathology classification system, replacing the term PMP by three diagnostic groups with decreasing prognosis: disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis with intermediate or discordant features (PMCA-I/D) and peritoneal mucinous carcinomatosis (PMCA). In our series DPAM patients showed a 3-year survival of 89% (n=38) whereas this was 37% for PMCA-I/D patients (n=24) (p=0.0002). DPAM and PMCA-I/D can be clearly distinguished from PMCA on pathological grounds. The prognosis of PMCA does not seem to differ from that of peritoneal carcinomatosis of ordinary appendix carcinoma or colon carcinoma. For this reason it is our opinion that this entity should no be included in the term PMP. PMCA-I/D takes an intermediate place; usually it presents as the same clinical appearance as DPAM, however with different pathological features and a different prognosis.

**Tumour markers in PM**

The measurement of tumour markers seems, besides Computed Tomography (CT), important during follow-up of PMP patients after cytoreductive surgery and HIPEC. As demonstrated in our study both elevated CEA and CA19.9 values were found preoperatively in a substantial part of the patients (75% and 58% respectively). CA19.9 appeared to represent a more useful marker than CEA during follow-up. Patients with pre-treatment elevated CA19.9 levels and (partially) normalised levels after surgery and HIPEC are probably best followed by physical examination and the measurement of CA19.9 only. Increase of CA19.9 raises suspicion for developing recurrent disease. The median lead-time of increased CA19.9 until detection of recurrence by means of CT was 9 months. Therefore, the number of CT-scans during follow-up of PMP patients can be limited according to our opinion. In case of pre-treatment elevated CA19.9 levels followed by normalisation after therapy, CT-scanning could be omitted. We recommend measurement of CA19.9 with 3-monthly intervals. Recurrences
of MPM can be treated with resection alone or even resection combined with a second HIPEC. Our experience in the treatment of PMP recurrences is, however, still limited. Further studies have to confirm our findings of the relevance of CA19.9 in the follow-up of PMP patients.

Future

Surgery combined with HITHOC has no place in mesothelioma patients. The possible value of this multi-modality treatment in pleural thymoma has to be awaited. Although our initial results are encouraging, larger groups of patients with adequate follow-up are necessary.

In PMP patients surgery and HIPEC has gained wide acceptance as treatment option, notwithstanding the absence of randomised studies. Meanwhile, a prospective randomised study on patients with peritoneal carcinomatosis of colorectal origin has been completed in our institute. This study compares cytoreductive surgery combined with HIPEC followed by systemic chemotherapy with systemic chemotherapy alone. The median survival was 21 months for the HIPEC arm versus 10 months for the systemic chemotherapy arm (p<0.05). A 5-year survival of 20-30% is to be expected for the HIPEC arm. Cytoreductive surgery and HIPEC therefore, is useful in patients with peritoneal carcinomatosis of colorectal origin. Although for PMP patients such a study is also desirable, this seems impossible to achieve due to the low incidence of this disease. Future studies should focus on better patient selection - the morbidity of HIPEC is considerable and on improvements of technique, like using promising new chemotherapeutic agents such as oxaliplatin. Pseudomyxoma peritonei still remains an entity attracted by many investigators; the apparent discrepancy between the abundance of mucous with just a few epithelial cells and the tendency to recur or to show progressive disease, is still not solved. May be that genetic profiling using the micro-array technique will help us to elucidate important aspects of this intriguing disease in near future.

References

General discussion and conclusion


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