

Tumor infiltrating lymphocyte (TIL) therapy for treating the solid tumors: Challenges and future perspectives

Sharma Bhartendra, Kaur Sukhbir, Sharma Vikas and Soni Sanjay

Dear Sir, immunotherapy is one of the effective methods discovered in the treatment of cancer and adaptive cellular therapy (ACT) is one among them. Chimeric antigen receptor (CAR) T-cell therapy is the primary form of ACT in which the patient's own T-Cells are modified for binding, attacking and eliminating the tumor antigen in hematological malignancies. But CAR T-cell therapy is not effective in treating the solid tumors. In this regard, the TIL therapy had provided good results in the global clinical trials and benefitted patients with different types of solid tumors. TILs are the naturally produced mononuclear cells which infiltrate the solid tumor microenvironment (TME). These are also called as the immune cells of the tumor [1]. TIL therapy was discovered by Steven Rosenberg in 1982. He had isolated TILs from the mouse tumor and proved that TILs, cyclophosphamide and interleukin (IL)-2 in combination is beneficial in hepatic and pulmonary metastasis treatment in the mice. Further, in 1988, first time Steven Rosenberg and his group administered TIL therapy in humans and noted favorable outcomes in patients with metastatic melanoma [2, 3]. Generally, there are two types of TILs, intratumoral (iTILs) and stromal (sTILs). iTILs are very rare and their detection is very difficult in tumor cells whereas sTILs are commonly present in tumor cells and their detection is very easy. TIL therapy involves isolation of the naturally infiltrating lymphocytes from tumor tissues, *in vitro* expansion and then infusion of these cells in patients for identifying and killing tumor cells. During reinfusion of TILs high dose of interleukin IL-2 is also administered parallelly. Prior to reinfusion, a non-myeloablative lymphodepletion NMA regimen is provided to the patients for suppressing the immune system and enhancing the effectiveness of infused TIL products. After the reinfusion significant anti tumor reactivity were noted. Therapeutic effects are increased with combined infusion of IL-2 and TILs. Globally, TIL therapy has been applied successfully in patients with metastatic melanoma, breast cancer, ovarian cancer, cervical cancer and other solid tumors and favorable outcomes are reported. In TIL therapy the T cells act directly against self-antigens and tumor specific neoantigens and multiple numbers of effector memory T cells, which express chemokine receptors after getting stimulated by the tumor antigen *in vivo*, thus making it easier for transfusion. It has low toxicity because it is obtained from patients without any genetic

manipulation [4]. In spite of having multiple benefits, this therapy also has limitations for many solid tumors. For isolating TILs surgery is needed for resecting the tumor which is very risky and distressful for cancer patients. And even after the surgery the tumor is not accessible always. Further for resecting tumor advanced technological set up and equipments are required which is not possible everywhere. There is lack of effector T cells consisting of antitumor activity, this can be overcome by adopting strategies like topical injections, bispecific molecules and combined use with checkpoint inhibitors. Further, multiple types of gene mutations are exhibited by the tumor cells which further generate different kinds of neoantigens. Therefore it becomes very difficult to formulate universal TIL for eliminating cancer cells. Another concern is the reduced elimination ability of tumor cells due to their immunosuppressive microenvironment which requires exploration of specific exhaustion markers such as single-cell level analytic technologies, new TIL subsets, single cell RNA sequencing, single-cell mass cytometry etc. Additionally, the survival time of infused TIL is short *in vivo*, for this modifications in TIL technology are recommended. In future, there is need for improving the isolation and expansion of efficient tumor-reactive T cells and exploring the alternative combined therapies [4].

AUTHOR CONTRIBUTIONS

Bhartendra Sharma conceptualized and designed the study, drafted/revised the manuscript, and approved the final manuscript. Sukhbir kaur acquired data and collected reviews. Vikas Sharma edited, drafted and revised manuscript Sanjay Soni reviewed and approved the final manuscript.

CONFLICTS OF INTEREST

Authors have no conflicts of interest to declare.

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Sharma Bhartendra: Department of Critical Care Nursing, Mahatma Gandhi Nursing College, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur, Rajasthan, India

Correspondence to: Sharma Bhartendra,
email: bhartendrasharma@mgumst.org

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