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The Use of Amifostine during Continuous Intraoperative Intraperitoneal Hyperthermic Chemoperfusion (CIIPHCP) for Peritoneal Carcinomatosis from Ovarian Cancer

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S u m m a r y. Continuous Intraoperative Intraperitoneal Hyperthermic Chemoperfusion (CIIPHCP), is a feasible treatment method, showing very encouraging results in the treatment of advanced primary or recurrent epithelial ovarian adenocarcinoma as well as in other intraabdominal malignancies. One of the most common complications after CIIPHCP with Cisplatin is renal dysfunction and failure. The fraction of the intraperitoneally infused chemotherapeutic drug, which is being absorbed from the peritoneum, cannot be calculated prior to the procedure and this fact makes the prediction of systemic exposure uncertain, but it seems that the fraction of the drug absorbed can be up to 77%. Among all patients, who have been treated in our Institution after we started to use Amifostine (Ethyol™) as a nephroprotective agent, no event of renal failure was noticed. We suggest the prophylactic administration of 1500 mg Amifostine, 30 min prior to the addition of Cisplatin into the perfusate during CIIPHCP.

INTRODUCTION

Continuous Intraoperative Intraperitoneal Hyperthermic Chemoperfusion (CIIPHCP) is a feasible treatment method, showing very encouraging results in the treatment of advanced primary or recurrent epithelial ovarian adenocarcinoma and in other rare ovarian cancers, as well as in some low-potential intraabdominal malignancies, which are confined to the peritoneal cavity for relative long time as pseudomyxoma peritonei. One of the most common complications after CIIPHCP with Cisplatin is renal dysfunction and – failure, with postoperative increase of serum urea and creatinine values (1,2). Cisplatin is a known nephrotoxic agent and it reaches considerable plasma levels after peritoneal administration (3). Antineoplastic drugs with molecular weight 5000-10000 are absorbed from the peritoneal cavity by the lymphatic vessels. Substances with smaller molecular weight are removed by the blood vessels. The peritoneal clearance for most of the chemotherapeutic drugs used in intraperitoneal chemotherapy is very small, leading to a high difference between the concentration in the peritoneal cavity and the plasma concentration. The peritoneal/plasma ratio after intraperitoneal instillation is 21±5 for Cisplatin and 10±7 for Carboplatin (4-7). The fraction of the intraperitoneally infused chemotherapeutic drug, which is being absorbed from the peritoneum, cannot be calculated prior to the procedure and this fact makes the prediction of systemic exposure uncertain. In a group of patients, with ovarian cancer, treated with continuous hyperthermic peritoneal perfusion with Carboplatin, the fraction of the drug absorbed varied from 27% to 77% (8). In another study, the ratio between the maximum drug concentration in the perfusate and plasma during intraoperative peritoneal chemohyperthermia, was 15±1 and the absorbed dose was about 75% of the administered dose (9).

Studies have demonstrated the protective effect of Amifostine against the nephrotoxic effects of Cisplatin and Carboplatin (10) and that

Amifostine does not affect the antitumor effect of those drugs (11).

METHODS

The purpose of the present study was the evaluation of CIIPHCP in the treatment of primary and recurrent epithelial ovarian cancer with peritoneal spread. 27 patients with advanced primary epithelial ovarian cancer and 20 heavily pretreated patients (with surgery and systemic chemotherapy) with recurrent epithelial ovarian cancer have been treated with a combination of cytoreductive surgery and CIIPHCP. The main goal of the study was the feasibility and effectiveness of the method, regarding the survival and the post-treatment course of the neoplasmatic ascites. Toxicity and morbidity of the method were also studied.

RESULTS

For the 27 patients with primary epithelial ovarian cancer, median survival for patients with residual disease less than 1.5 cm was 42.0 months, whereas for patients with residual disease equal or greater than 1.5 cm, the median survival was 10.0 months ($p=0.0023$). The neoplasmatic ascites disappeared postoperatively and median ascites-free period after the operation was 22 months.

For the 20 patients with recurrent epithelial ovarian cancer, median survival time for patients with residual disease less than 1.5 cm was 29.0 months, whereas for patients with residual disease equal or greater than 1.5 cm, the median survival time was 7.0 months ($p<0.05$). The ascites disappeared in all of the 13 pts with preoperative ascites. Median ascites-free period after CIIPHCP was 21 months (2).

Postoperative morbidity and toxicity was low. Renal failure occurred only in two of our patients but among all patients, who have been treated after we started to use Amifostine (Ethyol™) as a nephroprotective agent, no event of renal failure was noticed. Both events of renal failure occurred in the group of patients with recurrent disease, who were pre-treated with several Platinum-containing chemotherapy cycles.

CONCLUSIONS

In conclusion, the survival data and the disappearance of the malignant ascites postoperatively in combination with the limited morbidity, suggest that Continuous Intraoperative Intraperitoneal Hyperthermic Chemoperfusion (CIIPHCP) is an effective treatment option for patients with neoplasms confined in the peritoneal cavity for relatively long time. According to our experience, we suggest the prophylactic administration of 1500 mg Amifostine, 30 min prior to the addition of Cisplatin into the perfusate.

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