Current Status of Sporadic and Neurofibromatosis Type 1–Associated Malignant Peripheral Nerve Sheath Tumors

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Abstract

Malignant peripheral nerve sheath tumors (MPNSTs) are highly aggressive soft tissue sarcomas that rarely occur in the general population but have a lifetime incidence of 8% to 13% in those with neurofibromatosis type 1 (NF1). Complete surgical resection is the standard treatment for MPNSTs. Unresectable MPNSTs carry a poor prognosis, and survival appears to be worse in NF1-associated tumors than in sporadic tumors. The response rate of MPNSTs to standard chemotherapeutic agents used to treat pediatric and adult soft tissue sarcomas is unknown and is currently undergoing evaluation in a multi-institutional clinical trial. With an increasing understanding of the molecular pathogenesis of MPNSTs, clinical trials with targeted agents have become available and have established that histology-specific trials in this rare malignancy are feasible. This knowledge, coupled with the availability of preclinical MPNST models, likely will accelerate the development of effective treatments for this malignancy.

Introduction

Malignant peripheral nerve sheath tumors (MPNSTs), also called neurogenic sarcomas, malignant schwannomas, and neurofibrosarcomas, are soft tissue sarcomas that arise from a peripheral nerve or show nerve sheath differentiation and are associated with a high risk of local recurrence and hematogenous metastasis [1]. They account for 10% of all soft tissue sarcomas, and half of these malignancies arise in individuals with neurofibromatosis type 1 (NF1). Early diagnosis of MPNSTs is crucial, because only complete surgical resection has been shown to be curative. For NF1-associated MPNSTs, younger age at diagnosis and worse prognosis have been described [1–3]. This review describes the genetics and clinical manifestations of NF1 and the epidemiology, clinical presentation, diagnosis, and standard treatment of MPNSTs. Advances in the understanding of the molecular pathogenesis of MPNSTs are described, and the resulting histology-specific trials with targeted agents for MPNSTs are discussed.

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Epidemiology and Diagnosis of MPNSTs

MPNSTs account for 10% of all soft tissue sarcomas, and half of these malignancies arise in individuals with NF1, with a lifetime risk in NF1 of 8% to 13% [3]. Among individuals with NF1, those with a microdeletion of the *NF1* locus may have a higher incidence of MPNSTs [4]. The diagnosis of an MPNST should result in detailed clinical evaluation for NF1, unless this diagnosis is already established.

NF1, previously referred to as von Recklinghausen disease, is a relatively common (1:2500–1:3000) autosomal dominant, progressive tumor predisposition syndrome [5•,6,7]. It is caused by a mutation in the *NF1* tumor suppressor gene on chromosome 17q11.2, which comprises 60 exons spanning 350-kb genomic DNA [5•,6]. The gene product neurofibromin (2818 amino acids) contains a domain with significant homology to *ras* GTPase-activating proteins and thus regulates Ras activity. Neurofibromin accelerates Ras–guanosine triphosphate hydrolysis and thus functions as a potent negative regulator of Ras. Lack of functional neurofibromin in NF1 therefore leads to dysregulated Ras and tumorigenesis [8]. NF1 has 100% penetrance but features variable expressivity. The diagnosis of NF1 is based on clinical criteria including café-au-lait macules; axillary and inguinal freckling; presence of NF1-related tumors such as dermal neurofibromas, the hallmark clinical finding in NF1; and a family history of NF1 and can typically be made by 6 years of age [9]. Many *NF1* gene mutations but very few genotype–phenotype correlations have been described. Mutation analysis of the *NF1* gene in a Clinical Laboratory Improvement Amendments–certified laboratory has recently become available and allows identification of 95% of mutations, with a wide spectrum of mutations [10]. However, knowledge of the specific *NF1* mutation currently does not affect treatment decisions for individuals with NF1.

Importantly, individuals with NF1 have an increased risk of developing tumors of the central and peripheral nervous systems, including plexiform neurofibromas (25%–44%), dermal neurofibromas (> 99%), optic pathway gliomas (15%), brain tumors (2%–3%), MPNSTs (8%–13%), juvenile myelomonocytic leukemia (rarely), pheochromocytomas (2%), and rhabdomyosarcomas (1.5%–6%) [3,11,12].

Plexiform neurofibromas are benign nerve sheath tumors that grow along the length of nerves and involve multiple branches of a nerve [11]. These tumors are usually diagnosed early in life but may develop throughout life. Morbidity from plexiform neurofibromas includes substantial disfigurement, compression of vital structures, progressive neurologic deficit, and often unremitting pain. In addition, plexiform neurofibromas can undergo degeneration to MPNSTs, and most MPNSTs in NF1 develop in preexisting plexiform neurofibromas [1,13]. The only standard treatment for plexiform neurofibromas is surgery. However, given the location, infiltrative nature, high vascularity, and size of plexiform neurofibromas, complete surgical removal usually is not feasible, and up to 44% of tumors progress after the first surgery, most commonly in patients younger than 10 years with head and neck tumors [14]. There is no known effective medical treatment for patients with plexiform neurofibromas, but clinical trials with targeted agents have become available [15].

Early diagnosis of MPNSTs is crucial, because only complete surgical resection has been shown to be curative. However, the diagnosis of MPNSTs in NF1 is difficult to establish because clinical indicators of malignancy, such as pain, a growing mass, and neurologic compromise, may also be features of preexisting benign plexiform neurofibromas. The development of an MPNST within a plexiform neurofibroma may require several biopsies to successfully sample the malignant portion of the tumor (Fig. 1). Plexiform neurofibromas demonstrate high signal intensity on fat-suppressed MRI sequences and often show central areas of lower signal intensity (central dot sign) (Fig. 1). This may be lost in areas of malignant degeneration, and MPNSTs appear more heterogeneous. Heterogeneous enhancement on contrast-enhanced MRI may suggest malignancy [16]. [18]Fluorodeoxyglucose positron emission tomography (FDG-PET) has been identified as a sensitive and specific tool to assist in the diagnosis of NF1-associated MPNSTs [17••]. FDG-PET also may aid in establishing the diagnosis of MPNSTs by determining the area of greatest FDG uptake for a biopsy [18]. In addition, whole-body MRI is being evaluated as a tool to monitor the neurofibroma burden in NF1 over time with the goal to identify malignant degeneration [19•,20]. Studies suggest that the presence of internal neurofibromas, high whole-body neurofibroma burden [20,21], and the presence of numerous subcutaneous neurofibromas [22] may be associated with a greater risk for MPNST development.

The epidemiology and outcome of NF1-associated MPNSTs may be different from those of sporadic MPNSTs in that several studies report a younger age at diagnosis and worse prognosis for NF1-associated MPNSTs (Table 1). Reasons for the potentially worse outcome of NF1-associated MPNSTs are unknown. Two studies indicate that NF1-associated MPNSTs may develop more frequently as central nonextremity lesions, which might affect outcome because central lesions are less amenable to surgery [23,24]. A recently published large retrospective review of 126 individuals with MPNSTs treated in Italian and German studies between 1975 and 1998 found that response to chemotherapy was lower in NF1-associated MPNSTs (3 of 17 individuals [17.6%] responded) than in sporadic MPNSTs (26 of 47 [55.3%] responded). Details regarding the chemotherapeutic agents used were not provided [2]; however, it is not clear that NF1-related MPNSTs have a worse prognosis when adjustments are made for the known prognostic features. For example, one recent study describes excellent survival in patients with MPNSTs, with no difference between sporadic and NF1-associated tumors [25]. Potential reasons for the favorable survival compared with other reports are not discussed in this report, but 70% of the MPNSTs described were extremity lesions, compared with 30% in a central location. Although NF1-associated MPNSTs appear to have a worse outcome than sporadic tumors, gene expression profiling of NF1-associated (n = 25) and sporadic (n = 17) MPNSTs did not identify a molecular signature that could reliably distinguish between the two types [26].

Postirradiation MPNSTs, which have been described with an incidence of 5% to 11% [18], are associated with poor outcome. The potentially greater risk for individuals with NF1 to develop MPNSTs after radiation led to the recommendation that these patients avoid radiation if possible [27].

The diagnosis of MPNSTs can be established only by histopathologic evaluation. Two commonly used grading systems are the US National Cancer Institute system [28] and the Federation National des Centres de Lutte Contre le Cancer, developed by the French Federation of Cancer Centers Sarcoma Group [29]. Both systems evaluate the tumor's histologic type or subtype and amount of necrosis but also consider cellularity, nuclear pleomorphism, and mitosis. Most MPNSTs are high-grade tumors, and only MPNSTs with perineurial cell differentiation are low grade [30]. MPNSTs are spindle cell neoplasms. MPNSTs with rhabdomyoblastic or other divergent differentiation, called malignant triton tumors [31], may have a more aggressive clinical course than other MPNSTs [32]. Immunohistochemical stains against several antigens, including S-100, Leu7, CD34, p16, p53, p27, MIB-1, and topoisomerase IIα (TOP2A) [13], are used to delineate MPNSTs. A high Ki67 proliferation index (> 25%) was reported to be associated with reduced survival in patients with MPNSTs [33].

Like other soft tissue sarcomas, MPNSTs are most commonly staged using the American Joint Committee on Cancer staging system [34], which includes tumor grade (1–4), tumor size (5 cm or 5 cm), location (superficial versus deep), and the presence of distant metastases at the time of diagnosis. Large tumor (> 5 cm), deep location, and the presence of distant metastases are associated with poor outcome. Based on a postoperative nomogram for the 12year sarcoma-specific death risk, the presence of an MPNST carries the highest risk of sarcoma-specific death compared with other histologic types of soft tissue sarcoma [35].

The most frequent sites of MPNST metastasis are lung, liver, brain, soft tissue, bone, regional lymph nodes, and retroperitoneum [23]. Thus the diagnostic evaluation should include MRI of the primary lesion and CT of the chest to evaluate for pulmonary parenchymal disease. In individuals with NF1 and large neurofibroma burden, FDG-PET scanning may be of value as a baseline study before initiating therapy.

Treatment of MPNSTs

Treatment of MPNSTs follows the treatment of other adult soft tissue sarcomas. Only complete surgical resection has been shown to be curative, and it remains the cornerstone of therapy [34,36]. The goal of surgery is to resect the MPNST with wide negative margins. However, the local recurrence rate of MPNSTs is high, ranging from 32% to 65% [18]. Radiotherapy is used in situations in which the sarcoma is not amenable to surgical resection, but when radiotherapy is used as primary treatment, large doses are needed and the control rate is only 30% to 60%. Clinical trials have demonstrated that external beam radiation or brachytherapy in addition to limb-sparing surgery improves local control in patients with soft tissue sarcomas [37,38]. Thus, adjuvant radiotherapy is recommended to improve local control for intermediatet- high-grade lesions greater than 5 cm after a marginal excision [5•,37,39].

The role of chemotherapy for MPNSTs is not yet defined. In adult soft tissue sarcomas, only doxorubicin, dacarbazine, and ifosfamide were consistently associated with response rates of 20% or more in patients with soft tissue sarcomas, and the combination of ifosfamide and

doxorubicin produced response rates as high as 46% [40]. However, adjuvant doxorubicinbased chemotherapy did not demonstrate statistically significant improvement in overall survival [40]. In patients with advanced metastatic soft tissue sarcomas, doxorubicin and ifosfamide have the highest activity. The overall response rate for single-agent doxorubicin was 19% (range, 16%–27%), and for ifosfamide, response rates of 36% and 28% were reported [40,41].

Responses to chemotherapy have been described in children and adults with MPNSTs [42–44], but the response rate of MPNSTs to chemotherapy has not been determined prospectively. These tumors are thought to have intermediate chemosensitivity and to be less responsive than synovial sarcoma but more responsive than refractory diseases such as alveolar soft part sarcoma [45].

A recent retrospective review of individuals with MPNSTs described better response to ifosfamide-containing regimens and less response to chemotherapy for those with NF1-associated MPNSTs compared with those with sporadic MPNSTs [2].

The primary objective of an ongoing US Department of Defense–sponsored phase 2 clinical trial is to prospectively determine the rate of response of high-grade unresectable chemotherapy-naïve MPNSTs to standard chemotherapy agents (doxorubicin, ifosfamide, and etoposide) used to treat pediatric and adult sarcomas. Because the response to chemotherapy may differ between sporadic and NF1associated tumors, this trial stratifies for the presence of sporadic versus NF1-associated MPNSTs. Depending on its outcome, this trial may serve as a platform for future targeted therapies for MPNSTs.

Molecular Features of Tumorigenesis

With an increasing understanding of the molecular pathogenesis of MPNSTs, targeted treatment trials have become available. Surgical specimens and cell lines from patients with MPNSTs and NF1 demonstrate complete inactivation of NF1 and high levels of Ras activity [46–48]. Benign plexiform neurofibromas also demonstrate complete inactivation of *NF1*, with evidence suggesting that the Schwann cells represent the neoplastic element [49,50]; therefore, additional genetic alterations and abnormalities of other pathways likely contribute to progression to malignancy. Immunohistochemical analysis and molecular studies have implicated p53, p16, p27, and epidermal growth factor receptor (EGFR) as potential contributors to malignant transformation in peripheral nerve sheath tumors [1,51]. Further highlighting the unique pathogenesis of this tumor type, *NF1* and homozygous *p16* deletions appear to be relatively restricted to MPNSTs compared with other spindle cell sarcomas with overlapping morphologic features [51].

EGFR has been identified as an upstream activator of Ras in NF1. Although EGFR normally is not expressed by normal Schwann cells, its expression was demonstrated in benign neurofibromas, MPNST cell lines established from NF1 patients [52], and tumor cell lines derived from *Nf1: p53* mice. Cell lines responded to epidermal growth factor with activation of the downstream signaling pathways. The growth of these cell lines could be blocked by an EGFR antagonist [53]. EGFR's potential role in peripheral nerve tumor formation was

subsequently demonstrated in transgenic murine Schwann cells expressing EGFR, which elicited features of neurofibromas. In addition, genetic reduction of EGFR in $Nf1^{+/-}$ $p53^{+/-}$ mice that developed sarcomas significantly improved survival [54]. In individuals with MPNSTs, overexpression of EGFR was associated with worse outcome [55].

Angiogenesis also has been implied in MPNST progression. Mutations in *ras* can upregulate vascular endothelial growth factor (VEGF) expression [56,57], and VEGF and basic fibroblast growth factor also are highly expressed in neurofibromas from patients with NF1 at the mRNA and protein levels [58]. Furthermore, VEGF expression and tumor vascularization are significantly increased in MPNSTs [59]. Use of a specific small molecule inhibitor of VEGF receptor 2 in a mouse explant model of neurogenic sarcomas showed a reduction in tumor growth due to decreased tumor angiogenesis with subsequent reduction in tumor cell proliferation and an increase in apoptosis [59].

Recent studies have demonstrated that *NF1* regulates mammalian target of rapamycin (mTOR) pathway activation. *NF1* loss in mouse embryonic fibroblasts and primary mouse astrocytes resulted in Ras- and phosphoinositide 3kinase/Akt–dependent mTOR pathway activation, which could be inhibited by sirolimus [60,61]. Increased proliferation associated with loss of neurofibromin expression in human MPNST cell lines also was reduced dramatically with sirolimus treatment [61]. Using a genetic mouse model of NF1-deficient MPNST development, sirolimus completely inhibited the growth of these tumors in vivo [62••]. Similarly, the mTOR inhibitor RAD001 decreased growth in MPNST cell lines and prevented growth of subcutaneously implanted MPNSTs in mice [63]. A negative feedback loop between mTOR and Akt was not found in an NF1 optic glioma and in MPNST preclinical models after treatment with sirolimus [62,64].

Microarray analysis of MPNSTs recently identified *TOP2A* as the most overexpressed gene in MPNSTs compared with benign neurofibromas, and *TOP2A*-expressing tumors were associated with poor cancer-specific survival and the presence of metastasis [65]. Topoisomerase II is a primary target for several anticancer agents, including doxorubicin and etoposide. Thus there is a strong rationale for evaluating etoposide (in addition to doxorubicin) in MPNSTs, and the ongoing chemotherapy trial for individuals with chemotherapy-naïve MPNSTs includes both agents.

Gene expression profiling, immunohistochemistry, and/or Western blot analysis of human MPNSTs showed expression/overexpression of EGFR [26], platelet-derived growth factor receptor (PDGFR)-α and PDGFR-β [66,67], c-Kit [67,68], and matrix metalloproteinase 13 (MMP13) [69]. To identify events contributing to malignant transformation, several studies were performed comparing human Schwann cells with MPNSTs [70••] and plexiform neurofibromas with MPNSTs [65,70••,71,72]. The studies determined that MPNSTs differentially expressed neural crest stem cell markers SOX9 and TWIST1 [70••]; genes involved in cell proliferation (*MKI67*, *TOP2A*, *CCNE2*), apoptosis (*BIRC5/Survivin*, *TP73*), and extracellular matrix remodeling (*MMP13*, *MMP9*); and genes involved in the Ras (*RASF2*, *HMMR/RHAMM*) and Hedgehog-Gli signaling pathways (*DHH*, *Ptch2*). In addition, high-resolution array comparative genomic hybridization was used to compare dermal neurofibromas, plexiform neurofibromas, and MPNSTs. This technique revealed

amplification of some genes, including *PDGFRA*, *MET*, *TP73*, and *HGF*, and deletions in *NF1*, *MMP13*, *p16INK4A*, and *TP53*, demonstrating its potential in identifying MPNST markers [73]. Analysis for somatic mutations in MPNSTs from NF1 patients showed loss of heterozygosity across the *TP53* region and *TP53* mutation in 14 of 20 tumors [74].

Preclinical and Clinical Trials in MPNSTs

Until recently, few histology-specific clinical trials for MPNSTs were performed. A phase 2 trial of the EGFR inhibitor erlotinib was completed recently in patients with NF1-associated and sporadic MPNSTs [75]. Although erlotinib did not demonstrate activity in MPNSTs, this study demonstrated that timely completion of MPNSTspecific trials is feasible [75]. A phase 2 trial of sorafenib, an inhibitor of Raf kinase and other receptor tyrosine kinases, in adults with several soft tissue sarcoma strata, including an MPNST stratum, was completed recently and reported two minor responses in MPNSTs [76]. These trials required multiple participating sites with sarcoma expertise for completion. A recently established Department of Defense–sponsored NF Consortium has as its primary goal the development of an infrastructure for the timely conduct of NF clinical trials, and it may facilitate trials for individuals with MPNSTs. Likewise, the Children's Tumor Foundation is funding a preclinical NF consortium to accelerate the identification of effective therapies for NF-associated tumors. The availability of xenograft [63] and transgenic NF1 MPNST mouse models [62••,77] will allow researchers to validate candidate drugs in these models, with the goal of moving the most promising agents to clinical trials [78•].

Conclusions

MPNSTs are highly aggressive soft tissue sarcomas associated with poor outcome, particularly in individuals with the genetic tumor predisposition syndrome NF1. Although complete surgical resection remains the cornerstone of curative treatment, recent advances in the understanding of the molecular pathogenesis of MPNSTs have led to the first targeted treatment trials for MPNSTs. This, coupled with an organized approach toward evaluation of targeted agents in preclinical models of MPNST, will likely accelerate the development of effective treatments for this malignancy.

Acknowledgment

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Figure 1.
Malignant peripheral nerve sheath tumor arising in a neck/brachial plexus plexiform neurofibroma, shown on coronal short T1 inversion recovery MRI. The "central dot sign" *(1)* is not present in the malignant portion of the tumor *(2)*.

Table 1.

Epidemiology and outcome of sporadic versus neurofibromatosis type 1–associated malignant peripheral nerve sheath tumors

Study	Patients, n		Average age at diagnosis, y		5-Year survival, %	
	NF1	Sporadic	NF1	Sporadic	NF1	Sporadic
Sordillo et al., 1981 [24]	65	100	32	48	23	47
Ducatman et al., 1986 [23]	62	58	29	40	16	53
Hruban et al., 1990 [79]	23	20	36	44	38	42
deCou et al., 1995 [80]	11	17	13	16		39
Wong et al., 1998 [39]	32	102		37	36	57
Evans et al., 2002 [3]	21	37	26	62	21	42
Cashen et al., 2004 [25]	18	62	31	37		85 *
Carli et al., 2005 [2]	29	138	—	—	32	55

*
At 11 years, there was no difference between sporadic and NF1-associated malignant peripheral nerve sheath tumors. NF1—neurofibromatosis type 1.