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ORIGINAL ARTICLE

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in pediatric ovarian tumors: a novel treatment approach

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Abstract
Purpose Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been used in adults with ovarian carcinoma proving overall survival benefit in randomized trials, but measured in months. Diffuse peritoneal disease from pediatric type ovarian tumors is rare. We applied CRS and HIPEC to pediatric girls with diffuse peritoneal disease as part of a clinical trial.
Methods In all patients complete cytoreduction was followed by HIPEC using 100 mg/m^2 of cisplatin for 90 min in a closed technique. All received neoadjuvant chemotherapy. Patients with disease outside of the abdominal cavity were excluded.
Results Of 101 pediatric CRS and HIPEC operations, 8 had ovarian primary tumors and multifocal peritoneal disease. There were three yolk sac tumors (germ cell, mixed teratoma), one Sertoli–Leydig, one PNET of the ovary, one choriocarcinoma, one juvenile granulosa cell tumor and one adenocarcinoma. Age ranged 4–18 years. Three of the 8 (37 %) recurred and died. The remaining 63 % are disease free 2–6 years post HIPEC. Overall survival and relapse-free survival in this cohort was 64 and 62 %, respectively [CI 0.64 (0.34, 1); 0.62 (0.37, 1)].
Conclusions This is the first report of CRS and HIPEC in pediatric ovarian tumors. HIPEC may be effective in pediatric-type ovarian tumors. More study is needed in a larger cohort.

Keywords Ovarian tumor · Pediatric · HIPEC · Recurrent · Metastatic

Introduction

Cytoreductive surgery (CRS) followed by delivery of intraperitoneal chemotherapy is used commonly in adult patients with diffuse ovarian carcinomatosis. Even with aggressive surgical therapy combined with intraperitoneal chemotherapy, survival in these adult patients can be measured in months [1]. However, randomized trials have shown, without surgical resection and intra-peritoneal chemotherapy, survival is shortened [2].

Childhood neoplasms of the female genital tract account for <1 % of all pediatric tumors. The main histologic categories are germ cell and non-germ cell tumors. Germ cell tumors include teratomas (mature and immature), gonadoblastomas, yolk sac tumors, endodermal sinus tumors, embryonal carcinomas and choriocarcinomas. Non-germ cell tumors, sex cord stroma tumors in girls mostly include Sertoli–Leydig tumors and granulosa cell tumors. Juvenile granulosa cell tumors are different than their adult form and are most commonly benign. In a historic report by Imai [3], of 114 girls <18 years of age, only 20 % of tumor were malignant, or in 5 % potentially malignant. Of 114, 55 were of germ cell origin and 33 of epithelial origin.

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Table 1 Summary of patient outcome

Patient	Age (years) at Dx	Histology	Previous Tx	Surgical resection (CRS)	PCI	CR	Outcome
1	18	Mucinous poorly diff. adenocarcinoma	FOLFOX/Avastin, USO	PP, Oment, HIPEC	3	CCR0	A-74 months NED
2	17	Choriocarcinoma	BEP, USO	PP, POD, TAH, BSO, Oment, HIPEC	11	CCR0	A-15 months NED
3	18	Juv. granulosa	BEP, USO, CDDP/Tax, surg, radiation, SCT	PP, jejunal, R. colon, HIPEC	15	CCR1	DOD 12 months
4	10	Mixed germ cell	BEP, USO, Gem/Tax, SCT	PP, Oment, HIPEC	3	CCR0	A-32 months NED
5	14	Imm. teratoma PNET/ sarcoma	Ewing's chemo, USO, debulk surg, lung mets, rad	PP, HIPEC	4	CCR0	A-44 months NED
6	8	Sertoli–Leydig/undiff sarcomatoid	USO, BEP, debulk, carbo taxol Avastin	PP, HIPEC (no active tumor)	0	CCR0	DOD 5 months
7	3	Yolk sac	USO, CDDP, Dox, VP16, debulk, Ifos, CDDP, Tax, SCT	PP, POD, TAH large pelvic tumor, Oment, HIPEC	16	CCR1	DOD 11 months
8	11	Germ cell	USO, BEP, Gem Tax, Avastin	PP, POD, liver mets, Oment, TAH, USO, HIPEC	13	CCR0	A-13 months NED

A alive, *NED* no evidence of disease, *DOD* dead of disease, *PP* pelvic peritonectomy, *POD* pouch of Douglas resection, *debulk* debulking surgery, *USO* unilateral salpinghoophorectomy, *TAH* total abdominal hysterectomy, *BEP* bleomycin, etoposide, cisplatin, *Gem* gemcitabine, *Tax* paxitaxel, *SCT* high dose chemotherapy with stem cell transplant/rescue, *CDDP* cisplatin

Rarely, girls present with recurrent and/or diffuse peritoneal disease. The histologies in these cases vary. In a multi-institutional report of 67 girls with ovarian tumors, over a 23-year time span, only 8 had metastasis to the peritoneum at diagnosis or in the recurrent setting [4]. Since our group has been performing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in pediatric sarcomas [5–9], we hypothesized that girls with diffuse ovarian abdominal disease may benefit from prolonged survival after CRS and HIPEC.

Methods

All patients were treated on, or identical to our institutional review board (IRB) approved phase 1 or 2 investigator-initiated protocol for CRS and HIPEC. Patients who were not enrolled in the trial could not comply with on-site follow-up visits. Patients were included who were at least 1 year of age, had excellent performance status, had no liver or renal dysfunction, no cardiovascular contraindications to a general anesthetic, and no detectable FDG-avid disease by positron emission tomography imaging (PET) outside the abdominal cavity at the time of CRS and HIPEC.

Complete (CR0) or near complete (CR1 < 2.5 cm of tumor remaining) cytoreduction was achieved before HIPEC. All patients underwent closed technique HIPEC using 100 mg/m^2 of cisplatin for 90 min at 41 °C. In all patients, four fiberoptic temperature probes were sutured to the peritoneum in the following positions: right abdominal wall, left abdominal wall, sigmoid colon mesentery in the pelvis, and ligament of Treitz. As a control, a needle temperature probe was placed in the right lobe of the liver to verify the core temperature. These probes were connected to a standard computer, giving a constant reading of the temperature in each area for the duration of the 90 min HIPEC.

Results

Girls ranged in age from 3 to 18 years. All patients were previously treated with surgery, chemotherapy, and one patient had abdominal radiation before CRS and HIPEC. Table 1 outlines the results. Overall survival and relapse free survival in this cohort were 64 and 62 %, respectively [CI 0.64 (0.34, 1); 0.62 (0.37, 1)].

There were no perioperative deaths. Surgical complications included two wound infections, and one urinary tract infection and one enterocutaneous fistula in two different patients. Six patients (75 %) had no complications. The patient with the enterocutaneous fistula had juvenile

granulosa cell tumor that had repeatedly recurred over the previous 8 years and had undergone high-dose total abdominal radiation therapy and at the time of surgery had a 'frozen abdomen'.

Conclusions

In this first study of CRS and HIPEC in girls with peritoneal dissemination of ovarian tumors, we show CRS and HIPEC is safe. CRS and HIPEC has not been previously performed in pediatric patients for disseminated peritoneal disease secondary to primary ovarian tumors. We have previously shown in a phase 1 trial of HIPEC in children, CRS and HIPEC using cisplatin is safe [10]. This further study begins to demonstrate complete resection and HIPEC may be effective in some girls with ovarian disease and peritoneal spread.

From our data, it appears that more heavily pretreated patients, who were offered HIPEC at the third or fourth relapse, did worse, and all died. In the patients who had a long-term survival (between 1 and 6 years) the survival in this cohort of pediatric patients is much better than that of adult ovarian patients. In adult ovarian patients, various forms of complete cytoreduction and intraperitoneal chemotherapies resulted in a prolongation of survival that was measured <1 year [2, 11, 12]. Also in adults, the amount of disease burden and completeness of resection correlate with survival [2]. Here in the pediatric patients, this correlation may also be true. Two of the three patients who died of disease, had <2 cm of disease that was unresectable left behind. All but one patients with complete resection survived long term (the patient who died, patient #8 had a remnant of one ovary left in place at the time of HIPEC by parent request, and this is where the recurrence occurred).

Complete surgical resection, CRS and HIPEC is an approach that should be considered in pediatric patients with diffuse peritoneal disease from ovarian origin. Since these are very rare tumors, the sample size is small and no definitive conclusions can be made. Further study on a larger group of patients is needed.

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