Natural Killer and Cytotoxic T Cell Immune Infiltrates are Associated with Superior Outcomes in Soft Tissue Sarcomas

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Background

Immunotherapy has been a game changer in cancer treatment; however, there is currently a lack of effective immunotherapies for soft tissue sarcomas (STS). Although the majority of current cancer immunotherapies focus on amplifying the anti-tumor properties of T-cells, natural killer (NK) cells have been shown to be promising targets due to their innate cytotoxic characteristics, their ability to target cells without prior sensitization, and their ability to respond to diverse stimuli. Tumor infiltrating lymphocytes (TILs) have been shown to predict survival in STS, but the contribution of specific lymphocyte subsets such as NK and memory T cells to STS outcomes is undefined[1,2].

Objectives

To characterize the extent of NK and T cell infiltration in STS and to determine the correlation of these cytotoxic immune cells to patient outcomes

Methods

Archived tumor tissue from 90 STS patients collected from 2008-2020 was evaluated. Tissue microarrays (TMAs) were constructed, and immunohistochemical (IHC) analyses were performed by an STS pathologist for CD3, CD8, CD45RO, NKp46, TIGIT, and MHC-I. TIL scores of H&E slides were calculated. Metastasis-free survival (MFS) and overall survival (OS) were analyzed by Kaplan-Meier method.

Results

Figure 1: Representative IHC staining

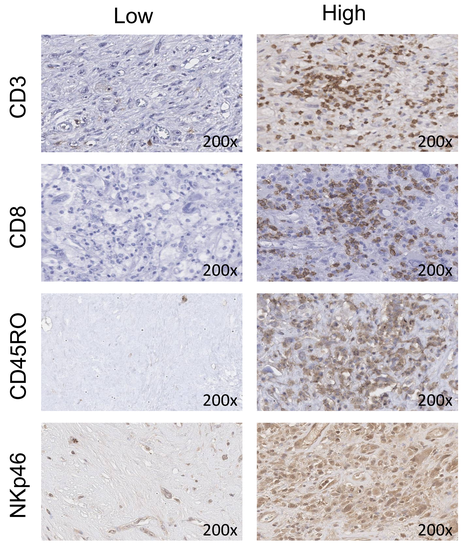


Table 1: Patient and clinical characteristics

	N = 90
Age (years)	62 (22 – 89)
Male	58%
Tumor size (cm)	13.2 (1.8 – 36)
Tumor site	
Extremity	58%
Retroperitoneal	23%
Trunk	16%
Tumor histology	
Liposarcoma	29%
Myxofibrosarcoma	23%
Pleomorphic sarcoma	20%
Leiomyosarcoma	7%
Other	21%
Survival	
Distant recurrence	53%
Died	28%
Median follow-up (months)	46 (0 – 143)
Median MFS (months)	25
Median OS (months)	91

Figure 3: Correlation of lymphocytic infiltrates with immunomodulatory markers MHC-I and TIGIT. MHC-I – stimulatory for T cells and inhibitory for NK cells; TIGIT – immune cell exhaustion marker

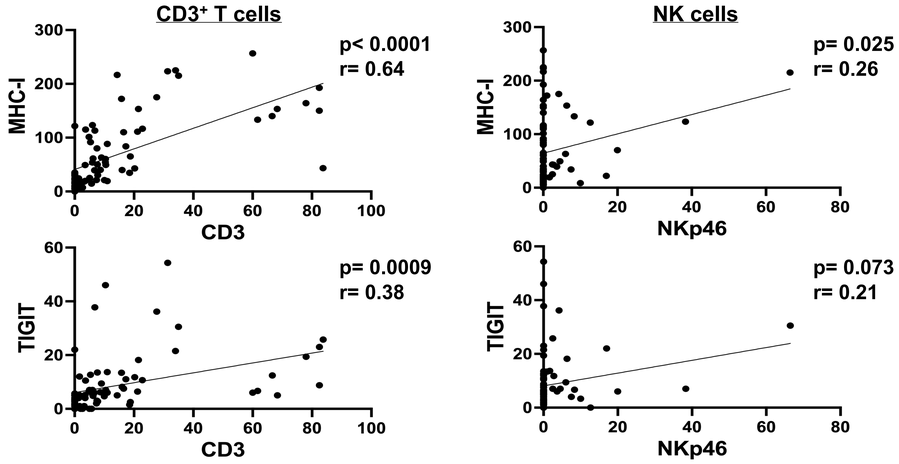


Figure 2: Patient overall survival and metastasis-free survival.

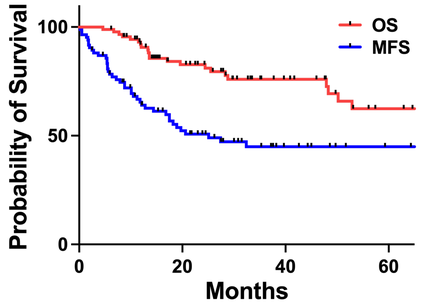
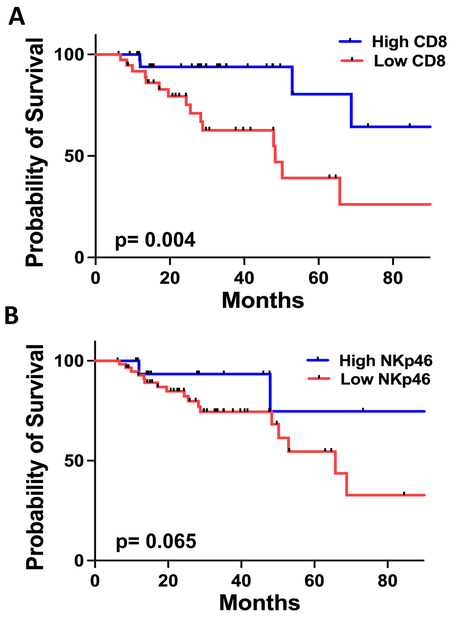


Figure 4: Cytotoxic lymphocyte subsets and overall survival. A) CD8 is a marker for cytotoxic T cells. B) NKp46 is a marker for NK cells



Conclusions

- We confirmed a positive correlation between TILs and improved outcomes in STS, including cytotoxic cells.
- We noted a trend of higher NKp46 scores to correlate with superior overall survival.
- Immune infiltrates, including NK cells, are prognostic in STS.
- These results may be relevant in other checkpoint resistance tumors, like pancreatic and colorectal cancer.

Future Directions

Further characterization of immune infiltrate in STS and other cancers is needed. Potential clinical translation includes:

- Biomarkers of prognosis
- Immune targeting

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References

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