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Case Report

Trametinib Combined with Pazopanib for Treating Malignant Peripheral Nerve Sheath Tumor in NF-1 Patients: A Case Report and A Review of the Literature

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Abstract

Neurofibromatosis type 1 is a pathological condition due to the mutation of the NF1 gene that occurs in one to 3000 newborns, in many ethnic groups, in both males and females equally. Almost all individuals with NF1 develop peripheral plexiform neurofibroma and about 10% of them will undergo malignant transformation to malignant peripheral nerve sheath tumors (MPNSTs). Rarely this kind of tumor localizes intracranial (not associated with any cranial nerve and more common in the supratentorial region) and may begin with unexplained spontaneous intracerebral bleeding without any other symptoms before. Since NF1 is also associated with intracerebral vascular malformations and Moya disease, often this highly malignant and aggressive tumor is underestimated, and the diagnosis is mistaken until the histological analysis is made. Current knowledge about clinical presentation and best therapeutic management is limited by the restricted number of patients reported over a long period and treated with various modalities. However, recent progression in genomic analysis allows highlighting the incidence of genomic alterations on intracellular signaling pathways leading to aberrant cell proliferation and targeting them with a targeted therapy. The current study presents the case of an 18-year-old man with MPNST without a family history of NF-1. The studies were retrospectively reviewed, and the patient's clinicopathological data, including tumor site, treatment, follow-up, prognosis, and genomic profiling, were collected.

Introduction

Neurofibromatosis type 1

Neurofibromatosis type 1 is an autosomal dominant disorder caused by tumor suppressor gene NF1 mutations that could be inherited or appear de-novo in the germline. It occurs in 1/3,000 live births in many ethnic groups and affects males and females equally [1]. The clinical features are highly variable, even within the same family. Multiple café-au-lait spots are typical of almost all patients within the first two months after birth, whereas intertriginous freckling develops starting at 5 years of age. Adults develop multiple cutaneous and subcutaneous neurofibromas that increase in number and size with age and never become malignant. Other manifestations may include ocular manifestations such as optic pathway gliomas and iris hamartomas, known as Lisch nodules that usually develop before age 6 years, and rarely progress after that. Osteopenia, osteoporosis, bone overgrowth, short stature, macrocephaly, scoliosis, skeletal dysplasia, and pseudoarthrosis may be present. Intellectual development is usually not severely affected, but 50%-75% of the NF1 population presents cognitive deficits and learning difficulties. NF-1 is constantly associated with vasculopathy and cerebrovascular abnormalities, with a pathophysiology that is still not completely understood [2-5]. There are multiple case reports in the literature of individuals with NF-1 who developed cerebrovascular disease (CVD) associated with complications and long-term impacts. Following the onset of CVDs in NF-1 patients, heterogeneous neurological manifestations and several complications have also been described.

These events frequently result in high morbidity and mortality in NF-1 patients [6]. The association of NF-1 with CVD results in a wide range of pathologies, such as cerebral ischemia, aneurysms, and Moya Moya Syndrome (MMS). Several NF-1 cases have been reported in children, but the incidence of CVDs in NF-1 cases is still poorly recognized, which warrants more studies on the important topic [7]. A variant of neurofibromas is represented by plexiform neurofibroma, which is a benign tumor of peripheral nerves arising from a proliferation of all neural elements [8]. Plexiform neurofibroma are pathognomonic of neurofibromatosis type 1, may cause disfigurement, pain, and functional problems, are usually present at birth, and may become malignant later in life. In about 10% of NF1 patients, neurofibromas may transform into malignant peripheral nerve sheath tumors (MPNSTs), which are highly aggressive [9].

NF1 gene and Neurofibromin function

NF1 is caused by point mutations in the tumor suppressor neurofibromin 1 (NF1) gene (17q11.2) and in only 5% of cases by a 17q11 microdeletion [10]. Allelic variation, second-hit events in the NF1 gene, germline-specific genetic context, epigenetic changes, and tissue-specific functions of neurofibromin may account for the profound degree of clinical heterogeneity in Neurofibromatosis type 1 [11]. NF1 gene encodes neurofibromin, a 250 to 280 kDa multifunctional protein that is ubiquitously expressed with highest levels in neurons, non-myelinating Schwann cells, and oligodendrocytes, as well as in the adrenal medulla, leukocytes, and testis. Sequence analysis showed that neurofibromin is highly conserved in mammals suggesting a strong selective pressure on neurofibromin structure and function. The structure of neurofibromin is complex, with several functional domains that contribute to its role in cellular regulation. The well-characterized region of neurofibromin is the Ras-GTPase-activating protein (GAP)-related domain (GRD) that interacts with Ras proteins [12]. This domain is critical for its role in inhibiting the Ras signaling pathway. Located upstream of the GRD, there is a CSRD (Cysteine/Serine-Rich Domain): this domain's function is

not entirely understood but is believed to contribute to the protein's regulation and interaction with other molecules. Found downstream of the GRD, there is a Sec14 Homology Domain, thought to be involved in lipid binding and regulation [13] (Figure 1).

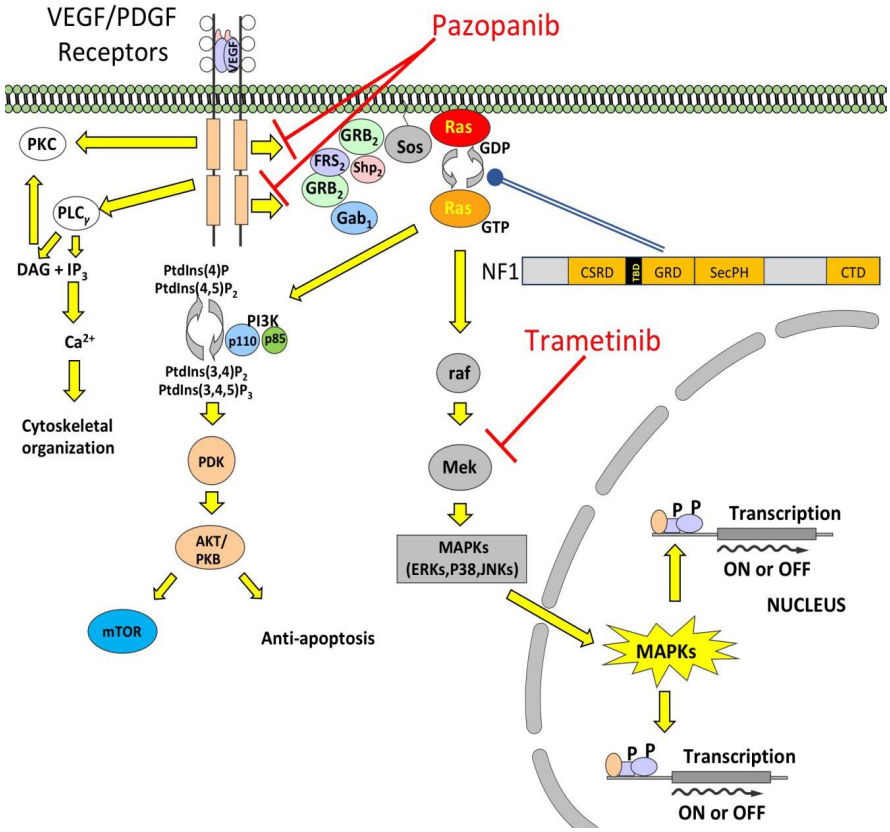

Figure 1: **Representation of NF1 roles within Ras and PI3K pathways**. NF1 regulates cell proliferation, differentiation, survival, and growth through the MAPK- and PI3K/mTOR pathway and cAMP signaling. NF1 functions as a GAP for RAS, increasing the speed of GTP hydrolysis and therefore reducing RAS's activation time. Ras also positively regulates cyclic AMP (cAMP), via PKCζ activation of G protein-coupled receptors (GPCR) and activation of adenylyl cyclase (AC), which controls cell survival. Loss of NF1 therefore activates RAS and downstream pathways dysregulating cell growth and tumorigenesis. The different inhibitors mentioned in the text and their targets are also shown in the figure.

Neurofibromin plays a critical role in regulating cell growth and differentiation, key functions include Ras GTPase-Activating protein (GAP) activity, tumor suppression, regulation of cell differentiation and migration, cytoskeletal organization, cognitive function, and learning. Neurofibromin mainly acts as a GAP for Ras proteins accelerating the conversion of active Ras-GTP to inactive Ras- GDP, and effectively downregulating Ras signaling. As a result, neurofibromin acts as a tumor suppressor preventing excessive cellular proliferation. Loss of neurofibromin function can lead to uncontrolled Ras activity, contributing to the development of tumors [14]. This is particularly evident in individuals with neurofibromatosis type 1 (NF1). These mutations lead to reduced or non- functional neurofibromin, increasing the risk of tumor formation. Moreover, neurofibromin interacts with cytoskeleton components, helping to regulate cell shape and motility. This interaction is important for maintaining the structural integrity of cells and for processes such as cell migration. Beyond its tumor-suppressing functions, neurofibromin is also involved in neural development and synaptic plasticity, influencing learning and memory. Loss of neurofibromin leads to cognitive deficits and learning disabilities, which are often observed in individuals with NF1 [15].

NF-1 associated MPNST

Malignant peripheral nerve sheath tumors (MPNSTs) are rare sarcomas, encompassing only 2% to 4% of all soft tissue sarcomas [16, 17]. The incidence of these tumors is 1:100000 in the general population. MPNST is a malignant tumor frequently associated with NF1; the risk of developing it during life is 8-13% in NF1 patients [16, 18, 19]. A slight predominance in males has been reported [20-23]. The peak incidence of these tumors differs between NF1-related tumors and sporadic tumors. NF1 patients have an incidence peak in the third and fourth decades, while sporadic tumors are usually diagnosed in the sixth decade. Few data are available on prognostic factors and on the best therapy for this kind of tumor. Still, maximal safe resection is crucial in both adult and pediatric cases. Reports on pediatric intracranial sarcomas, and in particular, MPNST, are

limited to single institutional case reports or small, single institutional case series, and in all of these, a complete tumor resection promotes the chances of patient survival. Furthermore, the vast majority of long-term survivors have received multimodal treatment to achieve local tumor control with radiotherapy and ifosfamide, carboplatin, and etoposide chemotherapy [24-26]. Various small targeted molecules were tested in small cohorts of MPNST patients, but trials have not yet progressed in treating this disease [8]. The survival of patients with metastatic or unresectable disease is poor, with a median progression-free survival of approximately four months and an overall survival of 13 months [9].

NF-1 associated MPNSTs Target Therapy

NF1 gene mutations are used as a diagnostic marker for neurofibromatosis type 1. Genetic testing can identify these mutations, aiding in early diagnosis and management. Understanding the pathways and mechanisms involving neurofibromin can help in developing targeted therapies for conditions resulting from its dysfunction, particularly tumors associated with NF1. Currently, no systemic drugs are specifically approved for patients with advanced MPNST, and the existing drugs used in soft-tissue sarcoma generally have a modest activity in this specific histologic subtype. Consequently, in those patients, the prognosis continues to be poor. NF1 individuals carry mutations in the NF1 gene, which are responsible for functional alterations in Neurofibromin 1 and consequently in the MAPK pathway. As detailed before, these subjects are more predisposed to develop neoplasms. With the advent of next-generation sequencing, other kinds of mutations in many genes that cooperate with the NF1 gene have been identified [27]. In particular, the loss of the tumor suppressor genes CDKN2A and/or PTEN, which control cell cycle progression [10, 27]; but, also oncogene activation, important for tumor progression, like PDGFRA, MET, c-kit, and epidermal growth factor receptor (EGFR) is frequently observed in MPNST [28, 29]. Another tumor suppressor gene involved in MPNST is TP53, although there are conflicting opinions regarding the frequency of mutations [30]. Moreover, epigenetic causes have also been found in the pathogenesis of the NF1-associated MPNST, such as mutations in SUZ12 or EED, which lead to inactivation of these two must components of polycomb repressive complex 2 (PRC2) [27].

Moreover, this kind of tumor is characterized by a high heterogeneity, meaning that different cells within the same tumor may respond differently to treatment. Thus, identifying a single target for therapy is therefore challenging, and, due to the rarity of MPNST, conducting large randomized trials is almost impossible. Since RAS proteins to be active should be associated with the plasmatic membrane, and this association is given by farnesylation, farnesyl transferase enzymes have been targeted in NF1-dependent MPNST cells, but in clinical trials, this strategy has not been successful [31]. An alternative to RAS inhibition is to target downstream of activated RAS. Sorafenib, a small-molecule RAF kinase and tyrosine kinase inhibitor has been shown to inhibit MAPK signaling and cell growth, inducing the cell-cycle arrest in G0/G1 phase in MPNST cell lines through B-Raf dependent inhibition [32]. However, sorafenib showed no significant response in a multicenter phase II trial, with overall survival of treated MPNST patients similar to controls [33].

MEK (MAP kinase) proteins are a family of kinases involved in the Ras-Raf-MEK-ERK (extracellular signal-related kinase) signaling pathway. This induces growth and survival in mammalian cells, activating alterations that drive cancer transformation. MEK proteins are kinases that phosphorylate in serine/threonine and tyrosine residue. They are classified into two isoforms, MEK1 and MEK2, ubiquitously expressed. Different mitogenic stimuli can bind to specific tyrosine kinase receptors (RTK), leading to its dimerization and autophosphorylation in tyrosine residues at the C-terminal domain. When activated, these activated receptors recruit and phosphorylate adaptor proteins such as Grb2 and SOS, which interact with Ras that function as molecular switcher GDP in GTP, causing its activation [34, 35]. Once activated Ras recruits and activates Raf kinases, which in turn interact and activate MEK1/2, which finally activates ERK1/2. Differently from the others, these latter have many cytosolic and nuclear substrates regulating different cellular processes, such as cell proliferation, survival, differentiation, motility, and angiogenesis [36]. While MEK 1/2 has not been considered an oncogene as long as activated MEK mutations are relatively rare in human tumors, MEK constitutive activation results in cellular transformation, and it is implicated in the progression of human tumors [37]. So, since 1995 new molecules that inhibit MEK activity have progressed into clinical trials (e.g., refametinib, selumetinib,

trametinib, cobimetinib). MEK inhibitors are commonly classified as molecules competing directly for the ATP–binding site (ATP-competitive), and the ATP non- competitive inhibitors bind to a unique allosteric site adjacent to the ATP site, ensuring their high specificity [38]. Despite about thirteen MEK inhibitors being tested and continuous screening or molecular modifications being made to improve the inhibitory activity, only trametinib (GSK1120212), a selective inhibitor of MEK 1/2, has been proven effective in a phase III clinical study.

MEK inhibitors: trametinib

Trametinib (GSK1120212, JTP-74057) is an allosteric inhibitor of MEK kinase. It falls into the second-generation non-competitive category, with potent activity against purified MEK 1/2 kinases [39]. In vitro preclinical studies demonstrate inhibition of tumor cell growth by cell-cycle arrest, through the de-phosphorylation of ERK 1/2. A trametinib phase I clinical trial on 206 patients with advanced solid tumors shows finite toxicities and a global response rate of 10% with 33% on B-Raf mutant melanoma [40]. These results bring researchers to carry out several phase II/III clinical trials of trametinib alone or in combination with other agents, especially on V600E/K B-Raf mutations in advanced melanoma, but also on advanced non-small cell lung cancer (NSCLC) which showed the same mutations. Results of these trials point out Trametinib extends the progression-free survival (PFS) of patients to 4.8 months, giving an 81% overall survival in patients with B-Raf mutated metastatic melanoma. Furthermore, combinations of Dabrafenib and Trametinib led to improved progression-free survival compared to single treatment [41]. In a randomized phase II clinical trial on NSCLC, Trametinib demonstrated similar efficacy to docetaxel in KRAS-mutant patients with moderate activity as a monotherapy [42]. Hence, the authors conclude that trametinib-based combination regimens may show improved efficacy. Only more recently, trametinib was used for the treatment of MPNSTs too. In vitro, results demonstrated the reduction of the MAPK pathway thanks to significant inhibition of p-ERK and downstream cyclin D1 levels [43]. Unfortunately, in vivo, tumor growth inhibition was transient. It resulted in resistance and reactivation of target pathways. In contrast, the combination therapy with other targets of interest in MPNST pathogenesis (mTOR, MNK, BRD, MET) demonstrated tumor regression with synergistic responses [44, 45]. A meta-analysis of 8 studies evaluates the effectiveness and safety of trametinib in NF1-related nerve tumors indicating a satisfactory stabilization but an inefficiency to shrink tumors in NF1-related nerve tumors [46]. Even though the safety profile of trametinib is satisfactory, there is no evidence that single-agent MEKi is effective in treating MPNST. Indeed, in NF-1 biallelic loss, it is capable alone to sustain a complete response to the metastatic recurrence in an adolescent patient in only 3 months of treatment. After 15 months after the second relapse, there was no recurrence of the primary chest lesion since the second surgery or at any other site [47].

Multitarget TK inhibitors: pazopanib

A significant role in the development of numerous human malignancies is carried out by tyrosine kinases Receptors (RTKs), such as vascular endothelial growth factor receptors (VEGFRs), fibroblastic growth factor receptors (FGFRs), and platelet-derived growth factor receptors (PDGFRs). In the last decade, many tyrosine-kinase inhibitors (TKIs) targeting osteosarcoma oncogenic pathways have been explored [48, 49]. Several studies have suggested that pazopanib may be effective against MPNST. Pazopanib is a tyrosine kinase inhibitor that blocks the vascular endothelial growth factor receptors (VEGFR-1/2/3), platelet-derived growth factor receptors (PDGFR-α/-β), and c-kit. In a phase II study on patients with relapsed or refractory advanced Soft Tissue Sarcoma (STS), Pazopanib showed interesting activity prolonging progression-free and overall survivals and was well tolerated in patients with relapsed, advanced STS [50]. A phase III clinical study was done randomly on 372 patients assigned to receive pazopanib or placebo, with no subsequent cross-over. Results indicated that the survival progression-free was a 3-fold increase in PFS over placebo. Overall survival grew in 2 months with pazopanib [51]. Since MPNST manifests in subjects who have lost the activity of NF1 or are deleted, and this lack leads to Ras activation, which in turn increases cells' dependence on the VEGF-VEGFR pathway, pazopanib may be effective against MPNST. Yoshihiro Nishida et al. examining the efficacy of pazopanib in a phase II clinical trial on 12 patients with advanced MPNST, demonstrated the effect of pazopanib against tumors with higher grades of malignancy, and thereby prolong life [52].

In light of this evidence, it is clear that monotherapy is not the right choice because the clinical activity of TKIs was relatively short due to primary or acquired resistance related to the activation of RTK downstream pathways [53], such as RAS/RAF/MAPK and/or PI3K-Akt-mTOR signaling pathways. Strategies involving combination therapies are being explored as potential approaches to treat MPNST. A vertical blockade combining upstream with the RTK inhibitor Pazopanib and downstream with the MEK inhibitor Trametinib should greatly suppress MAPK signaling. The antitumor activity was studied both in vitro and in vivo, demonstrating a synergistic antitumor activity through the strengthening of apoptosis and decreased ERK1/2 and Akt signaling activation in osteosarcoma, thyroid cancer, and advanced cholangiocarcinoma [54, 55]. Moreover, a phase Ib/II clinical study on the safety and efficacy of target therapy with Pazopanib and Trametinib was performed both in advanced solid tumors and differentiated thyroid cancers and in 25 patients with advanced soft tissue sarcoma. Although, no patient performed a complete response, a stable disease was obtained in the 48% of cases. Indeed, results demonstrated a progression-free survival median of

2.27 months (95% CI). The 4-month PFS rate was gained in 21.1% of cases with a median overall survival of 9.0 months [24, 56].

Case Report

An 18-year-old man presented with a massive intracranial hemorrhage and underwent surgical removal of the hematoma. The first diagnostic question was initially arteriovenous malformation, a widespread feature in NF-1 patients since 18F-fluorodeoxyglucose Positron Emission Tomography (18FDG-PET) was negative [57]. However, the final pathological diagnosis revealed eMPNST arising from peripheral nerves localized in the right parietal lobe, with a very high proliferative index (Ki67>70%). The histological analysis also revealed a high heterogeneity of the tumor tissue with Vimentin positivity, partial positivity to CD10 and CD56, and isolated positivity to S-100, HMB-45, and Melan A. After diagnosis, the patient was referred to the Department of Oncology due to the multiple recurrences and invasive nature of the tumor. Adjuvant radiotherapy was administered with a dose of 50 Gray (Volumetric Modulated Arch Therapy using high energy 15 MV photons for 30 seconds) in 30 fractions over 6 weeks (1 per day for 5 days a week). Subsequently, ICE chemotherapy was initiated according to the protocol published by Lafay-Cousin et al. in 2016 [24], consisting of ifosfamide 3g/m2 intravenously (IV) over 3 hours on day 1 and day 2; etoposide 150 mg/m2 IV over 1 hour on day 1 and day 2, and carboplatin 500 mg/m2 IV over 2 hours on day 3. Chemotherapy cycles were given every 21-28 days based on the blood cell count. Before treatment cell count was: 6.63 10^3 cells/µl of white blood cells (WBC); 5.32x10^6 cells/µl of red blood cells (RBC); 231x10^3 cells/µl of platelets (PLT). After the first cycle, the blood cell count was: 1.26x10^3 cells/µl of WBC; 4.63x10^6 cells/µl RBC, and 112x10^3 cells/µl PLT. Granulocyte colony-stimulating factor (PegfilGraStim 8mg) was administered to stimulate the proliferation of white blood cells. ICE therapy was interrupted after four cycles, due to a very low blood cell count (0.69x10^3 cells/µl WBC; 4.02 10^6 cells/µl RBC; 108x10^3 cells/µl PLT), necessitating discontinuation of the treatment. At the end of all treatments, a brain NMR for potential recurrence was performed, and the results revealed a recurrence of the disease (Figure 2 A and C). Meanwhile, genomic sequencing was performed on primary cells derived from tumor tissue. It resulted in two point mutations in the NF1 gene: deletion of glutamic acid in position 740 (E740*) in cysteine- and serine-rich domain (CSRD), leading to a truncate neurofibromin, and lysin deletion in position 2257 (K2257*) in C-terminal domain (CTD domain), that produces a variant missing of C-terminal domain. As a consequence of these mutations, the amplification of the following genes was observed: CCND2; KRAS; FGF23; FGF6; and KDM5A. Based on genetic results, we decided to treat the patient with a combined targeted therapy including pazopanib 400 mg in association with trametinib 2 mg, in a single administration per day as an alternative systemic treatment. The treatment was highly tolerated, and blood cell count was normal (4.45x10^3 cells/µl WBC; 4.40x10^6 cells/µl RBC; 354x10^3 cells/µl PLT). The only side effect was hair whitening. Serial disease response assessments by NMR imaging showed complete resolution of the lesion with a complete metabolic response 24 months after the start of the surgery (Figure 2).

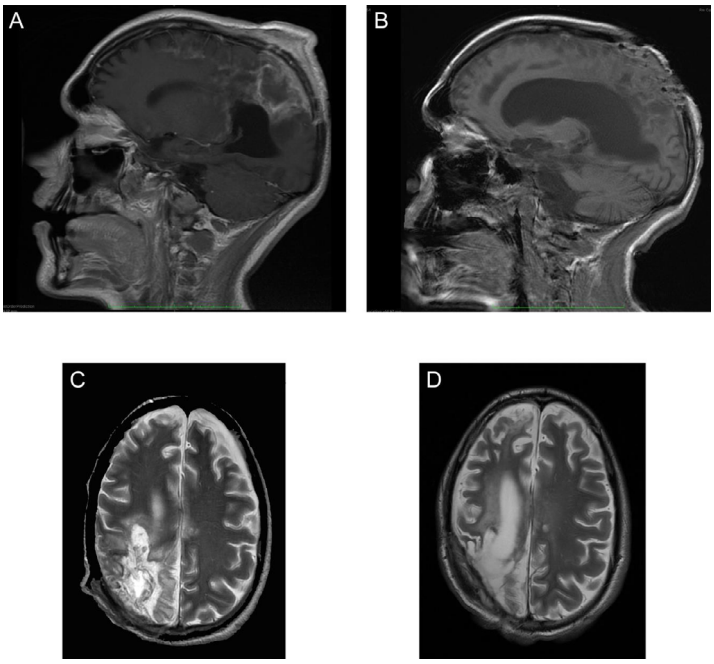

Figure 2: Brain MRI with gadolinium: A e C) Sagittal and axial section of early follow-up MRI (6 months after surgery) revealed evidence of recurrence disease; B and D) Sagittal and axial section of 16 months later the combinatory therapy with pazopanib and trametinib.

Discussion

Little data is available on prognostic factors and effective therapy for this tumor, but in both adult and pediatric cases, maximal safe resection is crucial. Reports on pediatric intracranial sarcomas, and especially on MPNST, are limited to single institutional case reports, and in all cases, a complete tumor resection promotes the chances of patient survival. Furthermore, the majority of long-term survivors have received multimodal treatment to achieve local tumor control with radiotherapy and chemotherapy [24-26]. Here we describe the comprehensive and multidisciplinary approach required to treat a complex and aggressive intracerebral MPNST in an 18-year-old NF-1 patient. The poor prognosis, high rates of recurrence and metastasis, and genetic heterogeneity of MPNSTs make them particularly difficult to treat with monotherapy. MPNSTs often harbor mutations and alterations in key signaling pathways that induce intrinsic or acquired resistance to single-

agent therapies. Thus, understanding the molecular basis of MPNST can lead to targeted therapies and personalized medicine approaches. In this contest, a vertical blockade combining upstream the RTKs inhibitor Pazopanib, and downstream with the MEK inhibitor Trametinib should greatly suppress MAPK signaling. The antitumor activity was studied both in vitro and in vivo, demonstrating a synergistic antitumor activity through the strengthening of apoptosis and decreased ERK1/2 and Akt signaling activation in osteosarcoma models [54]. Moreover, a phase Ib/II clinical study on the safety and efficacy of target therapy with Pazopanib and Trametinib was performed in patients with advanced sarcoma. Although, no patient performed a complete response, a stable disease was obtained in the 48% of cases. Indeed, results demonstrated a progression-free survival median of 2.27 months (95% CI). The 4-month PFS rate was gained in 21.1% of cases with a median overall survival of 9.0 months [56]. For the right management of this kind of malignancy, the network among neurosurgeons, pathologists, molecular biologists, and oncologists is crucial for significantly increasing overall survival. In this kind of network, the neurosurgeon is responsible for the surgical removal of the tumor, which is often the primary treatment for MPNST. Critical is the tumor complete resection for reducing the risk of recurrence, although the balance between the tumor removal and the preservation of nerve function is needed. The close work of pathologists with oncologists is important for diagnosing MPNST and determining its characteristics, which are essential for guiding treatment decisions and prognosis. Pathologists identify specific markers that can influence treatment options. They provide critical diagnostic information to oncologists for therapy decisions. Moreover, the interaction with molecular biologists is essential to reach, through advanced diagnostic techniques, the genetic and molecular characteristics of MPNSTs, including mutations, gene expression profiles, and molecular pathways involved in tumor growth and progression. This can help us to predict response and/or resistance to specific treatments. All these professional figures work together to develop and apply personalized targeted therapies. Combined target therapy represents a promising approach for treating MPNSTs. In particular, combining MEK and RTK inhibitors is promising for treating MPNSTs by targeting multiple critical pathways involved in tumor growth, survival, and progression. This approach could enhance anti-tumor efficacy, overcome resistance mechanisms, and improve patient outcomes. In this scenario, oncologists manage the overall treatment plan, including chemotherapy, radiation therapy, and novel therapeutic approaches. They monitor the patient's response to treatment and adjust protocols as needed, integrating the surgical outcomes from neurosurgeons, pathologists' diagnostic insights, and biologists' molecular findings. Moreover, this network fosters research into new treatments and understanding of MPNST, potentially leading to innovative therapies, improved patient outcomes, and ultimately improved patient prognosis and quality of life.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Credit authorship contribution statement

Conceptualization: AF and MTG; **Writing original**: draft AF and MTG; **Investigation**: GT, AdB, FM, AC, SB; **Methodology**: GT, AdB, AA, VM, AC, FM; **Formal analysis:** AA, APezone; **Data curation**: AC, APezone, AP, MM, PdM; **Writing review and editing**: AP, AP, MG, MM, PdP and MTG; **Supervision**: AP, MG, PdM and MTG; **Funding acquisition**: MG and MTG.

References

1. Monroe CL, Dahiya S, Gutmann DH. (2017) Dissecting Clinical Heterogeneity in Neurofibromatosis Type 1. Annual Review of Pathology: Mechanisms of Disease. 12: 53-74.
2. Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL, et al. (2017) Neurofibromatosis type 1. Nature Reviews Disease Primers. 3: 17004.
3. Napolitano F, Dell'Aquila M, Terracciano C, Franzese G, Gentile MT, et al. (2022) Genotype-Phenotype Correlations in Neurofibromatosis Type 1: Identification of Novel and Recurrent NF1 Gene Variants and Correlations with Neurocognitive Phenotype. Genes (Basel). 13.
4. Laycock-van Spyk S, Thomas N, Cooper DN, Upadhyaya M. (2011) Neurofibromatosis type 1-associated tumours: Their somatic mutational spectrum and pathogenesis. Human Genomics. 5: 623-90.
5. Nix JS, Blakeley J, Rodriguez FJ. (2020) An Update on the Central Nervous System Manifestations of Neurofibromatosis Type 1. Acta Neuropathologica. 139: 625-641.
6. Barreto-Duarte B, Andrade-Gomes FH, Arriaga MB, Araújo-Pereira M, Cubillos-Angulo JM, et al. (2021) Association Between Neurofibromatosis Type 1 and Cerebrovascular Diseases in Children: A Systematic Review. PLoS One. 16: e0241096.
7. Lehman LL, Ullrich NJ. (2023) Cerebral Vasculopathy in Children with Neurofibromatosis Type 1. Cancers (Basel). 15.
8. Grover DSB, S, Kundra R, Grover H, Gupta V, Gupta R. (2021) Imaging Diagnosis of Plexiform Neurofibroma—Unravelling the Confounding Features: A Report of Two Cases. Radiology Case Reports. 16: 2824-2833.
9. Marjanska A, Galazka P, Wysocki M, Styczynski J. (2020) New Frontiers in Therapy of Peripheral Nerve Sheath Tumors in Patients with Neurofibromatosis Type 1: Latest Evidence and Clinical Implications. Anticancer Research. 40: 1817-1831.
10. Wang W, Wei CJ, Cui XW, Li YH, Gu YH, et al. (2021) Impacts of NF1 Gene Mutations and Genetic Modifiers in Neurofibromatosis Type 1. Frontiers in Neurology. 12: 704639.
11. Bergoug M, Doudeau M, Godin F, Mosrin C, Vallée B, et al. (2020) Neurofibromin Structure, Functions, and Regulation. Cells. 9.
12. Dunzendorfer-Matt T, Mercado EL, Maly K, McCormick F, Scheffzek K. (2016) The Neurofibromin Recruitment Factor Spred1 Binds to the GAP-Related Domain Without Affecting Ras Inactivation. Proceedings of the National Academy of Sciences USA. 113: 7497-7502.

13. Barron VA, Lou H. (2012) Alternative Splicing of the Neurofibromatosis Type I Pre-mRNA. Bioscience Reports. 32: 131-138.

14. Mo J, Moye SL, McKay RM, Le LQ. (2022) Neurofibromin and Suppression of Tumorigenesis: Beyond the GAP. Oncogene. 41: 1235-1251.

15. Báez-Flores J, Rodríguez-Martín M, Lacal J. (2023) The Therapeutic Potential of Neurofibromin Signaling Pathways and Binding Partners. Communications Biology. 6: 436.

16. Martin E, Muskens IS, Coert JH, Smith TR, Broekman MLD. (2019) Treatment and Survival Differences Across Tumor Sites in Malignant Peripheral Nerve Sheath Tumors: A SEER Database Analysis and Review of the Literature. Neuro-Oncology Practice. 6: 134-143.

17. Chaix J, Karanian M, Corradini N, Merched M, Larousserie F, et al. (2023) Risk Factors in Pediatric Malignant Peripheral Nerve Sheath Tumors (MPNST): Results from the French Pediatric Oncology Society (SFCE) Cohort. EJC Paediatric Oncology. 1: 100013.

18. Knight SWE, Knight TE, Santiago T, Murphy AJ, Abdelhafeez AH. (2022) Malignant Peripheral Nerve Sheath Tumors—A Comprehensive Review of Pathophysiology, Diagnosis, and Multidisciplinary Management. Children (Basel). 9.

19. Pellerino A, Verdijk RM, Nichelli L, Andratschke NH, Idbaih A, et al. (2023) Diagnosis and Treatment of Peripheral and Cranial Nerve Tumors with Expert Recommendations: An EUropean Network for Rare Cancers (EURACAN) Initiative. Cancers. 15: 1930.

20. Doorn PF, Molenaar WM, Buter J, Hoekstra HJ. (1995) Malignant Peripheral Nerve Sheath Tumors in Patients with and Without Neurofibromatosis. European Journal of Surgical Oncology. 21: 78-82.

21. Zou CY, Smith KD, Liu J, Lahat G, Myers S, Wang WL, et al. (2009) Clinical, Pathological, and Molecular Variables Predictive of Malignant Peripheral Nerve Sheath Tumor Outcome. Annals of Surgery. 249: 1014-22.

22. Valentin T, Le Cesne A, Ray-Coquard I, Italiano A, Decanter G,et al. (2016) Management and Prognosis of Malignant Peripheral Nerve Sheath Tumors: The Experience of the French Sarcoma Group (GSF-GETO). European Journal of Cancer. 56: 77-84.

23. Ariel IM. (1988) Tumors of the Peripheral Nervous System. Seminars in Surgical Oncology. 4: 7-12.

24. Lafay-Cousin L, Lindzon G, Taylor MD, Hader W, Hawkins C, et al. (2016) Successful Treatment of Primary Intracranial Sarcoma with the ICE Chemotherapy Regimen and Focal Radiation in Children. Journal of Neurosurgery: Pediatrics. 17: 298-302.

25. Benesch M, von Bueren AO, Dantonello T, von Hoff K, Pietsch T, et al. (2013) Primary Intracranial Soft Tissue Sarcoma in Children and Adolescents: A Cooperative Analysis of the European CWS and HIT Study Groups. Journal of Neuro-Oncology. 111: 337-345.

26. Maher OM, Khatua S, Mukherjee D, Olar A, Lazar A, et al. (2016). Primary intracranial soft tissue sarcomas in children, adolescents, and young adults: single institution experience and review of the literature. J Neurooncol. 127: 155-163.

27. Somatilaka BN, Sadek A, McKay RM, Le LQ. (2022). Malignant peripheral nerve sheath tumor: models, biology, and translation. Oncogene. 41: 2405-2421.

28. Beert E, Brems H, Daniëls B, Wever ID, Calenbergh FV, et al. (2011). Atypical neurofibromas in neurofibromatosis type 1 are premalignant tumors. Genes Chromosomes Cancer. 50: 1021-1032.

29. Holtkamp N, Malzer E, Zietsch J, Okuducu AF, Mucha J, et al. (2008). EGFR and erbB2 in malignant peripheral nerve sheath tumors and implications for targeted therapy. Neuro Oncol. 10: 946-957.

30. Holtkamp N, Okuducu AF, Mucha J, Afanasieva A, Hartmann C, et al. (2006). Mutation and expression of PDGFRA and KIT in malignant peripheral nerve sheath tumors, and its implications for imatinib sensitivity. Carcinogenesis. 27: 664-671.

31. Rabab'h O, Gharaibeh A, Al-Ramadan A, Ismail M, ShahJ (2021). Pharmacological Approaches in Neurofibromatosis Type 1-Associated Nervous System Tumors. Cancers (Basel). 13.

32. Ambrosini G, Cheema SH, Seelman S, Teed A, Sambol EB, et al. (2008). Sorafenib inhibits growth and mitogen-activated protein kinase signaling in malignant peripheral nerve sheath cells. Mol Cancer Ther. 7: 890-896.

33. D'Adamo DR, Dickson MA, Keohan ML, Carvajal RD, Hensley ML, et al. (2019). A Phase II Trial of Sorafenib and Dacarbazine for Leiomyosarcoma, Synovial Sarcoma, and Malignant Peripheral Nerve Sheath Tumors. Oncologist. 24: 857-863.

34. Rauh MJ, Blackmore v, Andrechek ER, Tortorice CG, Daly R, et al. (1999). Accelerated mammary tumor development in mutant polyomavirus middle T transgenic mice expressing elevated levels of either the Shc or Grb2 adapter protein. Mol Cell Biol. 19: 8169-8179.

35. Shi ZQ, De-Hua Y, Park M, Marshall M, Gen-Sheng F (2000). Molecular mechanism for the Shp-2 tyrosine phosphatase function in promoting growth factor stimulation of Erk activity. Mol Cell Biol. 20: 1526-36.

36. Buscà R, Pouysségur J, Lenormand P. (2016). ERK1 and ERK2 Map Kinases: Specific Roles or Functional Redundancy? Front Cell Dev Biol. 4: 53.

37. McCubrey JA, Steelman LS, Chappell WH, Abrams SL, Wong EWT, et al. (2007). Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. Biochim Biophys Acta. 1773: 1263-1284.

38. Wallace EM, Lyssikatos JP, Yeh T, Winkler JD, Koch K (2005). Progress towards therapeutic small molecule MEK inhibitors for use in cancer therapy. Curr Top Med Chem. 5: 215-229.

39. Yamaguchi T, Kakefuda R, Tajima N, Sowa Y, Sakai T (2011). Antitumor activities of JTP-74057 (GSK1120212), a novel MEK1/2 inhibitor, on colorectal cancer cell lines in vitro and in vivo. Int J Oncol. 39: 23-31.

40. Infante JR, Fecher LA, Falchook GS, Nallapareddy S, Gordon MS, et al. (2012). Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol. 13: 773-781.

41. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, et al. (2012). Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med, 2012. 367: 1694-703.

42. Blumenschein GR, Smit EF, Planchard D, Kim DW, JCadranel J, et al., (2015) A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC)†. Ann Oncol .26: 894-901.

43. Gu Y, Wei C, Chung M, Li H, Guo Z, et al., (2022) Concurrent inhibition of FAK/SRC and MEK overcomes MEK inhibitor resistance in Neurofibromatosis Type I related malignant peripheral nerve sheath tumors. Front Oncol 12: 910505.

44. Lock R, Ingraham R, Maertens O, Miller AL, Weledji N, et al., (2016) Cotargeting MNK and MEK kinases induces the regression of NF1-mutant cancers. J Clin Invest 126: 2181-90.

45. Peacock JD, Pridgeon MG, Tovar EA, Essenburg CJ, Bowman M, et al., (2018) Genomic Status of MET Potentiates Sensitivity to MET and MEK Inhibition in NF1-Related Malignant Peripheral Nerve Sheath Tumors. Cancer Res, 78: 3672-3687.

46. Wang D, Ge L, Guo Z, Li Y, Zhu B, et al., (2022) Efficacy and Safety of Trametinib in Neurofibromatosis Type 1-Associated Plexiform Neurofibroma and Low-Grade Glioma: A Systematic Review and Meta-Analysis. Pharmaceuticals (Basel), 15.

47. Nagabushan, S., Lau LMS, Barahona P, Wong M, Sherstyuk A, et al., (2021) Efficacy of MEK inhibition in a recurrent malignant peripheral nerve sheath tumor. NPJ Precis Oncol,. 5(1): p. 9.

48. Duffaud F, Mir O, Boudou-Rouquette P, Piperno-Neumann S, Penel N, et al., (2019) Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol, 20(1): 120-133.

49. Davis LE, Bolejack V, W Ryan C, Ganjoo KN, Loggers ET, et al., (2019) Randomized Double-Blind Phase II Study of Regorafenib in Patients With Metastatic Osteosarcoma. J Clin Oncol, 37(16): 1424-1431.

50. Sleijfer S, Ray-Coquard I, Papai Z, Le Cesne A, Scurr M, et al., (2009) Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol, 27(19): 3126-32.

51. van der Graaf WT, Jean-Yves B, Chawla SP, Dong-Wan K, Bui-Nguyen B, et al., (2012) Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet, 379(9829): 1879-86.

52. Nishida Y, Urakawa H, Nakayama R, Kobayashi E, Ozaki T, et al., (2021) Phase II clinical trial of pazopanib for patients with unresectable or metastatic malignant peripheral nerve sheath tumors. Int J Cancer 148(1): 140-149.

53. Chiabotto G, Grignani G, Todorovic M, Martin V, Centomo ML, et al., (2020) Pazopanib and Trametinib as a Synergistic Strategy against Osteosarcoma: Preclinical Activity and Molecular Insights. Cancers (Basel),. 12(6).

54. Ball DW, Jin N, Xue P, Bhan S, Ahmed SR, et al., (2015) Trametinib with and without pazopanib has potent preclinical activity in thyroid cancer. Oncol Rep 34(5): 2319-24.

55. Shroff RT., Yarchoan M, O'Connor A, Gallagher D, Zahurak ML, et al., (2018) The oral VEGF receptor tyrosine kinase inhibitor pazopanib in combination with the MEK inhibitor trametinib in advanced cholangiocarcinoma. Br J Cancer, 118(2): e2.

56. Subbiah V, Meyer C, Zinner R, Meric-Bernstam F, Zahurak ML, et al., (2017) Phase Ib/II Study of the Safety and Efficacy of Combination Therapy with Multikinase VEGF Inhibitor Pazopanib and MEK Inhibitor Trametinib In Advanced Soft Tissue Sarcoma. Clin Cancer Res, 23(15): 4027-4034.

57. Milan G, Napoletano S, Pappatà S, Gentile MT, Colucci-D'Amato L, et al., (2017) GRN deletion in familial frontotemporal dementia showing association with clinical variability in 3 familial cases. Neurobiol Aging, 53: 193.e9-193.e16.