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Analysis of treatment sequence and outcomes in patients with relapsed malignant peripheral nerve sheath tumors

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Abstract

Background. Malignant peripheral nerve sheath tumors (MPNST) are aggressive soft tissue sarcomas originating from cellular components within the nerve sheath. The incidence of MPNST is highest in people with neurofibromatosis type 1 (NF1), and MPNST is the leading cause of death for these individuals. Complete surgical resection is the only curative therapeutic option, but is often unfeasible due to tumor location, size, or presence of metastases. Evidence-based choices of chemotherapy for recurrent/refractory MPNST remain elusive. To address this gap, we conducted a retrospective analysis of our institutional experience in treating patients with relapsed MPNST in order to describe patient outcomes related to salvage regimens.

Methods. We conducted a retrospective electronic health record analysis of patients with MPNST who were treated at Johns Hopkins Hospital from January 2010 to June 2021. We calculated time to progression (TTP) based on salvage chemotherapy regimens.

Results. Sixty-five patients were included in the analysis. Upfront therapy included single or combined modalities of surgery, chemotherapy, or radiotherapy. Forty-eight patients received at least 1 line of chemotherapy, which included 23 different regimens (excluding active clinical studies). Most patients ($n = 42$, 87.5%) received a combination of doxorubicin, ifosfamide, or etoposide as first-line chemotherapy. Salvage chemotherapy regimens and their TTP varied greatly, with irinotecan/temozolomide-based regimens having the longest average TTP (255.5 days, among 4 patients).

Conclusions. Patients with advanced or metastatic MPNST often succumb to their disease despite multiple lines of therapy. These data may be used as comparative information in decision-making for future patients and clinical trials.

Key Points

- Physician-selected chemotherapy regimens to treat relapsed malignant peripheral nerve sheath tumors (MPNST) have variable outcomes.
- Modest responses to irinotecan and temozolomide-based combinations were observed in several patients.
- When possible, patients with relapsed MPNST should be offered enrollment in clinical trials.

Importance of the Study

Outcomes for patients with malignant peripheral nerve sheath tumors (MPNST) remain poor, particularly in those with metastatic or recurrent disease, and MPNST is the leading cause of mortality in patients with neurofibromatosis type 1 (NF1). There is currently no evidence-based choice of therapy for patients with relapsed or refractory disease. To address this knowledge gap, we conducted a retrospective analysis of our single-institutional experience treating patients with relapsed MPNST. Our cohort of 65 patients represents one of the largest cohorts of patients with MPNST reported to date and is an important contribution to the literature to guide physicians in choosing regimens for this hard-to-treat population. Our study provides comparative information for decision-making for future patients and can inform the design of future clinical trials for MPNST.

Background

Malignant peripheral nerve sheath tumors (MPNST) are rare, aggressive soft tissue sarcomas (STS) of the nervous system with an estimated incidence of 1.46 per 1 million individuals.[1] Approximately 50% of cases occur in patients with neurofibromatosis type 1 (NF1) and another 10% are associated with prior radiation exposure, while the remaining 40% occur without an identifiable predisposition (sporadic MPNST).[2] The peak age of incidence of NF1-associated MPNST is the third and fourth decade of life, earlier than that of sporadic tumors which often occur in the seventh decade of life or later.[3]

Outcomes for patients with MPNST remain poor, especially in those with metastatic or recurrent disease. Reported 5-year overall survival (OS) rates for localized disease range from 35% to 62% and for metastatic disease, as low as 7.3%.[4,5] Currently, the only curative treatment is surgical resection with wide margins for localized disease; however, oncologic surgery is often not feasible due to tumor size or location among nerve bundles. About half of patients who receive curative-intent treatment for localized MPNST will experience progression to metastatic disease.[5–7] MPNST are more chemo-resistant compared to other STS. Phase II clinical trials have shown limited, but not durable, responses to combinations of doxorubicin, ifosfamide, and etoposide for newly diagnosed disease.[8] Radiotherapy at high doses is sometimes used for tumors 5 cm or greater and in the presence of microscopic positive margins, or gross residual tumor after resection, although evidence for its efficacy remains limited.[4,9,10] There is currently no FDA-approved chemotherapy for the treatment of MPNST.

In the past 2 decades, advances in the understanding of MPNST molecular biology have led to preclinical studies of targeted therapies that appear promising in cell-based and animal-model systems. Recurrent genomic alterations, most often loss-of-function events in tumor suppressors, are known to drive MPNST tumorigenesis and include alterations in *NF1*, *CDKN2A/B*, *TP53*, and the polycomb repressive complex (PRC2) genes *EED* and *SUZ12*.[11–14] Other putative genomic drivers of tumorigenesis include *TYK2*, *BRAF*, and receptor tyrosine kinases such as MET and EGFR. These discoveries provide opportunities for new therapeutic targets; however, tailored cytotoxic therapies and novel molecularly targeted therapeutics tested in clinical trials have not achieved clinical success.[15,16] Current treatment algorithms often follow that of general STS, based partly on physician choice, anecdotal experience, patient performance status, and comorbidities. These regimens have variable efficacy in the treatment of metastatic MPNST.[17] There are no data comparing the full menu of systemic therapies available for salvage treatment of recurrent or progressive MPNST. Here, we report our single-institutional experience in the treatment of patients with relapsed or refractory MPNST, with the goal of describing patient outcomes based on systemic chemotherapy regimens prescribed at the time of recurrent disease.

Patient and Methods

This retrospective electronic medical record study evaluated all patients diagnosed with MPNST who were treated at Johns Hopkins Hospital (JHH) from January 2010 to June 2021. Patients were included if they had a pathologically confirmed diagnosis of MPNST and received all or part of their treatment at JHH. Patients who received only surgical resection at JHH and had all additional therapy elsewhere were excluded. Clinical data were retrospectively obtained from medical records and included age, germline NF1 status, date of diagnosis, location of primary tumor, location of known metastasis, pathology reports, tumor genetic information, treatment course (ie, surgeries, chemotherapy, and radiation therapies), local and distant relapses, and date of death. Chemotherapy regimens, which encompassed systemically administered drugs with anticancer effects (ie, cytotoxic or conventional agents, targeted therapies, and immunotherapies), were recorded, including the combination of agents, dates of initiation, and duration each regimen. Particulars of dosage, length of cycles, and number of cycles administered were at the discretion of the treating physician. The institutional review board of Johns Hopkins University approved this retrospective clinical data extraction and analysis.

Possible outcomes as the next event after a particular line of therapy included remission, local or metastatic relapse, progressive disease, or death. Remission was determined in patients that have no evidence of MPNST burden at their last documented follow-up or at the time of our

data cutoff. Relapsed disease was defined as recurrence of disease (locally or metastatic, as seen on subsequent imaging) only after the completion of definitive treatment, as determined by the treating provider. Progressive disease, also referred to as refractory disease, was defined as evidence of increased disease burden during therapy that prompted change in treatment plan. OS was calculated from the date of diagnosis to the date of death from any cause or the last follow-up visit.

Results

Patient Characteristics

Between January 2010 and June 2021, 76 patients at JHH were diagnosed with histologically proven MPNST. Eleven patients were excluded from the analysis due to lack of disease-directed therapy (n = 3) or lost to follow-up (n = 8). Lost to follow-up patients included those who received treatment recommendations at our institution and were subsequently treated elsewhere. Sixty-five patients received treatment for MPNST, of which 48 received at least 1 line of systemic chemotherapy (Figure 1). Our cohort included pediatric and adult patients, with a median age of 49 years (range 5–75 years). About two-thirds of patients had known germline *NF1* alterations or a clinical diagnosis of NF1. A majority of the patients (n = 40, 61.5%) had localized, high-grade MPNST at presentation, most commonly in the extremity (n = 16, 24.6%), followed by the head and neck (n = 12, 18.5%) and pelvic (n = 12, 18.5%) regions. A small number of patients (n = 9, 13.8%) had histologic variants identified in the tumor pathology (Table 1). The 5-year OS in our cohort was 51.7% with a median survival of 65 months (95% confidence interval [CI]: 36, NA) (Supplementary Figure S1A). The OS for patients with NF1 syndrome versus those without were similar (hazard ratio: 0.80; 95% CI: 0.35 to 1.80; P = .59) (Supplementary Figure S1B).

Upfront Therapy Choices and Outcomes

The most common upfront therapy included a combination of 3 modalities: surgery, chemotherapy, and radiotherapy (n = 22), followed by surgical intervention only (n = 16). We determined the immediate outcome following upfront therapy and categorized them as achieved remission, local or metastatic relapse, progressive disease while on therapy, or death as the next event (Figure 2). Most patients who achieved remission had surgery as part of their upfront therapy (n = 27/28, 96.4%), although only 49.1% (n = 28/57) of patients who had surgery as part of upfront therapy achieved remission. Overall, patients with MPNST received a variety of single or multimodal therapy as their upfront therapy and in our cohort, there was no apparent

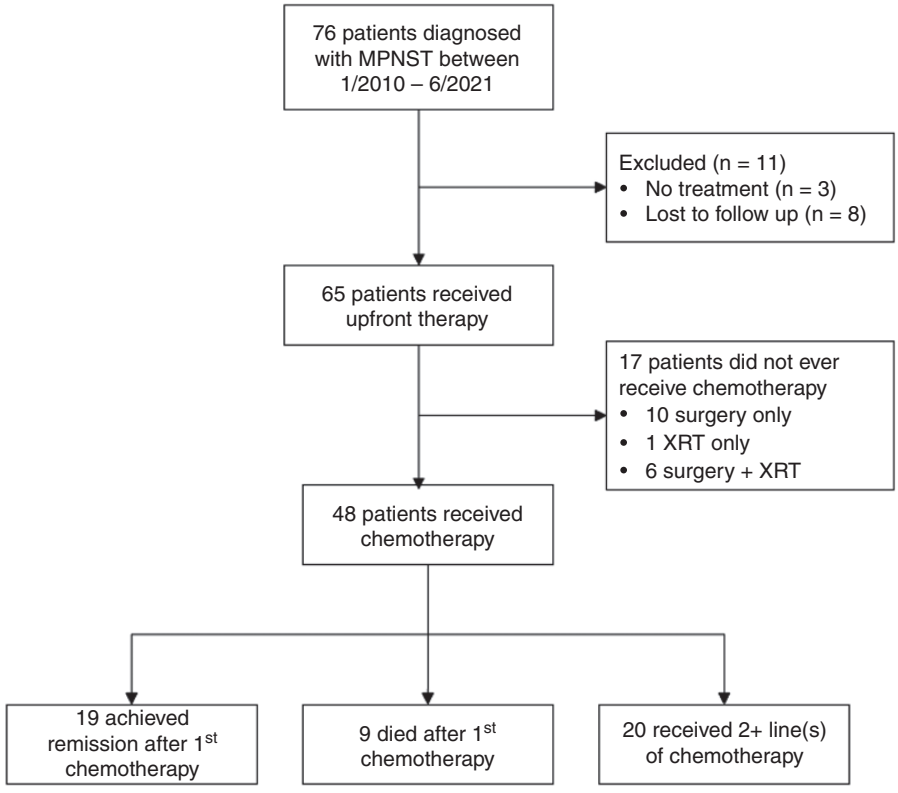

Figure 1. Patients included in our analysis. Seventy-six patients with histologically confirmed MPNST were identified, of which 11 were excluded due to not receiving any treatment for their diagnosed MPNST or were lost to follow-up. A total of 65 patients were included in our analysis. Abbreviation: XRT = radiation therapy

Table 1. Clinicopathologic Features of the Study Population, Including the Entire Cohort ($n = 65$) and Then Those That Achieved Remission ($n = 28$) or Had Relapsed or Progressive Disease ($n = 29$) Following Upfront Therapy

Characteristics		All Patients ($N = 65$)	After Upfront Therapy	
			Patients Who Achieved Remission ($n = 28$)	Patients Who Had Relapsed/ Progressive Disease ($n = 29$)
Age (median)		49 (range: 5–75)	37 (range: 5–75)	40 (range: 10–74)
Sex	Female	31	12	12
	Male	34	16	17
Germline NF1 mutation*	Yes	41	18	20
	No	24	10	9
Metastatic disease at diagnosis	Yes	8	1	5
	No	57	27	24
Grade by histology	Low	4	3	0
	High	51	22	23
	Not reported	10	3	6
Location of primary tumor	H&N	12	2	7
	Chest	6	3	2
	Abdomen	8	3	4
	Paraspinal	11	3	7
	Pelvis	12	5	6
	Extremity	16	12	3
Histologic subtypes	No variant histology reported	56	23	25
	Triton	5	3	2
	Epithelioid	1	1	0
	Other^	3	1	2
Outcome after upfront therapy	Remission	28		
	Relapsed disease	20		
	Progressive disease	9		
	Death	8		

Abbreviation: H&N = head and neck region.
*Germline NF1 mutation status was based on patients meeting clinical diagnosis criteria and/or confirmatory genetic sequencing results.
^Other histology included: 1. A mixed pattern of "bland spindled cells" and "small round blue cells with neuroblastoma-like rosettes." 2. A divergent differentiation with "heterologous elements in the form of well-differentiated glands, chondromyxoid changes and possible osteoid formation." 3. A component of "chondroid metaplasia."

correlation with clinical outcome. The choice of upfront therapy was multifactorial, often driven by multidisciplinary review, and tailored to address performance status, symptoms, location of tumor, and patient or physician preferences. These choices and their outcome did not vary with the presence of germline *NF1* mutation in our patient cohort (Supplementary Figure S2A).

In this cohort, 28 patients achieved remission following upfront therapy, 29 patients received additional therapy for relapsed/refractory disease (defined as relapsed or progressive disease), and 8 patients died after or during upfront therapy (of which 5 were due to disease progression). Table 1 shows the patient characteristics of those who achieved remission versus those who had relapsed/refractory disease. Of the 29 patients who had relapsed/refractory disease, 9 patients had progressive disease despite upfront therapy and 20 individuals initially achieved remission with a median time of 18 weeks (range 1 week to 4.6 years) to recurrence. A majority of these patients received chemotherapy, although 7 patients had surgical intervention and/or radiotherapy as part of their salvage regimen (3 had surgery, 2 had radiotherapy, and 2 had both modalities). These individuals received a median of 3 lines of therapy in total and up to 6 lines of therapy in 2 patients. One-third of patients who had non-NF1-associated MPNST and about half of patients with NF1-associated MPNST received multiple lines of therapy (Supplementary Figure S2B).

First-Line Systemic Chemotherapy

In total, 23 chemotherapy regimens were used among 48 patients who received systemic chemotherapy as any part of their treatment sequences (Figure 3A, B). The 8 patients who received 1 or more drugs as part of a clinical trial that does not yet have reported outcomes were excluded from this analysis. Of note, first-line systemic chemotherapy

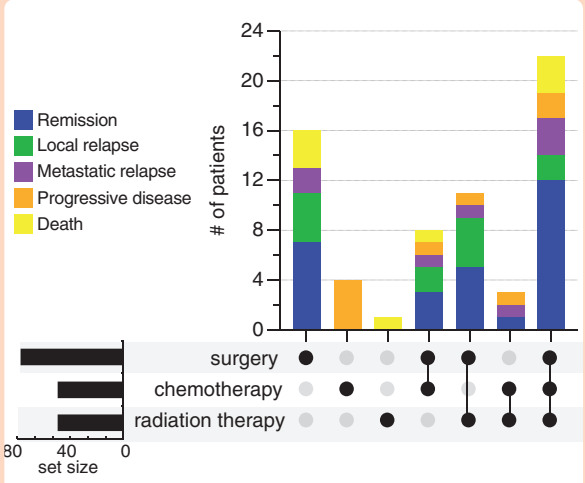

Figure 2. Clinical outcomes after upfront therapy. Patients are segregated as having received treatment modalities including surgery, radiation, or chemotherapy, or any combination of these, as indicated in the UpSet plot.[53] The immediate clinical outcome following upfront therapy for each patient was then categorized as remission, local or metastatic relapse, progressive disease while on therapy, or death.

was not always included as upfront treatment, and it is annotated in our study as the first-line chemotherapy regimen a patient received within the whole course of their treatment. Of the regimens analyzed, 8 were used as first-line chemotherapy (Figure 3A). A majority of patients (n = 41/48, 85.4%) received ifosfamide-based combinations, either as a single agent, in combination with doxorubicin, with or without etoposide (ie, ifos; ifos/doxo; or ifos/doxo + ifos/etop) as first-line chemotherapy. Some patients (n = 3/48, 6.3%) received single-agent pazopanib as first-line chemotherapy.

Time to the subsequent event, either disease progression or death, was used as a marker of clinical outcome following each chemotherapy regimen. The most common first-line regimens, ifos/dox and ifos/dox/etop, had longer average times to event, at 361.4 and 276.5 days, respectively, compared to salvage regimens (Figure 3A). This time course may reflect a prospective decision to treat with a defined number of cycles, such as 6 or 8, and a greater frequency of patients receiving multimodal therapy with first-line chemotherapy than with later salvage regimens.

Salvage Chemotherapy Choices and Outcomes

Twenty patients received salvage chemotherapy. There was overall more variation in second or greater line chemotherapy regimens (Figure 3B). Patients who received vincristine/irinotecan/temozolomide (VIT) (n = 3) had an average time to progression (TTP) or death of 317 days. This cohort included 1 patient who was initially receiving VIT plus metformin on a clinical trial,[18] for a total of 100 days, and subsequently stopped due to dose-limiting toxicity of metformin-related anorexia and continued with VIT only. Two additional patient received irinotecan/temozolomide (IT). One patient was actively in treatment at the time of data cuteoff and the other remained progression-free for over 300 days. Excluding the patient on active therapy, there were 5 instances of IT-based regimens among 4 patients, and these regimens had the longest TTP ranging from 14 to 47 weeks. Another notable regimen was pazopanib plus temozolomide, with an average TTP or death of 208.3 days in 3 patients. Overall, we observed a range of chemotherapy regimens for relapsed MPNST, and clinical outcomes were variable, with TTP or death ranging from 26 to 316.5 days. We also sought to further define the sequence of therapy for individual patients with relapsed disease and identify the reasons for stopping or changing chemotherapy regimens.

We analyzed the treatment sequences of 20 patients (3 non-NF1 MPNST, 17 NF1-associated MPNST; median age 28 years) who received at least 2 lines of chemotherapy to understand how patients responded to salvage regimens (Figure 4; all patients [n = 48] who received chemotherapy are included in Supplementary Figure S3). In this subgroup of patients, the OS was 45% and 20% at 12 and 24 months, respectively (Supplementary Figure S4). At the time of data cutoff, 4 patients were actively undergoing treatment, 15 patients had died due to disease progression or related complications, and 1 patient (patient #10) had died of a non-MPNST-related cause. After second-line chemotherapy, only 2 patients received other therapy modalities, consisting of surgery and radiation, or radiation alone, to metastatic sites.

Clinical next-generation sequencing (NGS) information was available from tumors of 8 of these 20 (Supplementary Table S1). Five tumors demonstrated mutations in *NF1* (all from patients with NF1 syndrome). Other notable mutations identified in clinical NGS included 4 instances of *CDKN2A/B* homozygous loss, 2 *SUZ12* alterations, and 1 *EED* alteration, recurrent genomic events that are commonly associated with MPNST.[19–21] Lower than expected frequencies of these mutations may be due to limitations of clinical NGS assays. Two patients (patient #29 and #35) received targeted therapies based on tumor sequencing results. One patient with a tumor with *EGFR* duplication received lapatinib as second-line therapy but experienced progression. Another patient, whose tumor harbored a gain-of-function *PIK3CA* mutation, received LY3023414 through single-patient compassionate use as third-line therapy and had rapid progression of disease.

Discussion

We conducted a retrospective analysis of patients with MPNST treated at JHH over a decade and report on clinical outcomes following physician-selected chemotherapy regimens. In our cohort, the most commonly administered first chemotherapy regimens were combinations of ifosfamide, doxorubicin, and/or etoposide. Doxorubicin plus ifosfamide was shown to have favorable outcomes over single-agent doxorubicin in patients with chemotherapy-naïve MPNST.[22] Similarly, the Children's Oncology Group phase II trial (ARST0332) assessed risk-adapted treatment outcomes in 529 pediatric patients with

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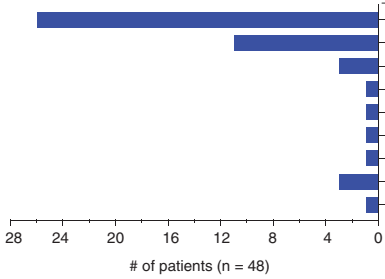

Chemotherapy regimen	Received on study	Avg time on therapy, days (range*)	Avg time to progression or death, days (range*)
Ifos + dox	N	101.3 (20–242)	361.4 (20–1895)
Ifos + dox + etop	N	113.5 (24–183)	276.5 (111–530)
Ifos + etop	N	47.7 (28–68)	180 (82–284)
Ifos	N	51	55
Dox	N	141	159
Gem + docetaxel + ontuxizumab	Y[54]	42	42
Everolimus + bevacizumab	N[55]	110	133
Pazopanib	Y [27,^]	59.7 (53–68)	68
Study drug(s) under investigation	Y[%]	112	186

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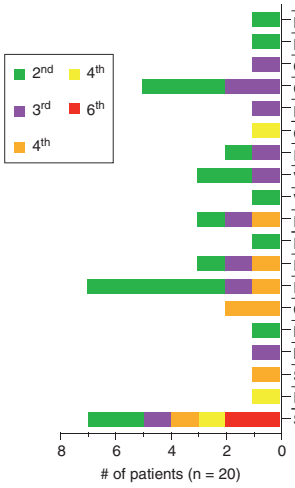

Chemotherapy regimen	Received on study	Avg time on therapy, days (range*)	Avg time to progression or death, days (range*)
Dox	N	20	36
Dox + olaratumab	Y[52]	48	63
Oral etop + cyclophosphamide	N	36	36
Gem + docetaxel	Y[53,#]	62.5 (28–94)	144 (34–385)
Docetaxel	N	108	108
Gem + dacarbazine	N	41	48
IT	N	56	313
VIT	N	194.7 (108–278)	316.5 (302–331)
VIT + metformin	Y[18]	100	100
Everolimus + bevacizumab	Y[55]	46 (38–51)	72.3 (58–100)
Everolimus + ganetespib	Y[42]	75 (47–103)	90.5 (49–132)
Pazopanib + temozolomide	N	166.3 (36–393)	208.3 (38–517)
Pazopanib	Y[27,^]	55.9 (33–119)	66.8 (26–93)
Cabozantinib	N	164	164
Lapatinib	N	77	62
LY3023414	N[&]	19	27
Selumetinib	N	26	26
Pembrolizumab	N	177	177
Study drug(s) under investigation	Y[%]	53.4 (7-124)	70.6 (15–124)

Figure 3. Time on therapy and time to progression associated with the chemotherapy regimens used in the treatment for MPNST as (A) first-line chemotherapy among 48 patients; and (B) salvage chemotherapy among 20 patients. Time on therapy includes time from start to end of therapy, in days. Time to progression or death includes time from start of therapy to the event, also measured in days. Where more than 1 patient received a regimen, values are reported as average (range in days); if only 1 patient received the regimen, the value in days is indicated for that patient. Some patients received multiple regimens as different lines of chemotherapy (second, third, fourth, fifth, or sixth), and these are indicated by color as shown in legend. Abbreviations: ifos = ifosfamide, dox = doxorubicin, etop = etoposide, gem = gemcitabine, IT = irinotecan, temozolomide, VIT = vincristine, irinotecan, temozolomide. *Ranges are included in groups that include more than 1 patient, but are not calculated for patients who remained on therapy at date of data cutoff. #2 of the 4 patients received this drug on study. ^1 of the 10 patients received this drug on study. &Received this drug through single-patient compassionate use based on the patient's tumor genetic testing results. %To date, the results from included clinical trials have not been published.

nonrhabdomyosarcoma STS, including 58 with MPNST, and showed benefit of neoadjuvant ifosfamide/doxorubicin and radiotherapy in patients with nonmetastatic, high-grade or initially unresectable tumors.[23] Subsequently, the SARC006 phase II clinical trial in pediatric and adult patients with MPNST demonstrated that neoadjuvant chemotherapy with ifosfamide, doxorubicin, and etoposide resulted in partial responses (PR, *n* = 9) and stable disease (SD, *n* = 24) in 48 patients with chemotherapy-naïve tumors.[8] These results suggested that upfront, neoadjuvant chemotherapy may improve outcomes and as a result, ifosfamide with doxorubicin and etoposide has become a common standard chemotherapy regimen used in patients with newly diagnosed MPNST for whom chemotherapy is considered appropriate. Another regimen that deserves consideration, but was not identified in our retrospective analysis, is neoadjuvant ifosfamide and epirubicin, which was associated with RECIST responses in 3 of 5 patients with MPNST in a single-institution retrospective cohort.[24]

The second most common upfront chemotherapy used in our patient cohort was the multi-tyrosine kinase inhibitor pazopanib. Although typically reserved for STS in the recurrent setting, its selection for some patients may be driven by the advantages of oral administration and good tolerability.[25,26] Pazopanib is a multitarget receptor tyrosine kinase inhibitor and is FDA-approved for patients with metastatic STS after failure of first-line treatment.[26] Less is known about its role as upfront therapy. One open-label, single-arm phase II study investigated the use of pazopanib as first-line therapy in patients with advanced STS and results showed a median progression-free survival (PFS) of 3.67 months with 1 complete response (CR) and 4 PR in 56 patients.[27] In addition, in ARST1321, a COG trial for patients with STS, patients with "chemotherapy-insensitive"

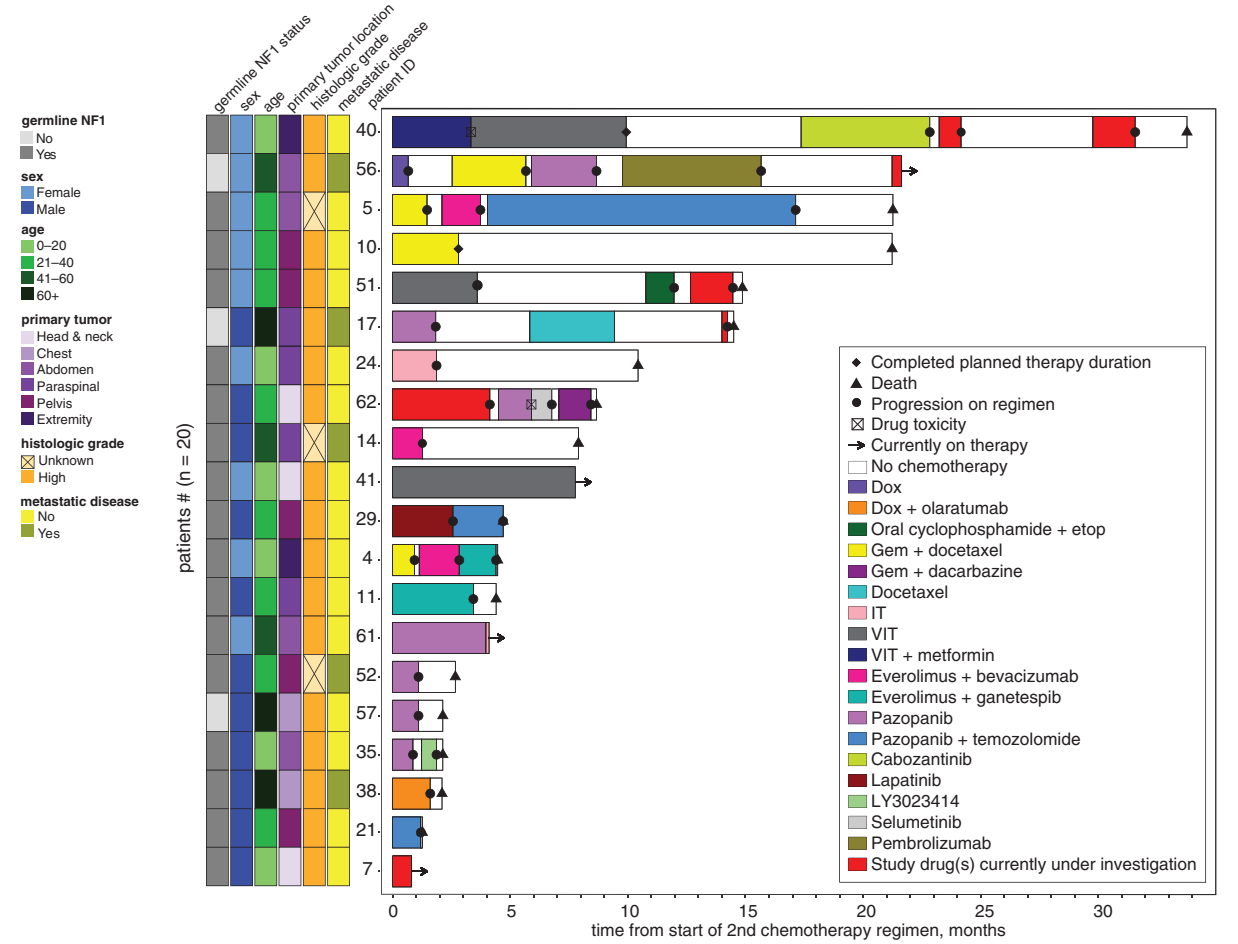

Figure 4. Sequence of salvage chemotherapy regimens used for patients with relapsed or refractory MPNST. Modified swimmer's plot representation includes patients (n = 20) who received at least 2 lines of systemic chemotherapy (including conventional or cytotoxic chemotherapy, targeted agents, or immunotherapy). Time starts at the beginning of the second-line systemic therapy. Regimens are shown in color, as indicated in the legend. White space indicates that the patient did not receive treatment during that time. Events are indicated by black symbols as shown in legend. Abbreviations: dox = doxorubicin, etop = etoposide, gem = gemcitabine, IT = irinotecan, temozolomide, VIT = vincristine, irinotecan, temozolomide.

tumors, including MPNST, were eligible for neoadjuvant pazopanib, which may have driven some interest in this treatment modality in our cohort.[28]

About half of the patients in our analysis who survived after upfront therapy for MPNST required salvage treatment for relapsed/refractory disease, consistent with reported literature.[29,30] Given the rarity of MPNST, additional chemotherapy regimens often follow algorithms established for general STS, and it is often included as a stratum within larger studies for STS. The disadvantage of this approach is that it fails to acknowledge the unique biology of diverse STS or harness the potential molecular vulnerabilities driving each sarcoma subtype. There is currently no comprehensive comparison of the available chemotherapy regimens used in clinical practice to treat patients with relapsed or refractory MPNST. Patient outcomes from a limited number of clinical trials in MPNST have been reported.[12,15–17,31] In 5 phase II trials conducted by the Sarcoma Alliance for Research through Collaboration (SARC) for patients with recurrent or refractory MPNST, no objective responses were seen and the longest SD duration of 24 weeks occurred in a single patient treated with gemcitabine and docetaxel on SARC002.[32] The median PFS for patients with MPNST on these 5 studies was 1.77 months.[16] Similarly, clinical trials using targeted agents for patients with MPNST (including erlotinib, sorafenib, imatinib, dasatinib, alisertib, bevacizumab/RAD001, ganetespib/sirolimus) demonstrated no objective responses and a median PFS of 1.7 months.[15] Our retrospective analysis had similar outcomes and a median PFS of 2.2 months in patients who received chemotherapy for relapsed or refractory MPNST.

Among the salvage chemotherapy regimens used in our patient cohort, IT-based regimens (VIT, VIT plus metformin, or IT) demonstrated the longest TTP or death, up to 47 weeks, in 4 patients. To date, there have been no clinical trials investigating the activity of irinotecan and temozolomide specifically in patients with recurrent

MPNST. Clinical studies have shown its efficacy in other relapsed/refractory solid tumors, with encouraging responses seen in Ewing sarcoma.[33–36] Our findings and previously reported clinical responses suggest that there is potential benefit for IT-based regimens in relapsed/refractory MPNST; this combination may warrant further exploration in future clinical trials.

A majority of the patients in this study had known NF1 syndrome, which was expected given the high volume of patients with NF1 treated at the Johns Hopkins Comprehensive Neurofibromatosis Center. Germline *NF1* mutations predispose patients to developing benign and malignant peripheral nerve sheath tumors. Studies looking at prognostic factors in MPNST have not consistently correlated known germline *NF1* mutations with poorer outcome.[4–6,37] However, the Italian and German Cooperative Group found that, in a series of 167 pediatric patients with MPNST, association with NF1 syndrome correlated with lower response to chemotherapy than non-NF1-associated tumors.[4] While SARC006 was not powered to detect a difference between sporadic versus NF1-associated MPNST response, lower response rates in NF1–MPNST were observed as well.[8] Our current study was also not statistically powered to find differences between NF1-associated and sporadic MPNST, but we observed that a higher proportion of patients with NF1 syndrome received greater than 2 lines of total therapy (17/41 NF1–MPNST versus 4/24 of non-NF1 MPNST). The OS between the 2 groups did not differ significantly; however, our study design limits our ability to draw any definitive conclusions regarding NF1 status. It is a reasonable speculation that underlying NF1 syndrome may alter responses to therapies given genomic and other biological differences in the tumors, and in these patients.[38]

A growing number of studies have unveiled the genetic and molecular aberrations driving MPNST, which have led to putative targets for therapeutic interventions. While earlier clinical trials using targeted therapies have not resulted in durable clinical benefit, improved preclinical models and ongoing multicenter collaborations have led to the identification of novel, rational therapies in the pipeline for future clinical trials with promising preclinical evidence.[39,40] For example, the mammalian target of rapamycin (mTOR) was shown to be essential in the tumorigenesis of NF1-deficient tumors and its inhibition effectively, but only transiently, decreased growth of MPNST cells in preclinical models.[41,42] Therefore, further studies have looked at combinatorial strategies such as the addition of heat shock protein 90 (Hsp90) inhibition,[43,44] colony-stimulating factor 1 receptor (CSF1-R) inhibition,[45] or dual mTOR complex 1 and 2 inhibition.[46] Additionally, signal transducer and activator of transcription-3 (STAT3) has also been implicated in MPNST oncogenesis and so, tyrosine kinase 2 (TYK2), involved in STAT protein activation, inhibitors in combination with mitogen-activated protein kinase kinase (MEK) inhibitors have shown potential in models of NF1-associated MPNST.[47] Recently, the src homology region 2 (SH2)-containing protein tyrosine phosphatase-2 (SHP2) has gained attention in its role in adaptive signaling driven by receptor tyrosine kinase activation and preclinical data in MPNST demonstrate therapeutic efficacy of combined inhibition of SHP2 and MEK[48] or cyclin-dependent kinase 4/6 (CDK4/6).[49] Additionally, there is a growing interesting in immunotherapeutic approaches in the treatment of MPNST, alone or in combination with molecularly targeted therapies, although no clinical trials have demonstrated overall benefits of immune checkpoint blockade (ICB) to date in MPNST. Novel approaches used in preclinical models that have shown efficacy include the combination of ICB with CDK4/6 and MEK inhibition[50] and the use of virus-based immunotherapy.[51] There is an ongoing phase I clinical trial studying the use of neoadjuvant nivolumab plus ipilimumab for newly diagnosed MPNST (NCT04465643). Further insights on the tumor immune microenvironment will identify additional potential tumor-intrinsic factors that define subsets of patients with MPNST for whom specific immune-based therapies are most appropriate.[52]

Upcoming and future clinical trials will aim to leverage these preclinical data to design targeted therapy strategies, and it will be pertinent to recruit suitable patients who may benefit from these novel small molecules or immunotherapeutics. In order to do so, genomic sequencing and assessment of all patient tumors is necessary. A study of 186 patients with MPNST in the Foundation Medicine archives showed that 47% of the patients had an alteration in at least 1 gene involved in the RAS signaling pathway (excluding *NF1* or *BRAF*) and 46% had alterations in the PI3K pathway, highlighting the benefit of genomic assessment for all patients with MPNST.[14] In our current cohort, 8 of the 20 patients who had recurrent MPNST had clinical sequencing data available, of which 2 patients received targeted therapies based on their findings. Given the small sample size of patients with available NGS, we were unable to draw any meaningful correlations between tumor genetics and treatment responses or efficacy. The low rate of tumor sequencing is likely due to the time frame of our retrospective analysis and the evolution of clinically available NGS techniques. There are ongoing, promising preclinical studies in the pipeline for clinical trials and standardizing the use of tumor genetic assessments will help direct the most appropriate patients to such clinical trials.

There are a few limitations to our study. It is a retrospective analysis of the practices in a single institution and was not powered to find statistical significance between treatment regimens. The retrospective nature of our analysis, with regimens largely driven by physician choice, also limits the ability to draw definitive conclusions. However, our practice benefits from a large comprehensive neurofibromatosis center, in collaboration with pediatric, medical, surgical, and radiation oncologists and multidisciplinary sarcoma and NF specialist team in the coordinated care of these patients.

Conclusion

In summary, we report our single-institution experience in the treatment of patients with relapsed and refractory MPNST. We identified modest responses to IT-based regimens in relapsed/refractory MPNST. Future clinical trials may be designed to enhance further analysis of the effectiveness of these regimens, as well as the combination of chemotherapy along with novel targeted therapies that appear promising in preclinical models. Patients with

relapsed and refractory MPNST should be enrolled in clinical trials when possible.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

chemotherapy | malignant peripheral nerve sheath tumors | neurofibromatosis type 1 | salvage therapy | soft tissue sarcoma

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Conflict of Interest

K.M.L is an inventor on the patent (WO2022046910) for prodrugs of 6-Mercaptopurine (not relevant to the current manuscript). C.A.P. is an inventor on the patent application (WO2022234409A1) held/submitted by the Johns Hopkins University and Novartis that covers compounds and compositions for the treatment of MPNST (not relevant to the current manuscript). C.A.P. is a recipient of research grants from Novartis (not relevant to the current manuscript) and Kura Oncology (not relevant to the current manuscript) and has received consulting fees from Day One Therapeutics and Genentech (not relevant to the current manuscript). C.F.M. received royalties from UpToDate (not relevant to the current manuscript). J.O.B is a national co-investigator for clinical trials supported by Alexion, SpringWorks, and Takeda (none are relevant to this current manuscript). The other co-authors declare that they have no competing interests.

Authorship

Conceptualization: L.Z., K.M.L., C.A.P. Methodology: L.Z., K.M.L., A.C., R.V., A.H.S., C.F.M., J.O.B., C.A.P. Investigation: L.Z., K.M.L., A.C., R.V., A.H.S., C.F.M., J.O.B., C.A.P. Visualization: L.Z., K.M.L., A.C., J.O.B., C.A.P. Supervision: C.A.P. Writing—original draft: L.Z., K.M.L., C.A.P. Writing—review & editing: L.Z., K.M.L., A.C., R.V., A.H.S., C.F.M., J.O.B., C.A.P.

Data Availability

Deidentified data generated in this study can be made available upon reasonable request to the corresponding author.

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