CLINICAL CASE

Optimal treatment with systemic chemotherapy, complete surgical excision and hyperthermic intraperitoneal chemotherapy for a desmoplastic small round cell tumor in an adult male patient

Traitement optimal par chimiothérapie systémique, chirurgie de résection avec chimiothérapie intrapéritonéale hyperthermique chez un patient présentant une tumeur desmoplastique à cellules rondes du péricône


Digestive Oncology Unit, Department of Hepato-Gastroenterology, Rouen University Hospital, 1, rue de Germont, 76031 Rouen cedex, France
Department of Surgery, Rouen University Hospital, 1, rue de Germont, 76031 Rouen cedex, France
Department of Pathology, Rouen University Hospital, 1, rue de Germont, 76031 Rouen cedex, France
Department of Oncology, centre régional de lutte contre le cancer, Rouen cedex, France

Summary
Desmoplastic small round cell tumor (DSRCT) is a very rare but aggressive malignancy. It is usually observed in males during adolescent and early adulthood. The tumor primarily affects the intra-abdominal serosal and is characterized by distinctive histological and immunophenotypic features and by the specific reciprocal translocation EWS-WT1. Prognosis is mainly poor with a mean survival approximately of 2.5 years. However, long-term survivals have been reported using aggressive multimodal therapy based on complete surgical excision, systemic chemotherapy and radiotherapy. The addition of hyperthermic intraperitoneal chemotherapy in the multimodal approach has been reported in very few cases but no effect on survival has been clearly demonstrated. We report a case of a 51-year old adult patient presenting with a DSRCT treated with aggressive therapy based on systemic chemotherapy, complete cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy, resulting in a long term survival of 4 years.

© 2010 Elsevier Masson SAS. All rights reserved.

Résumé
Les tumeurs desmoplastiques à cellules rondes sont rares qui touchent préférentiellement les enfants et adultes jeunes masculins. Ces tumeurs sont grevées d’un pronostic sombre avec une survie moyenne de 2,5 ans environ. Des cas de survie prolongée ont été cependant

* Corresponding author.
E-mail address: frederic.di-fiore@chu-rouen.fr (F. Di Fiore).

0399-8320/$ - see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.gcb.2010.04.005
Introduction

Desmoplastic small round cell tumor (DSRCT) is a rare entity with less than 300 cases reported in literature. DSRCT is characterized by specific clinical, histological and molecular patterns and occurred preferentially in children or young patients during their second or third decade of life with a male to female ratio of 4:1 [1–6]. This neoplasm often involves the abdominal cavity with numerous peritoneal implants with a tendency to lymph node involvement and hematogenous metastasis dissemination, most frequently to the liver. Moreover, extra abdominal extent have been also reported on non-mesothelial tissue i.e. for bone, lung, salivary gland, ethmoid sinus or posterior cranial fossa [7]. The prognosis of the disease is poor and most of patients die within 3 years [2].

Clinically, DSRCT is commonly characterized by large abdominal masses leading to abdominal distension and pain, and in some cases to compression of adjacent organs such as intestinal obstruction, hydronephrosis and urinary/erectile dysfunction. At pathological examination, the tumor forms nests or undifferentiated small round cells embedded in desmoplastic stroma. Tumor cells are usually mitotically active with a complex immunophenotype proteins expression including epithelial, muscular and neural differentiation. The stroma is primarily fibroblastic with variable collagen deposits. At cytogenetic examination, the EWS-WT1 gene fusion has been identified as a specific molecular alteration of DSRCT [2,8,9].

Regarding the rare incidence of the disease, therapeutic options of DSRCT are not well codified and no curative treatment has been yet documented. However, it has been shown that an optimal multimodal therapy using combined systemic chemotherapy and complete surgical excision of the masses is the only strategy that led to a long-term control of the disease [10–15]. Although a complete cytoreductive surgery followed by hyperthermic intraperitoneal (HI) chemotherapy is considered as the best treatment in adults with resectable carcinomatosis secondary to ovarian, mesothelioma, appendiceal and colorectal carcinomas [16], the usefulness of this specific procedure in DSRCT remains unknown. To our knowledge, this multimodal therapy including IH chemotherapy has been only reported in two pediatric and 4 adult patients with DSRCT but the impact on survival was not demonstrated [1,17]. Here, we report and discuss a case of a 51-year old adult patient presenting with a DSRCT treated with aggressive therapy based on systemic chemotherapy, complete cytoreductive surgery associated with HI chemotherapy, resulting in a a long-term survival of 4 years.

Case

A 51-year old man was referred in our unit in October 2005 for an isolated abdominal carcinomatosis with undetermined origin. Main complaints were abdominal distension, diarrhoea and pain due to multiple palpable abdominal masses. Biological blood tests and common serum tumour markers level were not normal (CEA, CA19-9, CA-125, alpha fetoprotein). The abdominal CT scan examination revealed extensive peritoneal mass and ascites without distant metastasis or retroperitoneal lymphadenopathy. No extra abdominal tumor was found at gastroscopy, colonoscopy and CT-scan examinations. Biopsies were performed during an exploratory laparotomy that revealed widespread omentum and peritoneal implants. The pathological examination showed undifferentiated tumour cells associated with diffuse necrosis areas. At immunohistochemical analysis, tumor was positive for keratin, epithelial membrane antigen and vimentin. The diagnosis of an undifferentiated peritoneal adenocarcinoma of unknown primary was then suggested. Seven cycles of systemic chemotherapy using cisplatin-LV5FU2 combination (cisplatin 50 mg/m² at day 1, leucovorin 400 mg/m² at day 1, fluorouracil 400 mg/m² bolus at day 1 followed by a 2400 mg/m² infusion during 46 hours) were delivered leading to a major clinical and radiological response with a reduction of more than 50% of abdominal mass (Fig. 1). No extra abdominal extent of the disease was observed at both CT scan and TEP scan. Patient underwent surgery and a complete cytoreductive excision of the peritoneal implants was performed followed by an HI chemotherapy using cisplatin and mitomycin combination. Histology assessment revealed the same patterns associated with chemotherapy-induced necrosis areas. A postoperative chemotherapy was delivered during 5 months using folfiri regimen due to renal insufficiency. A peritoneal disease recurrence was observed 9 months after the surgical procedure. A third exploratory laparotomy was performed after seven cycles of systemic chemotherapy using folfiri regimen but the surgical excision was not possible mainly due to the right hemidiaphragmatic extent of the disease. Pathological examination showed an abundant dense stroma reaction with demarcated nests blue tumor cells expressing keratin and desmin (Fig. 2). At this time, considering these particular histological findings and the unexpected survival,
the diagnosis of DSRCT was then suggested and confirmed by the identification of the specific genetic translocation t(11,22)(p15, q12). Four cycles of ifosfamide 3 g/m², MESNA (3 g/m²/day) and etoposide 75 mg/m² were delivered after surgery. Partial response was observed at CT-scan and TEP-scan and patient was still alive after 4 years of follow-up.

Discussion

DSRCT is a very rare entity, which is mainly reported, in young male patient with abdominopelvic malignancy. The disease is commonly diagnosed during the second or third decade of life and there were very few cases of DSRCT reported in adult patients. The histopathology and immunocytochemistry of the disease have been well documented with the presence, as in our case, of a specific genetic abnormality characterized by a reciprocal translocation EWS-WT1. Prognosis of DSRCT is poor and no curative treatment has been yet established. Disease mortality is evaluated at 70%-85% and most patients die within the 3 years from diagnosis [1–6].

However, long-term survivors have been reported in non-metastatic DSRCT with the use of a multimodal therapeutic procedure based on extensive surgery, systemic chemotherapy and in some cases abdominal radiation [2,5,14]. The major goal of the cytoreductive surgery combined with systemic chemotherapy is to delay the peritoneal recurrence of the disease. A 3-year survival rates of approximately 50% were reported in series including patients treated with the multimodal strategy as compared to approximately 30% when these three modalities were not combined [14]. When feasible, surgical procedure should be extensive aiming at complete macroscopic cytoreduction as well as resection greater than 90% of peritoneal mass [2,14,15]. Chemotherapy protocols are commonly based on ifosfamide, etoposide, cyclophosphamide, doxorubicin and vincristine combinations with approximately 40% of tumour response but early disease recurrence often within the 6 months is the rule except in two reported cases with good response and survived 55 and 101 months using systemic chemotherapy alone [1,2].

The continuous HI chemotherapy associated with complete surgical excision was evaluated in several peritoneal malignancies including gastric cancer, ovarian carcinoma, and colon cancer [16]. The use of HI chemotherapy infusion in the multimodal approach has been reported in very few cases of DSRCT and effect on survival has been clearly demonstrated. In DSRCT occurring in adult patient, the result of HI chemotherapy was reported in a series of seven patients with only four of them who had complete surgical removal of the disease [2]. In these series, median overall survival of these patients ranged from 13 to 55 months but authors did not found a clear survival advantage using this approach. Surprisingly, they observed the longest survival of 101 months in a patient who benefit from surgery combined to systemic chemotherapy but without HI chemotherapy. In DSRCT occurring in pediatric cases, Hayes-Jordan et al. reported two cases treated with extensive surgical excision followed by intraperitoneal chemotherapy using cisplatin with only 10 months and 6 months of follow-up, respectively [17]. More recently, Aguilera et al. reported a disease-free survival of 18 months in a 5-year old patient treated with a multimodal therapy including neoadjuvant chemother-
apy, cytoreductive surgery with intraperitoneal infusion using cisplatin and post operative abdominal 30 Gy radiation [18].

In conclusion, although systemic chemotherapy and extensive surgery should be proposed in non metastatic DSRCT, the benefit of the addition of the HI chemotherapy in the management remained undefined given the small number of reported cases in literature. However, as shown in our case where patient had a survival longer than 4 years, the use of HI chemotherapy in the multimodal therapy of DSRCT occurring in adult patient appears to be feasible and promising. Nevertheless, the 9 months of disease-free survival that we observed in our patient also highlights that further evaluation of new experimental agents used during perioperative and intraoperative settings may be probably useful to delay the disease recurrence and to improve patient’s survival.

Conflict of interest

All authors have no conflicts of interest for this manuscript.

References