

Limited activity of metronomic cyclophosphamide and pembrolizumab for soft tissue sarcomas

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Provenance: This is a Guest Editorial commissioned by Editor-in-Chief Jia-fu Ji, MD, FACS (Peking University School of Oncology & Beijing Cancer Hospital, Department of Gastrointestinal Surgery, Beijing, China).

Comment on: Toulmonde M, Penel N, Adam J, *et al.* Use of PD-1 Targeting, Macrophage Infiltration, and IDO Pathway Activation in Sarcomas: A Phase 2 Clinical Trial. *JAMA Oncol* 2018;4:93-97.

Received: 01 December 2017; Accepted: 12 December 2017; Published: 15 January 2018.

doi: [10.21037/tgh.2017.12.09](https://doi.org/10.21037/tgh.2017.12.09)

View this article at: <http://dx.doi.org/10.21037/tgh.2017.12.09>

Outcomes for patients with sarcoma remain poor with overall survival for patients in the metastatic setting typically in the range of 12 to 18 months (1). Programmed death 1 protein (PD-1) has become one of the most important targets in cancer immunotherapy (2), particularly for the many inflammatory cancers that contain PD-1 expressing T cells or cells expressing its ligand (PD-L1) (3). While recent studies have shown that some sarcoma patients may respond to PD-1 blockade, responses are highly subtype specific. Even in highly inflammatory subtypes such as undifferentiated pleomorphic sarcoma (UPS), responses are only seen in a minority of patients demonstrating the need for combination therapies that further improve patient outcome (4).

Regulatory T cells (Tregs) may be important for resistance to checkpoint inhibitors in some tumors. While sarcomas rarely have FoxP3 expressing cells, this may be different in PD-L1 high tumors receiving checkpoint inhibitors (5). Metronomic low dose cyclophosphamide inhibits Treg activity and spares effector lymphocytes (6,7). Indeed, anti-PD-1 therapy synergizes with metronomic cyclophosphamide in murine studies by enhancing the clonal expansion of antigen-specific CD8+ T cells. Additionally, combined therapy may even improve the responses in animals with low pre-existing intratumoral PD-L1 expression or that were previously nonresponsive to anti-PD-1 therapy alone (8). Thus, anti-PD-1 agents combined with metronomic cyclophosphamide was anticipated to be a potential

treatment targeting PD-1.

Metronomic oral cyclophosphamide has an established role in the treatment of sarcomas. Dr. Olivier Mir and colleagues treated 26 elderly patients, a PFS of 6.8 months and a response rate of 26.8% were observed (9). Given the baseline activity of metronomic cyclophosphamide, there were hopes that PD-1 antibodies would work in concert with cyclophosphamide to further enhance its antitumor effects.

Dr. Toulmonde and colleagues recently published a phase 2 clinical trial using a Simon two-stage design to assess the efficacy of immunotherapy targeting PD-1 with the combination of metronomic cyclophosphamide chemotherapy in sarcomas (10). Fifty-seven patients with advanced soft tissue sarcoma were enrolled across seven French Sarcoma Group centers. The patients were separated into 4 cohorts: Leiomyosarcoma (LMS, N=15), (UPS, N=16), other sarcomas (others, N=16), and gastrointestinal stromal tumor (GIST, N=10). The patients received cyclophosphamide 50 mg bid 1 week on and 1 week off, as well as 200 mg of intravenous pembrolizumab every 3 weeks. Seven of the 57 patients were excluded from the efficacy analysis due to (I) no prior previous line of chemotherapy in palliative setting; (II) prior treatment with cyclophosphamide; or (III) receiving cyclophosphamide treatment exclusively without receiving pembrolizumab.

The primary endpoint was the 6-month non-progression and objective response rate. The study had the potential to recruit 30 patients in each of the “LMS”, “UPS”, and

“others” cohort, requiring either 8 objective responses (ORs) or 20 non-progressions for a significant result. Following the recruitment of the first 15 patients, each cohort would only continue if there were at least 3 ORs or 7 non-progressions. Unfortunately, none of the cohorts reached these criteria with negative results and the study subsequently concluded. Both the “LMS” and “UPS” had 0% 6-month non-progression. Only two of the 14 patients in the “others” (14.3%) was progression free after 6 months, one patient with endometrial stromal sarcoma and one with solitary fibrous tumor.

A separate analysis was performed for GIST patients. They had planned to recruit 28 GIST patients and required at least 13 non-progressions for a significant result. Following the recruitment of the first 10 patients, the study would only continue if there were at least 4 non-progressions. Only one patient out of the eligible 9 patients (11.1%) showed non-progression and subsequently the study was halted.

While this study had a negative result in terms of clinical responses, these results raise important questions regarding pembrolizumab's antitumor activity in advanced sarcoma. Given that only three out of 50 patients showed clinical benefit here, it may be that the cyclophosphamide actually reduced the activity of pembrolizumab rather than enhancing it by lymphodepleting CD8+ T cells in addition to the Treg cells. Other potential problems include the lower than expected PD-L1 expression. In other cancers, tumors have been seen to be more responsive to pembrolizumab when higher percentage of tumor cells express levels of PD-L1 (11).

The study also anticipated resistance to treatment through the tumor promoting effects of M2 macrophage and indoleamine-2,3-dioxygenase (IDO). PD-1/PD-L1 interactions can drive macrophages towards an M2 phenotype with high levels of IDO expression (12-14). IDO has been established as a key mediator of immune evasion through catabolization of tryptophan into kynurenine and resultant suppression of T cells and NK cells while enhancing Treg cells (15). The authors propose conducting future studies of incorporating IDO targeted therapy to anti-PD-1 regimen. Further work testing new combinations will be critical to find effective immunotherapy regimens.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/tgh.2017.12.09

Cite this article as: Lien IC, Pollack SM. Limited activity of metronomic cyclophosphamide and pembrolizumab for soft tissue sarcomas. *Transl Gastroenterol Hepatol* 2018;3:4.