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Chemoimmunotherapy and withdrawal of immunosuppression for monomorphic post-transplant lymphoproliferative disorders

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Abstract

Introduction—Monomorphic post-transplant lymphoproliferative disorders (PTLD) are the most aggressive type of PTLD occurring after solid organ transplantation (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 non-standardized and RIS as an initial strategy may 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 chemo-immunotherapy and complete withdrawal of immunosuppression in treating 22 patients with monomorphic PTLD between January 1995 and August 2012.

Results—12 of 22 patients (55%) received CHOP-R every 2 weeks (dose dense CHOP-R) and 10 patients received other doxorubicin-based regimens. There was no treatment related mortality (TRM). Complete response (CR) was seen in 91% of patients. Median overall survival was 9.61 years with 95% CI (5.21-10.74). Median progression free survival (PFS) was 5.39 years with 95% CI (2.10-10.74). The graft-rejection rate was 18% with 95% CI (0.03-0.34).

Conclusion—We conclude that the use of aggressive chemo-immunotherapy in combination with withdrawal of immunosuppression approach yields excellent results and should be prospectively studied in a multi-institutional setting.

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Keywords

solid organ transplantation; rituximab; organ rejection; graft loss; treatment related mortality

Introduction

Post-transplant lymphoproliferative disorders (PTLD) 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). The majority of PTLD are associated with the presence of Epstein-Barr virus (EBV), a ubiquitous human herpesvirus that infects over 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 when EBV-negative recipients, predominantly children, receive organs from EBV-positive donors (6).

The 2008 WHO classification of PTLD includes the following types: early lesions, polymorphic lymphoproliferations, 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 involve extra-nodal sites as well as the allograft and causes significant morbidity and mortality (9). There is no universally accepted treatment strategy for monomorphic PTLD as 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 as well as preservation of the transplanted organ, particularly in situations where replacement therapy such as in liver, lung and heart transplants is not available. Accordingly, we employed 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 providing 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 1st of 1995 and August 30th of 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. In order to prevent rejection, prednisone was given at a dose of 40-60 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 – 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-sulfamethoxazole and more recently, filgrastim or pegfilgrastim. Response was assessed by a combination of physical exam, CT scans and, in recent years, with PET/CT scans. After completing chemotherapy, all patients were started back on immunosuppression with the choice of agents at the discretion of the transplant physicians. 22 patients met the inclusion criteria above.

Patient demographic factors and disease characteristics were calculated using descriptive statistics. Overall survival (OS) and progression-free survival (PFS) were estimated using 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 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 last follow-up. The cumulative incidence of PTLD-specific death was estimated by considering death due to other causes as a competing risk. The analyses were conducted by using SAS version 9.2 (SAS Institute, Cary, NC) and R version 2.11.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient and tumor demographic information are seen 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 (DLBCL), 6 with Burkitt or Burkitt-like lymphoma (27%). 13 out of the 22 patients had EBV positive lymphoma (59%). Only one patient had early PTLD (< 1 year after SOT) which was EBV positive. 9 out of 21 patients with late PTLD had EBV negative tumors. 15 (68%) patients had advanced stage disease and 17 (77%) had extra-nodal involvement (two patients who developed PTLD after kidney transplantation had graft involvement with PTLD).

All patients were treated with a combined approach with 12 of them (55%) receiving CHOP-R every 2 weeks (dose dense CHOP-R). Other treatment regimens included CHOP-R or CHOP every 3 weeks, part A hyper-CVAD-R, EPOCH-R and ProMACE-Cytabom (Table 2).

Complete response (CR) was seen in all but two patients (91%). One patient had persistent subcutaneous disease after dose-dense CHOP-R and required radiation before achieving CR for an overall CR of 95%.

Five patients had recurrent disease after achieving CR, including three patients with CNS recurrence, two of whom died. The third patient with (isolated) CNS relapse initially received a high-dose cytosine-arabioside-based salvage chemotherapy but tolerated it poorly and then received whole brain radiation and remains in remission with good graft function more than two years after completing treatment. One patient with a cardiac transplant had two relapses after completing dose-dense CHOP-R. The first recurrence was treated with involved-field radiation and rituximab. The second recurrence was treated by withdrawal of immunosuppression and salvage chemotherapy with RICE (rituximab, ifosfamide, carboplatin, etoposide). This was then followed by high-dose BEAM (carmustine, etoposide, cytosine arabinoside, melphalan) and autologous stem cell transplant. The latter patient remains in remission more than two years after treatment and has a normal cardiac ejection fraction. The fifth patient had recurrence of Burkitt lymphoma/leukemia five years after being treated for the same diagnosis. Interestingly, immunoglobulin gene rearrangement from tumor cells at recurrence was different from the time of diagnosis, raising the question of a second lymphoma.

Median follow-up time was 2.42 years among patients who were still alive. Median OS was 9.61 years with 95% confidence interval (CI) (5.21-10.74) (Figure 1). Median PFS was 5.39 years with 95% CI (0.92-10.74) (Figure 2). Only 3 patients died due to PTLT: two within the 3 years after diagnosis and 1 (with CNS lymphoma relapse) 9 years after the diagnosis.

There was no treatment-related mortality (TRM). PTLT-specific death was calculated using the cumulative incidence function (CIF). The 4-year cumulative incidence of death due to PTLT was 10% with 95% CI (0.02-0.28) (Figure 3).

Out of the 22 patients, 4 patients (all after kidney transplantation) had graft loss due to rejection with graft loss rate of 18% with 95% CI (0.02-0.34).

Discussion

The dual goals of treatment of PTLT are cure of the lymphoma as well as preservation of the transplanted organ, with the latter a necessity in situations where replacement therapy is not available such as in liver, lung and heart transplants. In the absence of prospective clinical trials, standard therapy has evolved to a sequential approach first aimed at partially restoring cellular immunity by RIS, sometimes in combination with or followed by rituximab. If there is no response or if there is disease progression, chemotherapy is initiated (15, 17). Nevertheless, recommendations regarding the extent and duration of RIS have been vague and non-standardized. RIS is usually ineffective in late monomorphic lymphomas, particularly in patients with advanced disease and a high LDH (18). Moreover, RIS can be associated with disease progression and a significant risk of graft rejection (15, 18, 19). Rituximab, usually given with RIS, has been a major advance in the treatment of PTLT but responses are generally incomplete and organ rejection remains problematic (20-22). Chemotherapy, particularly in combination with rituximab has been effective as in other aggressive lymphomas and appears to prevent rejection by compensating for the withdrawal of immunosuppression (14, 15, 23, 24). However, as earlier reports described excessive treatment-related morbidity and mortality, chemotherapy has been generally relegated to the second or third tier of treatment (15, 17, 25).

All of our patients were treated with complete withdrawal of immunosuppression in addition to immediately beginning chemotherapy with or without rituximab. This strategy yielded an excellent CR rate of 90% with an additional patient achieving CR after radiation and was associated with no TRM. The majority of these patients (55%) received dose-dense CHOP-R, with aggressive infection prophylaxis including acyclovir, fluconazole, ciprofloxacin, trimethoprim-sulfamethoxazole and hematopoietic growth factors. The absence of TRM in our patient population is undoubtedly due to the deployment of aggressive supportive care as well as complete withdrawal of immunosuppressive drugs during the treatment period. Discontinuing calcineurin inhibitors during chemotherapy avoids stacking immunosuppression on top of myelosuppression. In addition, cyclosporine is known to enhance the myelosuppression of drugs such as doxorubicin and etoposide (26-28) and thereby potentially increase morbidity and mortality.

The high response rate to chemoimmunotherapy and low cumulative risk of death due to PTLT suggests that the treatment sensitivity of PTLT is at least as good as other aggressive lymphomas, an observation supported by the well documented high response rate of PTLT to rituximab alone (20-22). In fact, in our study group, the cumulative rate of death from other causes exceeded that due to PTLT and as most of these deaths were late, this would suggest that death did not occur as a consequence of treatment but rather from the cumulative burden of comorbidities in this population of patients (Figure 3).

The most commonly used chemotherapy regimen, particularly in the more recent study period, was dose-dense CHOP-R, a regimen that is probably only equivalent in efficacy to standard CHOP-R given every three weeks in patients with diffuse large B cell lymphoma (29). However, the two-week schedule is associated with a shorter duration of treatment and may further minimize the risk of graft rejection secondary to greater immunosuppression provided by more frequent chemotherapy. In our study, only 4 of 22 patients had transplant organ loss, all of whom had kidney transplants and with three of the four patients showing chronic kidney injury (creatinine ≥ 2 gm/dL) at the time of diagnosis of PTLT. This compares favorably to the rejection rate after RIS alone or with rituximab (15, 18).

A potential key advantage to the strategy of combined dose-dense chemoimmunotherapy and withdrawal of immunosuppression is that for the 10-12 weeks, in which calcineurin inhibitors and adjuvant drugs are held, the patient is receiving “protective” chemotherapy. Although data are lacking on the effect of chemotherapy on organ survival, Trappe et al. retrospectively studied renal transplant patients with PTLT sequentially treated with RIS and chemotherapy and found non-inferior graft function compared with untreated control patients (24). Taylor et al. used anthracycline-based chemotherapy as first line treatment in 18 patients with monomorphic lymphoma and reported no organ loss (16). In both of the latter studies, immunosuppression was reduced but not eliminated. However, Mamzer-Bruneel et al. treated 10 patients with late (> 12 months) PTLT with CHOP and reported no graft rejection despite completely stopping immunosuppression (14). A larger group of patients will need to be studied to determine whether chemoimmunotherapy-induced immunosuppression is sufficient to avoid organ rejection.

There are several limitations of our study including its small size and the retrospective nature of data collection. In addition, our results were achieved in patients with predominantly late monomorphic lymphoma, 41% of whom were EBV-negative. Patients with an earlier onset of monomorphic lymphoma may have a higher TRM and graft loss in association with chemo-immunotherapy and stopping immunosuppression. It would be interesting to explore the outcomes based on the tumor EBV status and timing of the diagnosis to see if treatment results perhaps are better for patients treated during the last few years of the study period taking in to consideration differences in not only therapy but also diagnostics. With a total of only 22 patients, 9 of whom were EBV positive, the number of recurrences and rejections is only 5 and 4, respectively. The small size makes these types of analyses unfeasible. Ultimately, a prospective multi-institutional trial will be necessary to compare our approach described above with the strategy of sequential rituximab and chemotherapy in patients not responding to RIS recently reported by Trappe et al (25). They reported partial and complete responses in 53 of 59 patients with 7 additional patients (11%) dying of TRM (25). In the 53 responding patients, the median response duration has not been reached. The latter group has proposed a tailored strategy of rituximab followed by CHOP-R in patients who do not achieve a CR after rituximab alone. Patients who achieve a CR with rituximab will receive maintenance rituximab (25, 30). In addition to PTLT outcome, preservation of organ function will be an important endpoint as the tailored approach being tested by Trappe et al. employs a period of RIS during which the graft is not protected by chemotherapy.

A combined treatment approach with aggressive chemotherapy predominantly with rituximab and complete withdrawal of immunosuppression yielded excellent results for patients with monomorphic PTLT after SOT and was associated with a low risk of organ rejection and no TRM. Given the promising results of this retrospective study, this treatment approach should be tested in a prospective multicenter clinical trial.

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Clinical viewpoints

- Monomorphic post-transplant lymphoproliferative disorders (PTLD) are the most aggressive type of PTLD occurring after solid organ transplantation (SOT).
- Currently accepted therapy includes sequential approach starting from reduction of immunosuppression, sometimes in combination with or followed by rituximab. Chemotherapy has been generally relegated to the second or third tier of treatment due to concerns about excessive treatment-related morbidity and mortality. Outcomes of this strategy are not satisfactory due to lower response rates, high graft loss rates and frequent disease progression.
- We advocate for a combination approach including complete withdrawal of immunosuppression together with administration of intensive chemotherapy with or without rituximab with goals of simultaneously treating the lymphoma and providing enough immunosuppression with the chemotherapy to prevent rejection.
- Our results indicate that with combination approach, patients may achieve excellent complete response rate with little risk of organ rejection and treatment related mortality.
- Given the promising results of our retrospective study, this approach should be prospectively studied in a multi-institutional setting.

Fig.1.
Kaplan-Meier analysis for Overall Survival (OS) of all patients.

Fig.2.
Kaplan-Meier analysis for Progression-Free Survival (PFS) of all patients.

Fig.3.
Estimated Cumulative Incidence of PTLD-specific Death versus non-PTLD related death.

Table 1

Patients Demographic and Clinical Characteristics

Patient characteristic	All patients (n=22)
Age at diagnosis	
Median-yr	50
Range-yr	20-73
Sex-no. (%)	
Male	13 (59)
Female	9 (41)
Transplanted organ [*] -no. (%)	
Heart	3 (14)
Kidney	17 (77)
Liver	2 (9)
Time from first SOT to PTLD diagnosis	
Group-no. (%)	
Early PTLD(<=1 year)	1 (5)
Late PTLD(>1 year)	21 (95)
Median-yr	5.6
Range-yr	0.8-20.5
Histology of PTLD-no. (%)	
Burkitt (or Burkitt like)	6 (27)
DLBCL ^{**}	16 (73)
Tumor EBV-no. (%)	
Negative	9 (41)
Positive	13 (59)
PTLD stage-no. (%)	
Early stage (I-II)	7 (32)
Advanced stage (III-IV)	15 (68)
Extranodal disease-no. (%)	
Yes	17 (77)
No	5 (23)
Survival status-no. (%)	
Alive	13 (59)
Dead	9 (41)

* One patient with multiple SOT was grouped based on the first transplantation (kidney transplantation in 1998 and pancreas transplantation in 1999)

** One patient had DLBCL of the CNS

Table 2

Frequency of Different Chemotherapy Regimens with/without Rituximab Used to Treat PTLN

Treatment	Frequency (%)
CHOP-R every 2 weeks	12 (55%)
CHOP-R every 3 weeks*	4 (18%)
CHOP	2 (9%)
ProMACE-cytaBOM plus radiation	1 (4.5%)
EPOCH-R	1 (4.5%)
part A hyper CVAD plus rituximab × 4 cycles, CHOP-R × 1	1 (4.5%)
part A hyper CVAD plus rituximab × 5 cycles	1 (4.5%)

R: Rituximab

* CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (one patient received etoposide instead of vincristine due to neuropathy)

ProMACE-cytaBOM: cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, and prednisone

EPOCH: etoposide, prednisone, vincristine, doxorubicin, cyclophosphamide, and rituximab

Part A hyper CVAD: cyclophosphamide, MESNA, vincristine, doxorubicin, and dexamethasone