Clinical Experience with Combination Chemo-/Immunotherapy using Trabectedin and Nivolumab for Advanced Soft Tissue Sarcoma

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Abstract

Immune checkpoint inhibitors revive pre-existing immune responses that are suppressed in cancer. To restore innate tumour surveillance that is lost in cancer patients, a tumoricidal agent may have synergistic activity with certain immune checkpoint inhibitors. Herein, we report on our clinical experience using two FDA-approved drugs, trabectedin, a marine derived natural alkaloid with pro-apoptosis and immune modulator properties, in combination with nivolumab, a PD-1 immune checkpoint inhibitor, in advanced Soft Tissue Sarcoma (STS). Twenty-eight heavily pre-treated STS patients received trabectedin (1.5 mg/m2 Continuous Intravenous Infusion, CIV, for 24 hours) every 3 weeks, and nivolumab (3 mg/kg IV over 30 minutes) every 2 weeks. Retrospective analysis of safety/toxicity was conducted using the NIH/NCI CTCAE v.4.03. Tumour responses were assessed by RECIST v1.1 and irRECIST. Histologic subtypes in 28 patients include undifferentiated pleomorphic sarcoma (UPS; n=7), myofibroblastic sarcoma (n=1), leiomyosarcoma (n=6), synovial sarcoma (n=4), liposarcoma (n=6), chondrosarcoma (n=2), and Ewing sarcoma (n=2). All patients had metastatic disease and a median of 4 lines of prior chemotherapy. Safety analysis (n=28): Grade 3 treatment emergent adverse events include anaemia (n=2), fatigue (n=1), decreased platelet count (n=1), decreased granulocyte count (n=1) and increased creatine kinase (n=1). Efficacy analysis (n=22): Twenty-two patients were followed for at least 6 months and their results are reported here. There were 4 partial responses (UPS=1, myxoid liposarcoma=1, chondrosarcoma=1, leiomyosarcoma=1), 12 stable disease and 6 progressive disease, with best overall response rate of 18.2%, median progression free survival (PFS) of >45.4 weeks (range: 10->95 weeks), median Overall Survival (OS) of >66.5 weeks (10->95 weeks), 6 month PFS rate of 68.2%, and 6 month OS rate of 95.4%. Taken together, the data suggest that paired administration of trabectedin and nivolumab is safe, and that this chemo-/immuno-therapy approach has synergistic activity that can lead to improved clinical outcomes.

Introduction

Soft tissue sarcoma is a rare heterogeneous group of malignancies that arise from the mesenchymal tissue. It comprises about 1% of all adult cancers. The American Cancer Society estimates 13,040 new cases of soft tissue sarcomas and 5,150 deaths due to soft tissue sarcomas in the United States for the year 2018 [1]. The most prevalent types of sarcoma in adults are undifferentiated pleomorphic sarcoma (formerly called malignant fibrous histiocytoma), liposarcoma, and leiomyosarcoma. Certain types occur more often in certain areas of the body, e.g., leiomyosarcoma is the most commonly found abdominal sarcoma, while liposarcoma and undifferentiated pleomorphic sarcoma are most likely seen in legs [2]. Surgical resection is the treatment of choice for localized disease, with radiation therapy given as first-line treatment for unresectable cases. However, about half the high-grade cases tend to recur [3].

For several years, soft tissue sarcoma management was limited to doxorubicin and/or ifosfamide, with an estimated median survival of 8-13 months, as per the results of randomized studies conducted over the last 2 decades [4-7]. Targeted therapies like pazopanib (Votrient®) showed a significant, but modest benefit in Progression Free Survival (PFS) for patients with locally advanced unresectable or metastatic soft tissue sarcoma [8]. The USFDA approval of trabectedin (Yondelis®) in 2015, showed further promise for improving the quality of life and progression free survival of patients with soft tissue sarcoma [9-13].

Trabectedin (ET-743), a marine derived natural alkaloid, has a complex mechanism of action that not only affects key cell biology processes in tumour cells but also the tumour microenvironment via direct effects on tumour-associated macrophages and tissue-resident histiocytes [11,12,14].
It binds to the minor groove of DNA, thereby affecting the function of DNA binding proteins, including transcription factors and DNA repair machinery. This results in induction of p53-independent apoptosis [15,16]. Further, several features of trabectedin’s clinical performance differentiate it from other oncologic agents. These include prolonged tumour growth stabilization, favorable outcomes in sarcomas with genetic mutations, durability of response—even upon treatment re-institution after interruption of therapy, and absence of cumulative toxicity [17].

Nivolumab (Opdivo®) is a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, which interrupts the interaction of PD-1 on T-cells with PD-L1 and PD-L2, both of which are expressed on tumor cells. Interruption of the PD-1 and PD-L1 pathway can help to restore antitumor immunity and enhance clinical activity resulting in better survival outcome in metastatic melanoma, non-small cell lung cancer, and renal cell carcinoma [18-20]. Up to 65% of different types of sarcomas have been reported to be positive for PD-L1 expression [21]. Earlier studies on the efficacy of nivolumab and other checkpoint inhibitors in soft tissue and bone sarcomas showed a clinical benefit in 50% of the evaluable patients [22] suggesting a rationale for further exploration. In the present study we report on our clinical experience using a combination treatment with two FDA-approved drugs, trabectedin and nivolumab in advanced soft tissue sarcoma.

### Method and Materials

Twenty-eight heavily pre-treated STS patients with metastatic disease who had a median of 4 lines of prior chemotherapy are included in this report. These patients had few to no other therapeutic options. All patients received trabectedin (1.5 mg/m² continuous intravenous infusion, CIV, for 24 hours) every 3 weeks, and nivolumab (3 mg/kg IV over 30 minutes) every 2 weeks. Retrospective analysis of safety/toxicity was conducted using the NIH/NCI CTCAE v.4.03. Tumour responses were assessed by RECIST v1.1 and irRECIST.

### Results

#### Patients and treatment

The patient demographics are displayed in (Table 1). All patients were previously treated with a median of 4 chemotherapy regimens. Disease characteristics include Undifferentiated Pleomorphic Sarcoma (UPS; n=7), myofibroblastic sarcoma (n=1), leiomyosarcoma (n=5), synovial sarcoma (n=4), liposarcoma (n=7), chondrosarcoma (n=2), and Ewing sarcoma (n=2) (Table 2).

#### Safety Analysis

The adverse events observed in this report are consistent with those previously described in the safety and toxicity profiles of drugs, trabectedin and nivolumab. The most common adverse events were grade 1 to 2 in severity (Table 3). Four patients experienced Grade 3 adverse events which include decreased hemoglobin levels (9.1%) and laboratory-based measurements of myelosuppression with decrease in granulocyte and platelet count (4.5%, 4.5%). Grade 3 CPK elevations were also observed (4.5%).

#### Efficacy Analysis

There were 4 Partial Responses (PR) including one patient with UPS, one with myxoid liposarcoma, one with chondrosarcoma, and one patient with leiomyosarcoma, 12 Stable Disease (SD), and 6 Progressive Disease (PD) with overall response rate of 18.2% and clinical benefit rate of 72.7%. Figure 1 illustrates the duration of response in a patient with pleomorphic sarcoma. The 6-month

### Table 1: Baseline patient demographics.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Median</th>
<th>Range (32-71)</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13 (46.5%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (53.5%)</td>
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<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>22 (78.5%)</td>
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</tr>
<tr>
<td>Hispanic</td>
<td>4 (14.5%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (3.5%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1 (3.5%)</td>
<td></td>
</tr>
<tr>
<td>Disease Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>28 (100%)</td>
<td></td>
</tr>
<tr>
<td>Performance Score (ECOG)</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>28 (100%)</td>
<td></td>
</tr>
<tr>
<td># Previous Chemotherapy Regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>4 (1-7)</td>
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</tbody>
</table>

### Table 2: Sarcoma subtypes (*Partial responders).

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Leiomyosarcoma*</td>
<td>5 (18.0)</td>
</tr>
<tr>
<td>Liposarcoma*</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Synovial cell sarcoma</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>MFH/UPS*</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Chondrosarcoma*</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Ewing’s sarcoma</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Myofibroblastic sarcoma</td>
<td>1 (3.5)</td>
</tr>
</tbody>
</table>

**Figure 1**: Representative graph showing partial response with decrease in the sum of Longest Diameters (LD) of target lesions (y-axis) status post cycles of treatment with trabectedin and nivolumab (x-axis) as per RECIST v1.1 and irRECIST.
Progression Free Survival (PFS) rate was 68.2% with a median PFS was 45.4 weeks (range of 10 - > 95 weeks). The 6-month Overall Survival (OS) rate was 95.4% with a median OS of >66.5 (11 - >95) weeks (Table 4).

**Discussion**

First line treatment for advanced soft tissue sarcoma is still systemic chemotherapy options like doxorubicin and/or ifosfamide. Recently, newer compounds like gemcitabine, trabectedin and pazopanib have been used. Newer approaches, such as combination of immunotherapy or targeted therapy combined with chemotherapy are currently being evaluated. This retrospective analysis was conducted to analyze the outcome of combination therapy of trabectedin and nivolumab. Trabectedin, as monotherapy, has been associated with an improved PFS in sarcoma patients compared to dacarbazine, with a favorable toxicity profile [23]. Trabectedin gained accelerated approval in Europe in 2007 for advanced STS and full approval for advanced STS and ovarian cancer in 2015 [24], the same year that it gained full approval in the United States for leiomyosarcoma and liposarcoma [24]. Further, we previously reported our 10 years experience with trabectedin in advanced sarcoma wherein chondrosarcoma and synovial sarcoma were shown to have a median PFS of 4.5 and 6.8 respectively with trabectedin monotherapy [25], providing the rationale for using trabectedin for all advanced STS. The most common (≥5%) grades 3-4 laboratory abnormalities implicated with trabectedin are: neutropenia, increased...
ALT, thrombocytopenia, anaemia, increased AST and increased creatine phosphokinase [26]. Nivolumab by itself has not been shown to have any significant effect on previously treated metastatic sarcoma [27]. More severe adverse events related to nivolumab use comprise of immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies, nephritis and encephalitis [28].

The patient population included in this study suffered from a variety of sarcoma subtypes, and all were previously treated at least once. Within this patient population, trabectedin and nivolumab combination chemo-/immuno-therapy resulted in an ORR of 18.2% which is close to two-fold the ORR reported in a study conducted by Demetri et al. with trabectedin alone (ORR=9.9%) [23]. The clinical benefit rate, in terms of decrease in target lesion site (PR=4) along with Stable Disease (SD=12) was 72.7% versus 34 % with trabectedin alone. An improvement (68.2 %)in PFS rate was also noted when compared to a 37% PFS rate reported in the study conducted with trabectedin alone [23]. This benefit was observed irrespective of the disease pathology, previous line of treatment or patient demographics. Median PFS of the combination of these 2 treatment modalities together was >45.5 weeks (>11.3 months) which is greater than 4.2 months with trabectedin alone as reported by Demetri et al. [23]. Another retrospective analysis studying the effect of trabectedin on translocation-related tumours showed a clinical benefit response (tumour control rate) of 59 % along with a median PFS of 4.1 months and a 6-month PFS rate of 40%. This study presented a median OS of 17.4 months [29]. The safety and tolerability of the 2 drugs were consistent with prior extensive reports and trials [30-33]. The most common side effects noted were nausea, vomiting, anaemia, fatigue and myalgia (Table 3). The grade 3 adverse events noted were elevated transaminases, myelosuppression and increased CPK levels. Grade 3 adverse events were managed with dose reduction, supportive care and if necessary with withholding treatment (Table 3). There were no additional adverse events noted with the combination of the 2 drugs.

**Conclusion**

Taken together, the data supports the Prismatic Integration Principle proposed by Gordon and Brigham [34] that (1) killing the tumour and exposing tumour neoantigens in the tumour microenvironment and then (2) vaccinating the patient against one’s own tumour with an immune checkpoint inhibitor or a cytokine that evokes the cytotoxic T cell response, may be needed for induction of long lasting antitumor immunity. Although the number of patients treated was small, our clinical experience with this combinatorial chemo-immunotherapy regimen suggests such synergism and warrants further investigation. Improved overall responses and disease control were noted with the two-drug combination compared to monotherapy in heavily pre-treated soft tissue sarcoma. In contrast, there was no worsening of toxicity with the two-drug combination, even when the combination therapy was given for a long period of time in this small group of patients. Consequently, studies are now in progress to evaluate the safety and efficacy of trabectedin and two immune checkpoint inhibitors, ipilimumab and nivolumab, as first line therapy for advanced soft tissue sarcoma (ClinicalTrials.gov Identifier: NCT03138161).

**References**


