Desmoplastic Small Round Cell Tumor of the Pleura Successfully Treated with a Lower Dose of Pazopanib

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Abstract

Desmoplastic small round cell tumor (DSRCT) is an aggressive mesenchymal tumor which primarily affects the abdomen. Even a multimodal approach rarely achieves durable remission and the optimal therapy for extended disease is unknown. We herein describe a rare case of DSRCT arising from the pleura in a 32-year-old man. Initial therapy, which included chemotherapy, surgery and radiotherapy, achieved a partial response for only two months. Although salvage chemotherapies had no effect, pazopanib treatment shrank the tumors and was well-tolerated on an outpatient basis. From the viewpoint of quality of life, pazopanib may therefore be a good therapeutic option for this aggressive disease.

Key words: desmoplastic small round cell tumor, DSRCT, pleura, pazopanib


Introduction

Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive mesenchymal tumor that was first described in 1989 by Gerald and Rosai (1). DSRCT primarily affects young men with a peak incidence in the third decade of life (2). Microscopically, the tumors consist of nests of undifferentiated, small round or spindle cells surrounded by an abundant desmoplastic stroma (2, 3). The tumor cells show immunohistochemical evidence of epithelial, muscle and neural differentiation and are characterized by consistent chromosomal translocation t(11;22)(p13;q12), which results in the fusion of Ewing’s sarcoma (EWSR1) and Wilms’ tumor (WT1) genes (2, 3). DSRCT primarily occurs in the abdomen and pelvis; however, in rare cases it may arise extra-abdominally in locations such as the testes, ovaries and pleura (4).

Despite the current multimodal approach, which includes high-dose alkylator-based chemotherapy, adjuvant debulking surgery and radiotherapy and has been shown to achieve a favorable outcome (5), the prognosis remains poor (6). Moreover, the optimal therapy for extensive and recurred disease remains to be elucidated. Recently, several molecular-targeted drugs, including tyrosine kinase inhibitors, have been shown to have anti-DSRCT activities (7, 8).

We herein report a rare case of DSRCT of the pleura, in which a partial response was achieved with a newly developed multi-kinase inhibitor, pazopanib, in a patient with relapsed disease who had initially received multimodal treatments.

Case Report

A 32-year-old Japanese man, with no previous remarkable health problems, presented with a month-long dry cough and chest compression. The patient, who had no history of exposure to asbestos, had smoked a pack of cigarettes a day for seven years. Nearly all of the laboratory findings were normal; however, the levels of neural-specific enolase (NSE) (16.9 ng/mL) and cancer antigen 125 (CA125) (36.3 U/mL) were elevated. A chest X-ray at presentation revealed massive left pleural effusion (Fig. 1a). A chest X-ray (Fig. 1b) and computed tomography (Fig. 1c) following tube drainage of the left pleural fluid demonstrated multiple and widespread pleural masses accompanied by extensive tumor implantation throughout the left pleura. The patient’s tumors extended along the crura of the diaphragm into the retroperi-
Figure 1. (a) A chest X-ray at presentation shows massive left pleural effusion. A chest X-ray (b) and computed tomography (c) following tube drainage of the left pleural fluid demonstrates multiple tumors spreading throughout the pleural cavity. Note the presence of a small number of tumors which extend along the crura of the diaphragm to the retroperitoneal space (arrows).

Figure 2. Local anesthetic thoracoscopy revealed numerous white-tan colored tumors of varying sizes studding the pleural surface.

toneal region. No distant metastases were detected. Although pleural effusion cytology showed malignant cells, their origin could not be determined. Local anesthetic thoracoscopy (LAT) revealed numerous white-tan colored tumors of varying sizes located on the pleural surface (Fig. 2). Biopsy specimens were obtained for a microscopic examination, which demonstrated well-circumscribed nests of undifferentiated neoplastic cells with small, round to oval hyperchromatic nuclei and scanty cytoplasmos surrounded by an abundant amount of desmoplastic stroma (Fig. 3a). The tumor cells were immunohistochemically positive for pancytokeratin, desmin and NSE (Fig. 3b-d), which indicated polyphenotypic differentiation with the expression of epithelial, muscle and neural markers. The combination of all of these findings resulted in the diagnosis of DSRCT.

The patient received seven courses of an aggressive alkylator-based chemotherapy called “P6 protocol,” which consists of cyclophosphamide, doxorubicin, vincristine, etoposide and ifosfamide. He subsequently underwent adjuvant surgery to resect as much tumor mass as possible, however, a small amount of tumor outside the pleural cavity remained surgically unresectable. Following surgery, he received radiotherapy (50 Gy in 25 fractions) for the residual tumors of the left hemithorax. Two months after the completion of initial treatments, metastases developed in the left lower chest wall and the paraaortic lymph nodes. The re-occurred tumors did not respond to two courses of modified PAVEP consisting of pirarubicin, cyclophosphamide,
etoposide and cisplatin. He subsequently received pazopanib (800 mg/day), which caused side effects, including cardiogenic edema (Grade 3 according to the CTCAE version 4), hypothyroidism (Grade 2) and thrombocytopenia (Grade 1), early in the course of this therapy before an assessment of its efficacy had been made. Although the discontinuation of pazopanib plus the administration of diuretics and thyroid-hormone replacement therapy alleviated these conditions, pazopanib was not reinstituted at this time due to the concern that the patient would develop uncontrollable side effects. He was subsequently treated with topotecan and cyclophosphamide, however, computed tomography demonstrated an enlargement of the tumors that were previously identified in the lower left chest wall and paraaortic lymph nodes, along with the emergence of liver, mediastinal lymph node and disseminated lung metastases. All of these cytotoxic chemotherapies resulted in a prolonged hospital stay due to adverse effects such as anorexia, vomiting, neutropenic fever and thrombocytopenia. The patient preferred to be treated at home rather than in a hospital. He therefore selected to be treated with a reduced dose of pazopanib (400 mg/day). The best treatment response in the patient was a partial response (PR) that was achieved after the initiation of pazopanib (Fig. 4). At the time of this writing, the patient’s pazopanib treatment has continued for six months and mild side effects are being managed on an outpatient basis.

**Discussion**

We herein describe a young Japanese man with DSRCT of the pleura. DSRCT is a rare malignant tumor with an annual incidence rate of 0.1/1,000,000 (9). The pleura is a rare site of presentation (2); thus far, less than ten cases have been reported in the English literature (10-13). Only one (1.5%) case in a case series of 66 DSRCT patients (6) originated from the pleura, whereas no cases were reported in another case series of 41 patients (14). Despite its rarity, DSRCT should be included in the differential diagnosis of pleural malignant diseases with the accumulation of fluid, including disseminated pleural carcinomatosis and malignant pleural mesothelioma, due to the different treatment strategies that are used for these diseases. DSRCT tumor cells in effusion may be misidentified as small cell carcinoma or adenocarcinoma (10, 15). In our case, a cytological examination of the patient’s pleural fluid showed findings that mimicked metastatic non-small cell cancer. A histological examination is therefore essential for an accurate diagnosis. Although most

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**Figure 3.** Histopathological findings of the pleural tumor. (a) Nests of undifferentiated neoplastic cells with small, round to oval hyperchromatic nuclei and scanty cytoplasm surrounded by an abundant amount of desmoplastic stroma (Hematoxylin and Eosin staining, 200×). The tumor cells showed immunohistochemical positivity for (b) pancytokeratin (immunostaining for pancytokeratin, 200×), (c) desmin (immunostaining for desmin, 200×), and (d) neuron-specific enolase (NSE) (immunostaining for NSE, 200×).
of the reported cases were confirmed by a surgical biopsy under general anesthesia, the procedure is considered to be invasive due to the need for general anesthesia. A previous report demonstrated the successful diagnosis of a case using LAT (13). LAT is being increasingly adopted for the investigation of suspected benign and malignant pleural diseases. The diagnostic sensitivity of LAT for pleural malignancy is more than 90%, which is comparable with video-assisted thoracoscopic surgery (VATS) (16). In the present case, LAT obtained sufficient tissue samples for microscopic and immunohistochemical examinations to rapidly confirm the diagnosis of DSRCT without complications. The less invasive nature of this procedure and the good diagnostic results warrant the use of LAT in the diagnosis of DSRCT of the pleura.

The optimal therapy for DSRCT has not yet been established. Although a combination of aggressive alkylator-based regimens, debulking surgery to remove more than 90% of the residual masses and radiotherapy has been demonstrated to prolong the survival (5), durable remission is rare and the five-year survival rate for DSRCT is only 15% (6). Several studies have shown the feasibility of novel therapies such as hyperthermic intraperitoneal chemotherapy (HIPEC) and whole abdominal intensity-modulated radiation therapy (WAT-IMRT); however, such treatments are only recommended in a limited number of cases due to the small sample size of the studies and the toxicities of the procedures (4, 14). The optimal therapy for extensive or recurrent disease has yet to be determined, and new therapeutic strategies are thus needed.

The EWSR1/WT1 fusion gene has been confirmed to induce the upregulation of platelet-derived growth factor (PDGF) ligand and receptors, which might be responsible for the excessive production of desmoplasia that is described in DSRCT (17-19). Moreover, histopathologically-prominent stromal vascularity is present, ranging from complex capillary tufts to longer vessels with eccentric thickened walls (2), and vascular endothelial growth factor receptor (VEGFR)-2 and VEGFA have been shown to be overexpressed in this disease (20). DSRCT xenografts have been shown to be highly responsive to anti-VEGF agents such as bevacizumab (20). A study to investigate the impact of the addition of bevacizumab to existing high-dose alkylator-based chemotherapy is currently underway (21). Sunitinib, which is a multi-kinase inhibitor that blocks several tyrosine kinase receptors, such as VEGF receptors, PDGF receptors, KIT, fms-like tyrosine kinase 3 (FLT3) and colony-stimulating factor-1 (CSF-1), was tested in eight pretreated DSRCT patients. A PR was achieved in two patients (25%) and three patients (37.5%) had stable disease (SD) (22).

Pazopanib is an orally available inhibitor of the tyrosine kinases of VEGFR1-3, c-KIT, and PDGFR alpha and beta. The Ministry of Health, Labour and Welfare in Japan has approved the use of pazopanib in the treatment of advanced renal cell carcinoma and soft tissue sarcoma. A recent study demonstrated the activity of pazopanib in nine pre-treated patients with metastatic DSRCT, which is an unusual subtype of soft tissue sarcoma (8). Among the nine candidates, the best response was a PR in 2 patients, SD in 5 patients and progressive disease (PD) in 2 patients. The clinical benefit rate (PR + SD) was 78%. The median progression-free survival and overall survival were 9.2 (95%CI: 0-23.2) and 15.4 (95%CI: 1.5-29.3) months, respectively. The most common toxicities included neutropenia, anemia, fatigue, diarrhea, nausea, hypertension and an increase in liver enzyme levels; many of these toxicities were mild and manageable. A dose reduction was required in three of the nine patients.

Several other novel agents, such as insulin growth factor-1 receptor (IGF-1R) antibody ganitumab (23) and cixutumumab (IGF-1R antibody) with the mammalian target of rapamycin (mTOR) inhibitor temsirolimus (24), have been tested in patients with pretreated DSRCT. The drugs are reported to be well-tolerated and indicate durable antitumor activity.

DSRCT is an aggressive and miserable disease. Therefore, the goal of therapy should primarily be to preserve the patient’s quality of life. In this regard, pazopanib may therefore be a good therapeutic option for patients with recurrent and extended DSRCT.

**Figure 4.** (a) Computed tomography shows a metastatic tumor outside the spleen (arrow). (b) Four weeks of treatment with pazopanib reduced the tumor (arrow) in size by 40%.
The authors state that they have no Conflict of Interest (COI).

References


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