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Antitumor Activity of Cabozantinib in Metastatic Adult Ewing Sarcoma: A Case Report

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Abstract. *A 49-year-old male with Ewing sarcoma and bone, pleural, lung and mediastinal lymph node metastasis was treated with cabozantinib after four lines of previous systemic treatments. He responded objectively and subjectively well for 8 months. In this heavily pretreated patient, the daily starting dose of 60 mg had to be reduced to 30 mg because of adverse events. We conclude that treatment with cabozantinib administered in further-line was active in this particular patient with metastatic Ewing sarcoma. The underlying mechanism of action remains unclear. Because of a stable disease on a long-term treatment with pazopanib targeting an anti-angiogenic pathway common to both drugs previously administered in this patient, it is hypothesized that the action of cabozantinib could be ascribed to its action on the non-common receptors AXL and c-Met. The potential of cabozantinib should be further investigated more upfront in this disease either alone or in combination with other systemic treatments.*

Ewing sarcoma (ES) is a rare highly aggressive sarcoma of the bone, occurs predominantly in children and young adults and bears a poor long-term prognosis (1). Outcomes for patients aged more than 40 years also remain poor, but because of the extreme rarity of presentation in these patients, prognostic factors and treatment effects are much less documented. However, the prognosis of ES with pelvic lesions is markedly worse than those of limbs (2). Currently, the optimal treatment of pelvic ES is controversial but there is a trend for improved survival for patients treated with chemotherapy, radiotherapy and surgery (3). For adult patients with metastatic ES, chemotherapy based on vincristine, doxorubicin, cyclophosphamide (VAC) alternated with iphosphamide and etoposide (IE), has an outcome similar to pediatric cohorts (4). Another intensive regimen of alternating vincristine, doxorubicin, cyclophosphamide (VDC) and iphosphamide, carboplatin and etoposide (ICE) was shown to be feasible and effective (5). For patients with ES who relapse or develop refractory disease after primary treatment including chemotherapy it is actually unclear which cytotoxic treatment should be offered. Most studied regimens are based on cis- or carboplatin combinations, with or without cyclophosphamide or non-cis-or carboplatin combinations such as VDE (6). The dismal prognosis of patients with metastatic ES necessitates the development of novel strategies. A treatment with chemotherapy or more recently, immunotherapy or a tyrosine kinase inhibitor in or out of a clinical trial may be beneficial in metastatic ES. Newer multi-kinase inhibitors (TKI) that inhibit vascular endothelial growth factor receptor 1, 2, 3 (VEGFR1, 2, 3), platelet endothelial growth factor receptor-alfa and -beta and the stem cell factor receptor c-kit of which sunitinib (SNT) or pazopanib (PZP) are the best known examples used in the clinic in renal cell carcinoma (RCC) and soft tissue sarcoma (STS), are candidates to be used in ES. Cabozantinib (CBZ) targeting VEGFR-2, AXL, and c-MET, was shown to have a meaningful clinical activity in previously treated pediatric and adult patients with STS, including ES (7). We report here the antitumor activity of CBZ in an adult with metastatic ES of the iliac bone who had been previously treated with four lines of systemic treatment.

Case Report

A 49-year old male was diagnosed in February 2014 with ES of the left iliac bone. Because of the extent and the location of the tumor the patient was considered inoperable and a systemic treatment was started including four cycles of vinblastine, iphosphamide, epirubicin and etoposide (VIEE) followed by high dose chemotherapy and stem cell transplantation. Consolidation radiotherapy (2Gy per session, total dose 60 Gy) on the left iliac bone was performed. Based upon a fluorodeoxyglucose-positron emission tomography–computed

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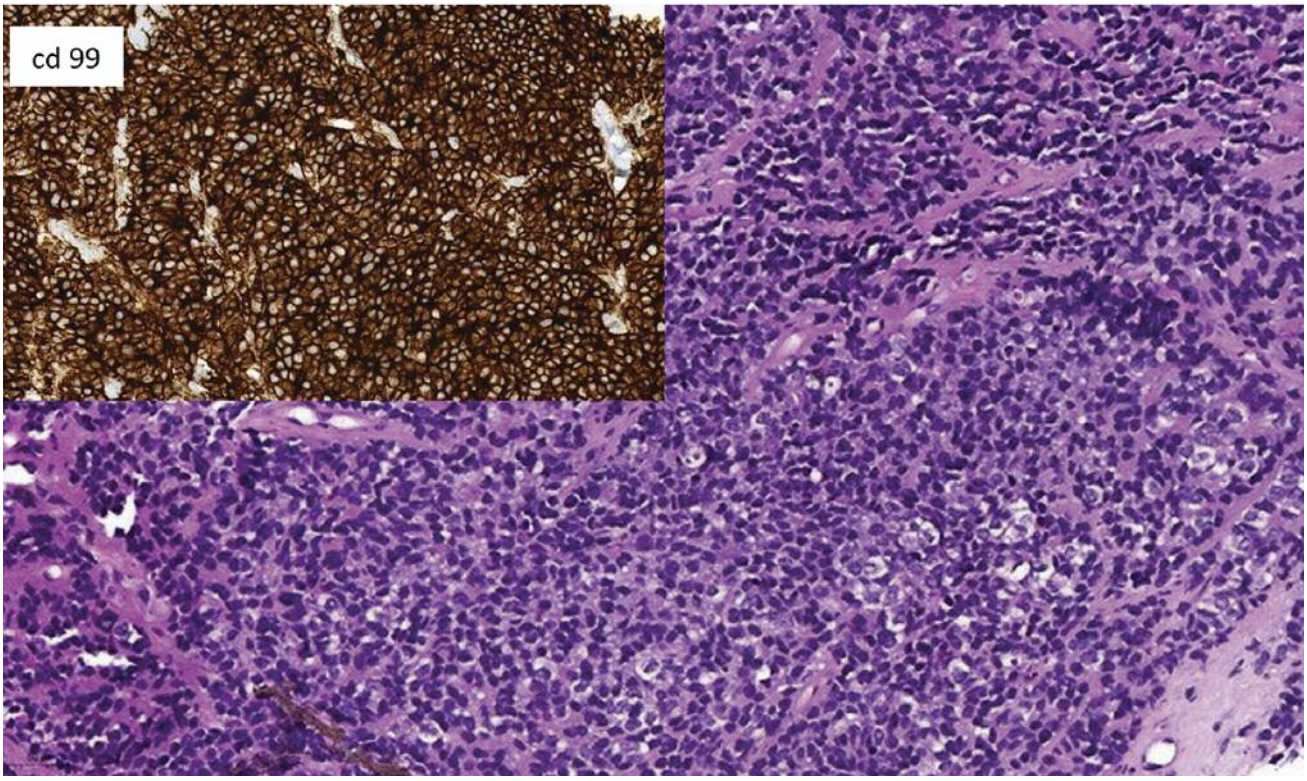

Figure 1. *Hematoxylin and eosin and cd99 immunohistochemical staining of the true-cut biopsy of the lung metastasis showing an undifferentiated small round blue cell tumor without any Homer-Wright rosettes (magnification ×20). The tumor is composed of highly compressed masses that grow in diffuse sheets. Nuclei possess round, even contours and smooth chromatin with inconspicuous nucleoli. Cd99 (insert) shows a distinctive strong diffuse membranous pattern.*

tomography acquired at the end of treatment, an objective response was demonstrated with the patient having a complete metabolic remission. In February 2016, a metastatic implant at the left orbita was irradiated (2 Gy, total dose 60 Gy). The patient developed asymptomatic lung metastasis in May 2016. The microscopic results of a true-cut biopsy of the lung metastasis are shown (Figure 1). CD 117 (cKIT) showed a moderate patchy membranous pattern; all the other markers were negative (Bcl2, S100, Tdt, Wt1, PanCK). Reticulin staining showed a typical dense network of fibers. Fluorescent *in situ* hybridization, using break apart probes identified a translocation of the *EWSR1* gene. Analysis for potentially druggable tumor drivers on the biopsy specimen of the primary tumor (Next generation sequencing and PDL1) was not contributive. PZP 800 mg per day controlled the metastatic sites for 20 months, however without achieving an objective response. Because of mainly intra thoracic asymptomatic progression after PZP [increase in volume and number of lung nodules, mediastinal lymph nodes and (sub) pleural nodules], he received consecutively three cycles of gemcitabine/docetaxel on days 1 and 8, respectively at the dose of 900 mg/m^2 and 60 mg/m^2 in a 3-weekly schedule, four cycles of trabectidine 1.5 mg/m^2 on a 3-weekly schedule and four cycles of the combination immunotherapy of ipilimumab and nivolumab every 3 weeks at the respective doses of 1 mg/kg and 3 mg/kg (medical need program Bristol Myers Squibb). However, a continuous radiological progression over the course of treatment was observed. In November 2018, the patient's clinical condition deteriorated rapidly [Karnofsky score (KS) was 60; fatigue and dyspnea were the main symptoms] and CT-scan demonstrated a right-sided pleural effusion, multiple intra thoracic lesions and severe tracheal compression (Figure 2A and B). CBZ 60 mg per day and low molecular weight heparin was initiated. After 1 week, CBZ was withheld because of side effects mainly global discomfort, anorexia and vomiting. Symptoms resumed 1 week after the interruption of CBZ, which was restarted at 30 mg per day, a dose that was well-tolerated and that was maintained hence. Two and a half months after initiation of treatment, skin toxicity became prominent and resumed with topical treatments. Already after 1 month of treatment, the PS rose to 90 and the dyspnea disappeared completely. On the CT-scan, a significant volume reduction of lesions was seen, the tracheal compression resolved and there was disappearance of the right-sided pleural effusion (Figure 2C

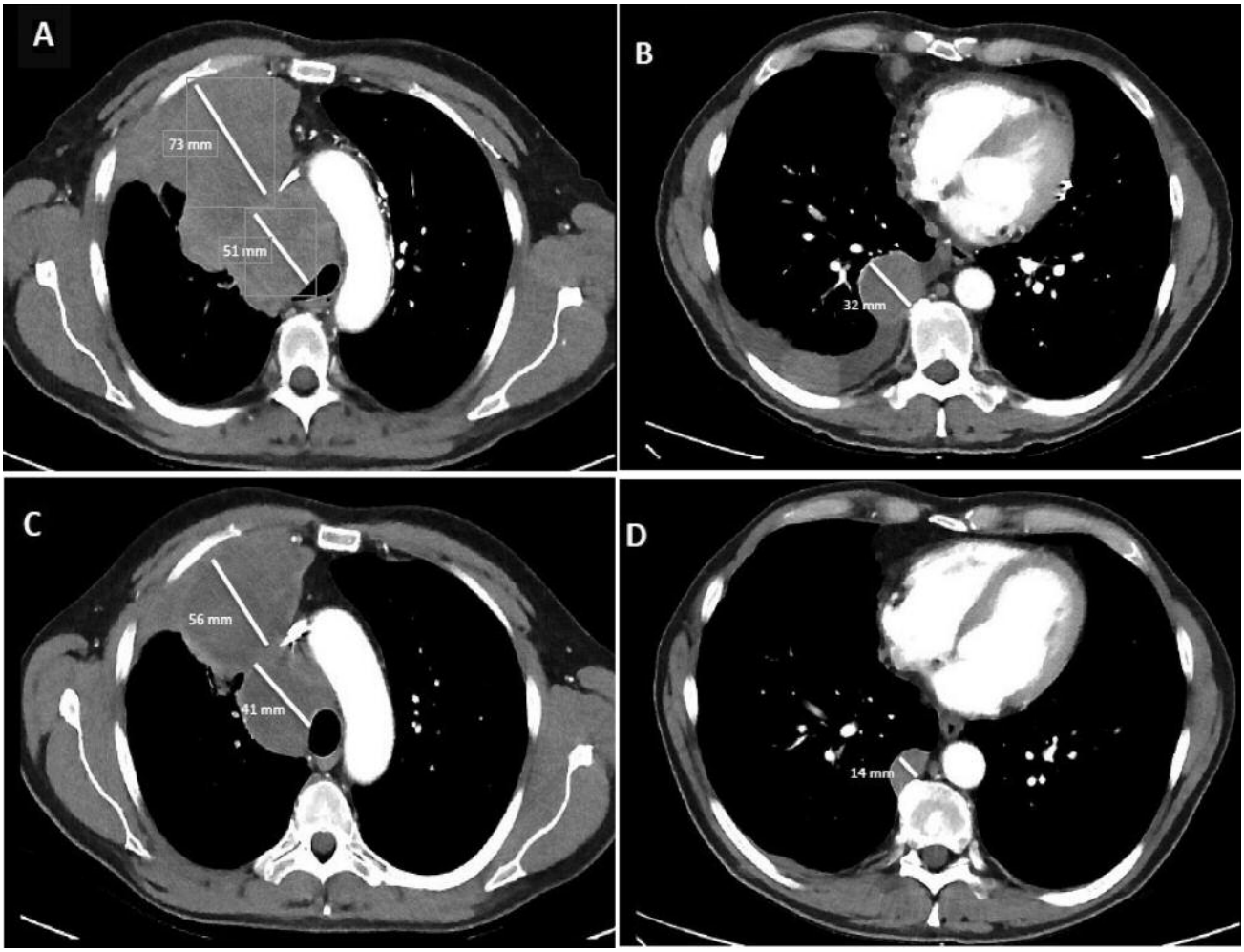

Figure 2. *Baseline thoracic pulmonary and mediastinal masses obstructing the main bronchial airway (unilateral diameters of 6.84 and 5.90 cm, respectively) (A) right paravertebral mass (unilateral diameter of 3.33 cm) and pleural effusion (B). Regression of thoracic pulmonary and mediastinal masses, reopening main bronchial airway (unilateral diameters of 5.97 and 4.15 cm, respectively) (C) and right paravertebral mass (unilateral diameter of 1.66 cm) (D).*

and D). According to the measurements of the largest unilateral diameters of the measurable lesions, a 40% reduction was observed corresponding to a partial response (PR) using the new response criteria (8). At eight months after the start of treatment with CBZ, the patient was admitted to the hospital in a severe general condition. The CT-graphic evaluation showed clear progressive disease in all existing intra thoracic lesions and multiple new bone metastases. Only palliative treatment was offered and he died soon afterwards.

Discussion

ES is a highly aggressive sarcoma of the bone and occurs predominantly in children and young adults (1). Treatment includes surgery, radiotherapy and chemotherapy. Because of the extreme rarity of presentation in adult patients, prognostic factors and treatment outcomes remain much less documented than in pediatric patients. The prognosis of pelvic lesions was shown to be markedly worse than of limb ES (2). Chemotherapy in ES in adults is based on VAC alternated with IE and outcomes are reported to be similar those in children (4). In the case presented, a simplified regimen of VIEE was administered as induction chemotherapy for the initially locally advanced tumor similar to the pediatric protocol currently used in our hospital. However, despite of the chemotherapy given, including high dose therapy and stem cell transplantation, the patient progressed with metastatic disease mainly in the thoracic cavity. Rather than repeating the first-line chemotherapy, it was decided to start PZB as second-line treatment. The decision was made based

on data of this drug in RCC and STS. Indeed, in large scale randomized trials involving patients with STS and RCC, these drugs were administered in 1st and 2nd-line, respectively and have shown promising results with manageable side effects (9-12). Regarding PZP, results of a randomized phase III study in 369 STS patients (excluding ES) who were considered progressive after 1st-line chemotherapy and received either PZP 800 mg daily or placebo (ratio: 2:1) as 2nd-line therapy (PALETTE), showed that PZP had a significantly higher antitumor activity than placebo, while quality of life and global health status were not significantly different (12). On the basis of the biologically plausible activity and the existing indication for other sarcoma types, one case of paravertebral ES that was metastatic and refractory to chemotherapy and received PZP, was published with an objective response lasting for 12 weeks (13). In our patient with metastatic disease, first-line PZP induced a long-term stable disease (SD) of 20 months in the absence of major toxicity. Preceding consecutive treatments consisting of chemo- and immunotherapy were ineffective. CBZ has been shown to have significant anti-tumor activity in preclinical models of ES, osteosarcoma and prostate cancer cell lines (*in vitro* and *in vivo*) (14, 15). A recent publication in Lancet Oncology (7) demonstrated significant efficacy in pretreated metastatic ES with ten responses out of 39 patients (OR: 26%), mainly partial response with a median progression free (PFS) and overall survival (OS) of 5.2 (range 3.2-7.4) and 9.8 months, respectively. Grade 3 adverse advents were noticed in less than 5% of the patient population (including ES and osteosarcoma). In the patient presented here, an objective response was demonstrated with a CT-scan and associated with an amelioration of clinical symptoms *e.g.* dyspnea and a dramatic increase in PS. The underlying mechanism of action of CBZ remains speculative. Of notice, our patient presented with a long-lasting SD on PZP, a TKI with activity on VEGFR (like CBZ). The non-overlapping target receptors of PZP and CBZ such as AXL and c-Met could be instrumental in the apparently differential effect of both. In our patient, molecular receptor analysis was not available. We conclude that CBZ can be associated with antitumor activity in patients with metastatic ES, pretreated with numerous lines of systemic therapy. CBZ could be a candidate for evaluation as a single agent therapy or in combination with other agents during earlier presentations of ES.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

DS: Drafted the manuscript; PL and HE: Provided critical revisions of the manuscript; DS, PL and HE: Provided final approval of the version to be published.

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