

Advanced Desmoplastic Small Round Cell Tumor: Near Complete Response with Trastuzumab-based Chemotherapy

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Case Report

Our patient, a 47-year-old Caucasian male, initially presented with complaints of progressive constipation. Computed tomography (CT) of the abdomen revealed a mass. At surgery, this was observed to be located in the mesentery involving the small intestine near the aorta, making it unresectable. Pathologic examination revealed a malignant neoplasm consisting of small blue cells in solid sheets with patchy necrosis and desmoplastic response. The tumor cells were positive by immunohistochemistry (IHC) for placental alkaline phosphatase (PLAP), vimentin, epithelial membrane antigen (EMA), desmin, and cytokeratin AE1/AE3 (focal), and negative for CD117 (c-kit), CD3, CD20, CD30, myogenin, and all other actins. The constellation of findings was consistent with a diagnosis of desmoplastic small round cell tumor (DSRCT).

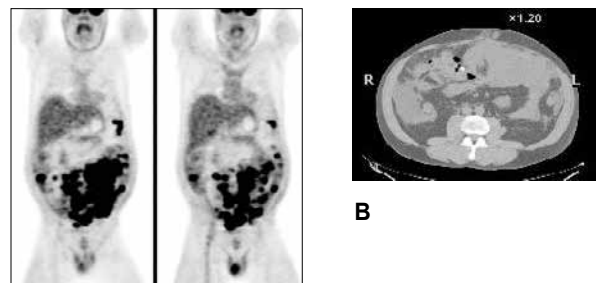
Neoadjuvant chemotherapy with mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) was initiated. No change in size of the tumor mass was evident after 2 cycles of treatment. Thereafter, the patient received 2 cycles of ifosfamide, cisplatin, and etoposide (ICE). This reduced the tumor size by 25%, making it amenable for surgical resection. He received 2 additional cycles of adjuvant ICE after surgery.

New abdominal masses were noted 3 months later on a positron emission tomography (PET) scan, 13 months after his first resection. The masses were again removed surgically. Four months later, multiple anterior abdominal masses, no longer amenable to surgical treatment, appeared on PET/CT imaging (Figure 1A and 1B).

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More detailed pathologic evaluation was undertaken. To confirm this unusual diagnosis, the Ewing's sarcoma-Wilm's tumor (EWS-WT1) translocation transcript, consequent to a chromosomal abnormality characteristic of DSRCT, was detected by reverse transcriptase-polymerase chain reaction (RT-PCR) analysis. The tumor cells were negative by IHC for c-kit and focally positive for platelet-derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR). Notably, all tumor cells (100%) over-expressed human epidermal growth factor receptor-2 (Her-2/neu).

Due to the PDGFR expression within the tumor and reports of activity of imatinib (Gleevec, Novartis) against this receptor,¹ the patient received imatinib therapy for 6 weeks. A CT scan revealed abdominal disease progression. Thereafter, due to strong Her-2/neu expression, the patient received therapy with carboplatin, etoposide, and a trastuzumab (Herceptin, Genentech) loading dose of



A

Figure 1. Positron emission tomography/computed tomography (PET/CT) imaging study prior to trastuzumab-based therapy. A) Coronal PET imaging reveals numerous anterior abdominal masses. B) Corresponding axial CT imaging showing the abdominal tumor not amenable to surgical resection.

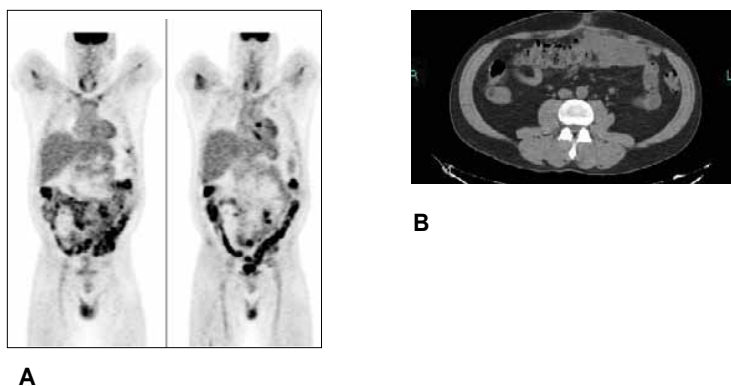


Figure 2. Positron emission tomography/computed tomography (PET/CT) imaging study obtained after trastuzumab-based therapy. A marked response is noted after 6 cycles of trastuzumab combined with cytotoxic chemotherapy, compared to pre-treatment imaging (Figure 1). A) Coronal PET imaging shows remarkable decrease in metabolic response of the tumor. B) Corresponding CT imaging shows decrease in the tumor masses in the anterior abdominal wall.

350 mg and maintenance dose of 180 mg for 2 cycles, which was changed to carboplatin, paclitaxel, and trastuzumab for 4 additional cycles.

After 6 cycles of trastuzumab-based therapy, PET/CT revealed a remarkable treatment response, with resolution of a majority of abdominal masses except for several small residual sites (Figure 2A and 2B). The patient then received maintenance treatment with single-agent trastuzumab, remaining in partial remission for 8 months before disease progression was documented. Subsequently, he withdrew from treatment and died 36 months after initial diagnosis.

Discussion

DSRCT, originally described by Gerald and coworkers in 1989, is a very rare tumor.² It usually presents in young Caucasian males as an abdominal mass.³ Histologic examination reveals nests, sheets, or cords of small round blue cells with indistinct cell borders, inconspicuous nucleoli, finely granular cytoplasm, metachromatic stroma, irregular nuclear membranes, and scant cytoplasm.⁴ Cytokeratin, desmin, EMA, vimentin, and neuron-specific enolase are typically detectable.^{5,6} PDGFR, Her-2/neu, androgen receptor, and c-kit expression have been described in some samples, although their expression is limited.⁷⁻⁹

DSRCT has a distinctive diagnostic chromosomal translocation. EWS-WT1 is the result of the fusion of *EWS* gene on chromosome 22q12 with *WT1* gene on chromosome 11p13. This can be detected in a number of ways, including RT-PCR to detect the consequent fusion mRNA and conventional cytogenetics or fluorescent in situ hybridization (FISH) to identify the chromosomal translocation directly.^{10,11} Detection of this pathognomic molecular abnormality provides definitive diagnostic confirmation.

The optimal treatment of DSRCT has not yet been defined due to the rarity of the disease and the relatively recent definition of DSRCT as a clinical entity. A variety of treatment regimens have been reported in case reports and small case series. As with most soft tissue sarcomas, complete surgical excision is the primary determinant of long-term survival.¹²⁻¹⁵ Unfortunately, advanced stage tumors are often not amenable to definitive surgery. Multimodality treatment with chemotherapy, cytoreductive surgery, and radiation therapy may improve the survival rate.¹²

Targeted therapies have been explored minimally so far. Various receptors that might be amenable to targeted therapy have been found to be expressed in some DSRCT samples, including Her-2/neu, c-kit, PDGFR, and the androgen receptor. Fine and colleagues reported use of androgen blockade in cases of DSRCT expressing androgen receptors.⁸ Partial or minor responses and stable disease were observed in treated patients who had normal testosterone levels prior to therapy initiation. Targeted therapy against other receptors, particularly Her-2/neu, has not been reported.

Her-2/neu is a transmembrane tyrosine kinase receptor that regulates cell growth and survival.¹⁶ Trastuzumab, a monoclonal antibody binding to the extracellular domain, leads to suppression of tumor proliferation, stasis, and apoptosis. Trastuzumab is approved for the treatment of high-risk and metastatic breast cancer where tumor cells have shown over-expression of the Her-2/neu target. In addition to breast cancer, trastuzumab has also been used for the treatment of urothelial, non-small cell lung, ovarian, and salivary duct carcinomas.¹⁷⁻²⁰ To the best of our knowledge, its use for the treatment of DSRCT has not been reported so far.

Our patient initially received 2 aggressive, multi-agent chemotherapy regimens, but soon had recurrent disease. Subsequent treatment with trastuzumab combined with

carboplatin and etoposide or paclitaxel yielded an excellent partial metabolic and tumoral remission, as documented by PET/CT scans. Progression occurred after 8 months of trastuzumab maintenance monotherapy.

We believe it is unlikely that the cytotoxic component of this therapy led to the patient's response given the patient's limited benefit from prior aggressive chemotherapy. Notably, prior chemotherapy according to the ICE regimen incorporated platinum- and etoposide-based therapy, to which the patient experienced a response prior to surgery, but disease recurred only 3 months after discontinuation of adjuvant therapy. In contrast, the trastuzumab-based regimen, incorporating maintenance trastuzumab therapy, did not lead to disease progression until 8 months after completion of cytotoxic therapy. The addition of trastuzumab to the therapy regimen of this Her-2/neu positive tumor is a biologically plausible explanation for the documented treatment response.

Conclusion

We here report a marked response to trastuzumab-based therapy in a case of DSRCT expressing Her-2/neu. Other treatment strategies directed at Her-2/neu, such as the tyrosine kinase inhibitor lapatinib (Tykerb, GlaxoSmithKline), may be relevant in the primary or secondary therapy of patients with Her-2/neu-positive DSRCT.²¹ More formal investigation of Her-2/neu-based therapy in DSRCT is warranted.

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Review

Desmoplastic Small Round Cell Tumor: Current Treatment Approach and Role of Targeted Therapy

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Chalasanani and colleagues¹ report a case of metastatic desmoplastic small round cell tumor (DSRCT), which progressed on various lines of conventional chemotherapies. Immunohistochemistry on the tumor cells was negative for c-kit and focally positive for platelet-derived growth factor receptor (PDGFR), but all the cells had overexpression of human epidermal growth factor receptor-2 (Her-2/neu). The patient received treatment with imatinib (Gleevec, Novartis) for 6 weeks directed to PDGFR expression, but the tumor further progressed. Subsequently, the patient was treated with trastuzumab (Herceptin, Genentech) in combination with chemotherapy, as Her-2/neu was universally overexpressed on all tumor cells, and had partial response. He continued on maintenance therapy with trastuzumab and remained in partial remission for a prolonged period of time.

DSRCT in General

DSRCT is a malignant small blue cell tumor typically involving the abdominal and/or pelvic peritoneum of children and young adults, occurring more frequently in males.¹ These tumors present as highly aggressive tumors with a tendency for peritoneal and omental spreads, may involve lymph nodes, and are found to metastasize hematogenously to the liver and other organs.² In various case reports and series, these tumor have also been described as arising from other mesothelial surfaces such

as pleura and tunica vaginalis, and other sites such as ovaries, kidney, pancreas, bone liver, central nervous system, and retroperitoneum.³⁻⁷

Radiologic differential diagnoses of this entity include peritoneal carcinomatosis from primary malignancies in the abdomen and pelvis, malignant mesothelioma, gastrointestinal carcinoid, malignant melanoma, soft-tissue sarcomas (MFH, desmoid fibromatosis), peritoneal tuberculosis, and fibrosing mesenteritis.

Since this is a rare tumor that shares similarities with other round cell tumors, the histologic differential includes Ewing's sarcoma (EWS), neuroblastoma, Wilm's tumor, rhabdomyosarcoma, and primitive neuroectodermal tumor.⁸ Distinctive cytologic, histologic, immunohistochemical, and cytogenetic characteristics are helpful for an experienced pathologist to make a diagnosis. On histologic and cytologic examination, the presence of small round blue cells with oval hyperchromatic nuclei and inconspicuous nucleoli and frequent mitotic figures with a background of fibrosclerotic stroma are striking morphologic features of DSRCT.⁸⁻¹⁰ The typical immunohistochemical profile is characterized by coexpression of epithelial, mesenchymal, myogenic, and neural markers. The tumor cells are positive for smooth muscle actin, neuron-specific enolase (NSE), epithelial membrane antigens, and cytokeratin.^{11,12} Cytogenetically, this tumor harbors a specific karyotypic abnormality, namely t(11;22)(p13;q12). These features distinguish DSRCT from other members of the family of small round cell tumors.^{8,9} Tumor markers such as CA 125 and NSE have been found to be elevated in these patients. Elevated CA 125 associated with DSRCT has not consistently been found to be useful in diagnosis or in monitoring response to treatment.¹³

The 5-year survival rate of DSRCT is only approximately 15%.¹⁴ Patients presenting with abdominal disease typically are in an advanced stage, with large masses and/or extensive seeding in the visceral and parietal peritoneal layers. Further, this tumor has a high recurrence rate after surgical resection.¹⁵

Current Treatment Options for DSRCT

The rarity of DSRCT is a limiting factor for gaining more experience of various therapeutic modalities in these tumors. There are no specific guidelines for management of this particular type of tumor, but the chemotherapy agents (mainly alkylating agents such as cyclophosphamide and ifosfamide) active for EWS are widely used for this tumor as well. Both tumors share a EWS fusion protein and may also share molecular mechanisms facilitating proliferation and survival pathways. Multimodality therapy including induction chemotherapy, aggressive

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surgical debulking, and external beam radiotherapy has been associated with improved survival.¹⁴ Surgery is the mainstay of management. Gross tumor resection has been associated with prolonged overall survival.^{14,16,17}

Various other chemotherapy agents are being used in combination for treatment, but curative outcomes and long-term survival has been difficult to achieve. High-dose chemotherapy with stem cell rescue was investigated in a phase II clinical study for various small round cell tumor groups, but the subset of DSRCT showed poor response as compared to other groups.¹⁸

Induction chemotherapy with alkylating agents (P6 protocol) has shown tumor response, and these patients can benefit subsequently by debulking surgery.^{19,20} The P6 protocol has 7 courses of chemotherapy. Courses 1, 2, 3, and 6 include cyclophosphamide, doxorubicin, and vincristine (HD-CAV). Courses 4, 5, and 7 consist of ifosfamide and etoposide.

Although this tumor is radioresponsive, the role of radiotherapy in these tumors is not very clear. Whole abdominopelvic irradiation has been associated with high rates of hematologic and gastrointestinal toxicities, but with unclear benefits.²¹

Targeted Therapies, Screening Tumors for Active Pathways, and Personalized Therapy

Since the advent of c-kit and the success of imatinib in gastrointestinal stromal tumor (GIST), there has been a constant search for therapeutic targets in other soft tissue sarcomas. In a series, c-kit positivity has been seen in synovial sarcomas, osteosarcomas, and EWS, but was negative in other sarcomas including DSRCT.²² Additionally, a phase II study with imatinib did not show activity in DSRCT.²³

The unique chromosomal rearrangement identified in DSRCT—t(11;22) (p13;q12)—juxtaposes 2 genes: the *EWS* gene on chromosome 22 and *WT1* gene at 11p13.^{18,24} The chimeric product of the fusion transforms in vitro and in vivo properties by a dysregulation of a critical group of target genes, such as platelet-derived growth factor-A, which stimulates fibroblasts and stromal desmoplastic reaction.²⁴ The presence of this specific fusion transcript may represent a possible target for selective molecular targeting therapies.

There have been anecdotal reports of use of other targeted agents for DSRCT. Predilection of this tumor in young males led to an investigation in the role of androgen receptors (AR) and testosterone; 37% of the patients were positive for AR.²⁵ Six patients in this series were treated with combined androgen blockade and 3 of them achieved clinical benefit. Longo and colleagues²⁶ reported a patient with refractory DSRCT who had overexpression

of epidermal growth factor receptor and vascular endothelial growth factor receptor. The patient was treated with a combination of monoclonal antibodies, cetuximab (Erbix, ImClone/Bristol-Myers Squibb) and bevacizumab (Avastin, Genentech), against these receptors without any objective response. Prolonged remission in 1 patient has been reported on maintenance therapy with a combination of cytostatic agents—histone deacetylase (HDAC) inhibitor valproic acid and mammalian target of rapamycin (mTOR) inhibitor rapamycin.²⁷ Preclinical data has indicated anti-tumor activity in these 2 agents.^{28,29} In a case report, mTOR inhibitor deforolimus (AP23573) has been shown to induce long-term stability in 2 patients with DSRCT.³⁰ Other agents that interact with the Akt/mTOR pathway, such as insulin like growth factor receptor (IGF-R1) antibodies and PIM kinase inhibitors, need to be explored for this tumor type.

Molecular profiling of these rare tumors needs to be further studied, as it may indicate active pathways and expression of surface molecules and receptors that may guide personalized therapies for these tumors. Chalasani and colleagues' case report has provided a unique example of a patient with Her-2/neu overexpression responding to trastuzumab. Of note, this patient was initially treated with trastuzumab in combination with carboplatin and paclitaxel. Combination of trastuzumab with carboplatin and taxanes (docetaxel) has shown synergistic activity in Her-2/neu overexpressing breast cancer cell lines.³¹ This combination should be further explored in this rare tumor.

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