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Case Report

Pazopanib in Primary Cardiac Angiosarcoma of the Right Atrium- A Case Report

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Abstract

Primary heart tumors are extremely rare oncological entity with primary cardiac sarcomas usually representing 20% of all primary cardiac tumorous lesions. Angiosarcoma is the most prevalent histology and despite multidisciplinary approach tends to have a dismal prognosis. Based on the prevailing literature we hereby want to report about a 48 year old woman diagnosed with primary metastatic cardiac angiosarcoma who showed severe hypersensitivity reaction to conventional chemotherapy with taxanes but excellent response to treatment with the multi-targeted receptor tyrosine kinase inhibitor pazopanib.

Keywords: Cardiac Sarcoma; Angiosarcoma; Soft Tissue Sarcoma; Right Atrium; Pazopanib

Case Report

In October 2014 a 48 year old woman was referred to the department of oncology at the Medical University of Vienna. Because of acute dyspnea, vertigo and precollaptic condition, the patient had been admitted to a peripheral emergency department two weeks before. Since pulmonary embolism was suspected, an immediate CT scan was performed which showed multiple pulmonary nodules and a circumferential pericardial effusion. Subsequent transthoracic echocardiography confirmed a pericardial effusion of three centimeters with an end-diastolic compression of the right atrium and ventricle besides normal performance and size of the left ventricle.

Because of rapidly worsening clinical condition due to tamponade physiology an emergency pericardiocentesis was done but the patient developed hemodynamic instability. Since iatrogenic trauma of the right atrium was suspected, the patient was transferred to the surgery department where an emergency sternotomy had to be performed. During surgery a 6 x 3 cm big right atrial mass was detected and subsequently entirely resected. The defect of the right atrium was restored with a non-vascularized pericardial auto-graft.

The patient's postoperative course was without any complications and a control echocardiography showed minimal pericardial effusion, a normal LV systolic function as well as normal ejection fraction. Since histology revealed cardiac angiosarcoma (tumor cells further stained positive for CD 34), the patient was transferred to our oncology department for further examination and treatment.

Besides progressive multiple pulmonary nodules, a postoperative CT scan of the chest and abdomen showed no further distant metastasis and no evidence of recurrence of the angiosarcoma in the right atrium. The patient had neither prior medical history nor concomitant medication and after careful consideration the patient was included in a clinical trial in which the combination of paclitaxel 70mg/m^2, d1, 8, 15 q28d, plus pazopanib 800mg/d is applied.

During the first administration of paclitaxel at the end of November 2014 the patient suffered from severe hypersensitivity anaphylactic reaction with dyspnea, hypotension and chest pain despite intensified pretreatment with cortisone, diphenhydramine hydrochloride, and ranitidine. An electrocardiogram revealed no cardiac problem and after additional i.v. corticosteroids, ranitidine, and i.v. hydration the patient's condition improved rapidly. According to the protocol paclitaxel treatment was stopped and the patient continued with pazopanib 800mg/d monotherapy. Pazopanib was tolerated well with the exception of newly diagnosed arterial hypertension grade I-II which however, was efficiently treatable with oral medication.

A CT (thorax/abdomen) in January 2015 showed stable pulmonary disease without recurrence of cardiac angiosarcoma and the patient continued with pazopanib 800mg/d. In March 2015 a CT (thorax/abdomen) revealed partial remission of pulmonary metastases (reduction of both number and size of pulmonary metastases) and a new liver metastasis. Therefore the patient was discontinued from the clinical study (as PD according to RESIST occurred). Pazopanib was maintained (800mg/d) and docetaxel was intended to be added. Despite intensified pretreatment with corticosteroids and anti-histamines the patient suffered from severe hypersensitivity reaction again and docetaxel was stopped immediately during the first application. However, pazopanib monotherapy (800mg/d) was kept.

A subsequent CT (thorax/abdomen) in June 2015 showed a complete remission of all pulmonary metastasis and a partial remission in the liver, both of which have been confirmed in a CT (thorax/abdomen) in October 2015. Thus pazopanib was continued (800mg/d) and the patient is in an excellent condition (ECOG 0).

Discussion

Primary heart tumors are an extremely rare oncological entity, occurring at a frequency of 0.11 -0.30% in surgical series [1]. Importantly 75% of all primary cardiac tumors are benign and only 25% malignant with Primary Cardiac Sarcomas (PCS) usually representing 20% of all primary cardiac tumorous lesions [1,2].

Angiosarcoma is the most prevalent histology accounting for 37%

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of all cases and is predominantly found arising from the right atrium [1,3]. Generally, primary cardiac angiosarcomas often afflict younger patients without predisposing factors and occur with non-specific symptoms such as dyspnea, chest pain, cough, syncope, arrhythmias, fatigue or even life-threatening intracardiac obstruction [4,5].

Despite multidisciplinary approach the overall prognosis of PCS remains poor with a median survival ranging from 11 to 18 months and a five-year survival of 20% [2,4]. Due to disease rarity, the level of evidence for the optimal therapy algorithm of PCS is low [4]. Furthermore multimodal management is often extrapolated from extra-cardiac Soft Tissue Sarcomas (STS), which however is problematic since cardiac surgery and radiation of dose-limiting organs like the heart and lungs are predominant features of PCS [4].

In elective cardiac sarcoma therapy, complete surgical excision remains the therapeutic mainstay, followed by radio- and/or chemotherapeutic regimen, the latter preferably containing anthracyclines, ifosfamide, or taxanes [2,4,5].

Importantly complete surgical resection is hardly achievable in PCS due to tumor inaccessibility and the vital role of cardiac structures, often requiring emergency surgery as described in our patient [4]. However, in a current retrospective series of 124 PCS patients of the French Sarcoma Group (FSG) by Isambert et al. [4] surgery was a major prognostic factor for survival, regardless of the quality of resection as well as metastatic status. This may indicate that even incomplete resection appears worthwhile for immediate vital reasons as well as tumor control. The primary aim of surgery in terms of survival in metastatic PCS however is probably a more functional short-term outcome than prolonged survival and should only be considered in oligo-metastatic patients [4].

Radiotherapy with or without sequential chemotherapy has been traditionally performed in PCS despite the risk of myocardial injury owing to the limited tolerance of the heart to ionising radiation [4]. Isambert et al. reported that radiotherapy with a median dose of 50 Gy was performed mostly for patients with un-resectable disease or in case of incomplete resection and was associated with better OS on univariate analysis and better PFS survival on multivariate analysis [4]. Since most PCS patients die of Loco-regional tumor progression, the trend for better OS with radiation therapy might be achieved through the improvement of Loco-regional tumor control [4].

Anthracycline-based chemotherapy regimens are still the gold standard for advanced and metastatic PCS and in the French case series anthracycline-based chemotherapy was significantly associated with better overall survival, in the overall population and in non-metastatic patients [4]. However recommendation of systematic adjuvant chemotherapy seems difficult and recent data suggest that taxanes are more beneficial than anthracycline-ifosfamide regimens in the treatment of angiosarcomas [4].

Primary cardiac angiosarcomas compared to other STS subtypes particularly prone to metastatic spread and survival outcome are described even less favorable with an estimated median survival of 14 months [4,5]. For the treatment of primary cardiac angiosarcoma, radio- and/or chemotherapy are usually reserved for inoperable or metastatic disease or given to patients as adjuvant treatment for those with residual tumor [6,7]. A multimodality approach including radiotherapy and chemotherapy may only be effective for a selected subgroup of patients and radiotherapy dosage is limited by the sensitivity of lung and heart to radiation injury [7,8].

Importantly, the well-known cardio-toxicity of anthracyclines can limit their use, especially in patients with intracardiac disease. Taxanes, as single-agent or in combination with Gemcitabine have shown high antitumor activity in angiosarcomas and some evidence on the efficacy of taxanes in primary cardiac angiosarcoma has recently been accumulated [5,9-11]. Furthermore taxanes can be used as radio-sensitizing agents decreasing the adverse effects of high-dose standard fractionated radiotherapy especially in patients in favour of radical surgery [9,10]. Despite these data the underlying mechanism of action of taxanes remains unclear- *in vitro* data suggest that taxanes may act as anti-angiogenic agents in cardiac angiosarcomas [12], especially when administered weekly.

As suggested by the clinical course of our patient, we hypothesize a sustained anti-angiogenic effect of pazopanib, a multi-targeted tyrosine kinase inhibitor, with activity against VEGF 1, 2 and 3, and Platelet-Derived Growth Factors [13]. Despite temporary progression in the liver pazopanib was maintained and has led to a confirmed complete remission of lung metastases and a confirmed partial remission of the liver metastasis. Thus a maintained VEGFR inhibition beyond progression might be of value in angiosarcomas.

The clinical efficacy of oral pazopanib in patients with metastatic STS was demonstrated in a randomized, double-blind, placebo-controlled, phase III trial. In the multicentre PALETTE trial, pazopanib 800 mg once daily significantly prolonged median PFS to placebo (4.6 *vs*. 1.6 months) in adults with progressive metastatic STS following standard chemotherapy [14]. At final analysis of the PALETTE trial, median overall survival was ≈2 months longer with pazopanib than with placebo, although this between-group difference was not statistically significant. Oral pazopanib was generally well tolerated with adverse events generally being grade 1 or 2 in severity [14] and therefore represent a valuable therapeutic option in cardiac angiosarcomas.

In conclusion PCS in general and cardiac angiosarcoma in particular are rare and aggressive and require major therapeutic challenges. The poor prognosis of PCS warrants extensive multidisciplinary approach as well as cohort studies to I. Promote earlier diagnosis, II. Achieve complete resection upfront and III. To improve local and systemic treatments towards the use of more personalized targeted therapies in specific histological subtypes. In order to guide treatment decisions for this complex malignancy, therapy should be tailored to each case and only be performed in specialized high volume centers as the subject of a multidisciplinary consultation.

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