Journal for ImmunoTherapy of Cancer

POSTER PRESENTATION Open Access

Enhanced tumor-infiltrating lymphocytes (eTIL) for cellular therapy of patients with pancreatic cancer or glioblastoma

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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

Purpose

The generation of T lymphocytes with specific reactivity against autologous tumor cells is a prerequisite for effective targeted cellular therapies. We established a protocol for tumor infiltrating lymphocytes (TILs) cultures from small biopsies or surgically resected material obtained from patients with pancreatic ductal adenocarcinoma (PDAC) and patients with glioblastoma.

Methods

Tumor specimens obtained from 17 patients with PDAC and 16 patients with glioma were cultured with TIL medium, containing IL-2, IL-15 and IL-21. Activity of TILs directed against shared tumor associated antigens (TAAs, mesothelin, survivin and NY-ESO-1, EGFRvIII) was detected by Intracellular staining (ICS). Cytotoxicity was measured using a Chromium-51 release assay and the specific activity of TILs against autologous tumor was measured by INF-γ production. TCRVb analysis was investigated by a multiplex antibody TCR Vb specific panel. TCR clonality was gauged by CDR3 region PCR analysis and subsequent sequencing. The T cell phenotype, as well as activation/exhaustion marker profile was tested by flow cytometry.

Results

We could reliably expand TILs, that resided predominantly in the central memory population ($CD45RA^-$, $CCR7^+$), from 33/33 patients. We were able to expand about 1.5 x 10e9 TIL from small PDAC biopsies. TIL showed reactivity to common TAAs, i.e. to mesothelin (16/17 in PDAC, 8/16 in glioma), survivin (12/17 in PDAC, 6/16 in glioma) or to NY-ESO-1(11/17 in PDAC, 6/16 in glioma) defined by intracellular cytokine staining. TIL cultures exhibited preferential usage of Vβ families (e.g. some TIL showed 99.3% Vb13.2, 99.60% Vβ2, 97.00% Vβ5.1 in $CD4^+$ or $CD8^+$ TIL). A PDAC $Vb13.2^+$, $CD8^+$ TIL clone strongly recognized autologous tumor cells, defined by INF-γ production, which could be blocked by the anti-HLA class 1 antibody (W6/32). TIL from glioma patients exhibited up to 25% IFN-γ and TNF-α production directed against autologous tumor cells, defined by ICS. TILs from PDAC and glioma showed strong cytolytic functions directed against autologous tumor cells, i.e. up to 70% specific lysis at an effector/target ratio at 25/1 by chromium-51 release assay.

Conclusions

We have optimized methods for generating pancreatic cancer and glioblastoma specific TIL cultures from small resected tumor specimens. Tumor specimens are currently sequenced to detect potential targets for anti-PDAC and anti-glioma directed T cell clones. A Phase I study to administer TIL for patients with pancreatic cancer or glioblastoma will start at Karolinska.

Published: 4 November 2015

doi:10.1186/2051-1426-3-S2-P35
Cite this article as: Meng *et al.*: Enhanced tumor-infiltrating lymphocytes (eTIL) for cellular therapy of patients with pancreatic cancer or glioblastoma. *Journal for ImmunoTherapy of Cancer* 2015 **3**(Suppl 2):P35.

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