Hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for the treatment of peritoneal carcinomatosis in pediatric solid malignancies: a single institution experience

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ABSTRACT

Background: Peritoneal carcinomatosis from abdominal tumors is an uncommon condition in children usually associated with dismal prognosis. Hyperthermic intraperitoneal chemotherapy (HIPEC) following complete macroscopic surgery has been demonstrated to be safe and of benefit in selected cases. Experience in pediatrics is scarce.

Methods: We retrospectively reviewed the medical files of patients under the age of 18 years with an abdominal malignancy and peritoneal carcinomatosis who had been treated with HIPEC in our institution between March 2001 and April 2012. HIPEC had been administered using the open technique with oxaliplatin (300 mg/m²) and irinotecan (200 mg/m²) or oxaliplatin alone (460 mg/m²) in the peritoneal cavity for 30 minutes at 43 °C and an intravenous perfusion of leucovorin (20 mg/m²) and 5-fluorouracil (400 mg/m²).

Results: Nine patients had undergone HIPEC. Grade 3–4 complications had occurred in seven patients and were intraabdominal (n = 3) or extraabdominal (n = 8). No procedure-related deaths had occurred. Four patients are alive and in complete remission after a median follow-up of 4.9 years (1.7–9.6). However, one relapsed after HIPEC and required additional salvage therapy.

Conclusions: HIPEC could be considered in patients with peritoneal carcinomatosis from primary abdominal tumors. Its complications are manageable by an experienced multidisciplinary team. There are four long-term survivors, one after a relapse.

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1. Methods

All consecutive patients under 18 years of age and diagnosed with peritoneal carcinomatosis and treated with HIPEC in the Pediatrics Department at the Gustave Roussy between March 2001 and April 2012 were considered eligible for this study. Data were collected retrospectively from medical files.

Patients had undergone a complete work-up at the time of the diagnosis and before performing the procedure to determine the extent of the disease and to rule out metastatic disease other than peritoneal carcinomatosis. The majority of patients (n = 8) had already undergone surgery and had received a variety of neoadjuvant chemotherapy regimens.

Patients diagnosed with peritoneal carcinomatosis considered as potential candidates for HIPEC were discussed in a multidisciplinary team meeting and the decision to perform the procedure was based on a unanimous agreement. Written informed consent had previously been obtained from the patient, parents or legal representatives before performing any procedure.
The procedure had been performed by the same surgeon (DE) over the years. Procedure guidelines, postoperative management and follow-up were identical throughout the study period.

Sixty minutes prior to HIPEC, patients had received an intravenous infusion of leucovorin (20 mg/m²) and 5-fluorouracil (400 mg/m²). Then, patients had undergone complete surgical resection of all macroscopic disease. HIPEC was performed using the Coliseum technique with an open abdomen and the skin pulled upward [7]. Chemotherapy had been administered as a heated oxaliplatin (300 mg/m²) and irinotecan (200 mg/m²) in seven cases or oxaliplatin alone (460 mg/m²) in two cases infused in 2 L/m² of 5% dextrose in the peritoneal cavity for 30 minutes at 43 °C.

After surgery and HIPEC, patients had been hospitalized in the intensive care unit (ICU) for a minimum of five days.

Data on postoperative morbidity and mortality had been collected until day 30 after the surgical procedure or patient discharge, whichever occurred later. Toxicities had been graded in accordance with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 4.03: June 14, 2010) [8].

Following cytoreductive surgery and HIPEC, the majority of patients had received a variety of treatments depending on their underlying condition and response to previous therapies. All patients had undergone a close clinical, biological and radiological follow-up.

Data were analyzed using SPSS 19® software (SPSS, Chicago, IL). Statistics are descriptive owing to the low number of patients and events. Data for the analysis were censored on the December 1, 2013.

2. Results

Nine consecutive patients with an abdominal tumor and peritoneal carcinomatosis without evidence of extraabdominal disease were identified from our records as having undergone HIPEC from March 2001 to April 2012. Baseline characteristics are depicted in Table 1.

The male/female ratio was 1/8. The median age at diagnosis of the malignancy was 13.1 years (range 8.7–16.9) and the median age at the time of procedure was 15 years (range 13.2–19.4).

The histologic types diagnosed were: malignant ovarian tumor (n = 3), papillary mesothelioma (n = 2), fibrolamellar hepatocellular carcinoma (n = 2), solid pseudopapillary tumor of the pancreas (n = 1), primary peritoneal adenocarcinoma (n = 1). All but one had received diverse treatments including chemotherapy and surgery before HIPEC.

Table 2 summarizes patient conditions before surgery, complications and outcomes.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at diagnosis (y)</th>
<th>Diagnosis</th>
<th>Number of treatment lines before HIPECa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>16.5</td>
<td>Primary peritoneal adenocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>13.1</td>
<td>Juvenile granulose cell tumour of the ovarian</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>12.5</td>
<td>Fibrolamellar hepatocellular carcinoma</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>12.6</td>
<td>Papillary mesothelioma</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>16.9</td>
<td>Papillary mesothelioma</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>11.8</td>
<td>Vitelline type ovarian tumor</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>14.4</td>
<td>Fibrolamellar hepatocellular carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>13.3</td>
<td>Ovarian small cell carcinoma of the hypercalcemic type</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>8.7</td>
<td>Solid pseudopapillary tumor of the pancreas</td>
<td>1</td>
</tr>
</tbody>
</table>

a Treatment lines included surgery alone or in combination with chemotherapy or chemotherapy alone.

HIPEC had been used as first-line therapy in one patient. It had been used as second, third or fourth line therapy in 4, 1 and 3 patients respectively.

Prior to the procedure, 2 patients had achieved a partial remission, 5 exhibited stable disease and disease was progressing in 2.

The median duration of the surgical procedure was 435 minutes (range 300–720). The median duration in the ICU after surgery was 8 days (5–19).

A complete macroscopic resection had been achieved in all patients.

No procedure-related deaths had occurred.

Grade 3–4 toxicities had occurred in 7 patients and were intraabdominal (n = 3) or extraabdominal (n = 8). Two patients had experienced both types of toxicities (Table 3). Only one patient (patient 8) had been readmitted to the ICU four days after discharge owing to a pneumoperitoneum and hemoperitoneum requiring an urgent laparotomy (grade 4). Patient 3 had developed a compartment syndrome in the calf at day 9 requiring an aponurectomy (grade 3) and a hemoperitoneum at day 13 that had required an urgent laparotomy (grade 4). Four patients had experienced a grade 3 hematological toxicity at a median of 7 days (6–12).

Once recovered from surgery, six patients had received different systemic therapies based on the nature of the disease and on previous response to chemotherapy (Table 2).

The median follow-up for the whole population from the time of the surgical procedure was 1.7 years (0.2–9.6). Two patients with the diagnosis of papillary mesothelioma (4 and 5) and one with a solid pseudopapillary tumor of the pancreas (9) were alive and in complete continual remission at 9.6, 6 and 1.7 years after the procedure respectively.

Patient 7 with a fibrolamellar hepatocarcinoma had relapsed 21 months later with multiple lesions in the peritoneum. She had received further chemotherapy and extended surgery. She had again relapsed with a solitary hepatic nodule that had been treated with radiofrequency ablation therapy. At the last follow-up, she was in complete remission twenty-five months after the last relapse. The median follow-up for patients who are alive is 4.9 years (1.7–9.6).

All the other five patients had relapsed after the procedure and eventually died. The median time to relapse was 5.9 months (1.8–20.7). Three patients had relapsed with diffuse peritoneal disease, one with diffuse peritoneal disease and extraabdominal disease and one with focal peritoneal disease and extraabdominal disease.

Median time to death from relapse was 6.1 months (0.9–23.2). Salvage therapy had been attempted in three cases. One of those patients had survived for a further 23 months.

Regarding the status of the disease before the procedure, the two patients with progressive disease had relapsed soon after HIPEC (1.8 and 2.2 months respectively) and had rapidly died after the relapse (0.2 and 0.5 years respectively). Among the seven patients who had either stable disease or had achieved a partial remission, three had remained in complete continual remission and one had been rescued with salvage therapy after the relapse.

Among the four patients who were alive at the last follow-up, two had been evaluated for a gonadal hormone deficit. One of them (patient 7) had experienced a gonadal hormone deficit five months after the procedure, requiring replacement therapy.

3. Discussion

Peritoneal carcinomatosis from abdominal tumors has a very dismal prognosis [1–3]. Systemic chemotherapy for peritoneal surface malignancies is largely ineffective because of its limited penetration in the peritoneum. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy can be considered as a tool for overcoming the drug limitations associated with systemic administration. The completeness of cytoreductive surgery is of major importance.
because drug penetration is limited to a few cell layers under the surface of the tumor. Intrapерitoneal chemotherapy should be administered immediately after surgery so that residual tumor cells do not get trapped in the postoperative fibrin adhesions [9]. In addition, hyperthermia has been shown to enhance the antitumor effects of several drugs (oxaliplatin, mitomycin C, cisplatin and irinotecan) [6,9]. Experience with HIPEC in pediatrics is very limited [3,10,11].

We opted for the open technique that ensures temperature homogeneity and complete spatial diffusion of the peritoneal infusate throughout the peritoneal cavity. In pediatrics, the open technique allows better control of the central temperature. Two drugs based on their safe and synergistic effect had been administered [12]. All these complications were manageable in a hospital context.

The 3-year overall survival rate is 23%–39% in adults with colorectal peritoneal carcinomatosis [4,21,22] and 20%–23% in patients with gastric tumors [4,23] treated with HIPEC. Furthermore, HIPEC had a significant impact on survival in a randomized trial evaluating systemic 5-FU/leucovorin ± palliative surgery versus cytoreduction, HIPEC and postoperative chemotherapy in patients with colorectal carcinomatosis (median survival 12.6 months versus 22.3 months, p = 0.032) [24]. In pediatrics, Hayes-Jordan et al. compared a historical cohort of patients (n = 9) with desmoplastic small round cell tumor (DSRCT) and mesothelioma. Their aggressive condition, less sensitivity to chemotherapy and tendency to present with disseminated disease, make them potential candidates for novel therapies. Because of this

<table>
<thead>
<tr>
<th>Complications</th>
<th>Patients (n)</th>
<th>Types (n) and grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>2</td>
<td>Hemoperitoneum: 2</td>
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<tr>
<td></td>
<td></td>
<td>(Grade 4)</td>
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<tr>
<td></td>
<td></td>
<td>Pneumoperitoneum: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Grade 4)</td>
</tr>
<tr>
<td>Extraabdominal</td>
<td>7</td>
<td>Compartment calf syndrome: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Grade 3)</td>
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<tr>
<td></td>
<td></td>
<td>Pleural effusion: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Grade 3)</td>
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<tr>
<td></td>
<td></td>
<td>Catheter-related infection: 1</td>
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<tr>
<td></td>
<td></td>
<td>(Grade 3)</td>
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<tr>
<td></td>
<td></td>
<td>Urinary tract infection: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Grade 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematologic toxicity: 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Grade 3)</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>2 patients had intraabdominal and extraperitoneal complications</td>
</tr>
</tbody>
</table>

* Different types of complications were associated in the same patient.
heterogeneity and the low number of patients, it is difficult to assess which specific tumor types could benefit more from this approach. This hypothesis is under investigation in a phase II trial in children and adolescents (NCT01277744).

Although encouraging, these results should be considered with caution. This is a small series of patients with heterogeneous diseases in whom HIPEC was performed along with intravenous chemotherapy that could have potentiated its effects. Furthermore, the majority of patients had received postoperative chemotherapy that could play a role in the consolidation of the results obtained with HIPEC. It is therefore difficult to assess the individual role of HIPEC in this particular population. Nevertheless, these data suggest that HIPEC is feasible and safe and as a part of a multimodal approach in pediatric peritoneal carcinomatosis, may afford a benefit to patients with disease otherwise deemed incurable.

Acknowledgment

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References