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Metastatic Myxofibrosarcoma with Durable Response to Temozolomide Followed by Atezolizumab: A Case Report

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

Key Words. Soft tissue sarcoma • Temozolomide • Immunotherapy • Antineoplastic drug resistance

Abstract

Myxofibrosarcoma (MFS) is a well-recognized histotype of soft tissue sarcomas that generally presents with localized disease. Herein, we describe the case of a patient with metastatic MFS who experienced durable response to sixth-line therapy with temozolomide. Upon further progression, his tumor was notable for a high tumor mutational burden, and he was subsequently treated with seventh-line immunotherapy, atezolizumab, achieving a second durable response. This case highlights the role of immunotherapy after administration of alkylating agents. Review of the literature indicates that recurrent tumors treated with alkylating agents often experience hypermutation as a means of developing resistance and that checkpoint inhibitors are subsequently effective in these tumors. ***The Oncologist*** 2021;26:549–553

Key Points

- To the authors' knowledge, this is the first report of a patient with myxofibrosarcoma with high tumor mutational burden after administration of temozolomide monotherapy.
- Hypermutation may be a resistance mechanism for patients with soft tissue sarcoma who develop resistance to alkylating agents.
- Checkpoint inhibition may be effective therapy in patients with soft tissue sarcoma with high tumor mutational burden as a consequence of alternate systemic therapy resistance.

Introduction

Myxofibrosarcoma (MFS) is a relatively common histotype of sarcoma, comprising 5% to 10% of all soft tissue sarcomas (STS) [1]. It is typically diagnosed in the elderly and often presents as an enlarging mass in the extremities [1]. This disease is locally aggressive with a high rate of recurrence and overall 5-year survival of 61% to 77% [1]. For individuals with metastatic disease, 5-year survival may be as low as 25% [2]. In local disease, surgical resection and radiotherapy is the standard of care [1]. For those with metastatic disease, anthracycline-based regimens are considered first-line therapy [3]; however, there is an emerging literature exploring alternative agents including immunotherapies [4, 5]. Here, we present a case of a patient with MFS that demonstrated a durable response to temozolomide (TMZ) and, on progression, was found to have a high tumor mutational burden (TMB) with subsequent durable response to atezolizumab.

Patient Story

The patient is a 63-year-old man who presented in 2013 with a T3N0M0G2 stage IIIB, 10.9 × 6.2 × 5.8 cm posterior left thigh mass. He underwent 50 Gy of neoadjuvant radiation to the thigh, followed by an R0 surgical resection. Pathology was consistent with a grade 2 MFS without lymphovascular invasion.

The patient was monitored with serial computed tomography (CT) imaging for 18 months, at which point he was found to have metastatic recurrence in the right middle lobe of his lung. Positron emission tomography scan confirmed oligometastatic disease. He underwent a right middle lobe wedge resection, and pathology was consistent with metastatic MFS. The mass was 1.4 cm in greatest dimension, with an R2 visceral pleural margin. Recurrence was found 6 months later, with a 3.2 cm mass along the surgical staple line.

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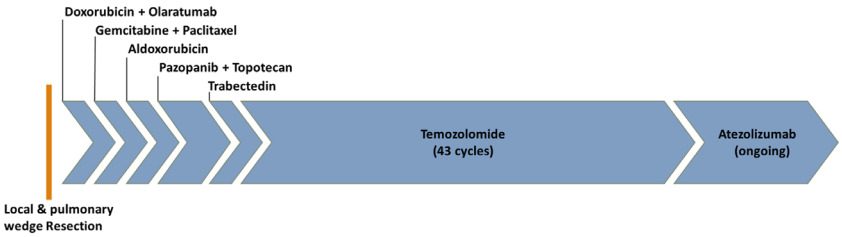

Figure 1. Treatment course. Sizing proportional to time on each treatment.

At this time, following tumor board recommendations, he was determined not to be a candidate for further local therapy. After discussion and shared decision-making, he was started on a clinical trial (NCT02326025) of doxorubicin followed by olaratumab. Progression of pulmonary disease was noted after two cycles, and he was subsequently treated with multiple lines of experimental and standard treatment regimens to which he was primarily refractory (Figs. 1 and 2; Table 1).

After failure of five prior systemic therapies, he was started on TMZ (150 mg/m^2 on days 1–5, with 28-day cycles) with decrease in the dominant right pulmonary mass from 9.7 × 11.4 cm to 3.5 × 4.8 cm after two cycles (Fig. 2). After eight cycles he had complete resolution of his pulmonary lesions with stable pulmonary effusion and stable axillary and mediastinal lymphadenopathy. He continued TMZ with minimal side effects for 43 cycles, or 38 months, before experiencing recurrence of pulmonary disease. On CT of his chest he was found to have a new 7.6 × 1.8 × 4.4 cm mass, resulting in destruction of the adjacent ribs. The lesion was biopsied and sent for next-generation sequencing analysis with Foundation One (Foundation Medicine Inc, Cambridge, MA) and Guardant360 (Guardant Health, Redwood City, CA). Results demonstrated tumor molecular burden with 889 mutations per megabase (Mb), but microsatellite stable, with no dominant, targetable somatic alterations. Sequencing data were also notable for a negative O^6 methylguanine-DNA methyltransferase (MGMT), which may contribute to the accumulation of mutations. Based on these results he qualified for, and was enrolled in, clinical trial (NCT02091141) and started on atezolizumab, which is ongoing with stable disease status after 22 cycles (Figs. 1 and 2; Table 1).

Use of TMZ in STS

TMZ is an oral imidazotetrazine prodrug approved for use in the treatment of high-grade gliomas and metastatic melanoma, with few studies evaluating its efficacy in patients with STS [6].

With respect to STS, a 2003 phase II trial of 26 patients with metastatic STS treated with TMZ demonstrated a progression-free survival (PFS) of 2.0 months, although patients with leiomyosarcoma had a PFS of 3.9 months [7]. A 2005 double arm phase II trial including 45 patients with STS treated with TMZ, demonstrated a 15.5% partial response rate, which was also primarily confined to individuals with leiomyosarcoma who had a partial response rate of 46% [8]. Neither of these studies enrolled patients with MFS. Lastly, to explore whether TMZ may have additional benefit if paired with targeted therapy, a small study of 14 patients with metastatic hemangiopericytoma and malignant solitary fibrous tumor treated with TMZ and bevacizumab found a PFS of 9.7 months [9].

Use of Checkpoint Inhibitors for STS

Immunotherapies that target checkpoint signaling have shown promise in sarcoma treatment [4, 5, 10]. In a phase II trial of nivolumab with or without ipilimumab in 85 patients with advanced sarcoma, 16% of those who received nivolumab and ipilimumab had an objective response, and overall survival was 10.7 months in the monotherapy group and 14.3 months for the combination therapy [10]. Another phase II study of 20 patients with locally advanced or metastatic sarcoma who received talimogene laherparepvec plus pembrolizumab found that 35% of patients had an objective response at 32 weeks, and the PFS was 17.1 weeks [11].

The effectiveness of checkpoint inhibitors in sarcoma may be partially explained by evidence that sarcomas express PD-1/PD-L1, with expression ranging from 0% to 33% across all sarcomas and up to 18% in MFS [12]. There remains, however, a need to identify biomarkers to determine who will respond to these therapies [4]. Of the 35% of patients who had a complete response to talimogene laherparepvec plus pembrolizumab, only one patient expressed PD-L1 before enrolling in the trial [11].

One promising marker of response to PD-1/PD-L1 inhibitors, regardless of cancer type or PD-1/PD-L1 expression, is the TMB, or the number of genomic mutations identified per coding area [13]. Moreover, using immunotherapy in patients with an elevated TMB has been shown to incur an overall survival benefit [14]. There is significant variability in TMB among different cancer types, ranging from less than one to thousands of mutations [15]. Our patient had an elevated TMB of 889 mutations/Mb; sarcomas typically have a low/intermediate TMB, with a median TMB for STS of 2.5 mutations/Mb [15].

Combination of TMZ and Atezolizumab

Current research, primarily in the setting of gliomas, suggests a role for the combination of alkylating agents and immunotherapy. There is emerging evidence that tumor genetic hypermutation, a form of tumor resistance to alkylator therapy such as TMZ, results in a tumor

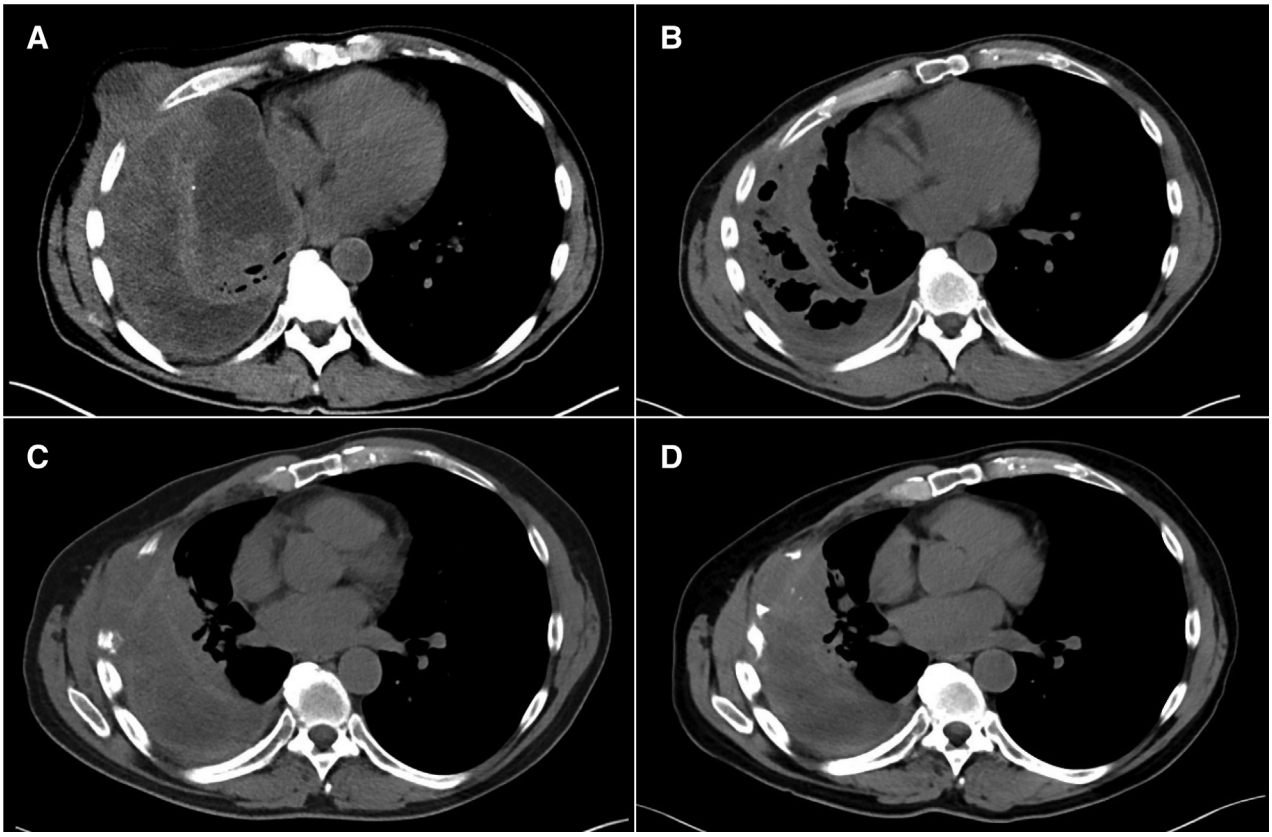

Figure 2. Progression of large metastatic pulmonary myxofibrosarcoma mass on computed tomography scans without contrast. **(A):** Depicting progression of disease after two cycles of trabectedin with 11.4 × 9.7 cm mass extending through the chest wall. **(B):** After two cycles of temozolomide (TMZ) with marked decrease in soft tissue component of lesion. **(C):** Recurrence of disease after 43 cycles of TMZ with a 7.6 × 1.8 × 4.4 cm mass resulting in destruction of adjacent ribs. **(D):** Stable to slightly decreased size of pulmonary mass after 16 cycles of atezolizumab.

Table 1. Summary of seven lines of treatment and a description of the radiologic features of the dominant right metastatic lung mass throughout treatment

Therapy	Clinical trial (if applicable)	Cycles until progression	PFS ratio[a]	Radiologic features of dominant right lung mass	
				Treatment response	Mass at progression
Doxorubicin followed by olaratumab	NCT02326025	2	—	No response	4.0 cm nodule in largest dimension
Gemcitabine/ docetaxel	—	2	0.9	No response	6.2 cm soft tissue mass in largest dimension
Aldoxorubicin	NCT02049905	2	1.0	No response	8.0 cm soft tissue mass in largest dimension with extension into the chest wall
Pazopanib and topotecan	NCT02357810	7	5.1	8.1 × 7.6 cm cystic mass (previously solid); solid component decreased to 5.3 × 3.6 cm	11.0 × 8.5 cm cystic mass with new destruction of anterior ribs and bronchopleural fistula
Trabectedin	—	2	0.2	No response	11.4 × 9.7 cm cystic mass with increase in solid component extending through the chest wall
Temozolomide	—	43	29.2	Complete resolution of metastatic disease by cycle 9 with residual architectural changes and stable mediastinal lymphadenopathy	7.6 × 1.8 × 4.4 cm soft tissue mass along surgical staple line
Atezolizumab	NCT02091141	Ongoing with 22 previous cycles	—	Stable 5.0 × 1.1 cm soft tissue mass	n/a

[a]Progression-free survival ratio indicating the time to progression on current treatment relative to time to progression on previous treatment.
Abbreviation: PFS, progression-free survival.

microenvironment conducive to a good response to checkpoint inhibition [16, 17].

The therapeutic effect of TMZ comes from the alkylation/methylation of guanine at the O^6 location, which results in a mismatch pairing of the methylated/alkylated guanine with thiamine. The resulting mismatch activates the mismatch repair (MMR) pathway which removes the mispaired thiamine, only to have it replaced by another mispaired thiamine; a process that continues to repeat, ultimately resulting in a futile repair cycle and cell death [16, 18]. One pathway of tumor resistance to TMZ is acquired mutations leading to dysfunction of the MMR pathway, which inhibits the cell's ability to repair base mismatches and leads to the accumulation of genomic mutations [16, 19, 20]. A large majority of patients with post–alkylator therapy hypermutation have MMR pathway deficiencies [21, 22]. An additional mechanism of tumor escape involves the upregulation of MGMT, which actively repairs TMZ induced genetic alterations [16].

At the time of recurrence after treatment with TMZ, our patient's tumor pathology demonstrated MGMT methylation, or nonfunctional MGMT, suggesting that hypermutation was the mechanism of escape. This is an emerging area of interest, as 16% to 47% of recurrent TMZ treated gliomas exhibited hypermutation [19, 23]. One limitation to concluding that TMZ was driving hypermutation in our patient is that TMB data are not available prior to treatment with TMZ. It is possible that our patient had an elevated TMB at diagnosis or that another treatment regimen contributed to the elevated mutation burden.

Given the evidence that a high mutation burden portends a good response to checkpoint inhibitors, tumors that develop resistance to TMZ through hypermutation may be good candidates for PD-1/PD-L1 inhibitors. Current trials assessing these therapies have had mixed results [19, 24, 25]. A randomized trial of 35 patients with recurrent glioblastoma found that pembrolizumab, a PD-1 inhibitor, conferred a 486-day overall survival benefit when given in the neoadjuvant setting [24]. A recently published randomized trial of bevacizumab versus nivolumab in recurrent glioblastoma found no survival benefit; however, TMB was not assessed, and there was a trend toward improvement in overall survival for those with PD-L1 > 1%. Another recent study retrospectively looking at hypermutated gliomas also found no difference in median overall survival among patients with and without an elevated TMB treated with PD-1/PD-L1 inhibitors [19, 25]. Although initial data for gliomas remain inconclusive, the durable response to immunotherapy seen in our patient may indicate a targetable resistance pathway for patients previously responsive to alkylating agents.

Patient Update

As of the submission of this article, our patient has received cycle 22 of atezolizumab with the most recent CT demonstrating stable disease.

Author Contributions

Conception/design: Brian C. Schulte, Victoria Villaflor, Mark Agulnik
Provision of study material or patients: Susan Abbinanti, John P. Hayes, Mark Agulnik
Collection and/or assembly of data: Brian C. Schulte, Susan Abbinanti, John P. Hayes, Mark Agulnik
Data analysis and interpretation: Jason P. Lambden, Max F. Kelsten, Brian C. Schulte, Victoria Villaflor, Mark Agulnik
Manuscript writing: Jason P. Lambden, Max F. Kelsten, Brian C. Schulte, Susan Abbinanti, John P. Hayes, Victoria Villaflor, Mark Agulnik
Final approval of manuscript: Jason P. Lambden, Max F. Kelsten, Brian C. Schulte, Susan Abbinanti, John P. Hayes, Victoria Villaflor, Mark Agulnik

Disclosures

Victoria Villaflor: Takeda (RF), AstraZeneca, Bristol-Myers Squibb, Genentech (C/A); **Mark Agulnik:** Eli Lilly & Co., Adaptimmune, Regeneron, AstraZeneca (C/A), Bristol-Myers Squibb, Bayer (other—speaker's bureau). The other authors indicated no financial relationships.

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For Further Reading:
Gregory M. Cote, Jie He, Edwin Choy. Next-Generation Sequencing for Patients with Sarcoma: A Single Center Experience. ***The Oncologist*** 2017;22:234–242.

Implications for Practice:
The sarcomas are a heterogenous family of over 50 different mesenchymal tumors. Current practice for metastatic disease involves systemic chemotherapy or nonspecific kinase inhibitors such as pazopanib. Sarcomas typically lack the classic kinase alterations seen in many carcinomas. The role of next-generation sequencing in sarcoma clinical practice remains undefined.