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Autologous Lymphokine-Activated Killer Cell Therapy of Lymphoproliferative Disorders Arising in Organ Transplant Recipients

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B CELL lymphomas which often contain the Epstein-Barr virus (EBV) make up the preponderance of tumors that collectively have been termed posttransplant lymphoproliferative disorders (PTLD). The unusual susceptibility of PTLD to immune surveillance was first demonstrated in organ allograft recipients following reduction (or discontinuance) of immunosuppression[1] with its attendant risk of precipitating allograft rejection.

Restoration of tumor surveillance has recently been accomplished in bone marrow transplant recipients with PTLD by infusing naive cytotoxic T lymphocytes (CTL) obtained from the original donors into the tumor-bearing recipients. In these cases the tumors are invariably of donor origin, and HLA-restricted effector cells directed against viral targets are thought to be the main mediators of tumor regression.[2,3] The unavailability of naive pretransplant recipient leukocytes has precluded direct application of this technology to the PTLDs which develop after organ transplantation and which are almost always of recipient origin.[4] However, we report herein an approach whereby the anti-PTLD activity of the recipient's own cells can be intensified in vitro. Reinfusion of these cells has been associated with clinical tumor regression in several cases.

MATERIALS AND METHODS

Approval from the Institutional Review Board was obtained for lymphokine activated killer (LAK) cell therapy of six patients who had PTLD that had incompletely responded to reduced immunosuppression, and for one patient who could not tolerate lowering of immunosuppressive drugs without the penalty of rejection. All patients were treated on a compassionate need basis. Peripheral blood mononuclear cells were obtained by leukapheresis and cultured in the presence of $rhIL_2$.[5,6] An average of 2.1×10^{10} resultant LAK cells were administered to each patient. Cytotoxic activity of cells from both the leukapheresis samples and from the final LAK cell preparations was determined by 4-hour ^{51}Cr release assay. PTLD specimens were classified histopathologically as previously described.[7]

CLINICAL OUTCOME

The organ recipients (2 liver, 2 lung, 2 kidney, 1 heart) were 2 months to 12 years posttransplantation; all but one were beyond 1 year. The PTLD lesions involuted in 4 patients with EBV^+ PTLD. In two of these patients, this was coincident with allograft rejection 3 days and 3 weeks after LAK cell infusion. The rejections were easily controlled with prednisone therapy. The antitumor effect was particularly obvious in a patient whose lower extremity immunoblastic lymphoma nodules, which had developed 6 years postcardiac transplantation, could be seen to shrink almost overnight.

A third patient with an EBV^+ Hodgkins-like lymphoma, who had been allowed to reject the allograft 12 years posttransplantation, was given LAK cells when residual PTLD was found at the time of graft nephrectomy. She underwent successful retransplantation 9 months later. The fourth patient, a double lung recipient whose polymorphic PTLD of undetermined clonality originated in the allograft, died of pseudomonas pneumonia 41 days postinfusion. No tumor was found at the autopsy which was limited to the thorax.

The three surviving patients with EBV^+ lesions are well with no evidence of residual tumor 12 to 16 months post-LAK cell treatment, including the recipient of a second renal allograft.

Three additional organ transplant recipients had EBV^- large cell non-cleaved lymphomas. LAK cell infusion did not precipitate rejection in any of these patients. Because there was no discernible immediate effect on the tumors, chemotherapy ($n = 3$) or irradiation ($n = 1$) was started 3 to 14 days post–LAK-cell infusion. The short time interval between cell infusion and the superimposition of other therapies made evaluation of the efficacy of LAK cells impossible. One patient is alive with residual but stable tumor 7 months postinfusion; the other two died after 17 and 188 days.

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DISCUSSION

LAK cell therapy was clearly effective in four cases of PTLD which had in common the presence of intratumoral EBV. Because control of EBV replication in vivo is primarily by EBV-specific CTL[8,9] with a possible accessory role of NK cells,[10,11] the presence of both phenotypes in the LAK cell infusate was reassuring.

Three patients had posttransplant lymphomas in which no evidence of EBV was detectable. The underlying cause of EBV negative PTLD remains problematic and is likely multifactorial. Viruses other than EBV may be operative in these tumors, or the lesions in some cases may simply represent sporadic lymphomas. Antigenic stimulation by allogeneic cells, either of parenchymal or of hematolymphoid origin, may also be a cofactor in such cases. Indeed, the state of functional tolerance which is associated with microchimerism[12] has been shown to be an active process in murine models[13,14] and such subclinical immunostimulation may itself provide the environment which predisposes to proliferative lymphoid processes.[15]

Although no response to LAK cell treatment was seen in the three patients with EBV$^-$ tumors, we suggest that the early supervention of other inherently immunosuppressive antilymphoma therapies following LAK cell infusion retarded the return of natural surveillance upon which long survival presumably depends. Such tumors in our experience have undergone involution following a period of reduced immunosuppression and, indeed, this had been demonstrated earlier in the courses of two of the three failed LAK cell cases. For this reason, we believe that LAK cells, perhaps repetitively administered, should continue to be offered as a therapeutic option for EBV PTLD.

In summary, we conclude that the administration of autologous LAK cells appears to be of benefit in PTLD. This effect is clearly shown in patients with EBV positive tumors. Additional work is necessary to define the mechanism and extent of this effect, and to clarify the role of LAK cell therapy, particularly in patients whose PTLD do not have the EBV genome.

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