Original Study

Chemoimmunotherapy and Withdrawal of Immunosupression for Monomorphic Posttransplant Lymphoproliferative Disorders

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Abstract

Current treatment guidelines for monomorphic posttransplant lymphoproliferative disorders (PTLDs) occurring after solid organ transplantation (SOT) are vague with regard to management of immunosuppression. Based on the outcomes of our retrospective cohort of 22 patients we argue that chemoimmunotherapy in combination with withdrawal of immunosuppression yields excellent results including high response rate, low treatment-related mortality, graft loss, and risk of death because of PTLD.

Background: Monomorphic PTLDs are the most aggressive type of PTLD occurring after SOT. Current guidelines for treatment suggest a stepwise approach that includes a reduction of immunosuppression (RIS) with or without rituximab, followed by chemotherapy if there is no response. Nevertheless, recommendations regarding the extent and duration of RIS are nonstandardized and RIS as an initial strategy might be associated with an unacceptably high frequency of graft loss and disease progression. **Patients and Methods:** We reviewed the outcome of a combination program of aggressive chemoimmunotherapy and complete withdrawal of immunosuppression in treating 22 patients with monomorphic PTLD between January 1995 and August 2012. **Results:** Twelve of 22 patients (55%) received CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) every 2 weeks (dose-dense CHOP-R) and 10 patients received other doxorubicin-based regimens. There was no treatment-related mortality. Complete response was seen in 91% of patients. Median OS was 9.61 years (95% confidence interval (CI), 5.21-10.74). Median progression-free survival was 5.39 years (95% CI, 2.10-10.74). The graft rejection rate was 18% (95% CI, 0.03-0.34). **Conclusion:** The use of aggressive chemoimmunotherapy in combination with the withdrawal of immunosuppression approach yields excellent results and should be prospectively studied in a multiinstitutional setting.

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Introduction

Posttransplant lymphoproliferative disorders (PTLDs) represent a spectrum of lymphoid proliferations that develop as a consequence of pharmacological immunosuppression. They are, after nonmelanoma skin cancers, the second most common tumors seen in patients after solid organ transplantation (SOT).[1] The incidence of PTLD is lowest in adult kidney transplant recipients (1%-2%) and is higher in patients with heart/lung and multivisceral transplants, probably secondary to more intensive immunosuppression.[2,3] Most PTLDs are associated with the presence of Epstein-Barr virus (EBV), a ubiquitous human herpes virus that infects more than 90% of the adult population.[4] It is postulated that therapeutic immunosuppression causes a decrease in the EBV-specific cytotoxic T-cell response and, as a result, there is an increase in the proliferative potential of EBV in latently infected B-cells.[5] The setting posing the highest risk of PTLD is that in which EBV-negative recipients, predominantly children, receive organs from EBV-positive donors.[6]

The 2008 World Health Organization classification of PTLD includes the following types: early lesions, polymorphic lymphoproliferations,

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monomorphic lymphomas, and classical Hodgkin lymphoma.[7] Those who develop early or polymorphic PTLD, frequently associated with EBV and occurring early after transplant, usually have a good prognosis and respond well to reduction of immunosuppression (RIS) and possibly antiviral therapy.[8] Monomorphic PTLD is indistinguishable from a subset of aggressive B-cell and much less frequently T-cell lymphomas that occur in immunocompetent individuals. Monomorphic PTLD in SOT patients frequently involves extranodal sites and the allograft, causing significant morbidity and mortality.[9] There is no universally accepted treatment strategy for monomorphic PTLD because randomized trials are lacking with most of the data coming from retrospective cohort studies evaluating heterogeneous populations of patients.[10-16]

Successful treatment requires eradication of lymphoma and preservation of the transplanted organ, particularly in situations in which replacement therapy such as in liver, lung, and heart transplants is not available. Accordingly, we used intensive chemotherapy and complete withdrawal of immunosuppressive agents with the goal of simultaneously treating the lymphoma and providing enough immunosuppression with the chemotherapy to prevent rejection. This retrospective study was designed to assess the outcome of such a strategy in monomorphic PTLD patients treated at the Yale Cancer Center (YCC) over a 17-year period.

Patients and Methods

We identified patients with PTLD after SOT by searching the Yale-New Haven Hospital Tumor Registry and by interviewing YCC hematology/oncology physicians who provide care to lymphoma patients. Patients were eligible for selection if they were 18 years of age or older and diagnosed with monomorphic PTLD after SOT between January 1, 1995 and August 30, 2012. We analyzed the outcomes among patients treated with a combined approach of intensive chemotherapy predominantly in combination with rituximab and complete withdrawal of immunosuppression. Before beginning chemotherapy, the calcineurin inhibitors such as cyclosporine and tacrolimus, were discontinued, as were adjuvant drugs such as mycophenolate and azathioprine. To prevent rejection, prednisone was given at a dose of 40 to 60 mg daily until the concentration of the calcineurin inhibitors was very low or absent. Steroids were then given per the lymphoma regimen with the exception that prednisone was continued at a dose of 7.5 to 10 mg daily between cycles for adrenal replacement. Rituximab (in the past several years) was often started during the initial drug washout. Supportive care included acyclovir, ciprofloxacin, fluconazole, trimethoprim-sulfamethoxasole, and more recently, filgrastim or pegfilgrastim. Response was assessed using a combination of physical exam, computed tomography (CT) scans and, in recent years, with positron-emission tomography/CT scans. After completing chemotherapy, all patients again received immunosuppression therapy with the choice of agents at the discretion of the transplant physicians. Twenty-two patients met the inclusion criteria.

Patient demographic factors and disease characteristics were calculated using descriptive statistics. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method. OS was measured from the date of the biopsy establishing PTLD diagnosis to death from any cause, censored at the date of the last follow-up. PFS was measured from the date of the biopsy establishing PTLD diagnosis to disease progression or death without progression, censored at the date of the last follow-up. The cumulative incidence of PTLD-specific death was estimated using death from other causes as a competing risk. The analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC) and R version 2.11.1 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1 Patient Demographic and Clinical Characteristics

Characteristic	Value
Age at Diagnosis, years	
Median	50
Range	20-73
Sex, n (%)	
Male	13 (59)
Female	9 (41)
Transplanted Organ, n (%)[a]	
Heart	3 (14)
Kidney	17 (77)
Liver	2 (9)
Time From First SOT to PTLD diagnosis	
Group, n (%)	
Early PTLD: $\leq$ 1 year	1 (5)
Late PTLD: $>$ 1 year	21 (95)
Median, years	5.6
Range, years	0.8-20.5
Histology of PTLD, n (%)	
Burkitt (or Burkitt-like)	6 (27)
DLBCL[b]	16 (73)
Tumor EBV, n (%)	
Negative	9 (41)
Positive	13 (59)
PTLD Stage, n (%)	
Early stage I-II	7 (32)
Advanced stage III-IV	15 (68)
Extranodal Disease, n (%)	
Yes	17 (77)
No	5 (23)
Survival status, n (%)	
Alive	13 (59)
Dead	9 (41)

All patients, n = 22.
Abbreviations: DLBCL = diffuse large B-cell lymphoma; EBV = Epstein-Barr virus; PTLD = posttransplant lymphoproliferative disorder; SOT = solid organ transplantation.
[a]One patient with multiple SOT was grouped based on the first transplantation (kidney transplantation in 1998 and pancreas transplantation in 1999).
[b]One patient had DLBCL of the central nervous system (CNS).

Results

Patient and tumor demographic information are listed in Table 1. Out of 22 identified patients, 17 received kidney (including 1 kidney and pancreas), 3 heart, and 2 liver transplants. Sixteen patients (73%) were diagnosed with diffuse large B-cell lymphoma, and 6 with Burkitt or Burkitt-like lymphoma (27%). Thirteen out of the 22 patients had EBV-positive lymphoma (59%). Only 1 patient had early PTLD ($\leq$ 1 year after SOT) which was EBV-positive. Nine out of 21 patients with late PTLD had EBV-negative tumors. Fifteen