VIA MEDICA

CASE REPORT

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Advanced solitary fibrous tumour of the pleura — a case report and literature review

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ABSTRACT

The solitary fibrous tumour (SFT) is a rare tumour, which usually occurs in the pleura. Patients with an advanced SFT have a poor prognosis. The treatment options for recurrent disease are especially limited. We present the case of a 55-year-old female patient with a malignant SFT of the pleura, who received conventional chemotherapy and targeted therapy. This paper focuses on systemic therapy in the treatment of metastatic SFT.

Key words: solitary fibrous tumour, pleura, chemotherapy

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Introduction

The solitary fibrous tumour (SFT) is a mesenchymal tumour, which in most cases concerns the pleura [1]. These tumours constitute less than 5% of pleural tumours and less than 2% of all soft tissue tumours [1]. SFT occurs in men and women with similar frequency, usually in the sixth and seventh decade of life [1]. More than half of the patients present no symptoms, and lesions in the lungs are detected incidentally during follow-up radiological tests. For the other half of the patients, the disease usually manifests itself with dyspnoea and chest pain. Solitary fibrous tumours are usually well limited, benign lesions. Malignant variants with a tendency towards recurrence and metastases occur significantly less often (10–20%) [1]. An evaluation of the tumour's traits in radiological, pathological, and immunohistochemical testing allows for the diagnosis of its malignant character. The malignant form of the tumour is abundant in cells, with ample polymorphism and an increased mitotic activity — a mitotic index above four mitoses per large field of view, with the presence of widespread necrosis and bleeding. The basic treatment method for the SFT is excision [1]. In about 20–30% of patients, local recurrence or spreading may occur — in such a case there is no local treatment option, and systemic treatment must be considered [2]. Data pertaining to systemic treatment are limited; the present work aims to review the literature and summarise the knowledge on the topic of systemic treatment in solitary fibrous tumours of the pleura.

Case report

In August 2013, a 55-year-old female presented at the oncology clinic, with a history of mediastinal tumour that was excised and diagnosed as a malignant SFT. The patient was in good condition (grade 1 on the ECOG scale), presenting no weight loss, and obese (weighing 130 kg). She had a history of hypertension. Presenting complaints included weakness and sporadic cough lasting for several months. Physical examination and routine laboratory testing conducted on the day of the visit revealed no clinically significant abnormalities. Due to a positive surgical margin (R1), the patient

was qualified for radical adjuvant radiation. Intensity Modulated Radiation Therapy (IMRT) was applied to the right pleural area up to a total dose of 5600 cGy, in 28 fractions of 200 cGy each. After the completion of radiotherapy, the patient remained under observation. Two years after the diagnosis, in a control CT scan of the thorax, progressive disease (PD) was detected in the form of three small tumours of the left lung. A wedge resection was performed, with a histopathological confirmation of the recurrence of an SFT. Subsequently, in January and March of 2016, the patient underwent a thoracotomy due to the presence of further lesions in the lungs. In a CT of the thorax conducted two months after surgery, another recurrence was noted, in the form of numerous lesions in the lungs with maximum dimensions of 20 × 15 mm. Due to a lack of radical treatment possibilities, after a multi-specialist consultation, the patient was qualified for palliative chemotherapy with cisplatin (80 mg/m^2) in conjugation with doxorubicin (40 mg/m^2) at 21-day intervals. Four courses of treatment were applied, attaining stable disease (SD). In November 2016 imaging showed another instance of progressive disease. The patient remained in good condition. Tests such as ECG, echocardiography and blood biochemistry showed no abnormalities that would be contraindications of another course of systemic treatment. Treatment with pazopanib was initiated at a dose of 800 mg/day, attaining SD once again. The treatment was continued for a year, until progression. In November 2017, at a multi-specialist session, progressive disease was confirmed at level 1.1 according to the RECIST criteria (Response Evaluation Criteria in Solid Tumours) — a single metastatic lesion appeared in segment IV of the liver. Stereotactic radiotherapy was applied (5000 cGy in five fractions at 1000 cGy), and subsequently chemotherapy with the use of gemcitabine and docetaxel was initiated. After the third treatment cycle, PD was found. The chemotherapy was changed to a doxorubicin, dacarbazine, and cyclophosphamide regimen. In May of 2018 PD was noted once more in the thorax and abdomen. Another line of chemotherapy using ifosfamide showed no effect. The patient remains in good overall condition (ECOG-1). The patient complained only of an increase in exercise intolerance. Previous treatment was conducted with no significant complications.

Discussion

Singular fibrous tumours are usually well-limited benign lesions, with malignant forms occurring significantly less often (10–20%) [1]. Benign SFTs of the thorax are characterised by a high cure rate, with the rate of local recurrence being 8% [1]. The rate of recurrence in the case of a malignant SFT reaches 14–68%, usually in the first two years of observation (even after radical resection) [1, 2]. However, recurrences can also occur even after 17 years [3]. Metastases within the thorax are detected in 0–36% of patients, and metastases outside of the thoracic cavity occur in 0–19% of patients with this diagnosis. The most common sites of metastasis are the lungs and the liver [1]. Less commonly, it metastasises to the mediastinum, pancreas, kidney, and bone [1]. The evaluation of the tumour in imaging, and pathological and immunohistochemical testing allows for the prediction of its malignant character. There are classifications that evaluate not just the histological type (benign/malignant form), but also the type of growth that the tumour is presenting (pedunculated *vs.* wide-based). They were proposed as a means of predicting recurrence after surgical treatment [1]. The rate of recurrence ranges from 2 to 63%, depending on the attributed grade. A complete resection of the primary lesion still remains the most important prognostic factor [3]. Metastatic or locally recurring SFTs may require repeated surgical treatment, radiotherapy, or systemic treatment. The preferred method of treatment in the case of localised lesions is local treatment. Solitary fibrous tumours are commonly considered to be neoplasms of low chemotherapeutic susceptibility [4]. The present work aims at a review of the literature pertaining to the systemic treatment of SFTs of the pleura.

Chemotherapy

The role of chemotherapy was evaluated in a retrospective work including a group of 21 patients with advanced SFT, unqualified for surgical treatment [4]. Most patients were Caucasian (81%), and the average age was 56 years. The most common sites of the primary lesion were the abdomen and pelvis. In 19% of patients, the lesions occurred primarily in the pleura of lungs. Primarily advanced disease occurred in 81% of the patients, and local recurrence affected 5% of patients. Chemotherapy as the first line of treatment was prescribed in 72% of the study participants. 24% of them received the second line of treatment, and one patient received the third line of chemotherapy. Fifteen patients (60%) received doxorubicin-based chemotherapy as the first line of treatment. The most commonly applied regimen was doxorubicin (75 mg/m^2) with ifosfamide (10 g/m^2). About 7% of the patients received doxorubicin and cisplatin chemotherapy. The other regimens and treatment responses are presented in Table 1 [4]. No patient attained objective response, no matter the applied regimen. 89% of the patients who received the first line of chemotherapy achieved stable disease, with 31% achieving stable disease for longer than six months. After the second line of treatment, 67% of patients achieved stable disease. Median progression-free survival time for the first line of chemotherapy was 4.6 months (95% CI 3.7–5.6 months) [4]. In conclusion, the authors point

Table 1. Chemotherapy response evaluated according to the RECIST criteria RECIST 1.1 [4]

Chemotherapy regimen	SD — N (%)	PD — N (%)
First-line treatment	16 (89%)	2 (11%)
Doxorubicin regimen	14	1
Doxorubicin + ifosfamide		
Doxorubicin + dacarbazine		
Doxorubicin + cisplatin		
Doxorubicin in monotherapy		
Gemcitabine regimen	1	1
Gemcitabine+ docetaxel		
Gemcitabine in monotherapy		
Paclitaxel	1	1
Second-line treatment	4 (67%)	2 (33%)
Gemcitabine in monotherapy		
Paclitaxel in monotherapy		
Third-line treatment	0 (0%)	1 (100%)
Gemcitabine		

PD — progressive disease; SD — stable disease

Table 2. Choi response criteria

	Choi
CR	Disappearance of all target lesions
PR	≥ 10% decrease tumour size or ≥ 15% decrease in tumour attenuation at CT
SD	Does not meet criteria for CR, PR, PD
PD	≥ 10% increase in sum of longest diameters of lesions does not meet the criteria for partial response by virtue of tumour attenuation, new intratumoural nodules

CR — complete response; PR — partial response; SD — stable disease; PD — progressive disease

out the role of chemotherapy as a therapeutic option with patients with locally advanced or metastatic SFT enabling disease control.

Trabectedin is an alkaloid extracted from the sea squirt *Ecteinascidia turbinata.* The substance binds to the minor groove of the DNA helix, and its biological mechanism of action involves modulating transcription factors and interaction with proteins responsible for repairing DNA [5]. Trabectedin is a drug registered for the treatment of patients with diagnoses of advanced soft tissue sarcoma. In Poland, contrary to many other EU countries, this drug is reimbursed only for its liposarcoma and leiomyosarcoma subtypes [5]. In a case report of a 39-year-old male diagnosed with advanced SFT, trabectedin was used after a failed first-line treatment intervention. The drug was administered at a dose of 1.5 mg/m^2 in 21-day intervals. After the third course of treatment, a decrease in the size of the metastatic lesions in the lungs was observed [3]. In a French study the treatment effectiveness of trabectedin was evaluated for 11 patients with diagnoses of advanced SFT (the second and third line of treatment) [6]. PR was achieved with one patient (9.1%) and SD for seven patients (72.7%). Median progression-free survival time was 11.6 months. Three patients (27.3%) exhibited toxicity at level 3 or higher — mainly haematological and hepatic toxicity (increased hepatic enzyme activity) [6].

Molecular-guided therapy

Pazopanib is a multi-kinase inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and stem cell growth factor receptor (KIT). The effectiveness of pazopanib in the treatment of SFTs in preclinical and clinical trials was evaluated by Stacchiotti et al. [7]. In the paper, pazopanib showed lower antitumour activity in mouse models (in comparison to sorafenib, sunitinib, regorafenib, axitinib and bevacizumab). Among the six patients who received pazopanib, three achieved SD and three PD (as evaluated with RECIST criteria). All PD cases were patients with a malignant form of SFT. Evaluating the response with Choi criteria (Table 2), one achieved partial response, two cases of SD, and three cases of PD. Median progression-free survival was three months (1–15 months) [7]. The effectiveness of pazopanib in treating soft tissue sarcomas (including SFTs) was also assessed in the PALETTE analysis [8]. This analysis was an international, multicentre, double-blind, placebo-controlled phase III trial. It compared treatment

responses *vs.* placebo of patients with advanced disease after at least one line of chemotherapy. The patients were randomly assigned to one of two groups: those receiving placebo (n = 123) or those receiving pazopanib at a dose of 800 mg once a day (n = 246). All of them had undergone anthracycline treatment. Median PFS was 4.6 months (95% CI 3.7–4.8 months) for pazopanib and 1.6 months (0.9–1.8) in the placebo group (HR, hazard ratio 0.31, 95% CI 0.24–0.40; $p < 0.0001$). The differences in overall survival were not substantial between the groups ($p = 0.25$) and were: 12.5 months in the pazopanib arm and 10.7 months (median) in the placebo arm. 67% of patients who received pazopanib achieved SD (38% in the placebo group). The treatment was well tolerated. The most commonly reported side effects were fatigue (65%), diarrhoea (58%), nausea (54%), weight loss (48%), and arterial hypertension (41%) [8]. In Poland, because of this research, it is possible to use pazopanib to treat advanced (unresectable or metastatic) sarcomas within the National Health Fund (NFZ) drug program. In 2018, a paper evaluating the effectiveness and safety of pazopanib treatment in patients with a diagnosis of recurrent or metastatic SFT as the first or second line of treatment was published [9]. The response was graded according to RECIST and Choi criteria. The responses were, respectively, 0% and 50%, depending on the applied response criteria. The percentage of patients who achieved disease control was 88.9% and 75%, respectively. Median PFS was 6.2 months (95% CI 3.2–8.8 months). Two patients (22.2%) exhibited a level 3 or higher increase in hepatic enzyme activity [9]. A different analysis presented the effects of pazopanib application in second-line and third-line treatment [10]. No objective responses to treatment were observed, and SD, being the best response, was observed in three out of six treated patients. Two patients receiving had no PD after six and eight months [10].

From among molecular-guided drugs, promising results were obtained also for sunitinib and figitumumab [11]. Sunitinib is a multi-kinase inhibitor of, among others, the VEGF receptor. Six treated patients (60%) with advanced, chemotherapy-resistant SFT achieved PR (Choi criteria). For most of them the response lasted for longer than six months [11]. Insulin-like growth factor-1 (IGF-1) undergoes excessive expression in some cases of SFT. Treatments with figitumumab, a human monoclonal antibody against the IGF-1 receptor, yields promising results [11].

Chemotherapy + molecular-guided therapy

The effectiveness of combining temozolomide with bevacizumab (VEGF monoclonal antibody) was evaluated retrospectively for 14 patients with locally advanced or metastatic SFT or HPC (haemangiopericytoma) [12]. For three patients the disease was primarily localised in lungs or pleura. Five patients had received earlier chemotherapy. In the work, the patients received temozolomide at a dose of 150 mg/m^2 orally on days 1–7 and 15–21 and bevacizumab at 5 mg/m^2 IV on days 8 and 22 in 28-day cycles. Objective response according to Choi criteria was achieved in 11 (79%) patients. Two (14%) exhibited SD and one (7%) PD. The response was also evaluated using RECIST criteria. This time, most patients (12 patients) achieved SD. Median PFS was 9.67 months (Choi PFS). The most commonly observed toxicity was bone marrow suppression [12].

Immunotherapy

In a case report of a 50-year-old patient with a diagnosis of malignant form of SFT of the pleura, after many lines of systemic treatment (carboplatin + paclitaxel, gemcitabine + docetaxel, temozolomide + bevacizumab), treatment with pembrolizumab was introduced [13]. The drug was administered in two doses at 2 mg/kg IV every three weeks. After two cycles of treatment a partial regression of lesions was achieved. The patient is currently continuing the therapy (the last entry — 31 cycle) and is tolerating the treatment very well [13].

About 20% of patients with diagnosed SFT experience local recurrence or distant metastases [12]. The first line of treatment should be resection of lesions, which is not always possible. Available options for treating nonresectable tumours are limited. Radiotherapy can only be used in selected cases. Chemotherapy using doxorubicin and ifosfamide is used in many subtypes of soft tissue sarcomas. Another treatment regimen can be a combination of gemcitabine and docetaxel. However, objective responses to standard chemotherapy treatments are rarely reported [12]. In patients treated with first-line anthracyclines we can consider using pazopanib. Promising results can also be found for other molecular-guided drugs [11, 12] and immunotherapy [13]. However, further research is needed for larger groups of patients, which could confirm the effectiveness of these therapies. The presented patient, after an attempt to treat her locally, finally required systemic treatment. The applied chemotherapy regimens resulted in only short-term disease stabilisation or progression, which confirms the low sensitivity of SFTs to this form of systemic treatment. Treatment with pazopanib led to SD (RECIST criteria 1.1) that was maintained for a year. Unfortunately, retrospective evaluation with Choi criteria was not possible. Currently, the patient is experiencing another PD. She remains under observation and symptomatic care. We can ask ourselves whether the application of consecutive lines of systemic treatment was appropriate. We do not have sufficient information regarding the effects of chemotherapy on

general survival of patients with diagnosed SFT of the pleura, and the PALETTE analysis showed that the differences in overall survival of patients in both groups were statistically insignificant. The presented patient tolerated the treatment very well and she remains in overall good condition. However, we are unable to assess if the applied treatments changed her prognosis and whether we should consider the significantly longer progression-free time and/or the increase in objective response as clinically significant.

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