Rational combinations of active and passive immunotherapy mobilize immune and clinical responses in terminal cancers

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Abstract

Solid tumors encroach on the. Strategies to enhance the specificity of the endogenous T cell population against tumors have been met with limited clinical success. We aimed to devise a 2-tier protocol coupling in vivo whole antigen priming with ex vivo cellular expansion to clinically evaluate survival in patients following re-infusion of primed, autologous T cells, determining treatment efficacy. Treatment commenced with the acquisition of whole tumor antigens from tumor cell lines corresponding with patients??? primary malignancy. Lysate mixture was inoculated intradermally while Peripheral Blood Mononuclear Cells (PBMCs) were periodically extracted via phlebotomy and expanded in culture ex vivo for re-infusion. Post treatment tumor-specific T cell response and cytotoxicity was confirmed via ELISpot and Real-Time Cell Analyzing (RTCA) Assay. Serum cytokine levels and cytotoxicity scores were evaluated for associations with survival status and duration. There was significant increase in cytotoxicity exhibited by T cells measured using both ELISpot and RTCA following treatment. Correlation analysis determined significant association between higher post treatment cytotoxicity scores and survival status (R=0.52, p=0.0028) as well as longer survival duration in months (R=0.59, p=0.005). Our use of whole cell antigens proved effective in its task of in vivo priming, thereby greatly facilitating the ex vivo cell expansion as previously noted. The unique PBMC culture system used in this study achieved over 85% CD8+ lymphocyte concentration post expansion. The data showed a clear increase in tumor-specific cytotoxicity post treatment (p=0.037), which directly translated to an improved survival rate both categorically (p=0.0028) as well as duration in months (p=0.005). This same trend was backed up by the IFN-? ELISpot count which demonstrated a positive association of the IFN-? ELISpot score with survival duration (p=0.04). In the future, dedicated studies in the recruitment of sufficient patients of specific cancers will streamline this process host???s immune microenvironment to favor its own proliferation and allow more in-depth analysis of post treatment changes segregated by each defined tumor cell line chosen. Conduction of formal randomized controlled trials will be the direction to take in future studies.

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