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Brief Communications

Selinexor, a First in Class, Nuclear Export Inhibitor for the Treatment of Advanced Malignant Peripheral Nerve Sheath Tumor

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Malignant peripheral nerve sheath tumor (MPNST) is a highly malignant neoplasm arising from peripheral nerve or its attendant sheath and is derived from Schwann or pluripotent cells of neural crest origin. Patients with recurrent, unresectable, or advanced stage disease have limited treatment options, and current therapies are associated with little benefit. In this article, we report nine cases of MPNST treated with selinexor, an orally bioavailable, selective inhibitor of nuclear export, accompanied by tumor stabilization or regression. ***The Oncologist*** 2021;26:e710–e714

Introduction

MPNST is rare, representing approximately 5%–10% of all soft-tissue sarcomas. They often afflict young to middle-aged adults. Approximately half of all MPNST cases are associated with neurofibromatosis type 1 (NF1), whereas the rest are attributed to sporadic or postradiation subtypes. This tumor is very aggressive, and surgery remains the only curative treatment for localized tumors [1]. MPNST has a high propensity for distant metastasis following tumor resection. In this setting, standard treatments such as chemotherapy and radiotherapy are often of little benefit, with an average prognosis of less than 12 months [2]. Advances in our understanding of the molecular pathogenesis of these malignancies have revealed multiple signaling pathways and epigenetic regulators, which have been a focus for recent targeted therapy development including inactivation of tumor suppressor pathways [3]. Selinexor (XPOVIO) is a first-in-class oral inhibitor of exportin-1 (XPO1) and is approved in refractory multiple myeloma. Selinexor results in nuclear retention and activation of tumor suppressor proteins (TSPs) across several tumor types, including sarcomas [4]. In this article, we report nine MPNST cases treated with selinexor as single or combination treatment with evidence of partial response or stable disease.

Materials and Methods

We performed a retrospective search in the database of Princess Margaret Cancer Centre (Toronto, Canada), University Campus Bio-Medico (Rome, Italy), and Memorial Sloan Kettering Cancer Centre (New York) for patients diagnosed with MPNST who received selinexor (as a mono- or combotherapy) between January 2015 and July 2020. All patients who received selinexor within a trial protocol or single-patient use (SPU) were eligible to be included. Identified patients were then cross checked with the patient database available at Karyopharm Therapeutics to ensure accurate patient identification. Data collected included patient demographics, disease characteristics, previous line of therapies, selinexor treatment details, and clinical outcome.

Results

Between January 2015 and July 2020, nine patients with MPNST with unresectable or metastatic disease received

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Table 1. Patient demographics, disease characteristics, and treatment summary

Patient characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Treatment regimen	Selinexor with doxorubicin	Selinexor with doxorubicin	Selinexor monotherapy	Selinexor monotherapy	Selinexor monotherapy	Selinexor monotherapy	Selinexor monotherapy	Selinexor monotherapy	Selinexor monotherapy
Drug source	NCT03042819	NCT03042819	SPU	NCT01896505	SPU	SPU	SPU	SPU	SPU
Gender	Female	Female	Male	Female	Male	Male	Male	Female	Male
Age, years	63	30	79	56	38	54	41	63	23
Ethnicity	White	Asian	White	White	White	White	White	Hispanic	Hispanic
ECOG PS	0	1	1	1	1	1	1	1	2
Relevant history	Sporadic	NF1 germline	Sporadic	NF1 germline	NF1 germline	NF1 germline	NF1 germline	Sporadic	NF1 germline
Primary lesion site	Left axilla	Right gluteal	Left gluteal	left iliosacrum	Left sciatic nerve	Neck	Lumbar	Retroperitoneum	Retroperitoneum
Initial local treatment	Radiotherapy (30 Gy/10)	Nil	Surgery	Surgery	Surgery	Surgery	Surgery	Surgery	Surgery
Molecular profile	BRAF wild type, unknown MDM2	Negative MDM2	Focal MDM2 positivity, FISH amplification	Focal MDM2 positivity	Negative MDM2	Negative MDM2		KRAS G12dup PIK3CA E542K	NF1 germline. TP53BP, EED, EZH2, CDKN2A/B, and others
Adjuvant chemotherapy	No	No	No	No	No	No	No	No	No
Adjuvant radiotherapy	No	No	No	Yes (50 Gy/25)	No	No	Yes	Yes	Yes
Presentation at advanced disease setting	Multiple metastasis	Multifocal local disease	Multiple metastases	Multiple metastasis	Multiple metastasis	Multiple metastasis	Multiple metastasis	Multiple metastasis	Multiple metastasis
Site of distant metastases	Lungs, bone, liver	Multiple pelvic masses	Lungs and pleura	Lungs	Lungs	Soft tissue	Bone, peritoneum	Abdomen and pelvis, lungs	Lung, pleura, brain
No. of prior therapy to selinexor	0	0	2	1	2	1	1	3	3
First-line chemotherapy			Doxorubicin and olaratumab	ENMD-2076	Epirubicin and ifosfamide	Doxorubicin	Epirubicin and ifosfamide	Pembrolizumab + investigational drug	Doxorubicin and Olaratumab
Best response with first-line chemotherapy			PD	SD	PD	PD	PD	PD	PD
Time to response and duration of response, mo			NA	NA	NA	NA	NA	NA	NA
Reason of discontinuation			PD	PD	PD	PD	PD	PD	PD
Second-line chemotherapy			Carboplatin - etoposide		Pazopanib			Doxorubicin and olaratumab	Pazopanib

(continued)

Table 1. (continued)

Patient characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Best response with second-line chemotherapy			PD		PD			Mixed response	PD
Time to response and duration of response			NA		NA			3.5	NA
Reason of discontinuation			PD		PD			PD	PD
Selinexor treatment details									
Dose	80 mg/wk + doxorubicin 75 mg/m^2	80 mg/wk + doxorubicin 75 mg/m^2	60 mg twice weekly	60 mg twice weekly	60 mg twice weekly	60 mg twice weekly	60 mg twice weekly	60 mg twice weekly	60 mg twice weekly
Dose reduction (if any)	No dose reduction	60 mg/wk; due to neutropenia	40 mg twice weekly; due to GI toxicities	No dose reduction	60 mg/wk; due to fatigue and nausea	None	None	40 mg and 20 mg weekly	None
Toxicities (attributable to selinexor)	Anemia, neutropenia, glucose intolerance, hyponatremia, weight loss, and nausea	Neutropenia, neutropenic fever, low EF, anorexia, fatigue, and anemia	Nausea, fatigue, loss of appetite, and weight loss	Nausea, loss of appetite, anemia, fatigue, diarrhea, and blurred vision (cataract)	Nausea, fatigue, and mild cognitive impairment	Nausea, and fatigue	Fatigue	Fatigue, anorexia, blurry vision, and dizziness	Fatigue, and anorexia
Worst grade of toxicities	G2	G3 (neutropenic fever)	G2	G2	G3	G1	G2	G2	G3
Best response by RECIST 1.1	PR	SD	PR	SD	SD	PD	SD	PR	PD
% of target volume decrease	−45	−12	−40	−11	−10	NA	−10	−56	NA
Best response by Choi	PR	SD	PR	SD	SD	SD	SD	NA	NA
% Hounsfield Unit change	−32.70	−23.60	−50	−35.70	−19	−18	NA	NA	NA
Duration of response, mo	3.5	NA	3	NA	NA	NA	NA	8+	NA
Time to progression, mo	3.5	4.2	3	13.5	3.3	2.5	NA	NA	1.5
Reason of selinexor discontinuation	PD	PD	Noncompliance	PD	Death	PD	Selinexor ongoing	Selinexor ongoing	PD and death

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; EF, ejection fraction; G1, grade 1; G2, grade 2; G3, grade 3; GI, gastrointestinal; mo, months; NA, not applicable; NF1, neurofibromatosis type 1; PD, progressive disease; PR, partial response; SD, stable disease; SPU, single-patient use.

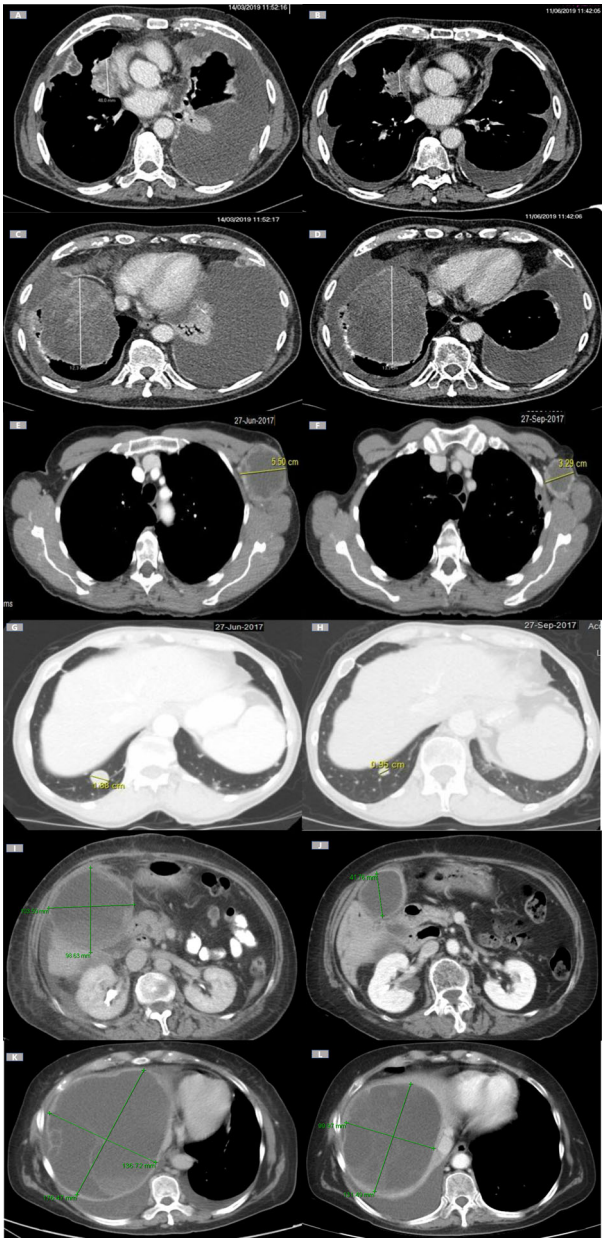

Figure 1. Representative images demonstrating response. **(A):** Baseline computed tomography (CT) scan of the first target lesion (patient 3). **(B):** Reduction in the tumor size after 3 months of selinexor by 40% according to RECIST version 1.1, with an increase in the necrotic component estimated at around 50%. **(C):** Baseline CT scan of the second target lesion (patient 3). **(D):** Slight dimensional increase in the second target lesion in the order of 1 cm with an increase in the necrotic-colliquative component estimated at around 45% after 3 months of selinexor. **(E):** Baseline CT scan of the first target lesion (patient 1). **(F):** Decrease in the first target lesion size 45% according to RECIST 1.1 with an increase in the necrotic component estimated at around 32.7%. **(G):** Baseline CT scan of the second target lesion (patient 1). **(H):** Decrease in the second target lesion size 49% according to RECIST version 1.1. **(I):** Baseline CT scan of the first target lesion (patient 8). **(J):** Decrease in the first target lesion size 56% according to RECIST 1.1. **(K):** Baseline CT scan of the second target lesion (patient 8). **(L):** Decrease in the second target lesion size 35% according to RECIST version 1.1.

selinexor. All nine patients had their tumor specimens reviewed by a sarcoma pathologist. Seven of these patients received selinexor monotherapy at 60 mg orally twice a week (SPU and clinical trial NCT01896505), whereas two others received 80 mg once weekly in combination with doxorubicin at 75 mg/m^2 (clinical trial NCT03042819). The patient demographics and disease characteristics are summarized in Table 1.

Of the nine patients, three patients had a partial response (PR), four had stable disease, and two had progressive disease as per RECIST v1.1. The three patients with PRs were treated with selinexor monotherapy (n = 2) as well as in combination with doxorubicin (n = 1). The duration of disease control for three patients with partial response was 8+, 3, and 3.5 months, respectively. A patient with NF1–associated MPNST had durable stabilization on monotherapy selinexor lasting 13.5 months. In seven patients, the mean duration of disease control was 4.5 months (range, 2.5–13.5). Additionally, the target lesion assessments at the time of best response showed a reduction in tumor size in seven patients, ranging from −10% to −56%; favorable changes in tumor density were also noted (Table 1; Fig. 1). One patient with NF1–associated MPNST had disease stabilization in the lung but failed to control rapidly progressing brain metastases, and the patient died within 7 weeks of starting selinexor.

The treatment with selinexor was associated with a number of well-described clinical toxicities such as fatigue, anorexia, and hematological and/or biochemical changes, but most are limited to grade 2 toxicities. In one patient, neutropenic fever was observed, but this patient also received concurrent doxorubicin. In four of nine patients, dose reduction occurred because of high or intolerable grade toxicities. Details of for selinexor treatment are also summarized in Table 1.

Discussion

MPNST develops in 8%–13% of NF1 patients, and this cancer represents one of the leading causes of death in this patient population [5]. MPNST can be associated with loss of function for multiple TSPs, including, but not limited to, NF1, *CDKN2A*/p16, and TP53. Recently, recurrent mutations in polycomb repressive complex 2 (PRC2) components suppressor of zeste 12 homolog and embryonic ectoderm development protein (EED) have been identified in MPNST, and loss of the PRC2 product, histone H3 lysine 27 trimethylation (H3K27me3), has been implicated in the pathogenesis of MPNST from plexiform neurofibromas [6].

Several chemotherapy and targeted therapies have been studied in MPNST. Standard chemotherapy is often associated with low therapeutic benefits. Targeted therapies have been investigated in this disease but with little success. For example, EGFR inhibition with erlotinib failed to induce any responses, and sorafenib in combination with dacarbazine was also limited in terms of efficacy [7, 8]. In our report, selinexor resulted in partial responses for three patients and a durable stable disease. However, one of these three patients, a sporadic case, received

selinexor in combination with the chemotherapy agent doxorubicin as first-line treatment and is thus more likely to respond to cytotoxic chemotherapy compared with patients with NF1–related cases. XPO1 is responsible for shuttling proteins from the nucleus to cytoplasm, including multiple TSPs. More than 200 different proteins harbor nuclear export signal motifs and are cargo proteins for XPO1, including CDKN1A/p21, CDKN1B/p27, p53, MDM2, BRCA1/2, NFKB1A, FOXO3, SMAD4, AKT1, WEE1, and APC. Inhibition of XPO1 by selinexor results in nuclear accumulation of TSP, therefore restoring normal cell-cycle checkpoints, and induces apoptosis in malignant cells, which may explain the antitumor activity seen in this patient population [9, 10].

Despite limited by numbers, these patient series represent a novel and interesting potential therapeutic avenue for this hard to treat disease. This preliminary data is encouraging, and based on this series, an investigator-initiated study of selinexor in patients with MPNST is currently being developed.

Conclusion

Advanced MPNST is a rare and highly aggressive sarcoma. It has a high propensity for metastases and resistance to the traditional treatments. Selinexor may be active as targeted treatment of advanced, metastatic MPNST.

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