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Case Report

Sporadic Metastatic Malignant Peripheral Nerve Sheath Tumour with an NF1 Mutation Responding to Trametinib: A Case Report

Nadia Hitchen[a, b] Matthew Cross[a] George Laking[a, b] Joanna Connor[a] Clement Korenbaum[a]

[a]Medical Oncology Department, Auckland City Hospital, Te Pūriri o Te Ora, Auckland, New Zealand; [b]Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

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Abstract
Sporadically occurring malignant peripheral nerve sheath tumours (MPNSTs) can have a variety of genomic alterations including altered NF1, leading to activation of the RAS-RAF-MEK-ERK signalling pathway. Trametinib is an inhibitor of MEK1 and MEK2. Here we present a case of a patient diagnosed with sporadic MPNST with an identified NF1 gene treated successfully with trametinib.

Introduction

Malignant peripheral nerve sheath tumours (MPNSTs) are a type of soft tissue sarcoma with a high propensity to metastasize [1, 2]. MPNSTs make up approximately 10% of soft tissue sarcomas; they can occur sporadically, be associated with radiotherapy, or more commonly be associated with neurofibromatosis type 1 [3].

Sporadically occurring MPNSTs can have a variety of genomic alterations. In a cohort of 201 patients, 52% had an inactivating mutation of neurofibromin 1 (NF1), a tumour suppressor protein, which results in increased RAS/RAF activity [4]. Despite accumulating evidence on the clinical activity of mitogen-activated protein kinase (MEK) inhibitor in the

Correspondence to:
Nadia Hitchen, NHitchen@adhb.govt.nz

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treatment of NF1-related plexiform neurofibromas, very little data are available on their malignant counterpart MPNST [5, 6].

In general, MPNSTs are poorly responsive to chemotherapy, and standard of care is complete surgical resection which often is not possible in a metastatic setting [2]. Doxorubicin and ifosfamide have modest activity and are a considered regimen in the first-line setting. While biological rationale for MEK inhibitors (MEKis) in MPNST exists, there are no clinical trials supporting their use. There is currently a phase 2 trial using MEKi selumetinib and mTOR inhibitor sirolimus, but results of this are awaited (NCT03433183). Here we report the case of a 63-year-old male treated with trametinib after progression on pazopanib and multiple lines of cytotoxic chemotherapy. The CARE checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000528743) [7].

Case Report

In 2003 a previously well New Zealand European male presented with right calf swelling from an underlying soft tissue mass. Histology revealed an MPNST, confirmed by sarcoma pathologist. He was treated with preoperative radiation and surgical resection with clear margins. There were no clinical features of neurofibromatosis. Between 2011 and 2018, he underwent several surgical resections for isolated recurrent disease in the distal pancreas, right arm, mediastinum, upper abdomen, and left buttock. Adjuvant radiation was given following the distal pancreatectomy due to positive margins, and all cases were histologically confirmed as relapsed sporadic MPNST.

At the end of 2018, a positron emission tomography scan identified unresectable recurrence in the mediastinum and left flank (shown in Fig. 1). The patient received six cycles of doxorubicin to cumulative dose of 495 mg/m^2. Two months after finishing doxorubicin, a computerized tomography scan showed progression in the mediastinum and retroperitoneal disease. The patient commenced pazopanib 800 mg daily; however, progression occurred in these same areas after 4 months.

As third-line systemic treatment, the patient received four cycles of gemcitabine and docetaxel with a best response status of partial response after six cycles. Three months later, progression occurred in the mediastinal and retroperitoneal disease; the patient remained asymptomatic. The patient commenced fourth-line systemic treatment in the form of ifosfamide and etoposide; after three cycles, there was progression in the retroperitoneal/perinephric lesions.

Given the progression through four lines of systemic treatment, consideration was given to further resection; however, this was deemed not technically feasible. The patient self-funded next-generation sequencing (NGS; FoundationOne® CDx analysis, Roche). NGS identified a pathogenic NF1 mutation (T1557fs*7) of therapeutic interest. Of note, family history for neurofibromatosis was negative. Germline testing was not performed. Other genomic findings were an EGFR T90M mutation which was subclonal and an FGFR1-TACC1 fusion; these were not considered targetable.

Despite progressive disease, the patient remained well with an ECOG performance status of 0. In August 2021, the patient commenced trametinib at a dose of 2 mg once daily. Computerized tomography scans at month 2, 4, and 7 after commencement of trametinib showed response in all known sites of disease, retroperitoneal/perinephric lesion and mediastinal lesion (shown in Fig. 2).

Peak toxicity across the initial 6 months of treatment was grade 2 folliculitis (CTC-AE Version 5), successfully controlled with doxycycline. In March 2022, the patient stopped

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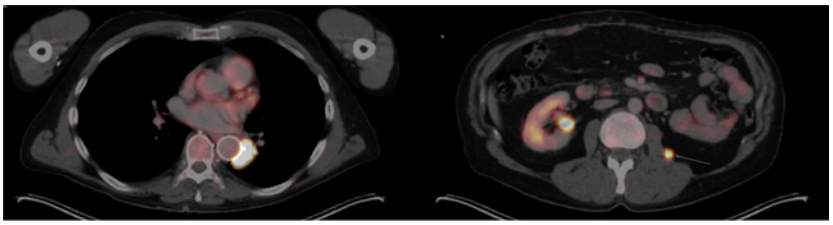

Fig. 1. PET scan December 2018 demonstrating recurrent unresectable metastatic disease in mediastinum (left) and flank (right). PET, positron emission tomography.

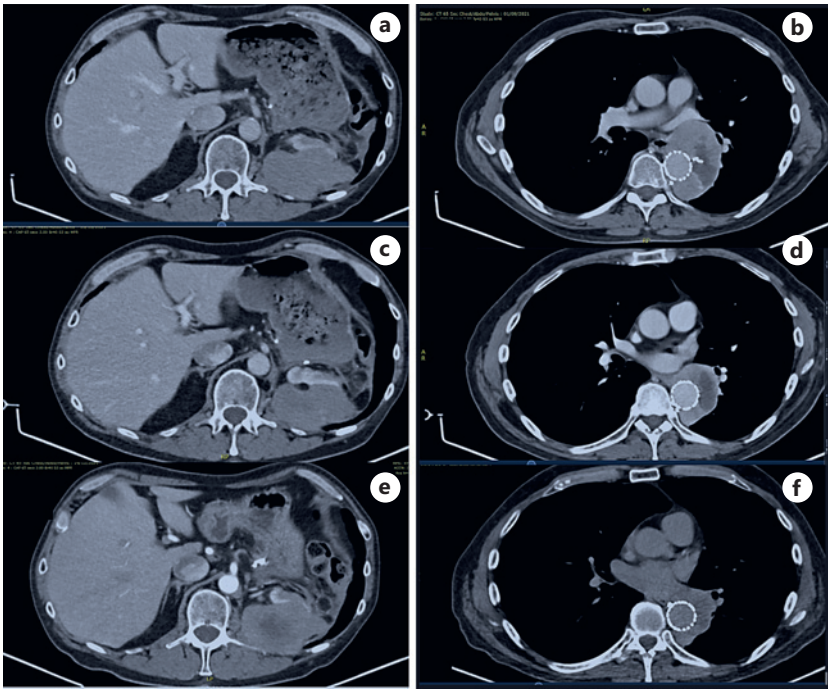

Fig. 2. Radiological response with trametinib in perinephric/retroperitoneal lesions and mediastinal lesion at month 2 (**a**, **b**), 4 (**c**, **d**), and 7 (**e**, **f**).

trametinib due to asymptomatic but severe left ventricular systolic impairment (LVEF 25–30%) detected on routine echocardiogram. Despite cessation of trametinib and maximal medical cardioprotective therapy, there was no improvement in LVEF; therefore, re-initiation of trametinib was not attempted.

The patient developed progressive disease 3 months after discontinuation of trametinib. He received further radiation to the abdominal and mediastinal disease and is due to commence palliative temozolomide. In summary, the patient achieved response to disease at all sites on trametinib for 10 months, the most durable response of all his systemic treatments (shown in Fig. 3).

Discussion

Historically, many sarcoma subtypes have been grouped together for diagnosis and treatment purposes, leading to suboptimal outcomes. Recent studies have highlighted the

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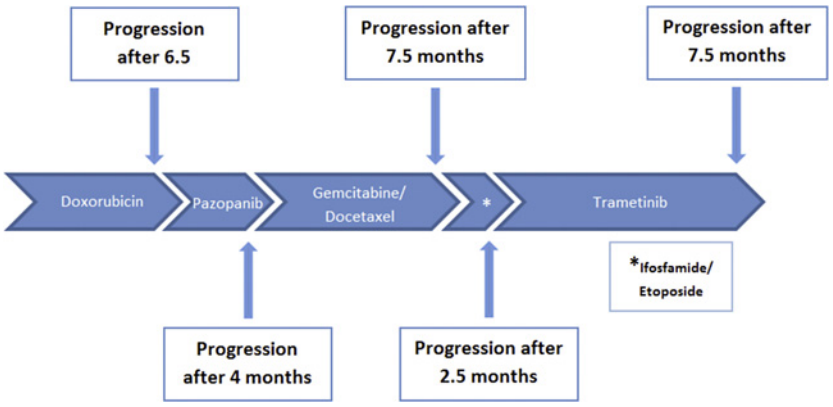

Fig. 3. Summary of systemic treatment in incurable setting for patient and times to progression.

importance of molecular characterization to improve diagnostic accuracy and impact treatment plans [8]. At present, the use of NGS in soft tissue sarcomas has not been defined but is likely to become more widely used.

MPNSTs are rare and heterogenous. The NF1 gene is commonly affected in sporadic MPNSTs, resulting in constitutional activation of the RAS/RAF/MAPK pathway [9]. This upregulates several downstream tyrosine kinases, resulting in biological rational and clinical activity from MEKi as has been shown in this case.

Pre-clinical mouse models demonstrated the biological rationale for MEKi in NF1-mutated MPNSTs [10, 11]. A phase 1 trial of selumetinib in 24 paediatric patients albeit with neurofibromatosis-related disease demonstrated an objective response in 71% [12]. Clinical trials are lacking within the sporadic MPNST space. Current clinical evidence exists in a single case report in which a 14-year-old with recurrent MPNST treated with trametinib achieved a complete remission for more than 15 months [13]. A phase 1b trial of trametinib with everolimus in 2015 included 2 patients with MPNST, although these were grouped as "other" tumour types, so efficacy for MPNST is not able to be ascertained [14]. Given the pre-clinical evidence and biological rationale for targeted treatments along these signalling pathways, early phase clinical trials are underway including the phase II SARC031 trial combining an MEKi and mTOR inhibitor (NCT03433183). There is also the COTESARC trial, which combines PDL1 with an MEKi (NTC04216953); additionally, the phase II MULTISARC (NCT03784014) uses NGS in advanced soft tissue sarcoma patients to identify genomic changes and subsequently match to targeted therapy. Trametinib is one of the treatment strategies within this trial.

A meta-analysis in 2019 demonstrated the addition of an MEKi to BRAFi increased risk of pulmonary embolism, decrease in LVEF and arterial hypertension [15]. Review of large-scale clinical trials in melanoma has demonstrated up to a 12% risk of reduction in LVEF with MEKi and was the limiting toxicity in this case [16].

In conclusion, sporadic MPNST is a rare subtype of soft tissue sarcoma that has a high propensity to metastasize. Surgery is the only curative option, and response to cytotoxic chemotherapies is poor and short-lived. While data remain scant, this case adds to the existing published data of response to trametinib in NF1 sporadic MPNSTs. It also supports the molecular relationship with plexiform neurofibroma, their benign counterpart, in which MEKi have demonstrated meaningful activity. The case also highlights the value of molecular characterization of soft tissue sarcomas to guide treatment decisions with the patient in this case achieving a longer response to trametinib than any of the four prior lines of systemic treatments.

Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and the accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Funding was not required; hence, funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Clement Korenbaum made the conceptualization. Nadia Hitchen, Matthew Cross, and Joanna Connor wrote the first draft. All authors edited the final manuscript and treated the patient discussed in this article.

Data Availability Statement

All data generated or analysed are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

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