

POINTS TO CONSIDER

TECHNICAL ABSTRACT

Improvements in radiochemotherapy have correspondingly improved the prognosis of patients with EBV-positive Nasopharyngeal carcinoma (NPC). However, patients resistant to the standard therapeutic approaches have a poor outcome. Moreover, life expectancy and quality of life of patients cured of NPC are both significantly reduced by treatment related mortality and morbidity. These limitations of current treatment protocols illustrate the need for more effective and less toxic therapeutic approaches. In NPC, almost all undifferentiated carcinomas have been shown to carry EBV-DNA and express EBV-genes.

We have evaluated the use of EBV-specific cytotoxic T cells (EBV-CTL) in patients with refractory or high-risk NPC in two Phase I clinical studies.^{1,2} In the first clinical study, EBV-specific CTL were given alone and in the second clinical trial patients received a monoclonal antibody prior CTL infusion to enhance T-cell expansion in vivo. Patients with EBV-positive NPC were eligible if they had recurrent, locally advanced stage disease, or metastatic disease. To date, 21 patients have received CTL and completed their evaluation. On both studies, no dose limiting toxicities were observed and patients have been treated on all dose levels. Six patients were in remission at the time of EBV-CTL infusion and remain in remission 6 to 50 months post CTL infusion. In the 15 NPC patients with active disease we have observed responses in 10 of 15 patients: 4 patients are in complete remission 12 – 42 months after CTL infusion. Of the other 11 patients, 4 had stable disease (2 to 32 months), 1 had a partial response (12 months) and 6 had progressive disease.

At present the anti-NPC activity of EBV-CTL is limited by several factors, including the dominance of T-cells clones in EBV-CTL lines generated by standards methods that react to lytic (BZLF1 and BRLF1) and latent (EBNAs 3A, 3B, and 3C) EBV proteins not expressed by NPC tumor cells.³ NPC tumor cells, like EBV-associated lymphomas in immunocompetent patients, express only 3 EBV proteins (LMP1, LMP2, and EBNA1).^{4,5} Of these, only LMP1 and LMP2 are potential targets for CD8-positive T cells. Since CTL escape mutants have been described for tumors as well as viruses and the expression of LMP1 and LMP2 in NPC tumors is heterogeneous, we propose in this clinical trial the infusion of LMP1- and LMP2-CTL to generate the broadest CTL response possible against the malignant NPC cells.

For this clinical trial we have established a polyclonal LMP1- and LMP2-CTL expansion protocol that is currently being used in our ongoing RAC and FDA approved clinical studies to treat EBV-positive lymphomas with LMP2-CTL. Out of 6 lymphoma patients with detectable disease at the time of LMP2-CTL infusion 5 had clinical responses. These results indicate that LMP2-CTL are safe, accumulate at tumor sites and have anti-tumor activity.^{6,7} To further improve the anti-tumor activity of T-cells against EBV-positive lymphoma we have recently opened a RAC and FDA approved clinical trial (RAC 0604-771) to test the safety and efficiency of LMP1- and LMP2-CTL. In the clinical trial proposed here, NPC patients will receive escalating doses of autologous LMP1- and LMP2-CTL that have been manufactured according to the same cGMP specification as in our ongoing study for lymphoma patients.

Of note, the adenoviral vector used for CTL generation is the same as in an earlier RAC (RAC 0604-771) reviewed FDA approved protocol.