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REVIEW

Trends in systemic therapy for malignant peripheral nerve sheath tumors

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Abstract
Malignant peripheral nerve sheath tumors are a type of soft tissue sarcoma deriving from Schwann cells that usually appear in type 1 neurofibromatosis patients but also sporadically. Tumors frequently interest the nerves in the limbs. They represent a therapeutical challenge due to difficulty of resection and relative radio-resistance and chemo-resistance. The paper aims to describe targeted therapy used in this setting and news concerning the molecular changes that lead to carcinogenesis initiation and promotion. A short selection of literature data was made using PRISMA criteria on this topic. However, due to the rarity and heterogeneity of these tumors, personalized treatment is necessary.
Keywords: limb sarcoma, peripheral nerve sheath tumor

Introduction

Type 1 neurofibromatosis (NF-1) is frequently associated with benign plexiform neurofibroma (are usually present from childhood) that can lead to the development of malignant nerve lesions. The most frequent tumors associated with NF-1 are neurofibroma with atypia (not considered malignant), atypical neurofibromatosis neoplasm of uncertain biologic potential, low-grade malignant peripheral nerve sheath tumor (MPNST), and high-grade MPNST [1].

MPNST can appear in any peripheral nerve structure but are frequently located in limb nerves and their surgical treatment usually consists of radical excisions [2].

Multimodal treatment is most often necessary with the collaboration of orthopedic surgeons, imaging specialists, oncologists, radiotherapists, and pathologists.

In the case of unresectable or metastatic MPNST, systemic treatment is mandatory. The choice of the treatment, in this case, needs a profound understanding of the physiopathological and molecular mechanisms of this tumor. The most important conclusion of this review should be that prompt identification of tumors related to NF-1 and complete

resection of these tumors is paramount for a good outcome [3].

Localized disease

It is well known that MPNSTs arise from preexistent plexiform neurofibroma. It was therefore proposed that all plexiform neurofibroma are surgically removed when technically possible. Another important aspect is that usually, the first steps of malignant transformation take place during childhood, so special attention has to be given to these tumors at young ages [4].

Some trials that proposed prophylactic treatment with MEK inhibitors like selumetinib, aimed to prevent this malignant transformation, reported efficacy but with great financial cost [5].

The same results were reported with trametinib in the same scenario [6].

When the malignant transformation is pathologically confirmed, the mainstay treatment is radical resection with clear margins. This usually implies at least 1 mm from tumor to ink [7].

Very often, MPNSTs present in stages that radical resection is not possible up-front. To obtain efficient tumor shrinkage, the possibility to administer neoadjuvant treatment was taken into consideration, but data regarding this option is provided by retrospective small trials, so evidence-based decisions are hard to make. The most solid evidence is for ifosfamide and epirubicin in this setting. Some trials suggest that neoadjuvant chemotherapy is more efficient in sporadic MPNSTs, but some disagree [8,9].

Adjuvant radiotherapy should be considered in high-grade tumors or larger than 5 cm, but this is not a substitute for suboptimal surgery. There is some concern regarding the relative radioresistance of these tumors and the possibility that radiotherapy induces malignant transformation in preexistent plexiform neurofibroma [10,11].

Administration of chemotherapy after radical resection is also a matter of debate. Ifosfamide and epirubicin are considered the most efficient in this case as well, but data is still scarce. There is one trial, however, that reported important overall survival benefit for this regimen, but randomized prospective studies have to confirm this [9].

Metastatic disease

Standard therapy for metastatic disease is based on trials that include all types of soft tissue sarcomas. Doxorubicin based therapy is reported to have decent response rates – from 55 to 70%, and as much as 80% of the patients obtained stable disease with this type of treatment. However, even if the response is obtained, it is short-lived and reported overall survival in the metastatic setting is 1.2 years [12].

In these circumstances, the need for more efficient, targeted therapy is of utmost importance. Enrolment in clinical trials should be proposed to every patient with metastatic MPNST. One of the first pathways to be targeted was based on the observation that EGFR was overexpressed in many cases of MPNSTs, either NF-1 related of sporadic. However, a phase 2 trial showed no clinical benefit with erlotinib for metastatic MPNSTs [13].

Another tested possibility for targeted therapy was the combination of an antiangiogenic – bevacizumab with an mTOR inhibitor. 25 patients were enrolled in this trial, but the overall clinical benefit was only 12%, thus failing to continue testing this option [14].

In 2019, one particular tyrosine kinase inhibitor (TKI) – pexidartinib was associated with sirolimus in a phase 1 trial and the result was encouraging, with an important stable disease rate. The efficacy of this combination is to be tested in further trials [15].

The tumoral microenvironment is also a very attractive target, especially for soft tissue sarcoma. MPNSTs are no exception and some

important in vitro observations have been made recently: this environment always contains Schwann cells (quasi-normal ones), fibroblasts, perineural cells, and the heterozygosity for NF-1 for these cells, which play an important role in the malignant transformation. It was demonstrated that mice with heterozygous Schwann cells in the composition of plexiform neurofibroma are predisposed to malignant transformation rapidly, whereas homozygous ones only develop some hyperplastic lesions that interest cranial nerves. It is considered that this information is valuable for the prophylaxis of MPNSTs, but one therapeutic modality that targets these transformations has not been yet proposed [16].

The possibility to use oncolytic viruses for the treatment of soft tissue sarcoma is not a new idea. However, it is a very attractive therapeutic possibility since it triggers apoptosis directly by integration into the cell or indirectly by manipulating the immune system. Herpes viruses, for example, are more prone to infect RAS mutant cells, therefore it could be an interesting alternative for MPNST treatment, and phase 1 trials are under development [17].

Conclusion

Several advances have been made in better understanding the pathological and molecular development of MPNSTs. Even so, no standard of care that includes targeted therapy exists and chemotherapy remains the evidence-based option in both adjuvant and metastatic stages. Promising research is underway and aims to elucidate how to better trigger pathways in this disease. Personalized treatment and clinical trial enrolment should always be mandatory for these patients.

Conflict of Interest statements

Authors state no conflict of interest.

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