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Review

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and Cytoreductive Surgery (CS) as Treatment of Peritoneal Carcinomatosis: Preliminary Results in Croatia

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A B S T R A C T S

The purpose of our study was to evaluate initial results following introduction of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and Cytoreductive Surgery (CS). Twenty two patients with intraperitoneal malignancy undergone cytoreductive surgery (CS) and hyperthermic intraoperative chemotherapy (HIPEC) between January of 2007 and January 2010. Nine patients had adenocarcinoma of colorectal origin, 8 patients had ovarian cancer, and 5 had pseudomyxoma peritonei. Inclusion criteria were diagnosis of peritoneal carcinomatosis based on intraoperative assessment during first operative procedure for intraabdominal malignancy or follow-up diagnostic imaging proof. Excluded were patients with known malignant proliferation outside abdomen, liver metastasis and ASA score 4 and higher. All patients with pseudomyxoma peritonei diagnosis are alive, with mean follow-up time 24.8 months (range 15–35). In group of patients with adenocarcinoma from colorectal origin, 3 died, resulting in mean survival time 7.6 months (range 1–16). In group of patients with ovarian cancer, 2 died, resulting in mean survival time 13.8 months (range 0–31). Two patients died in early postoperative period. Most of the patients had some sort of mental disorder. Although HIPEC with CS improves survival, during introduction period higher morbidity and mortality could be expected.

Key words: *cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, peritoneal surface malignances*

Introduction

Surgery for peritoneal carcinomatosis in our institution, prior to introduction of cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in beginning of 2007, was considered only as palliative method, dealing with issues like intestinal obstruction and malignant ascites. Peritoneal carcinomatosis patients survival is usually less than 6 months[1–3]. Colorectal cancer patients with peritoneal carcinomatosis and palliative treatment had considerable less mean survival time, 5–7 months[4,5], compared to patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy resulting in 5-year survival rate 20–53%[6,7]. Reported median survival for patients with diffuse malignant peritoneal mesothelioma in high volume tertiary institution treated without CS and HIPEC was 15 months[8] compared to 31–75% disease free survival at five years with CS and HIPEC[9,10] and 57% overall survival[9]. Even better results are obtained for pseudomyxoma peritonei, resulting in 67–91% overall survival in 5 years[11,12] and 44% disease free survival[11]. Metastatic ovarian cancer median survival range from 12–25 months[13], and even in these cases better results are reported[14,15]. Possibility to perform CS in patients with peritoneal spread has a potential to remove macroscopic malignant diseases present intraperitoneally, and combined with HIPEC even microscopic malignancy up to 2.5mm can be annihilated[16].

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Methods

22 patients undergone cytoreductive surgery and hyperthermic intraoperative chemotherapy for peritoneal spread of pseudomyxoma peritonei, colorectal adenocarcinoma and ovarian cancer between January of 2007 and January 2010. Diagnosis were: colorectal origin of adenocarcinoma in 9 patients (primary tumor locations as follow: rectum (n=5), sigmoid colon (n=1), appendix (n=3)) of which 4 were recurrent; ovarian cancer in 8 patients (FIGO IIIc in 6 patients, IIIb in 2), of which 5 were recurrent; and pseudomyxoma peritonei in 5 patients, neither one recurrent. Inclusion criteria were diagnosis of peritoneal carcinomatosis based on intraoperative assessment during first operative procedure for intraabdominal malignancy or follow-up diagnostic imaging proof. Excluded were patients with known malignant proliferation outside abdomen, liver metastasis and ASA score 4 and higher. Preoperative assessment and possibility for complete cytoreduction was based on helical abdominal CT scan with intravenous contrast. All patients underwent cytoreductive surgery, based on principles introduced by Sugarbaker[17], with no macroscopic residual disease left, including intestinal resection and lymph node dissection. Removal of the omentum and involved peritoneum was carried on in all patients; this mostly involved paracolic spaces, pelvis, abdominal wall and both subdiaphragmatic and subhepatic areas. In 4 patients gastrectomy was necessary due tumor involment, and in 13 colonic resections with protective ileostomas. Gallbladder was removed in 8, spleen in 9 and liver capsule in 8 patients. Closed technique hyperthermic intraoperative chemotherapy through 4 abdominal tube drains (2 for inflow, and 2 for outflow) using cisplatin (40 m/L) and doxorubicin (15.25 mg/L) of perfusate (carrier solution was normal saline in all cases) during 60 min with target temperature of 42.5°C (3 thermocouples in abdomen were used) followed in patients with ovarian cancer, adenocarcinoma patients received oxaliplatin (460 mg/m^2/L) or combination of mitomycin C (35 g/m^2/L) and doxorubicin, and pseudomyxoma patients received mitomycin C. Mean flow of perfusate was 600–1000 mL/min, and volume varied between 4 and 6 L. After HIPEC bilateral thoracic tubes were inserted in all patients as fluid accumulation in the chest is expected as a result of peritonectomy and HIPEC. Postoperatively patients resumed chemotherapy with florouracil and leucovorin. Ovarian cancer patient's follow-up continued in dedicated gynecological institution. Peritoneal cancer index (PCI)[18] and completeness of cytoreduction scores (CC) were calculated for all patients following procedure[19]. Peri-operative mortality and complications were evaluated.

Results

Twent two patients underwent CRS and HIPEC in above mentioned period, 19 females and 3 males, mean age 56 years, (range 29–78, SD=10.98 years). Mortality, defined as death in the first month after operation, was 4.6% in our group of patients, but 2 patients died in early postoperative period (14th and 42nd day). First patient was operated because of intraperitoneal spread from ovarian cancer, she became hypotensive during procedure and suffered from multiorgan failure in the end. Second patient had intraperitoneal spread of adenocarcinoma from appendiceal origin, he developed thrombocytopenia and anemia leading to disseminated intravascular coagulopathy. Others were in good clinical condition discharged from hospital. Median total operation time was 347 minutes (range 150–515 min, SD 92 min). Median total blood loss was 727 mL (range 100–1400 mL, SD 366 mL). Mean hospital stay in days was 17 (range 9–42 days, SD=7.78). Median follow-up 20 patients were 15.1 months (range 1–35 months). All patients with pseudomyxoma peritonei are alive, with mean follow-up time 24.8 months (range 15–35). In group of patients with adenocarcinoma from colorectal origin, 3 died, resulting in mean survival time 7.6 months (range 1–16). In group of patients with ovarian cancer, 2 died, resulting in mean survival time 13.8 months (range 0–31). PCI was equal or bellow 10 in 13 patients, with median survival time 17.8 months (range 1–35, SD 9.7), PCI was above 10 in 9 patients with median survival time 7.9 months (range 0–24, SD 8.9). In group of patients with satisfactory cytoreduction, CC score 0, 14 patients, mean survival time was 17.5 months (range 0–35, SD 10.4), compared to group with CC score 1 and 2, which mean survival time was 7.1 months (range 0–21, SD 7.1). Nine patients out of 20 had postoperative complications (2 who died in early postoperative period are excluded). In 3 patients we had 2 anastomotic leaks, both suffered dehiscence of ileorectal anastomosis on 4th day, and one perforation of small bowel due to technical error obvious on 2nd postoperative day; 4 patients had intraabdominal collection of which 2 required operative evacuation; 1 patient required blood transfusion and reoperation for additional hemostasis; one patient was septic.

Although we didn't evaluate patient mental status during this operations, it became obvious that most of the patients did developed some sort of mental disorder, either anxiety or depression. In discussions experienced oncologic surgeons mentioned use of opiates as possible cause during postoperative period. All of our patients had epidural catheter for pain management, so this couldn't be case in our group. We intend to monitor this effect in the future.

Discussion

Peritoneal carcinomatosis is last stage for many intraabdominal malignancies. Survival of less than 6 months and palliative procedures dealing with intestinal obstruction were common for those patients, as were frequent visits to emergency room. Combined treatment of local heated chemotherapy, which allows exposure to high drug concentration capable to penetrate tumor bulges less than 2.5 mm thickness, and surgical removal of larger tumor deposits results in significantly improved survival in once untreatable patients. Obvious benefits of

HIPEC are: higher intraabdominal concentration which helps to overcome chemoresistance decreased systemic concentrations resulting in decreased side effects[20,21]. As described by Sugarbaker et al.[22] peritoneal spread for colorectal cancer occurs first in subdiaphragmatic areas, pelvis and greater and lesser omentum, latter in subhepatic, retrohepatic and paracolic space and Treitz ligament, with finally spread to liver, gallbladder, stomach, colon and small bowel with adjunct mesentery at last. Peristalsis, gravity and reabsorption considered main factors for abdominal spread of low grade mucinous tumors. As seen in many studies, great risks are present in special patient subgroups. Inability to determine those patients becomes obvious when one summary the results of developing team as ours. Those are known facts described in learning curve following every new procedure. Lower morbidity and better overall survival could be achieved with better patient selection. Two early postoperative deaths and rate of 45% of a major peri-operative complications in presented group of patients is high, and contributed mostly to newly adopted procedure, but is expected to come closer to usually reported incidence bellow 30%[23]. Peritoneal cancer index is good prognostic factor in patients with primary colon cancer with peritoneal carcinomatosis[18] predicting 48 months mean survival and a 50% survival rate in 5 years for group of patients with score 10 or bellow. In the other subgroups with score 11–20 and 20 or above, median survivals is 24 months with 20% in 5 years and 12 months with 0% in 5 years, respectively. Although we didn't treat only colorectal cancer patients with this method, survival distinction between patients is obvious for those with PCI 10 or bellow. The question is how to improve preoperative PCI assessment mostly based on helical CT imaging to avoid patients with poor prognosis. Male sex had been described as significant factor for morbidity[24], conclusion we are not able to investigate yet on our data. There is no consensus considering timing for bowel anastomosis, either to do it before or after HIPEC[25]. We did bowel anastomosis before HIPEC, finding this safe and less time consuming. International workshop on peritoneal surface malignancy held biannually made some consensus about HIPEC in general during 2006. Isotonic salt solutions and dexterous solutions are considered advisable for perfusate. Optimal range of temperature for solution is considered 41–43°C. And drugs for HIPEC used in our study are considered safe for routine clinical use by majority of experts[26].

Conclusion

CRS with HIPEC significantly improves survival of patients with peritoneal carcinomatosis and pseudomyxoma peritonei. Improvement in survival of ovarian cancer patients and colorectal origin adenocarcinoma patients exist, although not so encouraging as in pseudomyxoma group. Earlier referral from other national institutions, with performance of the procedure in earlier phase of the disease, would improve outcome. During introduction period higher morbidity and mortality could be expected, as our institution also encountered 2 deaths in short postoperative period in first 5 cases.

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HIPERTERMIČKA INTRAPERITONEALNA KEMOTERAPIJA (HIPEC) I CITOREDUKTIVNA KIRURGIJA (CS) KAO TERAPIJA ZA PERITONEALNI TUMOR: PRELIMINARNI REZULTATI IZ HRVATSKE

S A Ž E T A K

Svrha našeg istraživanja bila je iznijeti naše početne rezultate hipertermijske intraperitonealne kemoterapije (HIPEC) i citoreduktivne kirurgije (CS). Istraživanjem je obuhvaćeno 22 bolesnika s karcinozom peritoneuma ili primarnom zloćudnom tvorbom peritoneuma, u razdoblju od siječnja 2007. do siječnja 2010. Devet bolesnika imalo je adenokarcinom kolona kao primarni tumor, osam bolesnika karcinom jajnika, a pet pseudomiksom peritoneuma. Kriteriji za odabir bolesnika pogodnih za ovaj operativni zahvat bili su dijagnoza karcinomatoze peritoneuma za vrijeme prve operacije zbog maligne bolesti ili dijagnoza proširene intraperitonealne maligne bolesti na temelju radiološke obrade. Isključeni su bolesnici s prijeoperacijski poznatom proširenom malignom bolesti van abdomena, s metastazama jetre, i bolesnici čiji je anesteziološki rizik za operaciju bio ASA stadij 4 i više. Bolesnici s pseudomiksomom peritoneuma imali su srednje vrijeme praćenja 24,8 mjeseci (raspon 15–35), i do kraja praćenog razdoblja bili su svi živi. U skupini bolesnika s adenokarcinom kolona, troje je umrlo, što je rezultiralo srednjim vremenom preživljenja 7,6 mjeseci (raspon 1–16). U skupini bolesnika s karcinom jajnika, dvije bolesnice su umrle, što je rezultiralo srednjim vremenom preživljenja 13,8 mjeseci (raspon 0–31). Dvoje bolesnika umrlo je u ranom poslijeoperacijskom razdoblju. Većina bolesnika imala je poslijeoperacijski promjene psihološkog statusa određenog stupnja, najviše u vidu depresivnog sindroma. Iako HIPEC sa CS poboljšava preživljenje navedenih skupina bolesnika, tijekom razdoblja učenja ovog novog tipa operativnog zahvata može se očekivati veći morbiditet i mortalitet. Ranije upućivanje bolesnika u odabrane tercijarne ustanove vjerojatno bi pridonijelo smanjenju morbiditeta i mortaliteta.