T-Cell Therapy Delays Disease Progression for People With Advanced Melanoma

Patients treated with tumor-infiltrating lymphocytes saw a 50% reduction in disease progression or death.

September 22, 2022 By Liz Highleyman

Personalized treatment for advanced melanoma using tumor-infiltrating lymphocytes (TILs)—T cells with a proven ability to recognize and fight cancer—reduced the risk of disease progression or death compared with checkpoint inhibitor immunotherapy, according to research presented at the European Society for Medical Oncology (ESMO) Congress 2022.

"This study shows for the first time in a randomized, controlled trial that cell therapy can be efficacious and beneficial for patients with solid cancers," lead investigator John Haanen, MD, of the Netherlands Cancer Institute in Amsterdam, said in an ESMO press release. "For patients with melanoma, we see a 50% reduction in the chance of progression of the disease or dying from the disease, which is absolutely practice changing."

Melanoma is among the malignancies most susceptible to immunotherapy, treatment that helps the immune system fight cancer. Standard therapy for advanced melanoma may include the PD-1 checkpoint inhibitors Keytruda (pembrolizumab) or Opdivo (nivolumab), which restore T-cell activity against cancer cells, or the CTLA-4 inhibitor Yervoy (ipilimumab), which promotes T-cell proliferation.

Tumor-infiltrating lymphocyte therapy is a customized treatment that involves collecting T cells from a patient's tumor sample, multiplying them in a laboratory and reinfusing the expanded cells back into the body. TIL therapy is not new—it was developed at the National Cancer Institute in the 1980s—but while some patients had very good outcomes, the side effects could be severe, and it took a backseat to checkpoint inhibitor immunotherapy.

The Phase III M14TIL trial compared TIL therapy versus Yervoy in 168 adults with previously treated unresectable (inoperable) Stage IIIC to Stage IV melanoma, nearly 90% of whom had progressed despite treatment with a PD-1 inhibitor. This is the first randomized, controlled trial to compare TIL therapy against a checkpoint inhibitor.

“[Checkpoint inhibitors] have a very good safety profile and quite high efficacy and are now often given as first-line therapy,” Haanen said. “But if patients fail first-line treatments, then the options become very scarce, particularly for patients failing anti-PD-1 drugs, so there is a real unmet need.”

The participants were randomly assigned to receive a single round of TIL therapy or up to four doses of Yervoy administered by IV infusion every three weeks. Those assigned to the TIL group were hospitalized and underwent strong chemotherapy to reduce the number of existing lymphocytes and make room for the new ones. After the cell infusion, they received high doses of interleukin-2, a cytokine that stimulates T-cell growth and activity.

People treated with TIL therapy had significantly longer progression-free survival (PFS), meaning they were still alive without disease progression. The median PFS time was 7.2 months with TIL therapy versus 3.1 months with Yervoy, and the PFS rates at six months were 53% versus 21%, respectively. Overall survival also appeared to be longer in the TIL group (25.8 months versus 18.9 months), but follow-up is ongoing. The overall response rate, or tumor shrinkage, was more than twice as high in the TIL group (49% versus 21%), and the complete response rate, or full remission, was nearly three times as high (20% versus 7%).

TIL treatment was generally safe, but side effects were common. Everyone who received TIL therapy and 57% of those treated with Yervoy experienced Grade 3 or higher adverse events. Common side effects included white blood cell and platelet deficiencies, which can lead to infections and excessive bleeding. Most of the adverse events were attributable to the accompanying chemotherapy or interleukin-2 rather than the TILs themselves. However, Haanen noted, these side effects “are well manageable and most resolve by the time patients leave the hospital after their TIL therapy.”

Speculating about why TIL therapy is effective after PD-1 checkpoint inhibitors have stopped working, Haanen said, “We think that the mechanism of resistance to anti-PD-1 treatment is mostly delivered by the tumor microenvironment. So when we take these cells out of their natural environment, reactivate them in the laboratory, grow them up to very large numbers and give them back to the patients, we can overcome some of the escape mechanisms.”

Haanen added that TIL therapy has the potential to work against a wide variety of solid tumors, and clinical trials are currently underway for people with many malignancies, including lung, cervical and head and neck cancers.

However, the process is labor-intensive and expensive, which could limit its commercial potential. This study was conducted by academic researchers in the Netherlands and Denmark without pharmaceutical industry involvement. The Netherlands government has agreed to use TIL therapy, and the researchers are seeking approval from the European Medicines Agency. In the United States, the Food and Drug Administration has strict requirements for cell-based therapies, and it may be difficult to win approval without industry support for specific products. That was the path taken by CAR-T therapy, which modifies a patient’s T cells to make them better cancer fighters

rather than relying on naturally occurring immune cells.

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