Predicting response to immune checkpoint blockades in sarcoma

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[Scientific Abstract]

Background and Rationale: Sarcoma is an aggressive, highly heterogeneous (>70 subtypes) tumour resistant to systemic standard-of-care. Alternatively, a subset of sarcoma patients have benefited from a newer therapeutic approach using immune checkpoint blockade (ICB) based on the PD-1/PD-L1 axis, which triggers T cells to recognize and attack tumour cells in a patient's immune system. Despite the therapeutic advancements, predictive measures that play roles in the therapeutic responses need further improvement.

Objective(s): Our study aims to predict sarcoma patients who would respond to immune checkpoint blockades using quantifiable determinants from multi-omic datasets in sarcoma. The aims of our study include: (1) estimation of tumour cell-intrinsic features using genomic data; (2) estimation of tumour cell-extrinsic features using transcriptomic data; and (3) classification of immune checkpoint blockade therapy responders by integrating multi-omic data from our MOHCCN cohort and annotation-rich external cohorts.

Methods & Results: Within MOHCCN-PR2C, we established a multi-year, pan-sarcoma cohort of matched transcriptomes, proteomes, and genomes (134 sarcoma tumours; 116 patients; 28 subtypes), and collected external datasets (552 sarcomas; 1,267 normal tissues) with annotations of sarcoma immune classification and immunotherapeutic response groups.

To date, we analyzed transcriptomes from sarcoma tumours using: (1) deconvolution of expression patterns into biologically interpretable gene expression programs; (2) estimation of immune cell infiltration in tumour microenvironment; and (3) cross-cohort integration of these transcriptomes with the external sarcoma cohorts to transfer immunotherapy-relevant annotation labels.

Conclusion(s): Using multi-transcriptomic integration, our approach can stratify sarcoma patients with immunotherapy response determinants.

Anticipated Impact: Our study will enhance our understanding of sarcoma immuno-biology and leverage to learn about immunotherapy-relevant determinants of potential responders to immune checkpoint blockade therapy in sarcoma. Furthermore, this disease-agnostic approach has broad applicability to other cancers where ICB is a therapeutic option.

[Plain Language Summary]

Background and Rationale: Sarcoma can be divided into bone and soft-tissue sarcomas, and the subtypes can be further categorized by the location of tumour origin (>70 subtypes). Most sarcoma patients receive surgery, radiotherapy and chemotherapy for their treatments, however, they often experience metastases and recurrence at high rates. With a newer therapeutic approach using a patient's tumour-fighting immune cells (e.g., T cells), some sarcoma patients have benefited from longer survival.

Objective(s): Our study focuses on predicting responders to immunotherapy in sarcoma using a collection of patient data from multiple sources, including information on the immunotherapeutic responders and non-responders.

Methods & Results: Within the MOHCCN-PR2C research community, we have generated a large number of sarcoma patient data with different subtypes. Using various computational approaches, we have systematically analyzed the data and expanded our analyses to externally available cohorts with patient-related annotations (which can be used as factors to predict the immunotherapeutic responses). To date, we have successful cases in which we could accurately classify two sarcoma patients with recurrences to support biological evidence that these patients are likely to respond to immunotherapy.

Conclusion(s): Our computational analysis approach can classify sarcoma patients who would likely respond to immunotherapy.

Anticipated Impact: Our study will enhance our understanding of sarcoma tumour immuno-biology and leverage to learn about immunotherapy-relevant factors of potential responders to immune checkpoint blockade therapy in sarcoma. This impact can be extended to supporting evidence for patients at the time point of a recurrence and/or metastasis after conventional therapies.