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REVIEW

Desmoplastic small round cell tumor: review of therapy including surgery followed by continuous hyperthermic peritoneal perfusion of chemotherapy

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Abstract Desmoplastic small round cell tumor (DSRCT) is a very rare disease of children, adolescents, and young adults and involves the abdominal cavity. DSRCT has characteristic fusion gene involving EWS1 and WT1 translocation, t(11;22)(p13;q12). Unlike Ewing's sarcoma of bone, DSRCT usually presents with diffuse peritoneal implants that are prone to recur. The primary organ of origin of DSRCT is mesenchyme of the peritoneum. This makes it a very unique tumor that is difficult to treat because of the infiltrative and diffuse nature of the peritoneum. The challenge of local control is to remove dozens to hundreds of tumors studding the peritoneal cavity, and then eliminate microscopic disease. We review a sequential multimodality strategy to reduce macroscopic and microscopic disease including neoadjuvant chemotherapy, aggressive surgery including an emerging new therapy to use after surgery to treat microscopic residual disease: continuous hyperthermic peritoneal chemotherapy, then radiation and adjuvant chemotherapy.

Keywords Desmoplastic small round cell tumor · Ewing's family of tumors · Pediatric surgery · Hyperthermia · Intraperitoneal chemotherapy · Peritoneal metastases

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Introduction

Desmoplastic small round cell tumor (DSRCT) is a rare disease of children, adolescents, and young adults, and involves peritoneal surfaces. Less than 200 cases are reported in the world literature. Despite multimodal treatment, including aggressive surgical excision, chemotherapy, and radiotherapy, multiple series have shown that approximately 75% of patients succumb to their disease within 3 years [1–7]. The general pattern of treatment failure is recurrent disease first in the peritoneal cavity, then in the liver, and finally in distant sites. Patients typically are young (ages 5–30 years) at presentation and 80–90% are males [3, 8–11]. The reason for male preponderance is unknown. In one study androgen receptors were present in 10/27 (37%; $P = 0.0045$) [10].

Young people with DSRCT usually present with diffuse abdominal metastatic disease very similar in gross appearance to peritoneal carcinomatosis [12–15]. DSRCT can also involve or metastasize to other serosal locations including the pleura, ovary or testicle, and soft tissue (e.g., liver, kidney) [2, 16]. DSRCT was relatively recently described pathologically in 1991 by Gerald et al. [17]. Histologically, DSRCT consists of small round blue cell nests separated by desmoplastic stroma (Fig. 1; ref. [4, 8, 11]). The presence of a specific recurring translocation, t(11;22) (p13;q12) involving fusion of the Ewing sarcoma gene (EWS1) and the Wilms' tumor gene (WT1), confirms the diagnosis of DSRCT [11, 18–23].

Presentation and staging

The usual presentation involves abdominal disease at an advanced stage, with large masses and/or extensive seeding of the visceral and parietal peritoneum [5, 11]. Thus,

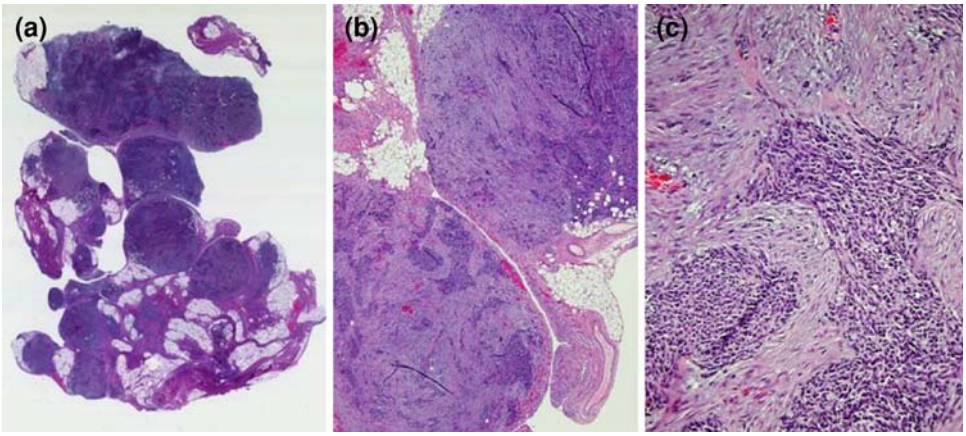

Fig. 1 Histologic appearance of DSRCT nodules removed from the peritoneum of a 6-year old male. **a** low power view. **b** high power view **c** nests of round cells in desmoplastic stroma. With permission from Sarcoma [36]

DSRCT, in the abdomen, is almost always disseminated regionally. Presenting symptoms may include abdominal pain and/or abdominal distension and possibly nausea or emesis. Vague abdominal pain is sometimes confused with constipation, but radiographic imaging readily reveals the diagnosis. The presence of ascites is the usual cause for the abdominal distension. Ultrasound, computed tomography scan (CT), magnetic resonance imaging, and/or PET-CT of the abdomen reveal multiple, always more than one or two and typically >20 tumor nodules "studding" the peritoneal cavity [24–28].

Once abdominal imaging reveals multiple tumors, imaging of the chest with CT scan and total body PET scan as part of the staging evaluation will confirm regional nature of the disease. PET-CT can in the future be used to evaluate "plateau of response" to neoadjuvant chemotherapy and timing of local control surgery or need to control relapse [29]. Percutaneous or open biopsy of the one or more peritoneal implants or analysis of malignant ascites with cytogenetics or FISH will confirm the characteristic t(11;22)(p13;q12) translocation involving EWS1-WT1.

Treatment: old and new strategies for DSRCT reduction, then elimination

Despite treatment strategies including chemotherapy regimens active for Ewings sarcoma, aggressive debulking surgery, adjuvant whole abdominal radiation, and even high-dose chemotherapy with autologous stem cell transplant [30], DSRCT survival remains low. Despite much time in the hospital and morbidity of the above interventions, DSRCT is chemotherapy responsive and many patients achieve a temporary marked reduction in disease burden and sometimes achieve "no evidence of disease status" (i.e., "NED"; a remission).

Chemotherapy agents with known activity in DSRCT are very similar to those active in Ewing's sarcoma and Wilms tumor. These small round blue cell tumors may share molecular mechanisms facilitating rapid, uncontrolled malignant proliferation, and apoptosis versus survival. Agents with activity in DSRCT are summarized in Table 1. Doxorubicin and alkylating agents such as cyclophosphamide and ifosfamide are important components of therapy. A well-recognized treatment schema has been reported by Kushner et al. who described results in 12 DSRCT patients [30]. This intensive alkylator-based therapy used cyclophosphamide, doxorubicin, vincristine alternating with ifosfamide, and etoposide. This chemotherapy combination with other treatment modalities such as aggressive complete surgical excision, total abdominal radiation, autologous stem cell rescue, or the combination of all of the above was used. The median survival time was 19 months. For those achieving complete response, the median follow-up in this series was 22 months. The toxicity for this regimen can be substantial and often includes hospitalization not only for chemotherapy, but also fevers associated with myelosupression. Weight loss is common.

New information on Ewing's sarcoma favors chemotherapy dose density (i.e., staying on schedule every 2 weeks) rather than dose intensity. In metastatic Ewing's, increased dose intensity had more toxicity and did not improve survival [31]. Mean values to provide outpatient chemotherapy with agents for DSRCT include use of dexrazoxane then doxorubicin to not only reduce heart toxicity but also reduce infusion times and continuous infusions of ifosfamide/mesna, then mesna or cyclophosphamide, and then mesna [32, 33].

Although DSRCT is a radiation-sensitive tumor, it is difficult to provide >30 Gy using whole abdominal radiation. Nevertheless, in the situations of relapse, adjuvant treatment after surgery (i.e., during low disease burden) and sites not amenable to surgery (e.g., porta hepatitis), radiation can be helpful. For tumors involving the liver, stereotactic radiation may be another new option to consider [34].

Table 1 Drugs and chemotherapy agents with activity in DSRCT

Regimen	Agent(s) dose/cycle + comments	Reference(s)
Pre-surgery (neoadjuvant)		
"P6" regimen HDCAV cycles 1, 2, 3, 6	Cyclophosphamide 4.2 gm/m^2, doxorubicin 75 mg/m^2, and vincristine 1 mg/m^2 max = 2 mg	[30]
	Note: cyclophosphamide doses divided G-CSF or pegGCSF recommended	
IE cycles 4, 5, 7	Ifosfamide/mesna 9 gm/m^2, etoposide 500 mg/m^2)	[36]
	Note: ifosfamide/mesna doses divided G-CSF or peg-GCSF recommended	
EuroEwings-like VIDE	Vincristine 1 mg/m^2 ifosfamide/mesna (9 gm/m^2) dexrazoxane (600 mg/m^2)/doxorubicin (60 mg/m^2) etoposide (150 mg/m^2)	[32, 33, 56]
	Note: ifosfamide/mesna doses divided G-CSF or peg-GCSF recommended	
	Outpatient therapy possible—if give ifosfamide/mesna as continuous infusion (daily clinic visits)	
Adjuvant (or relapse) or during radiotherapy		
Temozolomide + irinotecan	Temozolomide 100 mg/m^2 daily × 5	[37, 56]
	Irinotecan 10–20 mg/m^2 daily × 5	
Vinorelbine + cyclophsophamide	Vinorelbine 15–25 mg/m^2 (weekly × 3 of 4 weeks) cyclophosphamide 25–50 mg po daily	[38, 39]
Investigational		
R150	Anti-IGFR antibody	[57]

We presented an alternative more tolerable outpatient regimen similar to the widely used EuroEwing chemotherapy [35] in a DRCT case report [36]. In this report, neoadjuvant chemotherapy included vincristine, ifosfamide, dexrazoxane/doxorubicin, and etoposide. Continuous hyperthermic peritoneal perfusion (CHPP) with cisplatin was given immediately after extensive cytoreductive surgery. This was followed by irinotecan + temozolomide monthly × 2, then abdominal radiation 30 Gy with simultaneous temozolomide, then adjuvant irinotecan and temozolomide (9 months). The latter was done as "home chemotherapy." This outpatient chemotherapy resulted in a disease-free interval of nearly 2 years and permitted routine school attendance and full play activities with an excellent quality of life. For adjuvant chemotherapy or chemotherapy in relapsed patients both temozolomide + irinotecan and vinorelbine + oral cyclophosphamide are active outpatient combinations in Ewing's family of tumors including [32, 37–40].

Novel therapy including local control surgery with CHPP

Just as in Ewing sarcoma and Wilms tumor, aggressive cytoreductive surgery of DSRT is currently accepted to have an important role in the achievement of prolonged survival. This is similar to other malignancies involving the abdomen with peritoneal implants, i.e., peritoneal carcinomatosis [12, 13, 41–45]. In DSRCT LaQuaglia reported 3-year OS was 58% in gross total resection in comparison with 0% in the nonresection cohort [7]. Other therapeutic modalities such as CHPP also sometimes called hyperthermic intrapertitoneal chemotherapy (HIPEC), have been found to significantly improve outcome in cancer with carcinomatosis of the abdomen [42, 45–49]. However, many surgeons have been reluctant to embark on this very aggressive and potentially morbid operation without evidence of long-term control of microscopic disease. Since chemotherapy at 41°C can penetrate peritoneal surfaces, cytoreductive surgery followed by CHPP can potentially provide additional local control of microscopic disease in DSRCT.

We have recently treated children and adolescents with DSRCT and other malignancies involving the peritoneum on an experimental basis [12, 36]. Neoadjuvant chemotherapy was followed by complete cytoreductive surgery (removal of 5 tumor nodules up to 402 tumor nodules removed) followed by intraoperative CHPP using cisplatin. Six DSRCT patients treated with surgery + CHPP were compared to 12 historical controls that did not have CHPP chemotherapy following surgery. The additional treatment resulted in a 41-week improvement in survival. The estimated median was 3-year survival of 83% for CHPP versus 27% in those DSRCT patients who did not undergo CHPP.

Discussion

Continuous hyperthermic peritoneal perfusion is presently the preferred method of treatment in adults with carcinomatosis secondary to ovarian carcinoma, mesothelioma, and appendiceal and colon carcinoma [14, 15, 50–55]. In a

prospective randomized study on patients with gastric cancer, who, after gastrectomy, underwent CHPP, normothermic perfusion, or surgery alone, overall 5-year survival rates of CHPP, normothermic perfusion, and surgery-alone groups were 61, 43, and 42%, respectively [55]. In patients with gynecologic malignancies and persistent or resistant peritoneal carcinomatosis 1- and 3-year survival rates after surgery + CHPP were 79 and 63%, indicating some durability of response [51]. In mesothelioma the median progression –free survival after surgery + CHPP was 26 months and overall 2-year survival was 80%. There was minimal morbidity and no mortality associated with the procedure; some patients with recurrence were able to get surgery + CHPP a second time [55].

In conclusion, DSRCT treatment remains very challenging but is entering a new era. There are new treatment options that should be considered as part of an overall local control strategy and prolonged, but tolerable chemotherapy regimen: (1) CHPP immediately after surgery, and (2) new outpatient chemotherapy regimens. Using surgery + CHPP along with effective outpatient chemotherapy regimens has potential to improve not only survival, but also quality of life of young people with DSRCT.

Conflict of interest statement The authors declare that they have no conflict of interest to the publication of this article.

Appendix: description of HIPEC therapy

After removal of all visible and palpable tumors, seven temperature probes are inserted: One each in the right lobe of the liver, the ligament of Treitz, the pelvis, and the abdominal wall of the right and left upper and lower quadrants. This allows constant monitoring of the temperature in the peritoneal cavity in multiple locations to ensure equal distribution of the perfusate and to avoid elevated liver and core temperature secondary to hyperthermia. (If the temperatures of any area of the abdominal cavity are found to be too high, the perfusate temperature or flow can be adjusted). If the temperatures are below the target temperatures, more aggressive manual agitation to the corresponding portion of the abdominal cavity may be needed. The abdomen is then temporarily closed with a single-layer running stitch, and inflow and outflow cannulas are sewn into place and connected to a roller pump circuit (Fig. 2). The patient's body is cooled to approximately 35°C using ice and a cooling blanket. Sodium thiosulfate is then given intravenously to bind the cis-platinum that may escape into the circulation. The perfusate is warmed to the desired temperature while the abdomen is being constantly agitated to assure equal distribution of the perfusate. Once the desired temperature has been reached in all areas of the abdominal cavity, cis -platinum is added to the perfusate, and the abdomen continues to be agitated for 90 min. The perfusate is then evacuated, and the abdomen is reopened and irrigated. Although this is a very complex procedure, it has been done for >3 years at MD Anderson Cancer center in children as part of study MDACC 2005-0917.

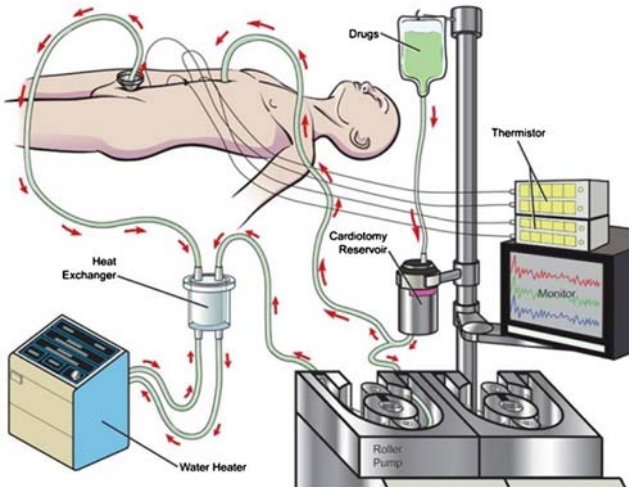

Fig. 2 Schematic of hyperthermic peritoneal perfusion set up as presently used to treat patients with DSRCT. With permission from Sarcoma [36]

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