Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Case Report

J. Exp. Clin. Med., 2019; 36(4): 131-135
doi: 10.5835/jecm.omu.36.04.006

Addition of hyperthermic intraperitoneal chemotherapy (HIPEC) after complete cytoreductive surgery in a child with desmoplastic small round cell tumour

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ARTICLE INFO

Article History
Received 03 / 09 / 2019
Accepted 17 / 01 / 2020
Online Published 02 / 03 / 2020

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Keywords:
Cytoreductive surgery
Desmoplastic small round cell tumour
Hyperthermic intraperitoneal chemotherapy
Pediatric patients

ABSTRACT

Desmoplastic small round cell tumour (DSRCT) is a rare and aggressive sarcoma. No curative treatment has been reported yet; however, multi-agent chemotherapy, an aggressive surgical approach and radiotherapy have been used. Hyperthermic intraperitoneal chemotherapy (HIPEC) is an additional strategy used to remove microscopic disease after cytoreduction, especially in patients with peritoneal carcinomatosis and colorectal cancer; however, its application in paediatric patients has been reported rarely. In Turkey, some HIPEC studies have been performed in adult patients but not in paediatric patients. A 10-year-old girl presented to the hospital with a mass palpated in the left lumbar region. The mass was reported as a primitive neuroectodermal tumour after the biopsy. Left radical nephrectomy and lymph node dissection were performed after she failed to respond to five months of neoadjuvant chemotherapy. The pathological examination revealed a DSRCT. A multi-agent chemotherapy regimen was applied to the patient for one year. Myeloablative chemotherapy and autologous stem cell transplantation were performed in the patient, who subsequently entered remission. During the third month of follow-up, high-dose multi-agent chemotherapy protocols were initiated because of disease relapse. At 6 months after recurrence, HIPEC with irinotecan and oxaliplatin was performed after the excision of all tumour foci by intracavitary cytoreductive surgery. No complications were observed. The patient was prescribed a tyrosine kinase receptor inhibitor (sunitinib maleate). The patient died 8 months later. In conclusion, although the benefit of HIPEC is still unknown and requires evaluation in a prospective trial, HIPEC can be used as an alternative treatment in paediatric patients with peritoneal carcinomatosis.

1. Introduction

Desmoplastic small round cell tumour (DSRCT) is a rare and aggressive sarcoma commonly seen in children and adolescents (Gerald and Rosai, 1989). The prognosis of this disease is poor, with a median survival of approximately 17 months. Although the tumour is thought to be mesothelial in origin due to its frequent association with serosal surfaces, its origin

remains controversial. It has been hypothesised to have originated from a primitive cell with multipotent differentiation (Kim et al., 2009).

Because of anatomical and pathological polymorphisms, the differential diagnosis should be made based on immunohistochemical and cytogenetic studies according to the clinical and histological features of the disease (Gerald et al.,1995).

No curative treatment has been reported yet; multi-agent chemotherapy, an aggressive surgical approach and radiotherapy are among the current treatment options. As a multifaceted approach, hyperthermic intraperitoneal chemotherapy (HIPEC) is an additional strategy used to remove microscopic disease after cytoreduction, especially in patients with peritoneal carcinomatosis and colorectal cancer, but this treatment has been reported in very few patients (Reingruber et al., 2007). In Turkey, adult patients with DSRCT have been treated with HIPEC; however, this treatment has not been used in paediatric patients.

In this case report, we present our first HIPEC experience in a 10-year-old child with DSRCT in Turkey.

2. Case

A 10-year-old girl presented to the hospital with month-long fatigue, anorexia and back pain. A physical examination revealed a mass of approximately 10 × 10 cm palpated in the left lumbar region. Magnetic resonance imaging (MRI) showed a mass lesion of approximately 80x92×118mm encompassing nearly the entire left kidney and extending posteriorly, with solid components and cystic necrotic areas with heterogeneous contrast enhancement, irregular lobular contours and shifts in the left renal collecting system (Fig. 1). A soft tissue mass (conglomerate lymph nodes) of approximately 30×36×79mm was observed in the left para-aortic area on the medial segment of the mass, surrounding and compressing the left renal artery. Positron emission tomography/computed tomography (PET/CT) revealed multiple hypermetabolic foci in the lung and abdominal lymph nodes and multifocal hypermetabolic osseous lesions. The tumour was staged as T2bN1M1.

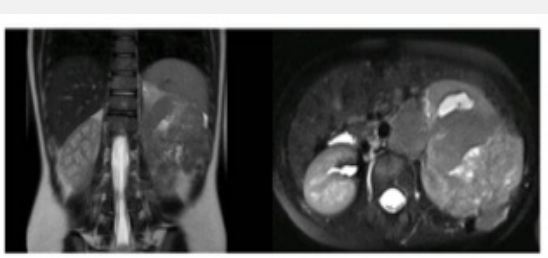

Fig. 1. MRI image of the mass.

An ultrasound-guided biopsy was performed on the mass, which was reported to be a primitive neuroectodermal tumour. Left radical nephrectomy and lymph node dissection were performed after six cycles of VIDE (vincristine 1.5 mg/m^2/day for 1 day, ifosfamide 3 g/m^2/day with mesna for 3 days and etoposide 150 mg/m^2/day for 3 days) administered according to the Euro-Ewing 99 protocol. Pathological examination using fluorescent in situ hybridisation of the nephrectomy material indicated a DSRCT with cytoplasmic reaction to the WT-1 dye and translocation of the ESWR gene. CEVAIE (carboplatin, epirubicin, vincristine, actinomycin-D, ifosfamide and etoposide), a multi-agent intensive chemotherapy regimen, was applied for approximately 1 year. At the end of the treatment, the fluorodeoxyglucose PET/CT findings were compatible with the radiological results and indicated a full remission with complete metabolic response. Because of the high risk of the disease metastasizing to sites other than the lung (tumour volume >100 ml), the decision to perform autologous stem cell transplantation was made by the council of the paediatric stem cell transplant centre. The procedure including busulfan (4 mg/m^2/d, 4 days) and melphalan (140 mg/m^2/d, 1 day) was successful. Three months after the transplantation, mass lesions were detected by abdominal MRI. A 19×16mm mass lesion with soft tissue intensity was detected in the liver in a subcapsular location at the anterior part of segment III. In addition, a 12×11mm mass lesion with soft tissue intensity and hyperintense in T2 series at segment IVB showed suspicious contrast enhancement after administering intravenous contrast agent. Furthermore, a 22×11mm mass at the medial, posterior and lateral parts of the spleen and at the hilus of the spleen between the pancreas and spleen and a 20×20mm soft tissue mass with hyperintensity and suspicious contrast enhancement was detected in the T2 series. Newly formed malignant hypermetabolic lesions were detected in the thorax, abdomen and skeletal system by PET/CT. Two cycles of salvage chemotherapy consisting of high-dose cyclophosphamide (2.1 g/m^2/d, 2 days) and topotecan (2 mg/m^2/d, 3 days) were applied to the patient. However, third-line chemotherapy, including irinotecan (175mg/m^2/d, 1 day) gemcitabine (1,000 mg/m^2/d, 1, 8, 15 days) and oxaliplatin (85mg/m^2/d, 1 day) (Carolin Hartmann et al., 2011), was performed due to the patient's poor response. However, widespread increased pathological metabolic activity (in multiple lung nodules and hilar lymph nodes, liver lesions, lesions adjacent to the spleen, abdominal lymph nodes, a mass adjacent to the rectum and foci of the skeletal system) was detected by PET/CT6 months after recurrence. This was interpreted as extensive progressive disease on abdominal MRI.

Cytoreductive surgery (CRS) and HIPEC were planned for the patient because of the overwhelming abdominal component. Informed consent was obtained from the patient's parents. Intraperitonealirinotecan (200 mg/m^2) and oxaliplatin (300 mg/m^2), which are activated by hyperthermia, were applied with the patient's prior chemotherapy protocol. Hypokalaemia caused by the tubular nephropathy, which developed from previously administered treatments, was corrected before the procedure. The high-dose saline infusion was applied before the procedure and continued for 48 hours after the procedure to reduce additional kidney toxicity potentially induced by the platinum-based drugs. First, omentectomy was performed by removing the omentum majus. The mass in the left upper quadrant was removed by mobilising the posterior part of the spleen. A portion of the distal pancreatic diaphragm was completely resected with the spleen. The liver metastases on both sides were excised by segmentectomy and transparenchymal dissection. The hilus of the liver and the lymph nodes on the hepatic artery were dissected. A peritoneal implant was detected, and a pelvic peritoneal mass between the bladder and rectum was excised. All parts of the abdomen were washed and haemostatic control was obtained. Because of diaphragm resection, a thoracic tube was placed and pulled out on day 2. Four drains/catheters were then placed to apply HIPEC to the abdomen. The abdomen was permanently closed with anatomical plans. HIPEC (41°C) was applied with a chemotherapy solution (130 mg irinotecan and 200 mg oxaliplatin) prepared for 60 minutes (Honoré C et al., 2017). During the procedure, the temperature of the delivered fluid, intraperitoneal temperature and body temperature were monitored. The body temperature was 36.5-37°C. No complications were observed in the patient, who was closely followed in the intensive care unit during the postoperative period for 1 night. Therapeutic options for patients with advanced disease are limited. There are data in the literature suggesting that sunitinib may be associated with clinical benefit, even in previously treated patients (Italiano et al., 2013). The patient was discharged 6 days after surgery and was prescribed a tyrosine kinase receptor inhibitor (sunitinib maleate). The disease recurred. The patient died 8 months later because of progressive disease.

3. Discussion

A DSRCT, first described in 1989, is a rare sarcoma that is difficult to diagnose because of its low incidence in the general population (Gerald et al., 1995). No more than 300 cases have been reported in the literature. This aggressive malignancy is usually found in paediatric and young adult patients, with a male:female ratio of 3:1. The age range of 73% of cases is 10–16 years (Jellouli et al., 2003).

The cells from which these tumours originate are unknown. However, DSRCT is frequently found on the mesothelial-coated surface, which is thought to be the origin. DSRCT usually arises from the abdominal or pelvic peritoneum and very rarely from the head and neck, base of the skull, paratesticular region, ovary, brain and internal thoracic organs (Biswas et al., 2005). Clinical manifestations are usually non-specific; the tumour does not present any symptoms until there is evidence of compression in surrounding structures or extensive invasion. Patients are diagnosed during the stage of extensive DSRCT progression. Symptoms include abdominal distress/distension, abdominal pain, weight loss or changes in bowel habits (Biswas et al., 2005).

The most characteristic imaging feature of abdominal DSRCT is not pathognomonic, with single or multiple lobular peritoneal soft tissue masses that are not derived from a specific organ (Pickhardt et al., 1999).

The diagnosis of DSRCT is difficult because of similar morphological manifestations in other small round cell tumours, such as Ewing's sarcoma, rhabdomyosarcoma, primitive neuroectodermal tumour, neuroblastoma and Wilms tumour (Ordóñez, 1998). Mutual translocation t(11; 22)(p13; q12) resulting in EWS–WT1 gene fusion has recently been reported as specific to DSRCT (Stuart-Buttlea et al., 2008).

Despite the search for a wide variety of therapies, there has been no dramatic improvement in the overall survival of patients with DSRCT. Treatment alternatives for abdominal DSRCT are not well documented because of the rarity of the disease. Due to the aggressiveness of the disease, DSRCT treatment relies on multimodal therapies, including comprehensive surgery when available, abdominal radiotherapy or systemic chemotherapy without abdominal radiotherapy (Stuart-Buttlea et al., 2008). The combination of these three methods showed better results compared with each method separately. The overall response rate was 39%, and the survival rate at 3 years was approximately 50% (Biswas et al., 2005; Stuart-Buttlea et al., 2008).

Despite surgical intervention, radiotherapy and multi-drug chemotherapy, the prognosis of DSRCT is poor (Bellah et al., 2005; Hiralal et al., 2007; Honoré et al., 2017). In recent years, chemotherapy regimens have been reported to extend the median survival by approximately 17 months (Lal et al., 2005; Stuart-Buttlea et al., 2008). In addition, percutaneous stenting (biliary) has also been reported in paediatric and adult cases to prolong life span and enhance comfort (Irwin et al., 2004). The effect of cytoreductive surgery on survival is unclear. Some authors suggest an improvement in survival for operative versus non-

operative tumours, with a median survival of 34 months versus 14 months, respectively (Biswas et al., 2005). Lal reported a significant effect of surgery on overall survival, with a 3-year survival rate of 58% compared with 0% in patients with unresectable disease. The surgical benefit is greater after complete resection, but this course of action is not always possible because of the widespread extent of the disease (Lal et al., 2005).

There are only a few reports on the use of chemotherapy for DSRCT. Multiagent chemotherapy leads to an approximately 40% reduction in tumour size (Biswas et al, 2005; Stuart-Buttlea et al., 2008). Chemotherapy may be beneficial for DSRCT patients; however, disease recurrence often occurs within 6 months (Lauridant-Philippin et al., 2010). Data on the use of radiation therapy for DSRCT are limited. This approach is primarily intended to destroy residual disease or relieve symptoms. Therapeutic use is limited by peritoneal spread to intra-abdominal organs and sensitivity to radiation (Jellouli et al., 2003; Stuart-Buttlea et al., 2008).

A recently used approach is multimodal therapy such as hyperthermia intraperitoneal chemotherapy. Conflicting findings have been reported from studies involving very few cases. In a series of seven adults treated with cytoreductive surgery and HIPEC, overall survival did not improve significantly (Gil et al., 2004). In a retrospective review, Hayes Jordan found shorter recurrence-free survival in patients with than in those without HIPEC (5.85 versus 8.85 months), but this difference was not statistically significant due to the low number of patients. A better outcome in paediatric patients was observed (Hayes-Jordan et al., 2010). For this reason, more patients need to be evaluated to determine the efficacy of HIPEC in DSRCT.

Complete resection of multiple intra-abdominal tumour implants is sometimes achieved by CRS and HIPEC, followed by hyperthermia chemotherapy at approximately 41 °C for a period of time. HIPEC may provide microscopic control of abdominal DSRCT after surgical resection and prevent, or prolong the time to recurrence (Msika et al., 2010).

Despite multimodal treatment, including CRS, neoadjuvant and adjuvant chemotherapy and radiotherapy, the mean 5-year survival rate in the majority of reported series is < 25%. Although the advantages of HIPEC after CRS are not absolutely known in these patients, HIPEC-associated CRS is being used as a new approach in paediatric patients (Reingruber et al., 2007).

HIPEC for adults is now a well-known procedure performed by experienced teams. Although there are studies related to HIPEC conducted in adults in Turkey, HIPEC has not been reported in paediatric patients. This procedure provides a local alternative approach to systematic treatment. Current observations and recently published articles suggest that CRS and HIPEC are practical procedures used in a multidisciplinary approach in paediatric patients. However, as there is insufficient experience and knowledge about implementing CRS and HIPEC in paediatric patients, this procedure should be used only after CRS.There is no more treatment option for patients with recurrent advanced disease. Our patient also survived 8 months after the HIPEC procedure. The experience of a small number of adult patients is similar with the average life expectancy. There is even less experience with this treatment option in pediatric patients.

In summary, HIPEC can be applied in paediatric patients for the treatment of resistant DSRCT. However, the benefit of HIPEC is still unknown and should be evaluated in a prospective trial. Further prospective studies are needed along with molecular analyses of DSRCT to determine a specific targeted treatment.

The authors declare no conflicts of interest.

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