ORIGINAL RESEARCH

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Multimodality Treatment in Malignant Peripheral Nerve Sheath Tumors

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ABSTRACT Objective: Malignant peripheral nerve sheath tumors (MPNSTs) are rare soft tissue sarcomas with poor prognosis. The treatment options, especially in metastatic cases, are limited. In this study, we aimed to investigate the treatment outcomes along with programmed death-ligand 1 (PD-L1) expression as a potential surrogate for immunotherapy benefit in our patients with MPNST. **Material and Methods:** In this retrospective study, 27 patients diagnosed with MPNST and treated at the Hacettepe University Cancer Institute between 2000 and 2016 were evaluated. Patient and tumor characteristics, survival data and treatment modalities were obtained from medical charts. The patient outcomes were assessed based on the treatment modality. Slides prepared from 4-mm diameter microarray tissue were stained for the PD-L1 antibody using Leica Bond Autostainer (Cell Signaling, E1L3N®). Membranous staining more than 5% of the cells were accepted as positive. **Results:** The median age of the patients was 36 years (range 19-89 years), and 37% of patients were male. The median tumor size was 8.7 cm, and 62% of patients had high-grade tumors. The most common tumor localizations were extremities (41%), trunk (48%), and the head-neck region (11%). Only two patients (7%) had distant metastases at the time of diagnosis. Seven patients (26%) had neurofibromatosis type 1 (NF1) and the presence of NF-1 was associated with partially worse overall survival (p=0.056). The majority of the patients underwent primary surgery (96.3%), and R0-R1 resection was achieved by 76% of patients. The median follow-up was 16 months (range 1 to 178 months). During the follow-up, 16 patients (59%) had recurrence (37% local, 22% distant recurrence). A 3-year disease-free survival (DFS) rate according to R0-R1 and R2 resection was 57% vs. 17%, respectively (p<0.001). After surgery, 48% of the patients received adjuvant therapy. Two patients (7%) received only chemotherapy, five patients (19%) received only radiotherapy (RT), and six patients (22%) received both. Patients who received both chemotherapy and RT had longer DFS compared to those who received either therapy alone and to those who received no adjuvant therapy (3-year DFS 100% vs. 14% vs. 44%, respectively, p=0.003) (Figure 3). PD-L1 expression was positive in 6 of 15 patients (40%) and was not associated with DFS. **Conclusions:** Multimodality treatment with surgery, chemotherapy, and RT may improve DFS in patients with MPNSTs. The PD-L1 expression is not associated with DFS.

Keywords: Malignant peripheral nerve sheath tumor; multimodality treatment; PD-L1 expression

Malignant peripheral nerve sheath tumor (MPNST) is an uncommon soft tissue sarcoma that originates from the peripheral nerves and is hypothesized to be of neural crest origin.[1] The incidence of MPNST is 1:100.000/year and accounts for 5-10% of all soft tissue sarcomas.[2] Approximately 50% of MPNSTs occur sporadically, the remaining arises secondary to prior radiation exposure and in patients with neurofibromatosis type 1 (NF1).[3-5] In the NF1 patients, MPNST usually originates from plexiform neurofibromas and atypical neurofibromas. The lifetime risk of developing MPNST in these patients is around 8-13%.[5-8] MPNSTs often arise from large and medium-sized nerves, located in the extremities in 33-

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46% of the patients, the truncal region in 31-41% and the head/neck region in 17-25%. MPNSTs are mostly high-grade with aggressive behavior.[9] For all patients with high-grade MPNST, overall 5-year survival rates range from 20% to 50% and with a mortality rate of up to 75%.[1,10] Current treatment for high grade localized MPNSTs is surgical resection with wide negative margins and adjuvant radiotherapy (RT). However, RT only reduces local recurrence risk but does not improve overall survival (OS).[11] Administration of adjuvant or neoadjuvant chemotherapy in the treatment of MPNSTs is still controversial.[12-15] Despite all these treatments, the local recurrence rate is 40-65% and the distant metastasis rate is 30-60%. Distant metastases are usually seen in the lungs.[13,16-18] Novel treatment agents and strategies are needed for this poor prognostic disease. But the rarity of the disease precludes conducting randomized controlled trials. Therefore, information related to treatment can be obtained from retrospective studies.

Programmed death-ligand 1 (PD-L1), CD274 or B7 homolog (B7-H1) is a transmembrane protein found mainly on lymphocytes and macrophages and plays a pivotal role in the regulation of cellular immune response. Activation of PD-1/PD-L1 complex leads to inhibition of antigen-specific T cell proliferation and induces apoptosis of these antigen-specific T cells, therefore, negates the cellular immune response. Neoplastic cells may express PD-L1 in order to escape from the immune system. Also, many studies showed PD-L1 expression in various cancer types, including sarcomas.[19,20]

In this study, we aimed to investigate patient and tumor characteristics, treatment outcomes in our patients with MPNST. We also assessed programmed death ligand-1 (PD-L1) expression and its association with survival.

MATERIAL AND METHODS

Patients with pathologically confirmed MPNST diagnosed and treated between 2000 and 2016 in Hacettepe University Cancer Institute were reviewed. Patients' demographic features, tumor characteristics including size, location, grade, stage, resection margin status, the presence of NF-1, and treatment protocols were obtained from patient files. The diagnosis of NF1 was confirmed by the presence of two or more clinical manifestations that met the National Institute of Health (NIH) consensus criteria.[3,21] The PD-L1 expression was determined using slides of microarray tissue that was stained for the PD-L1 antibody using Leica Bond Autostainer (Cell Signaling, E1L3N®). Membranous staining of more than 5% of the cells was accepted as positive. This study was approved by the Institutional Ethics Committee of Hacettepe University.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 21.0 (IBM, Chicago, IL, USA). We used the chi-square test for the comparison of categorical variables and the Mann-Whitney *U*-test and Student's *t*-test for numerical variables. The missing values were ignored in data analysis. The Kaplan-Meier analysis was used for estimating survival rates and the long-rank test for comparison of outcomes. Two-sided p values <0.05 were considered as statistically significant. DFS was defined as the time interval from the time of diagnosis to the first recurrence or death of any cause and OS was defined as the time period from diagnosis to death due to disease or any reason.

RESULTS

Twenty-seven patients were identified and evaluated, of whom 20 (74%) patients were sporadic and 7 (26%) were NF-1 associated. The patients mostly had localized disease (93%), high-grade tumors (63%), located in the trunk (48%) and median tumor size was 8.7 cm (range 2-20 cm). Patient characteristics are summarized in Table 1. Two patients (7%) had distant metastases at the time of diagnosis, at both the lungs. Surgery for the primary tumor was performed in 26 patients (96%) and R0 or R1 resection was achieved in 19 (76%) of the patients.

The median follow-up was 16 months (range 1 to 178 months). On follow-up, 16 patients (59%) experienced recurrence, 10 being local (37%), and 6 being at distant sites (22%). All distant recurrences were located in the lungs. The median DFS was 20 months [95% confidence interval (CI), range 5 to 168 months]. Disease-free survival was worse in NF1 patients but this difference did not reach statistical significance (43 vs. 9 months, p=0.056) but clinically

TABLE 1: Demographic characteristics of malignant peripheral nerve sheath tumor patients.

Characteristics		n (%)
Age (year) [Median (min-max)]		[36 (19-39)]
Gender	Male	10 (37)
	Female	17 (63)
Genetic Background	Sporadic	20 (74)
	Neurofibromatosis type–1 associated	7 (26)
Grade	Low- Intermediate	9 (37)
	High	15 (63)
Location	Extremity	11 (41)
	Trunk	13 (48)
	Head and Neck	3 (11)
Tumor Size (cm) [Median (min-max)]		[9 (2-20)]
Stage	Localized	25 (93)
	Metastatic	2 (7)
PD-L1 expression	Positive***	6 (40)
	Negative	9 (60)

*** Membranous staining over 5% of the cells was regarded as positive.

remarkable. The 3-year DFS rate according to R0-R1 and R2 resection was 57 vs. 17%, respectively (p<0.001) (Figure 1). The median OS was 56 months.

None of the patients received neoadjuvant treatment. After surgery, 13 patients (48%) received adjuvant treatment. Two patients (7%) received chemotherapy, five patients (19%) received radiotherapy, and six patients (22%) received both. Patients who received both chemotherapy and radiotherapy (chemoradiotherapy group, n=6) had longer 3-year DFS compared to those who received chemotherapy or radiotherapy alone (unimodality group, n=7) and to those who did not receive any adjuvant treatment. The 3-year DFS rates were 100% in the chemoradiotherapy group vs. 14% in the unimodality group and 44% in the surgery alone group (p=0.003) (Figure 2). Ten out of 16 patients who developed recurrence underwent surgery. The patients who underwent surgery after recurrence had better 3-year survival than those who did not (66% vs. 0%, respectively, p=0.02). Among the 15 patients in whom tumor PD-L1 expression was assessed, PD-L1 was positive in six patients (40%) (Figure 3). Even though the survival of PD-L1 positive and negative groups showed a clear separation especially after the

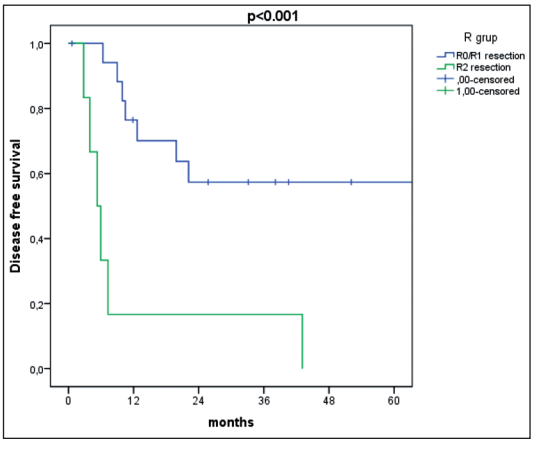

FIGURE 1: Disease-free survival according to the resection margin.

16th month of follow-up, the relationship between PD-L1 expression and DFS was not statistically significant (p=0.2) (Figure 4).

DISCUSSION

In this study, we have shown that multimodality treatment including surgery, chemotherapy, and radiotherapy is associated with improved DFS in patients with MPNST. Previous data on MPNST have principally been collected from single-center retrospective trials and the 5-year survival range is be-

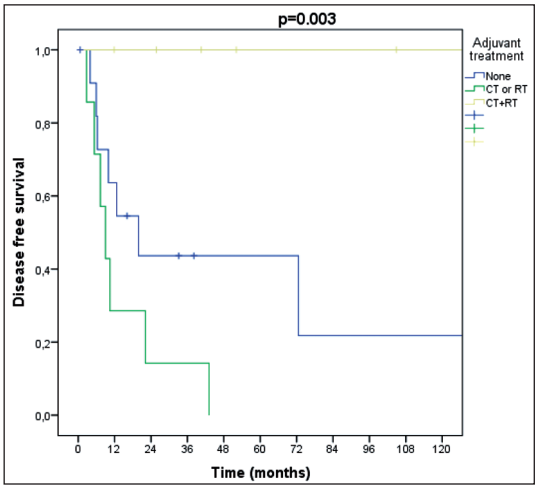

FIGURE 2: Disease-free survival according to adjuvant treatment. CT: Chemotherapy, RT: Radiotherapy.

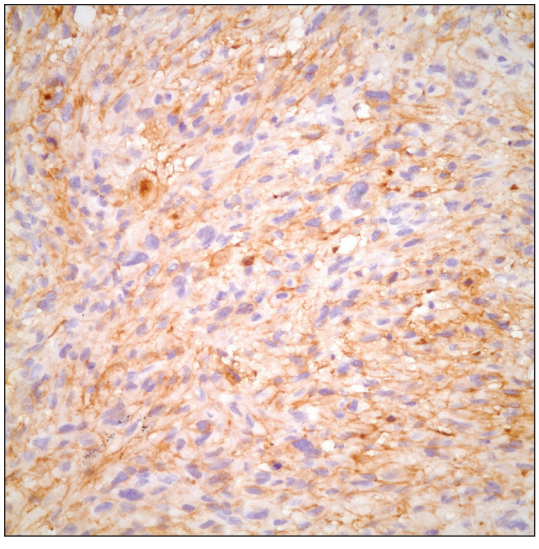

FIGURE 3: Membranous PD-L1 expression in neoplastic cells of MPNST (400x).

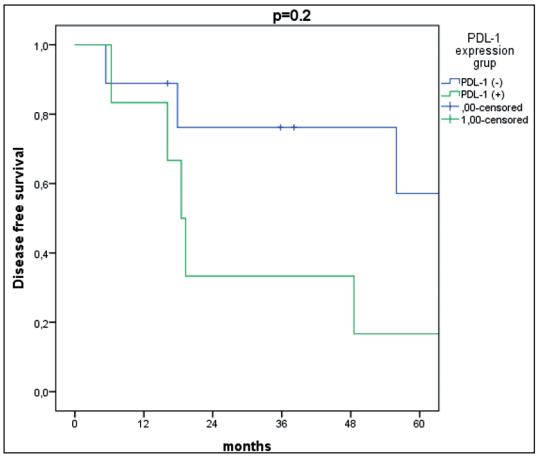

FIGURE 4: Disease-free survival according to the PD-L1 expression.

tween 15% and 50%, consistent with our results. In those studies, large tumor size (>5 cm), high tumor grade, truncal location, surgical marginal status, and local recurrence have been accepted as poor prognostic factors.[22-24] NF1 is an important risk factor for the development of MPNST, approximately 10% of all NF1 patients eventually develop MPNST but the prognostic impact of NF1 is controversial.[25] Previously, several studies have reported poorer outcomes among patients with NF1-MPNSTs, however, with the advent of imaging and diagnostic techniques, better surveillance, rapid intervention, prognosis have improved drastically.[26] The only definitive treatment for MPNST is surgical resection with wide negative margins. Almost all of our patients (96%) had undergone surgical resection. A better 3-year DFS rate was associated with total resection (R0-R1) compared with subtotal (R2) resection. However, in some patients, resection is not possible due to tumor size, localization, or patient morbidities.[27] The role of chemotherapy is not well-defined. In a retrospective study conducted by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group, first-line chemotherapy was evaluated in MPNST patients and the median progression-free survival was 17 weeks and the overall survival was 48 weeks. The doxorubicin-ifosfamide regimen had better response rates compared with doxorubicin alone.[28] Radiotherapy improves local control; the effect on survival has not been demonstrated.[14,15] Stucky et al. recommend the use of postoperative radiotherapy for tumors with greater than or equal to 5 cm, high grade, and R1 resection (microscopically positive), the closest margin within 2 mm, or R2 (macroscopically positive margin) margin status.[24] Both neoadjuvant chemotherapy and radiotherapy could be used to downstage borderline unresectable tumors and to determine in vivo chemosensitivity in selected cases.[29-32] Hirbe et al. showed in a retrospective study that patients receiving neoadjuvant chemotherapy had a response rate of 60% and a clinical benefit rate of 100%.[31] Similarly, in our study, a 3-year DFS rate was 100% in patients who received multimodal treatment. There are reports supporting our results and suggesting that multimodality treatment provides better

recurrence-free survival.[33] Randomized controlled trials are needed to prove the efficacy of this treatment.

Preclinical studies assessed tumor protein p53, retinoblastoma gene (RB1), phosphoinositide 3-kinase (PI3K), protein kinase B-mammalian target of rapamycin (Akt-mTOR), RAS-ERK and Wnt signaling pathways in the pathogenesis of MPNST.[34] Several targeted therapies such as erlotinib, sorafenib, imatinib, and dasatinib were investigated in histology-specific phase II trials but no clinical benefit was detected.[35] Recently, Ki et al. demonstrated that wild-type platelet-derived growth factor receptor alpha (PDGFRA) overexpression may be a key driver of MPNST development. Also, they found that sunitinib decreased tumor progression and increased apoptosis in PDGFRA wild-type transgenic fish model.[36] Sunitinib can be a promising agent for this disease. There are also ongoing studies with MEK inhibitors, small molecule inhibitors of colony-stimulating factor 1 and KIT.[37]

Immune-based treatments have shown significant therapeutic efficacy in numerous tumor types, such as advanced melanoma, Hodgkin lymphoma, and non-small cell lung cancer.[38] The PD-L1 expression is associated with a higher response to immunotherapy in some tumors including lung cancer. PD-L1 expression in sarcomas was reported to be present in a wide range of cases (6-65%).[19,20,39-44] This wide difference may be due to the use of different antibodies, the cut-off points varying between 1% to 10%, and the types of sarcomas studied. However, in most of them, MPNSTs are included in high PD-L1 expressing sarcomas (13-39%). In our series, the relationship between PD-L1 expression and DFS did not reach the statistical significance level (p=0.2), although there was a clear separation of survival curves after 16 months of follow-up, a larger series may help prove a possible correlation. Shurell et al. also investigated the relationship between PD-L1 status and clinical outcomes in patients with MPNST. PD-L1 staining in at least 5% cases was seen and it was 13% and more in MPNST compared with benign lesions (7/53 vs. 2/68, p=0.033). Consistent with our results, they did not find any association between PD-L1 expression and disease-specific and disease-free survival.[38]

In conclusion, MPNST is an entity with a poor prognosis. Surgery is the mainstay of treatment. We demonstrated that combined modality adjuvant therapy might improve outcomes. Previous studies on adjuvant treatment for soft tissue sarcomas are heterogeneous and include several histological subtypes. Further determination of the efficacy of chemoradiotherapy specifically in MPNST is needed. At present, PD-L1 expression appears to be unrelated to prognosis and survival in MPNST.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ömer Dizdar, Ayşe Kars, Yusuf Karakaş,;* ***Design:*** *Yusuf Karakaş, Alev Türker, Ömer Dizdar;* ***Control/Supervision:*** *Ömer Dizdar, Alev Türker, Ayşe Kars, Kemal Kösemehmetoğlu;* ***Data Collection and/or Processing:*** *Yusuf Karakaş, Utku Burak Bozbulut, Metin Demir, Gökhan Gedikoğlu, Figen Söylemezoğlu;* ***Analysis and/or Interpretation:*** *Yusuf Karakaş, Ömer Dizdar, Utku Burak Bozbulut, Metin Demir, Alev Türker, Ayşe Kars;* ***Literature Review:*** *Yusuf Karakaş, Kemal Kösemehmetoğlu, Utku Burak Bozbulut, Metin Demir, Alev Türker, Ayşe Kars;* ***Writing the Article:*** *Yusuf Karakaş, Ömer Dizdar, Gökhan Gedikoğlu, Figen Söylemezoğlu, Alev Türker, Ayşe Kars;* ***Critical Review:*** *Yusuf Karakaş, Kemal Kösemehmetoğlu, Ömer Dizdar, Ayşe Kars;* ***References and Fundings:*** *Yusuf Karakaş, Ömer Dizdar, Kemal Kösemehmetoğlu;* ***Materials:*** *Yusuf Karakaş, Ömer Dizdar, Ayşe Kars.*

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