Background
Adoptive T cell therapy with autologous tumor infiltrating lymphocytes (TIL) has demonstrated clinical efficacy in patients with metastatic melanoma and cervical carcinoma.

In some studies, better clinical outcomes have positively correlated with the total number of cells infused and/or percentage of CD8+ T cells.

Most current production regimens solely utilize IL-2 to promote TIL growth.

Enhanced lymphocyte expansion has been reported using IL-15 and IL-21-containing regimens.

This study describes the positive effects of adding IL-15 and IL-21 to IL-2 in a second generation TIL protocol recently developed by Iovance Biotherapeutics.

Generation of TIL using a novel process developed at Iovance

MATERIALS & METHODS

- The process of generating TIL includes a pre-Rapid Expansion Protocol (pre-REP), in which tumor fragments of 1-3 mm³ size are placed in media containing IL-2.
- During the pre-REP, TIL emigrate out of the tumor fragments and expand in response to IL-2 stimulation.
- To further stimulate TIL growth, TIL are expanded through a secondary culture period termed the Rapid Expansion Protocol (REP) that includes irradiated PBMC feeders, IL-2 and anti-CD3 antibody.
- A shortened pre-REP and REP expansion protocol was developed at Iovance to expand TIL while maintaining the phenotypic and functional attributes of the final TIL product.
- This shortened TIL-generation protocol was used to assess the impact of IL-2 alone versus a combination of IL2/IL15/IL21 added to the pre-REP step.
- These two culture regimens were compared for the generation of TIL grown from colorectal, melanoma, cervical, triple negative breast, lung and renal tumors.
- At the completion of the pre-REP, cultured TIL were assessed for expansion, phenotype, function (CD107a+ and IFNγ) and TCR Vβ repertoire.

RESULTS

IL-2/IL15/IL21 enhances the percentage of CD8+ cells in lung carcinoma, but not in melanoma

Expression of CD27 is slightly enhanced in CD8+ cells in cultures treated with IL-2/IL15/IL21

T cell subsets are unaltered with the addition of IL-15/IL-21

Enhancement in expansion during the pre-REP with IL-2/IL-15/IL-21 in multiple tumor histologies

The functional capacity of TIL is differentially enhanced with IL-2/IL-15/IL-21

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CONCLUSIONS

- This work demonstrates the ability of the IL-2/IL-15/IL-21 cocktail to enhance TIL numbers compared to IL-2 alone (>20%) in Iovance Generation 2 process, in addition to impacting phenotypic and functional characteristics.
  - The effect of the triple cocktail on TIL expansion was histology-dependent.
  - The CD8+/CD4+ T cell ratio was increased with the addition of IL-2/IL-15/IL-21 in lung tumors.
  - The addition of IL-15 and IL-21 enhanced CD107a expression and IFNγ production in TIL derived from lung tumors.
  - The addition of IL-2/IL-15/IL-21 altered the TCR Vβ repertoire in the lung.
- The Generation 2 Iovance TIL expansion process was used to encompass the IL-2/IL-15/IL-21 cytokine cocktail, thereby providing a means to further promote TIL expansion in specific tumor histologies, such as lung and colorectal tumors.
- These observations are especially relevant to the optimization and standardization of TIL culture regimens necessary for large-scale manufacture of TIL with the broad applicability and availability required of a mainstream anti-cancer therapy.

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