Long-term survival of a patient with aggressive sporadic malignant peripheral nerve sheath tumour presenting as haemothorax

Renata Zaucha, Aneta Waszczuk

Chair and Department of Oncology and Radiotherapy, Medical University of Gdansk, Poland

Malignant peripheral nerve sheath tumour (MPNST) belongs to the group of rare soft tissue sarcomas. High histological grade is a common feature, explaining its poor prognosis irrespective of the aggressiveness of local treatment. Standard therapy of inoperable local relapses or distant metastases has not been established, as phase II or III clinical trials are lacking and treatment strategies are based on anecdotal reports on the effectiveness of standard chemotherapy or different novel agents. Here we present a long-term survivor of the sporadic type of MPNST – a giant thoracic tumour with an uncommon presentation of haemothorax. Despite radical excision of the tumour, followed by high-dose radiotherapy to the tumour bed, the patient was diagnosed with multiple metastases located in the postpneumonectomy thoracic cavity and the right lung. First-line doxorubicin followed by somatostatin analogue resulted in a six-month PFS, while second-line ifosfamide-based chemotherapy resulted in good and long lasting symptom palliation.

Key words: malignant peripheral nerve sheath tumour, haemothorax, treatment.

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Introduction

Malignant peripheral nerve sheath tumour (MPNST) constitutes about 5% of all soft tissue sarcomas [1]. Approximately 25–50% of cases accompany neurofibromatosis type 1 (NF1) – a dominant autosomal defect in which a *NF1* gene product – neurofibromin – lacking RAS-GAP function, does not act as a tumour suppressor gene [2, 3]. Depending on the type of *NF1* mutation, 2–29% of carriers develop MPNST in their lifetime. Sporadic MPNST cases are not linked to any specific mutations; however, numerous chromosomal aberrations including –22 (in 40% of tumours), +3, +14, –13, –17 and –18 have been described [3]. Typical molecular changes include retinoblastoma tumour suppression pathway, aberrant expression of CHFR and aberrant expression of immune system-related genes [4–6]. The tumour originates from proliferating Schwann or perineural cells, most frequently surrounding sciatic, brachial and maxillofacial nerves [2]. The most common clinical presentation is a painful, invasively growing mass with accompanying neurological deficit [7, 8]. Spontaneous bleeding has been reported in *NF1* mutation carriers as a consequence of vascular abnormalities – aneurysm rupture or arteriovenous fistula [9, 10].

The aim of this paper was to present a long-term survivor of the sporadic type of MPNST – a giant thoracic tumour with an uncommon presentation of haemothorax – and to discuss different therapeutic options.

Case report

In August 2004 a 28-year-old man was admitted to the hospital with symptoms of rapidly progressing dyspnoea, cough, weakness and chest pain. His medical history was unremarkable, except for a dull back pain lasting for several months. Physical exam revealed tachycardia, tachypnoea and left pleural effusion up to the level of the third intercostal space, confirmed by a chest X-ray. A CT-scan of the chest showed pleural effusion and a large (18 cm) tumour located in the posterior mediastinum. Transthoracic fine needle biopsy suggested sarcoma. A radical excision of the tumour, left lung, thymus, mediastinal lymph nodes and distal parts of the 4th and 5th left ribs was performed and a histopathological examination established a diagnosis of high-grade (G3) MPNST, with positive staining of S-100 and vimentin at immunohistochemistry. The patient received postoperative radiotherapy at a dose of 66 Gy in 33 fractions. Four months later he developed dyspnoea, hectic fever and fatigue and a PET CT scan revealed a recurrent tumour infiltrating the chest wall in the left pericardial region, and multiple metastases in the right lung. Six cycles of palliative chemotherapy consisting of dacarbazine and doxorubicin resulted in stabilization of the disease. Six months later, in September 2005, a CT scan showed further progression. Of

note, the patient had moderate cardiac insufficiency with tachycardia and intermittent oedema of the scrotum making him incapable of further doxorubicin-based treatment. Additional immunohistochemical analysis performed at that time showed negative EGFR [11], negative VEGFR and equivocal CD117 expression. A tumour specimen was sent for sequencing of *cKit* (exons 9, 11, 13, and 17), *PDGFR-*α and *PDGFR-*β (exons 12, 14, and 18) coding genes [12, 13]. After obtaining the patients' consent and a positive opinion from a local Ethics Committee, a 3-month empirical treatment with imatinib given orally at a daily dose of 400 mg was administered. A CT scan performed 3 months later showed a dramatic progression of the disease. Additionally, mutations of *cKit* and *PDGFR-*α and *PDGFR-*β were not confirmed in a subsequent biopsy specimen. Owing to the deterioration of the patients' general status, second-line chemotherapy consisting of ifosfamide 3 g/m^2 IV with uromitexan, for 3 consecutive days every 28 days, was applied. After completion of 6 cycles a partial remission of the pulmonary lesions was achieved. Due to anecdotal reports on the possible role of somatostatin analogues in MPNST [14], we performed an octreoscan, which showed an increased uptake of somatostatin in the regions of the main lesion, accompanied by multiple metastatic tumours. Subsequently, octreotide treatment (20 mg every 28 days) was initiated. The disease was stable for 6 months, but then a CT scan again revealed progression (Figs. 1A, B). A third-line chemotherapy including doxorubicin, dacarbazine, cisplatin and ifosfamide was attempted, with no response. Instead, palliative reirradiation decreased dysphagia, chest pain and dyspnoea. Three months later, due to progression in the right lung, retreatment with ifosfamide was started. Because of haemoptysis after 2 cycles and evident progression of right lung metastases, the patient received 2 cycles of ecteinascidin. This therapy was also unsuccessful, whereas the re-administered ifosfamide unexpectedly resulted in symptomatic and radiological improvement. The patient, in a good general status (PS 80%), returned to work despite disseminated disease. After 8 cycles, ifosfamide treatment was discontinued due to disease progression, and in January 2009 the patient died.

Discussion

Malignant peripheral nerve sheath tumour belongs to the group of invasively growing soft tissue sarcomas with poor prognosis, high metastatic potential and limited radio- and chemo-sensitivity [15]. Incomplete resection, large tumour size, location (axial vs. peripheral), lymph node metastases, high-grade (G3), primary or recurrent disease and *NF1* mutations are predictive for early metastatic spread [7, 16–18]. In the largest reported series of patients, only negative surgical margins (R_0) and no history of irradiation remained significantly related to survival in multivariate analysis, including tumour size, grade and location, *NF1* mutation, mitotic rate, necrosis and histological subtype [7]. Adjuvant radiotherapy delivered in a total dose of less than 60 Gy does not improve the outcome significantly, whereas intraoperative brachytherapy seems to increase survival [7]. The reported 5- and 10-year survival rates are, respectively, 34% and 22%, despite aggressive local treatment. The risk of recurrence is high. Optimal therapy of locally advanced or disseminated MPNST has not been established. Palliative chemotherapy induces a response in about one-third of patients and its impact on survival is unknown. According to the results of the largest analysed group of 175 MPNST patients treated in 12 different clinical trials, only PS and the use of doxorubicin and/or ifosfamide are significant with regard to overall and progression-free survival [19]. The median survival of patients with *NF-1*-related or axial tumours does not exceed 12 months [1, 7].

Malignant peripheral nerve sheath tumour shows expression of at least one of the five somatostatin receptors – sst4 (in 32% of cases) and sst2 (in 15% of cases) [14]. This may suggest a beneficial role of somatostatin receptor analogues in the diagnosis and treatment; however, their usefulness has not been verified. Another possible area of investigation includes PDGFRB or EGF, or cMet pathways in both *NF1*-related and sporadic tumours, although data on such treatment efficacy are inconclusive [1, 11].

To conclude, more effective therapies are needed in MPNST, particularly in locally advanced and disseminated disease. Despite relative chemoresistance, systemic treatment provides a good palliation to some patients. Better

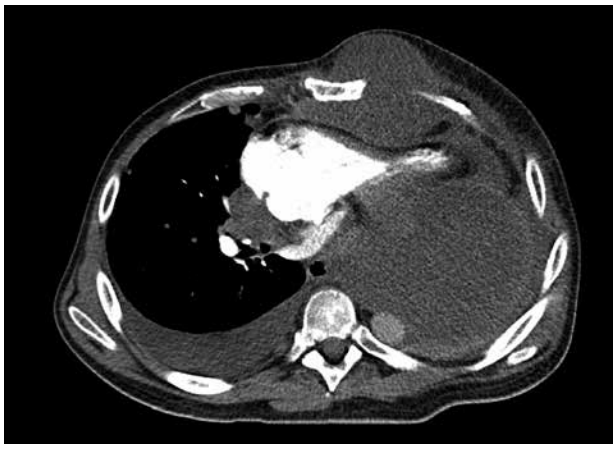

Fig. 1A. The CT scan of the patient showing giant recurrent tumor in the left thoracic cavity, chest wall, and right hydrothorax

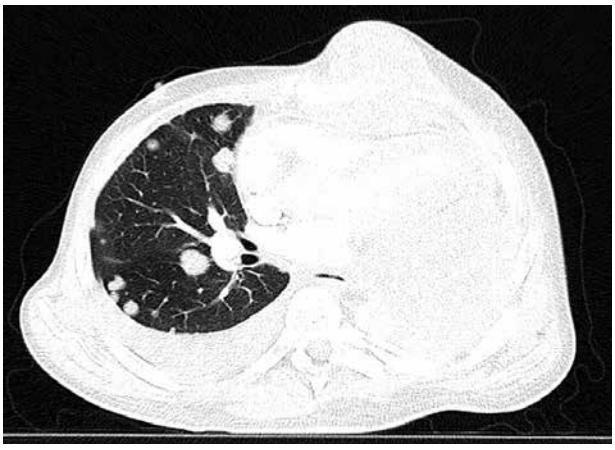

Fig. 1B. The CT scan of the patient showing multiple right lung metastases

knowledge of the molecular features of these tumours may provide the basis for the newly targeted agents.

Authors declare no conflict of interest.

References

1. Hagel C, Zils U, Peiper M, et al. Histopathology and clinical outcome of NF1-associated vs. sporadic malignant peripheral nerve sheath tumors. J Neurooncol 2007; 82: 187-92.
2. Rawal A, Yin Q, Roebuck M, Sinopidis C, Kalogrianitis S, Helliwell TR, Frostick S. Atypical and malignant peripheral nerve-sheath tumors of the brachial plexus: report of three cases and review of the literature. Microsurgery 2006; 26: 80-6.
3. Kobayashi C, Oda Y, Takahira T, et al. Chromosomal aberrations and microsatellite instability of malignant peripheral nerve sheath tumors: a study of 10 tumors from nine patients. Cancer Genet Cytogenet 2006; 165: 98-105.
4. Seeley SL, Bosco EE, Kramer E, Parysek LM, Knudsen ES. Distinct roles for RB loss on cell cycle control, cisplatin response, and immortalization in Schwann cells. Cancer Lett 2007; 245: 205-17.
5. Lee PR, Cohen JE, Fields RD. Immune system evasion by peripheral nerve sheath tumor. Neurosci Lett 2006; 397: 126-9.
6. Kobayashi C, Oda Y, Takahira T, et al. Aberrant expression of CHFR in malignant peripheral nerve sheath tumors. Mod Pathol 2006; 19: 524-32.
7. Wong WW, Hirose T, Scheithauer BW, Schild SE, Gunderson LL. Malignant peripheral nerve sheath tumor: analysis of treatment outcome. Int J Radiat Oncol Biol Phys 1998; 42: 351-60.
8. Ziółkowska E, Mross M, Biedka M, Makarewicz R. Guz złośliwy nerwów obwodowych – opis przypadku. Wspolczesna Onkol 2007; 11: 247-51.
9. Conlon NP, Redmond KC, Celi LA. Spontaneous hemothorax in a patient with neurofibromatosis type 1 and undiagnosed pheochromocytoma. Ann Thorac Surg 2007; 84: 1021-3.
10. Teitelbaum GP, Hurvitz RJ, Esrig BC. Hemothorax in type I neurofibromatosis. Ann Thorac Surg 1998; 66: 569-71.
11. Prayson RA, Yoder BJ, Barnett GH. Epidermal growth factor receptor is not amplified in schwannomas. Ann Diagn Pathol 2007; 11: 326-9.
12. Holtkamp N, Okuducu AF, Mucha J, et al. Mutation and expression of PDGFRA and KIT in malignant peripheral nerve sheath tumors, and its implications for imatinib sensitivity. Carcinogenesis 2006; 27: 664-71.
13. Dang I, DeVries GH. Schwann cell lines derived from malignant peripheral nerve sheath tumors respond abnormally to platelet-derived growth factor-BB. J Neurosci Res 2005; 79: 318-28.
14. Mawrin C, Schulz S, Hellwig-Patyk A, et al. Expression and function of somatostatin receptors in peripheral nerve sheath tumors. J Neuropathol Exp Neurol 2005; 64: 1080-8.
15. Cashen DV, Parisien RC, Raskin K, Hornicek FJ, Gebhardt MC, Mankin HJ. Survival data for patients with malignant schwannoma. Clin Orthop Relat Res 2004; 426: 69-73.
16. Gronchi A, Casali PG, Fiore M, et al. Retroperitoneal soft tissue sarcomas: patterns of recurrence in 167 patients treated at a single institution. Cancer 2004; 100: 2448-55.
17. Youssef E, Fontanesi J, Mott M, Kraut M, Lucas D, Mekhael H, Ben-Josef E. Long-term outcome of combined modality therapy in retroperitoneal and deep-trunk soft-tissue sarcoma: analysis of prognostic factors. Int J Radiat Oncol Biol Phys 2002; 54: 514-9.
18. Anghileri M, Miceli R, Fiore M, et al. Malignant peripheral nerve sheath tumors: prognostic factors and survival in a series of patients treated at a single institution. Cancer 2006; 107: 1065-74.
19. Kroep JR, Ouali M, Gelderblom H, Le Cesne A, Dekker TJA, Van Glabbeke M, Hogendoorn PC, Hohenberger P. First-line chemotherapy for malignant peripheral nerve sheath tumor (MPNST) versus other histological soft tissue sarcoma subtypes and as a prognostic factor for MPNST: an EORTC Soft Tissue and Bone Sarcoma Group study. Ann Oncol 2011; 22: 207-14.

Address for correspondence

Renata Zaucha
Chair and Department of Oncology and Radiotherapy
Medical University of Gdansk
Dębinki 1
80-211 Gdansk, Poland
e-mail: rzaucha@gumed.edu.pl

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