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Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Pediatric Ovarian Tumors: A Novel Treatment Approach

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Abstract

Purpose—CRS and HIPEC has 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 100mg/M2 of Cisplatin for 90 minutes 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 3 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 to 18 years. Three of the 8 (37%) recurred and died. The remaining 63% are disease free 2 to 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 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 less than 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, 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 less than 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.

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 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 PET imaging (Positron Emission Tomography) outside the abdominal cavity at the time of CRS and HIPEC.

Complete (CR0) or near complete (CR1= $\leq$ 2.5cm of tumor remaining) cytoreduction was achieved before HIPEC. All patients underwent closed technique HIPEC using 100mg/m² of cisplatin for 90 minutes at 41 degrees Celsius. In all patients, 4 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 minute 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 was 64% and 62% respectively. [CI 0.64(0.34,1);0.62(0.37,1)]

There were no perioperative deaths. Surgical complications included 2 wound infections, and 1 urinary tract infection and 1 enterocutaneous fistula in 2 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 3rd or 4th 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 adults ovarian patients. In adult ovarian patients, various forms of complete cytoreduction and intraperitoneal chemotherapy resulted in a prolongation of survival that was measured less than one year.[2, 11, 12] Also in adults, the amount of disease burden and completeness of resection correlates with survival.[2] Here in the pediatric patients, this correlation may also be true. Two of the 3 patients who died of disease, had less than 2 cm of disease that was unresectable left behind. All but one patient 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, no definitive conclusions can be made. Further study on a larger group of patients is needed.

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Table 1

Summary of patient outcome.

Patient	Age(yrs)at Dx	Histology	Previous Tx	Surgical Resection(CRS)	PCI	CR	Outcome
1	18	Mucinous Poorly Diff. Adenocarcinoma	FOLFOX/Avastin, USO	PP, Oment HIPEC	3	CCR 0	A-74 mo NED
2	17	Choriocarcinoma	BEP, USO	PP POD,TAH,BSO Oment, HIPEC	11	CCR 0	A-15 mo NED
3	18	Juv. Granulosa	BEP,USO,CDDP/Tax, surg, radiation, SCT	PP, jejunal, R. colon,HIPEC	15	CCR 1	DOD 12mo
4	10	Mixed germ cell	BEP, USO, Gem/Tax, SCT	PP oment, HIPEC	3	CCR 0	A-32 mo NED
5	14	Imm. Teratoma PNET/Sarcoma	Ewing's chemo, USO, debulk surg, lung mets, rad.	PP, HIPEC	4	CCR 0	A-44 mo NED
6	8	Sertoli-leydig/undiff sarcomatoid	USO, BEP, Debulk, carbo taxol avastin	PP, HIPEC (no active tumor)	0	CCR 0	DOD5mo
7	3	Yolk Sac	USO, CDDP,Dox, YP16, Debulk, Ifos, CDDP, Tax, SCT	PP, POD, TAH large pelvic tumor Oment, HIPEC	16	CCR 1	DOD- 11mo
8	11	Germ Cell	USO, BEP, Gem Tax, avastin	PP, POD, liver mets, oment, TAH,USO HIPEC	13	CCR 0	A-13 mo 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 salpingoophorectomy, TAH=total abdominal hysterectomy, BEP= bleomycin, etoposide, Cisplatin, Gem-=Gemcitabine, Tax=Paxitaxel, SCT=High dose chemotherapy with stem cell transplant/rescue, CDDP=Cisplatin