

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## Recent Advances in the Treatment of Transplant-related Lymphoma

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### **H&O** In what setting does transplant-related lymphoma generally occur?

**MC** Secondary lymphoma can occur after solid organ transplants or other situations involving profound immune suppression. Posttransplant lymphoproliferative disorder (PTLD) can occur after any solid organ transplant. Kidney transplants are associated with the lowest rate of PTLD, approximately 1–2%. This rate is higher among patients receiving pancreas-kidney transplants, liver transplants, lung transplants, small bowel transplants, and heart-lung transplants, with the highest rate of incidence being approximately 10%.

### **H&O** Why does PTLD develop?

**MC** The viral agent associated with PTLD is Epstein-Barr virus (EBV). Approximately 95% of adults in the United States have been infected with EBV, which initially enters through the nasopharynx and travels to the B lymphocytes, where it resides in latent form.

Normally, the few B cells that are infected with EBV will awake from their latent step, express new viral antigens on their cell surface, and begin to replicate. In individuals in whom the immune system is intact, this transformation is detected at a subclinical level, and the T lymphocytes eliminate these cells before any signs or symptoms of overwhelming infection or cancer manifest. Thus, this type of cancer is rare, if not nonexistent, among people with a healthy immune system.

However, following the immunosuppressive therapy that patients undergoing a solid organ transplant receive, the T cells that so effectively detect transforming EBV(+)

B lymphocytes are suppressed and therefore can't prevent the uncontrolled proliferation of EBV-infected transforming B cells and subsequent PTLD.

### **H&O** What have been the traditional approaches for treating PTLD?

**MC** Historically, the typical treatment approaches for PTLD have been chemotherapy or reduction of immune suppression. Reduction of immune suppression is a logical first step for treating a disease resulting from suppressed T cells. In some instances this approach can be highly effective and even curative, but graft rejection can be a serious or even fatal consequence. Alternately, malignancies that spread systemically, as PTLD does, have traditionally been curable only with systemic chemotherapy.

### **H&O** Have any chemotherapeutic regimens been successful in treating PTLD?

**MC** With the exception of few small studies, chemotherapy at low, intermediate, or high doses has not been consistently effective in treating PTLD. An exception may be the use of a low-dose chemotherapy regimen in children with PTLD, who appear to have a more favorable response rate after failing first-line reduction in immune suppression. The reasons for this generally poor response to chemotherapy are not entirely clear but likely relate to both the immune-suppressed state of the patient along with the viral origin of the cancer.

### **H&O** How has the treatment of PTLD changed in recent years?

**MC** The most recent developments relate to targeted cellular therapy. EBV expresses certain unique gene products. Therefore, malignant EBV(+) B cells contain proteins that are not expressed in any other cell in the body. T cells can generally detect viral-associated tumor cells among normal cells in individuals who have not received immunosuppressive therapy. In terms of treating PTLD, T cell-specific therapy against the EBV-infected malignant cell could be an effective approach.

## H&O Has this strategy been pursued?

**MC** This strategy has been pursued very effectively in PTLD arising after stem cell transplantation for cancers such as leukemia. Here, EBV lymphoma generally results from donor cells infused into the recipient. Typically, the normal donors who provided their stem cells in the transplant are available to provide additional EBV-specific T cells that can target the viral proteins and can be grown in the laboratory to be infused into the patient.

## H&O Is this strategy effective in solid organ transplant recipients?

**MC** In the setting of solid organ transplantation, EBV PTLD generally originates in the recipient. In this setting, the only immunotherapy that could be considered is reducing immune suppression in the patient to enable a T cell response, but this approach also risks organ rejection.

In the case of a seemingly fatal malignancy, the risk of organ rejection is warranted if the transplant is not critical to survival (ie, kidney or pancreas). With organs that are critical to survival—heart, lung, or liver—incurring serious risk of rejection is not an option.

## H&O Are there other treatment strategies being evaluated for patients whose transplantations involve the heart, lung, or liver?

**MC** Yes. One of the proteins expressed in EBV-infected B cells is viral thymidine kinase. This enzyme can convert drugs that are relatively nontoxic to normal cells into toxic forms. The presence of this enzyme exclusively in the EBV(+) cancer cells means that drugs that are not toxic to normal cells will pass in and out of normal cells without a problem. In the EBV(+) cells, the drug has the potential to be converted into a toxic form, thereby selectively killing the tumor cells. Using this approach, ganciclovir and zidovudine (AZT) have occasionally been effective. Much more needs to be learned about this experimental targeted approach to successfully treat PTLD.

Another targeted therapy that has been tried with only modest success to date is the anti-CD20 antibody rituximab. Choquet et al performed a prospective trial of single-agent rituximab in 46 PTLD patients who failed initial reduction in immune suppression, and reported an initial response rate of 44%. Interestingly, treatment with rituximab can lead to dramatic decreases in the EBV viral load found in peripheral blood, but this decrease does not show correlation to tumor response. Prospective trials of rituximab in combination with chemotherapy for PTLD have not been reported.

## H&O Why do some transplant recipients develop PTLD while others do not?

**MC** Experimental data suggest that whether or not a patient develops PTLD may be related to the number of T cells directed against EBV prior to organ transplantation. Other experimental findings suggest that a patient's endogenous cytokine profile also has an influence. It may be that a combination of the two is responsible. Again, prospective studies with large numbers of patients will be necessary to see if these hypotheses hold true.

## H&O How are these findings being applied to treatment strategies?

**MC** Ninety-five percent of adults in this country are EBV(+) and thus have some existing T cell immunity to the virus. It may be possible to counter a predisposition to PTLD by increasing the number of cytotoxic T cells prior to organ transplantation with something like a booster vaccine. Patients would still undergo immune suppression at the time of organ transplantation; however, with a greater number of circulating T cells directed against EBV, the likelihood of virally infected B cells successfully transforming into malignant cells could be much lower. If the patient were to develop EBV PTLD, a reduction in immune suppression might result in a more robust and specific anti-EBV response that could eliminate the tumor without necessarily rejecting the transplanted organ. In children who have not been exposed to EBV, this strategy would be considered a primary vaccination, not a booster vaccination.

We now know some of the viral antigens produced by EBV that are recognized by T cells in PTLD patients. In preliminary experiments using these viral antigens, the booster vaccine approach appears to hold merit, and clinical studies are soon to be underway.

## Suggested Reading

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