Treatment Response and Outcomes in Post-transplantation Lymphoproliferative Disease vs Lymphoma in Immunocompetent Patients

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ABSTRACT

Posttransplantation lymphoproliferative disorder (PTLD) after solid organ transplantation may carry a poorer prognosis than lymphoma in immunocompetent individuals, but comparative data are lacking. In a retrospective, single-center, case-control study, 21 cases of PTLD were identified in patients undergoing kidney transplantation since 2000, and compared to 42 nontransplanted controls cared for in the same institution and matched for age, prognostic index, and cerebral localization. Two-year and 5-year overall survival was 57% and 44%, respectively, in PTLD patients and 71% and 58% in controls (log-rank test $P = .20$). On multivariable analysis, overall survival was similar for PTLD and control patients (hazard ratio 1.71, 95% confidence interval 0.81 to 3.61, $P = .16$). Response rate to first-line chemotherapy was similar between the 2 groups. Death was due to progression of the disease in 46% vs 94% of PTLD and control patients, respectively ($P < .01$), or sepsis in 31% vs 0% ($P = .03$). Treatment-related mortality was significantly higher in PTLD (19%) than in controls (0%, $P = .03$). In conclusion, response to first-line chemotherapy and overall survival are similar in PTLD and control patients, whereas causes of death were significantly different. Better prevention and management of infectious complications could improve the results in PTLD patients.

TRANSPLANT recipients are at a markedly higher risk of cancer than the general population [1,2]. Post-transplantation lymphoproliferative disease (PTLD) is the most frequent malignancy in kidney transplant patients, with the exception of skin cancer, occurring in 1% to 2% of patients [2,3], but is also a common finding after liver (2% to 3%), thoracic (~2%), and lung (5% to 6%) transplant recipients [2].

PTLD differs from lymphoma in immunocompetent patients in some respects. Development of early PTLD (within the first year posttransplantation) is strongly influenced by the intensity of immunosuppression. It is usually associated with Epstein-Barr virus (EBV) infection, particularly if there is a mismatch in EBV serology, ie, the donor is seropositive but the recipient is seronegative [4,5]. Late PTLD, occurring after the first year of transplantation, is only rarely related to EBV infection. The pathogenesis of PTLD is based on a direct effect of viral latency proteins on core B-cell functions, and reduction (or loss) of T-cell control of EBV-induced proliferation associated with the intensity and duration of immunosuppression. Late PTLD shows a poorer prognosis than early PTLD [6], due to frequent extra-nodal involvement and cerebral localization.

Treatment of PTLD is not standardized. Reduction of maintenance immunosuppression, to allow partial reconstitution of antitumoral immunity, is conventionally considered to be the first step in PTLD management, and high response rates have been reported for early lesions and polymorphic PTLD [7,8]. However, reduction of immunosuppression alone leads to poor outcomes in aggressive monomorphic PTLD, necessitating more intensive therapy

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[9]. Retrospective analyses of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) have shown good long-term disease control [10,11]. Use of rituximab monotherapy has improved remission rates in patients with CD20-positive B-cells [12–14]. Therefore, until recently, combination therapy with rituximab plus CHOP (R-CHOP) has generally been proposed as first-line therapy for patients with B-cell PTLD [15–17]. This is the same approach as that used in immunocompetent patients with diffuse large B-cell lymphoma (DLBCL). Similarly, methotrexate based-chemotherapy is used to treat primary cerebral PTLD, identical to therapy in the nonimmunosuppressed population [18–20]. Conventional chemotherapy, however, which can be curative for lymphoma in the general population, appears to be associated with high rates of myelotoxicity and infectious complications in PTLD, leading to treatment-related mortality [10,11,21,22]. To our knowledge, there are no data in the literature comparing mortality and morbidity rates between PTLD and classic non-Hodgkin lymphoma.

In the present study, we retrospectively reviewed cases of PTLD diagnosed in our kidney transplant population since the introduction of rituximab therapy. We performed a case-control analysis of these patients vs immunocompetent patients treated for non-Hodgkin lymphoma who were matched for age, prognostic index, and cerebral localization. Particular focus was placed on response rates to first-line chemotherapy and overall survival, as well as on treatment-related complications and mortality.

METHODS

Study Population

Twenty-five diagnosed cases of PTLD were identified retrospectively among patients who had undergone kidney transplantation at the University Hospital of Montpellier, France. The analysis period started with the introduction of rituximab treatment in 2000 and ended with last follow-up in July 2013. Because cerebral localization is frequent in PTLD, we decided not to exclude patients with primary cerebral lymphoma (PCL). Three cases presented as Hodgkin's disease and 1 was treated in another hospital, all of which were excluded from the analysis.

All cases of DLBCL patients diagnosed by the Department of Hematology at the University Hospital of Montpellier from 2000 to 2012 were identified. Patients were excluded if they were HIV-positive, if they were treated in other hospitals, or if they had received intensified chemotherapy followed by autologous bone marrow transplantation. Each PTLD patient was then individually matched to 2 control patients from the remaining pool of DLBCL cases, using 3 criteria: central nervous system localization, age at diagnosis, and International Prognostic Index, which is the most widely used prognostic index in DLBCL [23].

Diagnosis and Evaluation

The diagnosis of lymphoma was based on examination of histological material. PTLD was classified according to World Health Organization (WHO) 2008 recommendations [24]. EBV status was detected in tumor tissue either by EBV early RNA in situ hybridization or by latent membrane protein (LMP1) immunohistochemistry. CD20 immunophenotyping and proliferation index measure (MiB1) were performed in all patients. Immunophenotyping classification (germinal center B-cell-like [GCB]– or activated B-cell-like [ABC]–lymphoma) was determined where possible according to the Hans classification [25].

All patients underwent a bone marrow examination and a thorough evaluation to detect disease localizations with computed tomography and/or positron emission tomography scan. Using these data, lymphoma staging was made according to the Ann Arbor classification.

Performance status was assessed according to the Eastern Cooperative Oncology Group scale. Bulky disease was defined as any mass with a maximum diameter >5 cm. International Prognostic Index, which includes 5 items (age >60 years, performance status >2, lactate dehydrogenase [LDH] greater than upper limit of normal, presence of extra-nodal sites, stages III/IV of the Ann Arbor classification), was calculated for all patients [23]. PTLD patients were classified as being at low, moderate, high, or very high risk for death according to a prognostic score recently developed (range from 0 for low-risk patients to 5 for very-high-risk patients) for kidney transplant recipients [26].

Data Collection

Data were obtained from hospital medical records, including demographic characteristics (age, sex), biological parameters (serum creatinine, serum albumin, LDH, hemoglobin), causes of death, thrombotic events, and complications of treatment. The date of lymphoma diagnosis was defined as the date of histological analysis.

Treatment and Definitions of Outcomes

Decisions concerning diagnostic procedures or treatment for transplant patients or controls were undertaken at the multidisciplinary team meetings of the Onco-Hematology Department, with the participation of transplant physicians when PTLD cases were discussed. Dose intensity was used to define the delivered drug dose per time unit and was expressed as mg/m^2 per week [27]; it was calculated for each patient and each drug, and was expressed as the percentage of the dose and duration recommended in protocols. Dose intensity is correlated to survival [28,29], and a cutoff of 85% is commonly used [30]. Granulocyte colony-stimulating factors (G-CSF) prophylaxis was assessed according to International Cancer Society guidelines [31,32].

Complete response, partial response, and disease progression were defined according to the International Working Group criteria [33]. Treatment-related mortality was defined as death occurring in the first year after diagnosis that could not be attributed to disease progression or relapse. Adverse events were retrospectively assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0) with a specific emphasis on hematological and infectious toxicities.

Statistical Analysis

Categorical variables were expressed as percentages and were compared using the Fisher exact test. Continuous variables were expressed as median (range) and compared using the Mann-Whitney U test. Survival rates (overall survival, event-free survival, progression-free survival, and disease-free survival) were calculated according to the International Working Group criteria [33], as was the rate of response to chemotherapy. Survival curves were constructed with the Kaplan-Meier method and compared