Immunotherapy To Treat Leukemia Possibly Ineffective for Advanced Disease

By Gunjan Sinha

Immunotherapy presents a promising approach for blood cancers resistant to treatment, but it may be effective only in patients with minimal residual disease. In a mouse model of chronic myeloid leukemia (CML), researchers at the University of Bern, in Switzerland, showed that adoptive transfer of cytotoxic T lymphocytes (CTLs) reduced numbers of leukemia stem cells (LSCs) when leukemia antigen levels were low. Paradoxically, in mice with more advanced disease, transferred CTLs induced LSCs to proliferate and caused the cancer to progress more quickly. Moreover, the study for the first time implicates gamma interferon (IFN-γ), a major cytokine that CTLs secrete, as a major player responsible for this dual behavior of CTLs.

The findings “have high translational relevance,” said Martin Bornhäusser M.D., at the Carl Gustav Carus University Hospital.
at Technical University in Dresden, Germany. Although previous studies have shown that T-cell immunotherapy is more effective for minimal residual disease, “that such therapy might harm patients with more advanced disease is entirely new,” Bornhäuser added.

Working with mice transfected with the human BCR/ABL gene, the Swiss researchers, led by Adrian Ochsenbein, M.D., tested several hypotheses (see J. Exp. Med. 2013;210:605–21). To investigate how specific effector CTLs interact with LSCs in mice with both minimal and high leukemia load, the researchers transplanted model mice with LSCs taken from donor bone marrow that expresses BCR/ABL and gp33 antigen—a model antigen targeted to activate T cells. Eighteen hours later, the researchers then adoptively transferred p14 effector CTLs to the mice. The transferred CTLs drastically reduced the number of leukemic cells in the blood and the number of LSCs in the bone marrow. Also, mice treated with CTLs survived, whereas untreated control subjects died after approximately 3 weeks. But when CTLs were transferred into recipient mice 20 days after LSCs were transplanted, total LSC numbers increased substantially. Moreover, treating mice with CTLs did not improve survival at this late stage.

To investigate how CTLs might induce LSCs to proliferate, the researchers studied IFN-γ. In mice treated with CTLs 18 hours after LSC transplantation, IFN-γ was undetectable in the blood, nor could the cytokine be detected in untreated mice. By contrast, when IFN-γ levels were analyzed in mice 16 days after LSC transplantation, levels increased in statistical correlation with the number of transferred CTLs. More important, when researchers injected CML mice with IFN-γ, leukemic granulocyte numbers in peripheral blood stabilized. The paradoxical and potentially troubling find was that in parallel, LSC numbers increased fivefold. When bone marrow from IFN-γ-treated mice was transplanted into recipient mice, they developed more severe disease and died sooner than control mice. “That’s the unexpected result,” said Ochsenbein. “The LSCs behave differently from all other cells in response to IFN-γ.”

“It’s very carefully done work,” said Richard Van Etten, M.D., Ph.D., chief of the Division of Hematology and Oncology and director of the Tufts Cancer Center in Boston.

The study findings align with clinical studies of immunotherapy in CML patients. Two years ago, for example, Bornhäuser published a study (Blood 2011;117:7174–84) in which 13 patients who did not respond to imatinib received infusions of T cells activated ex vivo against leukemia-derived antigens. The therapy was most effective in patients who had few leukemic cells, Bornhäuser said.

But caveats exist, Van Etten added. For one, the Swiss researchers used gp33 as a model antigen to activate T cells. But “it’s an artificial model because in CML we don’t actually know the antigens involved in the alloreponses,” he said. Also, the researchers identified LSCs by surface antigens, but most of these cells are not true stem cells but rather a mix of progenitor cells that include stem cells, Van Etten said. Consequently, the observed increase in LSCs after T-cell transplantation may have triggered proliferation of the progenitor cell population and not necessarily the LSC population. Also, the 18-hour window between LSC transplantation and adoptive T-cell transfer is too short, in Van Etten’s view. “It’s a time before the stem cells have really engrafted,” he said, and so one can’t be sure whether the T cells are mounting an inflammatory response to the engraftment or to the cancer. Nevertheless, the authors do offer supporting evidence that addresses these shortfalls, Van Etten said, and nicely showed in human CML cells that the IFN-γ effect is still seen.

The findings are substantial enough to warrant confirmatory studies, the researchers said. However, the results may not be clinically relevant in treating CML. Second- and third-generation tyrosine kinase inhibitors are so effective in treating nonresponsive patients that few are referred for transplantation, Bornhäuser said. “But there is potential translation to other cancers,” he added.

For example, Bornhäuser is investigating immunotherapy to treat acute myeloid leukemia. In light of the Swiss study, eradicating leukemia as much as possible directly before administering T-cell immunotherapy might be important to consider, he added. The Swiss researchers are also now turning their attention to acute myeloid leukemia.