


Recurrent desmoplastic small round cell tumor responding to an mTOR inhibitor containing regimen

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Abstract

Desmoplastic small round cell tumor (DSRCT) is a rare mesenchymal tumor that typically presents with multiple abdominal masses. Initial treatment is multimodal in nature. Patients with relapsed DSRCT have a poor prognosis, and there are no standard therapies. We report our experience with five patients treated with vinorelbine, cyclophosphamide, and temsirolimus (VCT). Median number of VCT courses delivered was 7 (range 4–14 courses), and partial response was observed in all patients. Median time to progression or relapse was 8.5 months (range 7–16 months). Neutropenia and mucositis were most common toxicities (n = 4 each).

KEYWORDS

childhood cancer, desmoplastic, recurrence, sarcoma, temsirolimus

1 | INTRODUCTION

Desmoplastic small round cell tumor (DSRCT) is a rare mesenchymal tumor thought to arise from the peritoneum. There is a strong male predominance, and DSRCT is associated with a characteristic translocation involving the EWSR1 and WT1 genes at t(11;22)(p13;q12).^{1,2} Patients typically present with multiple abdominal masses, and currently there is no universally accepted standard of care treatment plan. However, multimodal therapy using chemotherapy and cytoreductive surgery followed by hyperthermic intraperitoneal perfusion of heated cisplatin (HIPEC) or adjuvant radiation therapy has been described.^{3–7}

Once relapsed, the long-term prognosis for DSRCT is quite poor with no proven standard treatment. Separate case reports have described response using vinorelbine with oral cyclophosphamide or the mammalian target of rapamycin (mTOR) inhibitor, temsirolimus, independently.^{8,9} Also, there are emerging data describing mTOR pathway involvement in DSRCT.^{10,11} The Children's Oncology Group completed a clinical trial (ARST 0921) that evaluated vinorelbine, intravenous cyclophosphamide, and temsirolimus (VCT) in relapsed

rhabdomyosarcoma patients, which demonstrated the safety of this drug combination (ClinicalTrials.gov identifier: NCT01222715). Thus, our primary objective is to describe our observational experience of using an mTOR inhibitor containing regimen VCT in five patients with relapsed DSRCT.

2 | METHODS AND RESULTS

This retrospective study was approved by the Institutional Review Board and consent was obtained from the patient, parents, or guardians. Clinical medical records were reviewed for the five patients identified in this report. All patients received frontline therapy consisting of systemic chemotherapy followed by cytoreductive surgery, HIPEC, WART, and maintenance chemotherapy with irinotecan and temozolomide, although some patients received other regimens prior to VCT therapy. Time to first recurrence was defined from end of frontline therapy to date of relapse. All patients received vinorelbine 25 mg/m² IV on day 1 and 8 and temsirolimus 15 mg/m² on day 1, 8, and 15. Four patients also received cyclophosphamide 1,200 mg/m² IV on day 1, while one patient (Patient 3) received oral cyclophosphamide at 25 mg/m² daily. Clinical endpoint assessed was time from start of VCT therapy to date of disease progression or relapse. Response was assessed retrospectively using either Response

Abbreviations: DSRCT, desmoplastic small round cell tumor; FDG PET-CT, 18-fluorodeoxyglucose positron emission tomography fused with computed axial tomography; HIPEC, hyperthermic intraperitoneal perfusion of heated cisplatin; mTOR, mammalian target of rapamycin; RECIST, Response Evaluation Criteria in Solid Tumors; VCT, vinorelbine, cyclophosphamide, and temsirolimus

TABLE 1 Characteristics of patients treated with vinorebine, cyclophosphamide, and temsirolimus

Patient	Age at diagnosis (yr)	Gender	Sites involved at diagnosis	Chemotherapy received prior to VCT	Sites involved at time of VCT	Number of courses	Time to progression or relapse on VCT	Status
1	28	M	Abd, pelvis, liver	VDC/IE; Irino/Temo; Gem/Abraxane; DTIC; Pazopanib; HD Ifos	Abd, pelvis, liver, bone, lung	14	12 months	Dead
2	11	F	Abd, pelvis, liver	VID; Epi/Carbo; IE; Irino/Temo; Metformin/Sirolimus; Pazopanib	Liver, bone, lung	7	N/A	AWD
3	26	M	Abd, pelvis	VDC/IE; Irino/Temo	Abd, liver	7	10 months	AWD
4	13	M	Abd, pelvis	VEC/Vinc, Epi, Carbo; Irino/Temo	Abd, liver, lung	8	7 months	AWD
5	15	M	Abd, pelvis	VDC/IE; Vinc, Irino, Temo	Pelvis	4	16 months	Dead

VCT, vinorelbine, cyclophosphamide, temsirolimus; Yr, year; M, male; F, female; Abd, abdomen; VDC, vincristine, doxorubicin, cyclophosphamide; IE, ifosfamide, etoposide; Irino, irinotecan; Temo, temozolomide; Gem, gemcitabine; DTIC, dacarbazine; HD ifos, high-dose ifosfamide; VID, vincristine, ifosfamide, dactinomycin; Epi, epirubicin; Carbo, carboplatin; N/A, not applicable; AWD, alive with disease; VEC, vincristine, epirubicin, cyclophosphamide.

Evaluation Criteria in Solid Tumors (RECIST) 1.1 or metabolic response by 18-fluorodeoxyglucose positron emission tomography fused with computed axial tomography (FDG PET-CT) scan.¹² Toxicities were reviewed in the medical record and graded using NCI-CTCAE criteria version 4.0.

Clinical and treatment characteristics are summarized in Table 1. The median age at diagnosis was 15 years (range 11–28 years). The mean time to first recurrence was 13.6 months (range 3–31 months), and the sites of first recurrence prior to VCT therapy were lungs ($n = 3$), liver ($n = 2$), and bone ($n = 2$). Three patients received other relapsed treatment regimens prior to VCT exposure (Table 1).

With regard to VCT therapy, median number of courses delivered was 7 (range 4–14). Patient 2 received seven courses of VCT therapy and then returned to her home country and was changed to different therapy by her local treating physician due to lack of availability of temsirolimus. Patient 5 received two courses of therapy and then underwent local control surgery with complete resection of recurrent tumor. He then received an additional two courses of adjuvant VCT therapy but then refused further therapy. Unfortunately, he developed local and metastatic recurrence of disease 16 months after last course of VCT therapy.

Partial response by RECIST 1.1 criteria was the best achieved response to therapy, and it was observed in four patients, while patient 3 had stable disease. Patient 2 also had an FDG PET-CT scan that demonstrated partial metabolic response for a liver metastasis following two courses of therapy (Fig. 1). All evaluable patients progressed on therapy. Patient 2 was excluded from time to progression evaluation due to change of therapy in her home country; thus, median time to progression or relapse for the remaining four patients was 8.5 months (range 7–16 months). Observed toxicities included grade 2 fatigue ($n = 3$), grade 3–4 neutropenia ($n = 4$), grade 2–3 mucositis ($n = 4$), and grade 1 acute renal injury ($n = 2$) manifested by temporary elevation in serum creatinine lasting 1 month and 2 months, respectively. Patient 2 had two admissions for fever and neutropenia, and patient 4 had one admission for fever and neutropenia. Two patients died from progressive disease, while three patients are still alive with evidence of disease.

3 | DISCUSSION

DSRCT is an aggressive mesenchymal tumor, and the long-term prognosis for patients with DSRCT is extremely poor. One of the limitations for treating patients with relapsed DSRCT is the lack of data regarding potentially effective salvage regimens. Ferrari and colleagues described two patients who responded to vinorelbine and oral cyclophosphamide, while Thijs and colleagues described their experience with one patient who responded to temsirolimus. The Children's Oncology Group completed a clinical trial for recurrent rhabdomyosarcomas, which compared response rates between a regimen consisting of vinorelbine, intravenous cyclophosphamide, and temsirolimus versus vinorelbine, cyclophosphamide, and bevacizumab. The trial demonstrated that the temsirolimus combination was safe and tolerable. Given the lack of standard therapies for DSRCT, it would be of interest to determine if the VCT regimen was safe and demonstrated activity in DSRCT patients.

One limitation of this report is that we were unable to determine if the observed responses were due to a synergistic effect derived from this drug combination versus single agent activity. Since all of the patients had previously received vinca alkaloids and alkylator agents, the temsirolimus was the only new class of agent introduced. There are some data from single institution series to indicate possible involvement of the mTOR pathway in DSRCT.^{10,11} In a phase 2 study evaluating temsirolimus for adult patients with soft tissue sarcomas, only two of 40 patients demonstrated treatment response lasting 3 and 17 months, respectively, and resulting in a disappointing response rate of only 5%.¹³ While another limitation of this study is that this is a retrospective, observational series without a clear denominator of patients, the demonstrated response in these five DSRCT patients using this combination suggests the possibility of synergy with these agents that is better than the reported response rate for single agent temsirolimus. Unfortunately, we were unable to fully determine the response time course of this drug combination due to two patients having abbreviated therapy due to patient refusal and lack of drug availability in the patient's home country.

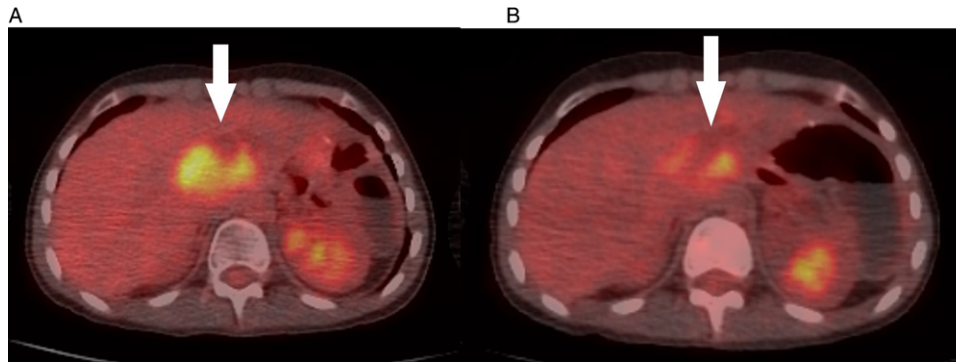


FIGURE 1 (A) Image from an 18-fluorodeoxyglucose positron emission tomography with computed axial tomography (FDG PET CT) scan of a 13-year-old female demonstrating a hypermetabolic metastatic lesion involving the liver. (B) Follow-up FDG PET CT scan image demonstrating metabolic response following two courses of therapy with vinorelbine, cyclophosphamide, and temsirolimus

In conclusion, we observed that the VCT regimen can safely be administered to patients with progressive or relapsed DSRCT and is well tolerated. Another advantage with the VCT regimen is that since we utilized an established Children's Oncology Group protocol, this treatment plan and guidelines for administration should be readily accessible to pediatric oncologists. Further study is needed to determine if this regimen can be utilized in newly diagnosed patients, and additional preclinical study is needed to determine the mechanism of action for this combination in DSRCT.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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