

## POINTS TO CONSIDER

### NON TECHNICAL ABSTRACT

While patients with nasopharyngeal carcinoma (NPC) may be cured by chemotherapy and radiotherapy, the outlook for patients who are resistant to this treatment or who relapse is poor. Almost all patients with undifferentiated nasopharyngeal carcinoma have the EBV virus in their tumors which may be a target for immunotherapy approaches. We have successfully used specialized immune system cells grown in the laboratory and trained to recognize and kill EBV infected cells (EBV-specific cytotoxic T-lymphocytes [EBV-CTL]) to prevent and treat another type of cancer called post transplant lymphoma that occurs after bone marrow transplant. In post transplant lymphoma, the tumor cells have 9 proteins made by EBV on their surface. However in nasopharyngeal carcinoma that develops in patients with a normal immune system, the tumor cells only express 2 EBV proteins that are much harder for the immune system to recognize. In a previous study we made EBV-CTL that recognized all 9 proteins and gave them to patients with NPC. For patients without evidence of active disease at the time of therapy, their disease remains in remission. For those patients with active disease at the time they received CTL, some patients had a partial response to this therapy, and only three patients had a complete response. We think the main reason for this is that many of the T cells reacted with EBV proteins that were not on the tumor cells, and the other is that the infused T cells have not enough space to grow.

The two EBV proteins present on NPC tumor cells that are good targets for T-cell therapies are called LMP1 and LMP2. We are therefore planning to generate T cells specific for LMP1 and LMP2 and infuse these cells into NPC patients. To make LMP1- and LMP2-CTL, we have obtained blood from the patients and grown special type of cell called a dendritic cell (DC) and EBV infected lymphoblastoid cells (LCL). We have then transferred an adenovirus vector that carries the LMP1 and LMP2 gene into the DC and the LCL. These DC and LCL are then treated with radiation so they cannot grow and are used to stimulate and expand LMP1- and LMP2-CTL. This stimulation trains the T cells to kill cancer cells with LMP1 and LMP2 on their surface.

To 'create space' for EBV-CTL growth after infusion in NPC patients we have already used a special protein called a CD45 antibody, which removes for a short period of time most of the patient's T cells. The preliminary results of this study is encouraging: the use of the CD45 antibody is safe and we observed enhanced EBV-CTL growth after infusion. In addition, all patients who has EBV-CTL growth had clinical responses.

In this study NPC patient will therefore first receive 4 days of treatment with CD45 antibody followed by one dose of LMP1- and LMP2-CTL. In this way we can learn if treating the patient first with the CD45 antibody will also let LMP1- and LMP2-CTL we give grow better. In addition, we will find out, if LMP1- and LMP2-CTL are safe and have enhanced anti-tumor activity in comparison to standard EBV-CTL.