Journal for ImmunoTherapy of Cancer

POSTER PRESENTATION Open Access

Level of PD-1 expression on CD8+ T cells influence prognosis and respond to PD-1 therapy in a murine model

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From 30th Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer (SITC 2015)
National Harbor, MD, USA. 4-8 November 2015

Introduction

Prognosis varies dramatically in head and neck squamous cell carcinoma (HNSCC) based on HPV status. In HPV^+ patients, programmed death (PD)-1 expression has been linked to a better clinical outcome. We hypothesized that extent of PD-1 expression may differentially impact T cell phenotype, patient prognosis and response to anti-PD-1 immunotherapy in a murine HPV^+ cancer model.

Material and methods

Freshly isolated tumor infiltrating lymphocytes (TIL) from HNSCC patients were stained by flow cytometry for expression level of PD-1 expression ($PD\text{-}1^{high}$ vs. $PD\text{-}1^{low}$), granzyme B, or IFN-y secretion by ELISPOT. The prognostic impact of $PD\text{-}1^{high}$ vs. $PD\text{-}1^{low}$ T cells was determined in a cohort of HNSCC patients (n=56, median follow up=19 mo). In a murine HNSCC model, $PD\text{-}1^{high}$ and $PD\text{-}1^{low}$ fractions were compared from $CD3^+$ $CD8^+$ $PD\text{-}1^+$ cells and analyzed according to different treatment groups (untreated, anti-PD-1 mAb, radiotherapy and 3 different anti-PD-1/radiotherapy combinations).

Results

CTLA-4 and PD-1 were significantly upregulated on both HPV^+ and HPV^- HNSCC patients' TIL, whereas $PD\text{-}1^+$ $CD8^+$ cells were significantly enriched in TIL from HPV^+ patients (p=0.006). Interestingly, $PD\text{-}1^{high}$ cells represented a more dysfunctional phenotype, with severely compromised IFN-γ secretion (phigh $CD8^+$ TIL were more likely to be HPV^- and had a worse disease free survival (HR = 2.25; 95% CI = 1.46 – 3.15; p < .0001), while high fractions of $PD\text{-}1^{low}$ T cells were associated with better clinical outcome (HR= 0.19, 95% CI = .07 - .49, p = .0006), and were seen preferentially in HPV^+ HNSCC patients. In the murine HNSCC model, anti-PD-1 mAb plus radiotherapy resulted in optimal tumor elimination, which was associated with an elimination of $PD\text{-}1^{high}$ $CD8^+$ T cells and – most importantly – increase in $PD\text{-}1^{low/intermed}$ T cell frequencies (p < 0.5).

Discussion

Consideration of different PD-1 expression levels on TIL segregates PD-1 expression as a marker of activated, competent tumor reactive T cells on the one hand (low/intermed expression), and as a marker of exhausted, dysfunctional cells in the tumor microenvironment on the other hand (high expression). These results emphasize the crucial role of differential PD-1 expression levels on HNSCC patients' effector T cells for prognosis and as a potential novel biomarker for anti-PD-1/PD-L1 based immunotherapy.

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Published: 4 November 2015

doi:10.1186/2051-1426-3-S2-P228
Cite this article as: Kansy *et al.*: Level of PD-1 expression on CD8+ T cells influence prognosis and respond to PD-1 therapy in a murine model. *Journal for ImmunoTherapy of Cancer* 2015 **3**(Suppl 2):P228.