TIL Therapy in Melanoma: Where We Stand

The Melanoma Research Alliance looks at the research, benefits and challenges of a cellular therapy using tumor-infiltrating lymphocytes (TIL) to treat the skin cancer.

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This blog post is by Tanisha Jackson, PhD, MRA Scientific Program Director.

Despite the incredible progress made to develop new treatment options for melanoma, almost 50% of patients are still not responding to the latest approved therapies. To address this important unmet need for patients with difficult to treat melanoma, clinicians are looking to new strategies including cellular therapy. Cellular therapies use the body's own immune cells, such as lymphocytes, to attack tumors. One type of cellular therapy, Tumor Infiltrating Lymphocytes – often shortened to "TILs" – are immune cells that are embedded within the tumor and have the potential to recognize and destroy tumor cells.

In TIL therapy, immune cells called lymphocytes are separated from a patient's surgically removed tumor, grown in large numbers in the lab over a set number of days, and then reinfused back into the patient. Prior to receiving their personalized TIL infusion, a patient's existing lymphocytes are depleted using chemotherapy. After the TIL infusion, patients are treated with a therapy that stimulates the immune system to grow and divide. The newly infused army of TILs go on to wipe out cancer cells in the body.

New TIL Therapy Clinical Trial Results

- Dr. John Haanen, of the Netherlands Cancer Institute, reported positive results from a phase 3 clinical trial in which patients with melanoma were treated with either ipilimumab (anti-CTLA-4 immunotherapy) or TIL therapy at the September 2022 ESMO Congress. Patients treated with TIL therapy had a median overall survival benefit of 25.8 months, compared to 18.9 months for those who received ipilimumab. This is notable because all patients enrolled in this study had received PD-1-based immunotherapies. These encouraging findings were also recently

published in the New England Journal of Medicine.

- Similarly, exciting data were also shared at the Society for Immunotherapy of Cancer (SITC) annual meeting by Dr. Amod Sarnaik of the Moffitt Cancer Center & Research Institute. Dr. Sarnaik reported on the largest Phase 2 study to date exploring the use of TIL therapy in patients with advanced melanoma who have progressed on or after treatment with checkpoint immunotherapy and/or BRAF/MEK targeted therapy. In this study, patients were treated with an experimental TIL therapy called lifileucel. Lifileucel is an individualized TIL therapy developed by Iovance Biotherapeutics that reinvigorates a patient's TIL so they can be deployed to fight cancer. In this process, a patient's naturally occurring TIL are collected from a portion of their own tumor and grown outside the body using Iovance's proprietary manufacturing process to produce the TIL therapy. The overall response rate for patients treated with lifileucel, which measures tumor shrinkage, was 31% with almost half of the responses lasting for more than 24 months. Based on these encouraging results, Iovance Biotherapeutics submitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) for lifileucel on March 24, 2023.[1] The FDA will soon begin evaluating the application and hopefully lifileucel TIL Therapy will be approved later this year.

- In the past melanoma patients with brain metastases have been excluded from many clinical trials including ones testing TILs. Also, at SITC, Dr. Allison Betof Warner of Memorial Sloan Kettering Cancer Center announced a new small clinical trial of 10 patients that just opened at MSKCC testing Lifileucel for patients with melanoma who have asymptomatic brain metastases (meaning they are not causing any neurological symptoms). This exciting pilot trial will help us understand safety and the potential efficacy of TIL therapy among this important patient population.

Advantages & Challenges of TIL Therapy

Clinical trial results show that TIL therapy creates robust and durable anti-tumor activity, even in patients who have been treated with BRAF/MEK targeted and immune-based therapies. In addition, most side effects of TIL therapy are caused by the chemotherapy regimen needed before the TIL therapy infusion or the IL-2 given after the infusion to jump start the immune response; both can be managed. TIL therapy is a truly personalized approach to treating melanoma.

However, a few challenges also exist:

- The production time for TILs is 2-3 weeks and treatment requires inpatient hospitalization;
- TIL therapies are expected to be expensive, following in the footsteps of other cell therapies approved in other cancer types, such as CAR-Ts;
- As seen with other melanoma treatments, resistance to TIL therapy can develop if melanoma cells reduce the expression of molecules on their surface that TILs recognize and target for killing, which can allow melanoma cells to escape immune system recognition and continue to divide.

Patient accessibility, optimization of physician care and the potential cost of TILs will need to be addressed and considered before scaling access to TIL therapy to patients outside of a clinical trial. However, biotech companies and clinicians are already thinking of alternative ways to deliver this therapy to improve access and potentially reduce cost. In addition, combining TILs with other immune therapies is being tested in a number of clinical trials to improve the potency of TIL therapy and perhaps combat resistance.

TIL Therapy for Advanced Melanoma

Clinical trials have shown that response rates to TIL therapy in patients with anti-PD-1 resistant melanoma are between 25–50%. In fact, in patients who do respond to TIL therapy, 80% experienced either a complete response, partial response, or stable disease. In addition, in several patients, the durability of the response was quite striking and lasted for many years. Taken together, these exciting clinical trial results highlight the many benefits of TIL therapy to patients facing melanoma.

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