# Using patients' own tumor-fighting cells to knock back advanced melanoma

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A small, early-phase clinical trial to test the effectiveness of treating patients with advanced melanoma using billions of clones of their own tumor-fighting cells combined with a specific type of chemotherapy has shown that the approach has promise. One patient of the 11 experienced a long-term, complete remission that has lasted more than three years, and in four others with progressive disease, the melanoma temporarily stopped growing. The results of the study are published in the Early Edition of the *Proceedings of the National Academy of Sciences* for the week of March 5.

The goal of the research, led by Cassian Yee, M.D., a member of the Clinical Research Divison of Fred Hutchinson Cancer Research Center, was to find the optimum cellular environment in which to infuse 15 billion to 20 billion cancer-fighting CD8+ T cells so that they persisted for as long as possible in the body to battle the tumors. The cells, which were extracted from the patients and multiplied in the lab before re-infusion, are a type of white blood cell that attacks a protein associated with the cancer.

All of the patients in this study had progressive metastatic melanoma that no longer responded to traditional therapy. Prior to the T-cell infusions, all were treated with high doses of cyclophosphamide to eradicate their lymphocytes, a type of white blood cell that is part of the immune system. This was done to stimulate the production of certain growth factors that help promote further expansion of the T cells within the body.

Eight of the 11 patients received low doses of interleukin-2 growth factor after the T cells were infused to further promote cell growth. Among these patients, one showed a complete remission and four patients, who had failed conventional therapy, experienced a temporary non-progression of their disease. The remaining three patients received higher doses of IL-2, which was found to be more toxic to the body. Two of these patients had temporary non-progression of their disease.

In all of the patients, except for the one who attained a complete remission, their disease eventually progressed within 12 to 19 weeks of T-cell infusion.

Individual variations between patients with regard to how long the infused T cells persisted within the body probably accounted for why some responded to treatment better than others. "Certainly there are differences between patients but we think that persistence of the infused T cells in the body has a lot to do with it," Yee said. "It tells us we certainly have a way to go."

Yee said the study has two key findings that point toward the optimum environment in which to use adoptively transferred tumor-specific T cells:

- The use of high-dose cyclophosphamide alone is a safe inpatient procedure and resulted in the T cells persisting much longer in the body compared to regiments used in previous studies that used different chemotherapy drugs or none at all. What was novel in this trial, according to Yee, was that high-dose cyclophosphamide alone was enough. Other studies have routinely used a combination of cyclophosphamide with fludarabine and/or radiation therapy to deplete lymphocytes, followed by high-dose IL-2, which is a far more toxic regimen

for patients who often require intensive care management during therapy. So-called lymphodepletion is important for engraftment of the infused cells so that the body produces IL-7 and IL-15 growth factors while rebuilding the lymphocyte population to normal levels. Low-dose IL-2 given on an outpatient basis following the cell infusions was found to be nontoxic.

- The CD8+ T-cell clones infused into the patients are long lasting and, the researchers theorize, are derived from central memory T cells, which can fight cancer and infections. "When we infused them as clones, they reverted back to an earlier memory type of T cell," Yee said. "This is important because these cell types have a high potential to proliferate in the patient."

In two of the patients the researchers found upregulation of the IL-7 growth factor receptor and CD28 levels – both of which are important for giving the T cells a growth advantage. A protein encoded by the CD28 gene is essential for T-cell proliferation and survival. The cloned cells showed the potential to become "help independent" from the need to use other growth agents.

"Our results confirm that if we can develop methods to grow these kinds of cells in the lab, then we can give these high-proliferating, helper-independent T cells to all patients for T-cell therapy," said Yee, who is a researcher in the Hutchinson Center's immunotherapy program. "Fortunately, we have been able to achieve this goal and are in the process of treating patients in an ongoing study with these helper-independent T cells."

Future studies may use different variants of interleukin growth factor and perhaps even vaccines to boost the body's response to the infused cells, he said.

**More information:** "Transferred Melanoma-Specific CD8+ T Cells

Persist, Mediate Tumor Regression and Acquire Central Memory Phenotype," *PNAS* (2012).

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