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Matched T cell repertoire analysis of peripheral blood and tumor-infiltrating lymphocytes (TILs) in early stage breast cancer (ESBC) patients (pts) treated with pre-operative cryoablation (cryo) and/or Ipilimumab (Ipi)

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Background

Cryo plus anti-CTLA-4 therapy induces antigen-specific clonal T cell expansion, enhanced survival, and long-term anti-tumor immunity in mice [1]. We recently demonstrated that pre-operative cryo and/or anti-CTLA-4 therapy with Ipi is well tolerated and clinically feasible in women with ESBC. Furthermore, cryo with or without Ipi generates a polyclonal influx of novel T cell clones within the tumor bed [2,3]. Here, we utilize T cell repertoire analysis to explore the impact of cryo and/or Ipi on clonal expansion within peripheral blood and TILs.

Methods

In a pilot study, women with ESBC were treated with cryo 7-10d before mastectomy (6 pts), single-dose Ipi (10 mg/kg) 8-15d before mastectomy (6 pts), or cryo+Ipi (6 pts). Peripheral blood mononuclear cells (PBMCs) and tumor tissue were obtained pre-mastectomy (immediately preceding cryo and/or 1-5d after Ipi), and at mastectomy. T cell repertoire analysis was conducted on extracted DNA using an Illumina® DNA deep sequencing platform and ImmunoSEQ™ software. Clones comprising ≥0.01% of sample DNA were analyzed, and results are reported descriptively.

Results

Cryo with or without Ipi was associated with decreases in absolute TIL count (median change: Ipi +6%, cryo -73%, cryo+Ipi -16%). However, cryo+Ipi was associated with the greatest expansion of TIL clones across the range of 10^2-10^4 amplicons (table 1), although no difference was observed by group in PBMC clones. Across all samples, a median of 523 TIL clones increased by ≥10^2 amplicons, and a median of 4 TIL clones increased by ≥10^3 amplicons. The Ipi/cryo group exceeded the median in 80% (4/5) of cases. 21% of all TIL clones were detectable in time-matched PBMC, whereas 16% of expanding (≥10^2) TIL clones were detectable in time-matched PBMC.

Conclusion

Cryo plus Ipi expands more TIL clones than either strategy alone. Therapy-associated clonal expansion may be difficult to detect in PBMCs. These data highlight the potential importance of TIL repertoire analysis for the monitoring of pts treated with cryo and/or Ipi in the preoperative setting. In a follow-up randomized study, we will evaluate whether TIL clonal expansion across the 10^2-10^4 range can be used to predict recurrence-free survival.

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Table 1 Therapy-associated T cell clonal expansion in TILs and PBMCs.

	Median # TIL clones expanding by			Median # PBMC clones expanding by		
	$\geq 10^2$ amplicons	$\geq 10^3$ amplicons	$\geq 10^4$ amplicons	$\geq 10^2$ amplicons	$\geq 10^3$ amplicons	$\geq 10^4$ amplicons
Cryo	199	2	0	697	1	0
Ipi	750	22	1	545	5	0
Cryo+Ipi	2010	85	1	830	1	0

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