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Cytoreductive surgery associated to hyperthermic intraperitoneal chemoperfusion for desmoplastic round small cell tumor with peritoneal carcinomatosis in young patients

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Abstract

Purpose: Desmoplastic round small cell tumor (DRSCT) is a rare intraabdominal mesenchymal tissue neoplasm in young patients and spreads through the abdominal cavity. Its prognosis is poor despite a multimodal therapy including chemotherapy, radiotherapy, and surgical cytoreduction (CS). hyperthermic intraperitoneal chemotherapy (HIPEC) is considered as an additional strategy in the treatment of peritoneal carcinomatosis; for this reason, we planned to treat selected cases of children with DRSCT using CS and HIPEC.

Methods: Peritoneal disease extension was evaluated according to Gilly classification. Surgical cytoreduction was considered as completeness of cytoreduction-0 when no macroscopic nodule was residual; HIPEC was performed according to the open technique.

Results: We described 3 cases: the 2 first cases were realized for palliative conditions and the last one was operated on with curative intent. There was no postoperative mortality. One patient was reoperated for a gallbladder perforation. There was no other complication related to HIPEC procedure.

Conclusions: Surgical cytoreduction and HIPEC provide a local alternative approach to systemic chemotherapy in the control of microscopic peritoneal disease in DRSCT, with an acceptable morbidity,

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and may be considered as a potential beneficial adjuvant waiting for a more specific targeted therapy against the fusion protein.

Desmoplastic round small cell tumor (DRSCT) is a rare intraabdominal mesenchymal tissue neoplasm in young patients; it generally occurs in patients, aged 35 and younger more often in males than in females [1,2]. This disease is because of a mutant gene, after reciprocal translocation between chromosome 22 and chromosome 11, particularly with a fusion between exon 7 of the former and exon 8 of the latter. The result is a chimerical transcript, the Ewing's sarcoma gene Wilms' Tumor (EWS-WT1), which can be detected with a reverse transcriptase-polymerase chain reaction [3].

This tumor has a tropism for mesenchymal tissues, and it develops on serosal surfaces even if it could be found elsewhere. The abdominal cavity is the most involved site, but this tumor may take place in other sites such as pleura [4] and ovary [5], and the starting point is usually unknown. Initially considered as a sarcoma, DSRCT is now identified as a polyphenotypic lesion with epithelial, muscular, and neuronal biomarkers. This led some authors to consider DSRCT almost as carcinomas, and thus, surgical cytoreduction (CS) was performed. Tumor is usually not capsulated, and its cells form clusters or bands, well defined, surrounded by hyperrepresented desmoplastic stroma. Development of the disease is extremely aggressive with rapid growth and local diffusion. Intraperitoneal masses are characterized by spreading off. Metastases are found in multiple sites such as lymph nodes, liver, lungs, and more rarely in bones, spleen, kidneys, and pleura [6].

Despite a multimodal therapy including chemotherapy, radiotherapy, and CS, mortality is high and the 5-year survival rate is around 15% [7]. The high recurrence rate after multimodal therapy and difficulties to clear up the local extension of the disease justify innovative approaches. Hyperthermic intraperitoneal chemotherapy (HIPEC) is considered as an additional strategy, which allows clearing up microscopic disease after cytoreduction particularly in colorectal cancer with peritoneal carcinomatosis. This increases disease-free and overall survival in some selected patients [8,9]. Hyperthermic intraperitoneal chemotherapy has been very rarely indicated as main treatment of DRSTC [10]. According to our experience, the prognosis of DRSTC in children is extremely bad. For this reason, we planned to treat selected children cases with DRSCT using CS and HIPEC.

However, this procedure requires a specialized team with a large learning curve; until now, we treated in our specialized referral center, 259 adult patients for peritoneal carcinomatosis (PC) with 307 CS + HIPEC. This enabled us to develop a pediatric multidisciplinary approach including oncologists and surgeons to treat children affected by PC from DRSCT.

1. Methods

1.1. Tumor staging

Peritoneal disease extension was evaluated according to Gilly classification [9]. Gilly 1 corresponds to neoplastic granulations less than 5 mm located in a half-abdominal space, Gilly 2 to neoplastic granulations less than 5 mm spread all over the peritoneal surface, Gilly 3 to neoplastic granulations with diameter between 5 and 20 mm, and Gilly 4 to neoplastic granulations more than 20 mm.

1.2. Completeness of cytoreduction

An extensive cytoreduction, defined as a surgical reduction of the tumoral mass in case of diffuse peritoneal disease, was realized before HIPEC. The CS was considered as completeness of cytoreduction (CCR)-0 when no macroscopic nodule was residual, CCR-1 when residual nodules were less than 5 mm, and CCR-2 when residual nodules were more than 5 mm [11].

1.3. Technique of hyperthermic intraperitoneal chemoperfusion

After completeness of CS, a rubber silo was sutured watertight along the skin of the open abdomen, and HIPEC circulation was performed using the coliseum technique with open abdomen. The equipment consisted of a device (Medtronic, RanD, Minneapolis, USA, Medolla (MO), Italy), including roller pomp and heat exchanger. The circulation was started under continuous heating. When intraperitoneal temperature reached 41° to 43°C, chemotherapeutic intraperitoneal drugs (mitomycin C, 120 mg, and cisplatinium, 75 mg/m^2 body surface) were administered with physiologic salted solution during 30 minutes. Central and intraabdominal temperatures were continuously checked, as central temperature can increase more rapidly in children than in adults. When perfusion was terminated, abdomen was washed out with salted solution. Digestive anastomoses were performed if necessary and the abdomen was closed with 3 drains.

The surgical procedure was the same for the 3 cases: extended cytoreduction of macroscopic disease associated to HIPEC, with intraperitoneal administration at 41°C to 43°C as described previously [8].

2. Patients and results

We report 3 patients operated on from June 2007 to September 2008.

2.1. Patient 1

A 16-year-old boy presented constipation, abdominal distension, and pain. A computed tomographic (CT) scan detected a 13-cm mass, located in lower left abdominal quadrant, associated to peritoneal lesions in the Douglas pouch and a secondary nodule in the right liver (Gilly 4). No thoracic masses were detected. Initial anatomopathologic diagnosis was rhabdomyosarcoma, but an additional analysis finally concluded for a DRSCT. The EWS-WT1 transcript was present in tumor cells. A chemotherapy protocol using cyclophosphamide/D-actinomycin/vincristine (CAV), followed by ifosfamide-etoposide (VP-I) during 6 months was established. Regional progression lead to a second-line therapy with vinorelbine-cyclophosphamide [12]. Imaging controls showed that lesion size had reduced. Recurrent hemorrhagic ascitis was found; decision of surgical treatment was taken (Fig. 1).

Laparotomy with intention of debulking and HIPEC has been realized (June 18, 2007). The main mass was broken, and the extension was classified as Gilly 4. Surgical cytoreduction was uncompleted (CCR-2). Partial peritonectomy, omentectomy, masses exeresis, and HIPEC were performed. Residual viable cells were discovered on pathologic specimens (Fig. 2). Postoperative course was uneventful. With support and palliative therapy, the patient died 5 months after operation, 12 months after initial diagnosis.

2.2. Patient 2

A 14-year-old girl has been admitted for ascitis. Ultrasonography and a CT scan showed hyperechogenic pelvic masses with ascitis and many peritoneal implants associated to aortocaval lymph nodes. The diagnosis was obtained by a needle biopsy targeting a mass in the abdominal central quadrant. Histologic results found a small round cell cancer, initially identified as rhabdomyosarcoma. Then, the specimen has been reevaluated, and the mutation of EWS-WT1 has been found confirming DRSCT. Additional evaluation by a total body CT and a positron emission tomography (PET)-CT permitted to find also some microlesions in the lungs and mediastinal lymph nodes. Initial treatment was chemotherapy by ifosfamide/vincristine/D-actinomycin/doxorubicin protocol, followed by CAV/VP-I.

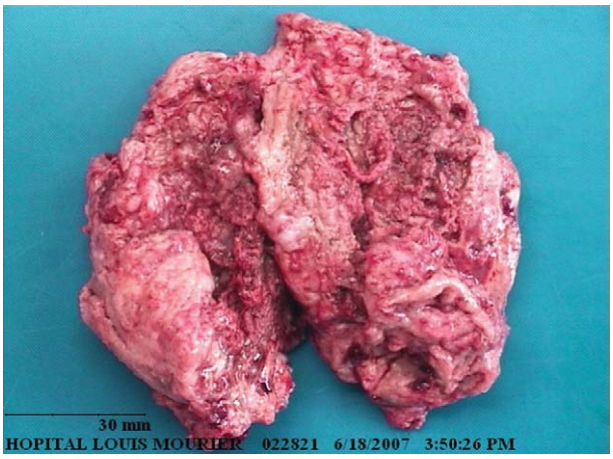

Fig. 1 Main abdominal mass after resection (patient 1).

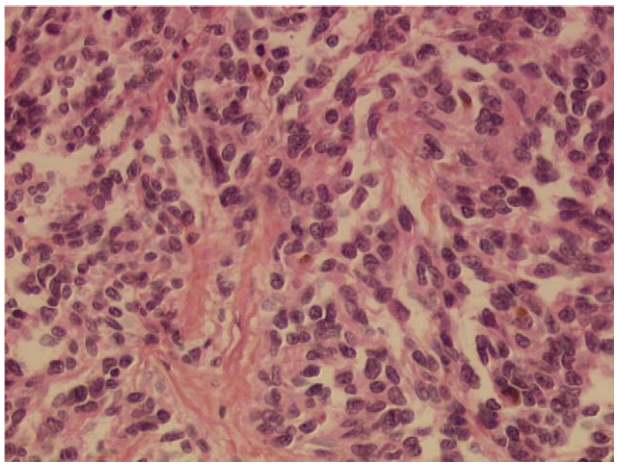

Fig. 2 Histologic aspect of main abdominal mass after resection (coloration H&E stain ×25) (patient 1).

Even then, chemotherapy allowed cleaning up thoracic lesions; abdominal masses were stable after 4 courses of chemotherapy. The patient then received vinorelbine-cyclophosphamide with initial partial response after 3 courses and secondary peritoneal progression after 6 courses. Laparotomy with intention of debulking and HIPEC has been decided and realized (June 27, 2007). Peritonectomy, omentectomy, left annexectomy, appendectomy, exeresis of a diaphragmatic lesion, and HIPEC with mitomycin C and cisplatin have been realized. Lesions were classified as Gilly 4 with ascitis. All visible masses were removed during this operation (CCR-0). Six globular sediments were administered postoperatively. At day 6, the patient has been reoperated on because of biliary peritonitis because of gallbladder perforation. A cholecystectomy was performed with abdominal toilette and drainage. Then, the course was uneventful. Anatomopathologist confirmed diagnosis of DRSCT, and residual viable cells were discovered on pathologic specimens.

The patient died 4 months after the last operation, with abdominal progression 14 months after initial diagnosis.

2.3. Patient 3

A 15-year-old boy presented constipation and a palpable abdominal mass. A CT scan confirmed the presence of the lesion located in pelvis as well as secondary multiple hepatic nodules. The PET-CT scan showed bone metastasis, at right femur and some right ribs. Diagnosis of DRSCT was made by needle biopsy of the mass. Anatomopathologist found desmoplastic small cells, and EWS-WT1 transcript was

present in tumor cells. Chemotherapy with CAV followed by VP-1 was the first treatment. A second PET-CT scan did not find any bone-enhanced focus. A first laparotomy confirmed that lesions previously detected had disappeared. Some small, calcified pelvic lesions with no residual tumor cells were found. The patient was clinically well, without digestive symptoms. Five weeks after initial surgery, a CT scan showed persistent calcified intraabdominal masses without thoracic involvement. A new CAV/VP-1 course was delivered. Additional radiologic evaluation detected some intraabdominal calcifications. A second look with intention of CS and HIPEC has been decided and realized (September 22, 2008). Partial peritonectomy, omentectomy, lymph node dissection, and HIPEC were performed. All histologic samples were negative for neoplastic cells, but necrosed, calcified clusters were found. The patient is actually alive and free of disease 10 months after surgery.

3. Discussion

The present observations and those reported recently confirm that CS and HIPEC could be considered as feasible procedures in the multidisciplinary treatment of DRSCT in children. However, as CS and HIPEC need an important learning curve, this procedure should only be used for patients with a hope to achieve a complete CS (CCR-0 or CCR-1).

Surgical cytoreduction and HIPEC are therapies that, in appropriate conditions, are associated with almost good results in the treatment of PC from colorectal origin in adults. In these cases, median survival time is 32.9 months if the CS is complete (CCR-0), 12.5 months in case of CCR-1 and 8.1 months for patients with a CCR-2 [8]. Desmoplastic round small cell tumor, which has particular tropism for mesenchymal tissues and especially for serosal surfaces, is usually diagnosed in young patients. Most of them are children. Despite multimodal therapy including CS, neoadjuvant and adjuvant chemotherapy, and radiotherapy, most of reported series showed a mean 5-year survival rate of less than 25%. Patients, who had a long-term survival, could hope for complete remission after chemotherapy. Most of the patients died of peritoneal recurrence. In these conditions, CS associated to HIPEC might represent a new approach as it is for adults [13].

Hyperthermic intraperitoneal chemotherapy in pediatric patients has been reported in only 2 series with a total of 3 patients. In one case, the tumor was a signet-ring cell carcinoma of the colon in a 12-year-old boy [13]. Authors showed that this procedure is feasible without any complications, but the patient died of progressive recurrent disease 13 months after HIPEC.

In the series of Hayes-Jordan et al [14], there were 2 consecutive children (6 and 11 years old) with DRSCT finally treated by CS and HIPEC after many cycles of systemic chemotherapy. In these 2 cases, CS was complete, without any surgical complications, unless there is a transient renal failure. These patients were still alive 6 and 10 months after the procedure without evidence of disease.

In our study, all patients received many cycles of systemic chemotherapy before CS and HIPEC. The procedure has been performed without perioperative mortality in all cases. However, in the 2 first cases, patients were almost in palliative conditions with severe hypoalbuminemia. One patient was reoperated on for biliary peritonitis at day 6 without further morbidity. The mean duration of the procedures was 9 hours. Complete cytoreduction (CCR-0/CCR-1) was obtained in 2 patients. One died 14 months after initial diagnosis of recurrent disease; the other patient is still alive, free of disease 10 months after the procedure. In this case, the CS was performed with a curative intent (CCR-0), and the patient had a good general condition. In the later case, the only residual lesions were intraperitoneal calcified nodules after chemotherapy. Complete CS of these lesions was histologically free of neoplastic cell. In DRSCT, calcified persistent nodules after chemotherapy could be considered as sterile lesions. In our opinion, systematic second surgical look has to be discussed in the therapeutic approach of DRSCT as used in other peritoneal carcinomatosis in adults. In this article, we discuss HIPEC for DRSCT in children after CS-CCR-0 or as systematic second look after complete response induced by multimodal combined therapy (chemotherapy and radiotherapy) in the absence of extraabdominal persistent tumor. Radiotherapy-induced peritoneal fibrosis may represent, on a pure theoretical basis, an obstacle to penetration of cytotoxic drugs in the tissue during HIPEC. However, previous radiotherapy does not represent, to date, a contraindication to perform HIPEC.

In our study, the patient who had a CCR-2 surgical reduction, died 5 months after operation, 12 months after initial diagnosis from progressive disease, was our first case. He received HIPEC as a palliative treatment of the hemorrhagic ascitis that was refractory to medical treatment. Transient resolution of ascitis and mass-related symptoms was indeed effective in the postoperative course. As we demonstrated for peritoneal carcinomatosis from gastric carcinoma [15], we do not recommend cytoreductive surgery and HIPEC in palliative conditions. As well as for adults, CCR is an important prognostic factor [16].

In the series of Hayes-Jordan et al [14], the authors used a closed technique for continuous hyperthermic peritoneal perfusion and administered *cis*-platinum as the unique chemotherapy drug to treat the 2 children. In the series of Reingruber et al [13], the authors used an open technique and administered mitomycin C as the unique drug. In our study, we used an open technique, administering both *cis*-platinum and mitomycin C. We used 2 drugs because of their synergic effect [17]. Doses were adapted to corporeal surfaces in the all the cases. Hyperthermia ranged from 41°C to 43°C in all cases. Duration of HIPEC is variable from one study to the other, between 30 and 90 minutes. We suggest that in children or teenagers, moreover, with

small weight and size, the open technique allows a better control of the central temperature as it can suddenly increase during the HIPEC procedure.

In the studies of Hayes-Jordan et al [14] and Reingruber et al [13], the patients were 6 to 12 years old. In the series of Feldmann et al [18], some teenagers have undergone intraperitoneal chemotherapy for mesothelioma, but none have been reported in children and adolescent younger than 16 years or those with disease other than mesothelioma. In our study, we operated on 3 teenagers from 14 to 16 with DRSCT, and this is the first cases reported.

As well as for adults, CCR is an important prognostic factor. Hyperthermic intraperitoneal chemotherapy for adults is now a well-controlled procedure in experienced teams. This provides a local alternative approach to systemic chemotherapy in the control of microscopic peritoneal disease. Provided CS is complete, HIPEC could be delivered in a curative intent with acceptable morbidity and absence of perioperative mortality. Experience and long-term follow-up in children and teenager patients is of course too short to draw definitive conclusions, but considering the dramatic poor prognosis of DRSCT in children and teenagers with the classical treatments, cytoreduction and HIPEC may be considered as potential beneficial adjuvants waiting for a more specific targeted therapy against the fusion protein. However, this approach should not be used for palliative purpose. More clinical data must be provided to confirm this opinion, particularly to demonstrate the effect of HIPEC, when associated to CS.

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