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Lymphoproliferative Disorders Arising Under Immunosuppression with FK 506: Initial Observations in a Large Transplant Population

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POSTTRANSPLANT lymphoproliferative disorders (PTLDs) encompass a range of benign to frankly malignant lymphoid tumors that occur in the immunocompromised state.[1] Many, but not all, are of B-lymphocyte origin and the Epstein-Barr virus is acknowledged to be an important cofactor in most cases.

The introduction of cyclosporine A (CyA) in the early 1980s brought with it concerns that this new immunosuppressant might also cause an inevitable increase in the number of transplant lymphomas.[2] These fears were not borne out, and PTLDs presently occur in about 2% of transplant recipients.

FK 506 is a new macrolide immunosuppressant that has been shown to be at least 100 times more potent than CyA by in vitro assays.[3,4] It is appropriate, therefore, to again ask whether or not the degree of immunosuppression exerted by such a powerful new drug carries with it an unacceptable price in the form of increases in the frequency or aggressiveness of transplant-associated lymphomas.

MATERIALS AND METHODS

Patient Population

Between March 1, 1989 and July 1, 1990, 679 patients received FK 506 at the University of Pittsburgh. An additional 100 or so patients are currently enrolled in a randomized trial of FK 506 vs CyA, and will not be included in the statistics. No PTLDs have been seen in that trial, however. Of the 679 patients, there were 516 liver recipients, 72 renal recipients, 40 patients who received livers with 1 or more other organs, 30 heart transplant patients, and 21 miscellaneous patients.

During the study period a total of 19 PTLDs were diagnosed. Five of these occurred in patients who were taking FK 506-containing regimens; the remainder were under CyA-based immunosuppression. An additional seven patients who had had previously diagnosed PTLD were also switched over to FK 506 during this time.

The relationship of FK 506 to the development and behavior of PTLDs was studied by subdividing the patients into three main groups. Group 1 patients received FK 506 as primary immunosuppression for their organ transplants and subsequently developed PTLD. Group 2 patients were converted from CyA regimen to FK 506 because of either intractable rejection or CyA toxicity. They had no evidence of PTLD prior to the switchover, but subsequently went on to develop a lymphoproliferation. Group 3 patients were switched over to FK 506 with no prior documented PTLD.

Pathological Studies

Routinely processed surgical and autopsy specimens were reviewed by one of us (M.N.). Clonal analysis is based on immunocytochemical studies done as a part of the pathological evaluation. Immunogenotypic data are not available at present on these cases. Likewise, EBV serologic data were used when available from the medical record.

RESULTS

Frequency of PTLD Arising Under FK 506

The median follow-up time for patients receiving FK 506 is 10.5 months, with a range of 1 to 16 months. During this time, three patients in group 1 (primary FK) and two patients in group 2 (switchover to FK 506) developed lymphoproliferative processes, for a frequency of 0.7%.

PTLD in Transplant Recipients Initially Receiving FK 506-Based Immunosuppression (Group 1)

The three patients who developed PTLD following primary FK 506 immunosuppression did so at 1.6, 2.6, and 5.9 months after transplant. Patient 1 was highly sensitized and received her first hepatic allograft on December 13, 1989. She required retransplant 3 days later due to primary nonfunction. In addition to FK 506, three courses of OKT3 and multiple steroid boluses were required to control rejection. She developed bacterial sepsis and her second liver was resected at the end of January. At that time, a nonclonal PTLD was found in the allograft liver and periportal nodes. The patient expired approximately 1 week following this third transplant, with widespread nonclonal PTLD.

Patient 2 was an 18-year-old white male who presented with a sore throat 2 1/2 months following his liver transplant. Unilateral tonsillectomy and adenoidectomy led to a diagnosis of polymorphic, polyclonal PTLD. He was treated with acyclovir and a reduction of FK 506. He is currently well at 7 months after diagnosis, with no evidence of residual disease.

The final patient in group 1 developed a phenotypically clonal PTLD in her allograft liver approximately 6 months after transplant. She presented at that time with fever and

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hepatic mass and on workup found to have a 10-cm tumor with a smaller satellite nodule, confined to the allograft. Resection was performed, immunosuppression reduced, and acyclovir administered. She has remained without evidence of disease for 3 months following tumor resection.

PTLD in Patients Switched Over from CyA to FK 506 (Group 2)

One of the two patients in group 2 received his first kidney in 1982, and by April 1989 had received his third kidney. The patient, who was highly sensitized, required CyA, Imuran, and repeated courses of OKT3 and steroids to control rejection. On July 14, 1989, he was started on FK 506 to rescue his kidney. However, renal function continued to deteriorate. Just before nephrectomy in mid-September, a CT scan showed changes in the mastoid, and a mastoidectomy was concurrently performed. Both *Aspergillus* and PTLD were found in the mastoid, and the allograft kidney contained PTLD. He was removed from immunosuppression at the time of allograft nephrectomy, but subsequently expired due to *Aspergillus* brain abscess approximately 4 months after tumor diagnosis. No clinical evidence of tumor was present at the time of death; however, autopsy was declined.

The second patient was a 5-year-old girl who received a liver for treatment of biliary atresia in August 1989 and was placed on FK 506 1 month later to control accelerated rejection. She did well until 8 months following transplant, at which time gastric biopsies showed evidence of clonal IgA lambda PTLD in that organ. CT of the head, chest, and abdomen was negative for tumor elsewhere. She received IV acyclovir 450 mg q8h and her FK 506 was dropped from 3 mg/d to 3 mg every third day. No elevation of liver enzymes was observed, and she has done well for the last 4 months, with no evidence of disease on follow-up biopsy. EBV serology at the time of diagnosis was consistent with a primary infection.

Patients with Prior Documented PTLD Who Were Later Switched to FK 506 (Group 3)

Seven patients who had had prior PTLDs were switched over to FK for various reasons. One patient had a monoclonal PTLD of the esophagus diagnosed in December 1987. This required several resections and radiotherapy for control. Despite temporary resolution, lesions invariably recurred near the same site. Further radiotherapy was planned but was canceled in October 1989. At the same time, the patient was also switched over to FK 506 for control of rejection secondary to the discontinuance of CyA. The lesion regressed while the patient was on this regimen and he has remained well without evidence of tumor for the last 10 months on FK 506. Three other patients were switched over to FK 506 for relief of renal dysfunction due to CyA. Two patients had a prior diagnosis of clonal PTLD at 75 and 44 months, and one had a diagnosis of nonclonal PTLD at 23 months, prior to FK 506 administration. None of these three patients had evidence of tumor at the time FK therapy was begun. No evidence of recurrent tumor has been seen with respective follow-up intervals of 8.5, 5.5, and 6.0 months.

Two additional patients had biopsies consistent with PTLD from the gut and lung, respectively, but no further pathologic studies were performed due to paucity of tissue. Both responded to conservative treatment and were switched to FK 506 at 3 and 5.5 months after diagnosis. Neither had PTLD at the time of the switchover and no evidence of tumor has developed at 7 and 11 months following the institution of FK-based immunosuppression.

The final patient was a 12-year-old boy who had PTLD present at the time of switchover to FK 506 therapy. He expired of DIC a short time thereafter, and at autopsy residual PTLD was found in lymph nodes.

DISCUSSION

The overall incidence of PTLD for all transplant recipients at the University of Pittsburgh is approximately 2%. In the general population of PTLD patients who did not receive FK 506, but almost invariably received CyA, the median time between transplant and tumor was 6.1 months, and 65% of the tumors occurred less than 10 months after transplant. Thus, the 0.7% frequency of PTLD seen with a 10.5-month-median follow-up time compares favorably with the general transplant population.

The brevity of the follow-up would indicate that the final frequency may be somewhat higher than at present. In this context, it is important to recall that the intensity of clinical surveillance may also introduce an important artifact when attempting to compare statistics from different eras. In older times, PTLDs were diagnosed when they were clinically and pathologically obvious. With greater awareness and understanding of the spectrum of this complication, subtle lesions which would have been missed or misdiagnosed as hyperplasia or rejection 10 years ago are now diagnosed with accuracy.

In summarizing our early experience with FK 506, several additional features are of interest. First, both clonal and nonclonal tumors occur relatively soon after transplant. This is similar to PTLDs occurring with CyA-based regimens.[5] In contrast, azathioprine-based regimens tend to produce early nonclonal disease, with clonal tumors arising some years following transplant.[5] The similarity to the CyA time course should not be surprising, since both CyA and FK 506 work on the peptidyl-prolyl isomerase system,[6,7] although by different routes. Second, individual cases appear to be B-cell lesions that involve the tonsillar region, gastrointestinal tract, and allograft, and are associated at least in some cases with active EBV infection. These data are currently being analyzed, but the features of these lesions appear to be similar to the currently accepted spectrum of this disorder. The early dissemination of widespread polyclonal disease in one

patient represents an unfortunate but well-established manifestation of this disease in a minority of cases. The occurrence of tumor in the allograft organ in three of five cases is of interest. This may represent a significant observation, or may simply be a sampling artifact due to small numbers. Allograft involvement is not uncommon in cases of PTLD. It may occur alone or as part of disseminated disease. In the present cases, there was no evidence of concurrent PTLD and rejection in the same organ. Therefore, the concept that organ rejection and PTLD occur at different extremes of immunosuppression remains a valid working hypothesis. Finally, the response of the tumors to the primary therapeutic approach of local surgery, reduced immunosuppression, and acyclovir is encouraging and appears to be similar to the results obtained with other PTLDs.[8] In summary, FK 506 is a powerful new immunosuppressant that is effective in preventing transplant rejection and shows no evidence to date of any increase in the risk of developing or succumbing to transplant-associated lymphoproliferations.

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