Late-onset post-transplantation lymphoproliferative disorders after kidney transplantation: a monocentric study over three decades

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Abstract

Background. Late-onset post-transplantation lymphoproliferative disorders (PTLDs) occur 1 year after transplantation and are associated with poor prognosis. Initial treatment usually involves a reduction in immunosuppressive treatment. While early-onset PTLDs have a good prognosis following RI, this approach is generally inadequate for late-onset PTLDs. We assessed the specific outcome of late-onset PTLDs after kidney transplantation during the past three decades.

Methods. We reviewed the clinical and biological data of 52 kidney transplant recipients who developed late-onset PTLDs at our centre between 1980 and 2010. We compared clinical features, long-term outcome and renal prognosis of late-onset PTLDs both before and after the era of rituximab.

Results. Before 2000, 38% of the patients underwent surgery and 76% received chemotherapy either immediately or after surgery. After 2000, rituximab was administered to 70% of the patients either alone (23%) or in combination with chemotherapy (77%). Chemotherapy alone was administrated in 26% of the cases. Before and after 2000, complete remission was achieved in 38 and 87% of the cases, respectively (P = 0.0005). The 5-year overall survival (OS) was 33.3 and 69% (P = 0.003), and 5-year disease-free survival was 37.5 and 80%, respectively (P = 0.19). Renal function was preserved in 70% of the cases at the end of the follow-up.

Conclusions. This study shows an increase in OS and low graft loss for patients with late-onset PTLDs during the last decade, which may be attributed to multiple changes in clinical practice, including a more standardized treatment and the use of rituximab in combination with chemotherapy.

Keywords: chemotherapy; kidney transplantation; post-transplantation lymphoproliferative disorders; prognosis; rituximab

Introduction

Post-transplantation lymphoproliferative disorders (PTLDs) are rare but potentially life-threatening complications of solid organ transplantation. The World Health Organization (WHO) classification included PTLDs from 2001 [1] and distinguishes between early lesions, polymorphic PTLD, monomorphic PTLD and classical Hodgkin’s lymphoma [2]. Early- and late-onset PTLDs are currently distinct from one another, and this distinction is supported by a bimodal incidence profile and differences in risk factors and in clinical features [3]. Early-onset PTLDs occur during the first year and are frequently localized to the graft [4]. The almost systematic association with Epstein–Barr virus (EBV) [5–7], the absence of architectural effacement and the monoclonal pattern of pathologic hyperplasia histologically confirm the
diagnosis. Although not required, molecular analysis mostly shows the absence of monoclonal immunoglobulin gene rearrangement [2]. In contrast, late-onset PTLDs occur beyond the first year after transplantation and have multiple localizations and are associated with poor prognosis. Initial treatment usually involves a reduction in immunosuppressive treatment (RI) [8–10]; however, although early-onset PTLDs have a good prognosis following RI [9, 11], this approach is inadequate for late-onset PTLDs. Very few patients achieve a complete remission [10, 12, 13], and most of them require aggressive chemotherapy [3, 14–16]. Moreover, RI exposes patients to graft rejection [17]. Some teams use chemotherapy alone or in combination with radiotherapy; however, the reported results are highly variable. Response rates vary from 65 to 100%, and 5-year overall survival (OS) ranges from 24 to 60% [18]. All of these data must be reconsidered since the introduction of targeted therapies. Four prospective studies have evaluated the effect of rituximab monotherapy [19–22]. The combination of rituximab and chemotherapy showed better results in several series of patients [18], and a recent prospective phase 2 study supported the use of sequential immunochemotherapy with rituximab followed by CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone) in PTLDs [23]; however, most studies do not distinguish between early- and late-onset PTLDs and include multiple types of organ transplantations, and few data are available about the safety and efficiency of the combination of rituximab with chemotherapy. For this reason, it is difficult to form conclusions about the specific response to treatment and the prognosis of late-onset PTLDs. We therefore chose to focus our work on late-onset PTLDs after kidney transplantation. They represent an important therapeutic challenge, because of their severity, and must therefore be evaluated in the era of targeted treatments. Ten years ago, our team first published on a series of 16 patients with late-onset PTLDs diagnosed between 1980 and 1999 [24]. To assess the changes in the management and prognosis of late-onset PTLDs in the past 10 years, we compared all patients treated for a late-onset PTLD, before or after 31 December 1999. In our experience, this date corresponds to the beginning of a more standardized treatment for patients in the haematology unit and to the introduction of rituximab into clinical practice.

Subjects and methods

Patients

We conducted a retrospective monocentric analysis of patients treated between January 1980 and December 2010 at Necker Hospital for late-onset PTLDs after kidney transplantation. This work was approved by the Institutional Review Board (IRB registration number: 00001072). Adult patients (age ≥18 years old) were included if they were diagnosed with late-onset PTLDs occurring over a year after transplantation. We divided the cohort into two series with a cut-off on 31 December 1999. Information was collected regarding the patient’s medical history, pre-transplantation viral serology, clinical and biological presentation at the time of diagnosis, WHO performance status (PS), Ann Arbor staging, LDH level, International Prognosis Index (IPI), treatment and outcome. Staging evaluation was completed by computerized tomography, systematic bone marrow evaluation and lesion biopsy for histological analysis. Retrospective chart review of all patients was performed to ensure uniform staging for all patients diagnosed before the application of the Ann Arbor staging. The first step of treatment consisted of RI. In the absence of response after 2 weeks, patients received chemotherapy either alone or in combination with radiotherapy, according to the staff decision. After 1999, rituximab at 375 mg/m² was used either alone or in combination with chemotherapy for patients with CD20-positive lymphoma. If rituximab was used as a single agent, patients were included in the ongoing protocol [20]; otherwise, rituximab was used in combination with chemotherapy, according to haematologist’s decision.

Pathological specimen

Diagnostic biopsy materials were retrospectively collected from the institutions where PTLDs had been first diagnosed. The formalin- and/or Bouin-fixed paraffin-embedded sections of each specimen were stained with haematoxylin and eosin, Giemsa and silver stains for histopathological analysis. All of the slides were simultaneously reviewed by three experienced pathologists (I.A, D.C. and N.B.) at our institution and were classified according to the 2008 WHO classification into the following groups: polymorphic PTLD, monomorphic PTLD or classical Hodgkin’s PTLD. The panel of antibodies included CD20, CD3, CD5, CD10, CD15, CD23, CD30, Bcl2, Bcl6, immunoglobulin kappa and lambda light chains (Dako, Copenhagen, Denmark) and Ki67 (Immunotech, Marseille, France). For EBV detection, latent membrane 1 (LMP1) expression was analysed in paraffin-embedded sections by immunohistochemistry using the immunoperoxidase technique in all cases. Immunoperoxidase staining was performed on formalin-fixed sections via the avidin–biotin peroxidase complex method. EBV-encoded RNA (EBER) in situ hybridization using EBER oligonucleotides was performed on formalin-fixed sections using the Dako hybridization kit (Dako, Copenhagen, Denmark). Burkitt lymphomas were confirmed by the detection of c-myc rearrangement.

Statistical analysis

Responses were classified as a complete remission (CR), partial response, stable disease or progressive disease based on the International Workshop criteria [25]. Patients’ OS was defined as the time between the date of PTLD diagnosis and the date of death or last follow-up. Disease-free survival (DFS) was defined as the time between the complete remission and the date of relapse, progression, death or last follow-up for patients. Data are described as median and 25th and 75th percentiles for quantitative variables, and frequency and percentage for qualitative variables. Characteristics of the patients and the PTLDs were compared across the two periods (1980–1999 and 2000–2010) using Wilcoxon sum-rank test or Fisher exact test. OS and DFS were computed by Kaplan–Meier estimator and survival curves compared with log-rank test. Prognosis variables were identified by a Cox proportional hazard regression model. All statistical tests were two-tailed with a significance level of 0.05. Analysis was performed with R 2.13.1

Results

Baseline characteristics

Altogether, 52 kidney transplant recipients were diagnosed with late-onset PTLD in our hospital. Patient characteristics are summarized in Table 1. All but three patients were on dialysis prior to transplantation. Between 1980 and 1999, 57% of patients received induction therapy before transplantation. Between 2000 and 2010, a larger proportion of patients (80%) received induction therapy (P = 0.022). Anti-rejection prophylaxis combined either two (corticosteroids, purin inhibitors or mycophenolic acid) or three drugs (adding calcineurin inhibitors). More patients received a tritherapy in the second cohort than in the first (84 vs. 62%, respectively). The median interval between transplantation and late-onset PTLD...
diagnosis was 97 [65–183] months in the first cohort and 115 [74–163] months in the second cohort (P = 0.54).

Clinical characteristics

Most patients had a PS of ≤1 (52 and 72% in the first and second cohorts, respectively). Fever, weight loss and asthenia were the initial symptoms in 29% of patients (15 of 52). Four patients had a macrophage activation syndrome. Late-onset PTLDs were extranodal in 86 and 87% of patients in the first and second cohort, respectively. Organ localizations included the digestive tract (38%), central nervous system (CNS; 21%), bone marrow (17%), liver (10%), lung (8%), upper respiratory tract (8%), skin (6%) and graft (2%). The sex ratio (M/F) was 1.47 for the entire cohort of PTLDs and 1.46 in the whole population of kidney transplant patients during the same period. This ratio was similar for all localizations except in the case of CNS involvement (sex ratio M/F = 0.57). There was no difference in the IPI score between both cohorts (P = 0.93). Clinical characteristics at diagnosis are summarized in Table 2.

Histopathological findings and EBV status

All patients underwent a lesion biopsy at the time of diagnosis. PTLDs were classified according to the new WHO 2008 classification. Monomorphic PTLD was diagnosed in 80% of patients. Three patients (6%) had classical Hodgkin’s lymphoma, and seven (14%) patients had polymorphic PTLD. Histological subtypes are described in Table 3. EBV was present in tumour cells in 52% of patients, either by LMP1 expression or by EBER detection. Among monomorphic PTLD patients, 45% were EBV related. Polymorphic PTLDs were EBV related in 86% of cases, and all classical Hodgkin’s lymphomas were EBV related. In the second cohort, the EBV genome was prospectively searched in whole blood samples from 83% of patients. In the first cohort, it was retrospectively tested in frozen blood samples from 52% of patients. Quantitative viral load was measured by polymerase chain reaction with a cut-off of 1000 EBV copies/mL. EBV viral load was positive in 57% of patients tested. In patients with positive viral load, EBV was detected in the tumour in 65% of cases, whereas patients with
In CD20-expressing lymphomas, rituximab was used alone or in combination with chemotherapy. Drug doses were adapted to serum creatinine levels. Two patients required surgery due to initial intestinal perforation. Four patients (13%) were treated with rituximab alone, 8 patients (26%) received chemotherapy alone and 18 patients (58%) received a combination of rituximab with chemotherapy. Only one patient underwent radiotherapy for CNS localization, and two patients received an intensification therapy with autologous stem cell transplantation. The details of treatments based on histology and lymphoma localizations are reported in Table 4.

Outcomes

The median follow-up after PTLD diagnosis was 155 and 43 months in the first and second group of patients, respectively. Between 1980 and 1999, 24% of patients died within the first 30 days, mainly due to either sepsis (4 of 5) or rapid disease progression (1 in 5). Three of these patients received surgery, and only one of them received chemotherapy. After 1999, only 6.4% patients died from uncontrollable sepsis within the first 30 days (P = 0.10). Complete remission (CR) was achieved in 38 and 87% of cases for Cohorts 1 and 2, respectively (P < 0.001). In the first cohort, partial remission was obtained in 10% of cases. Five-year OS was 33.3 and 69% for Cohorts 1 and 2, respectively (P = 0.003) (Figure 1A). Median OS was 16.2 months in the first cohort and was not reached in the second. Among patients who achieved CR, 5-year DFS was 37.5 and 80%, respectively (P = 0.19) (Figure 1B). Between 1980 and 1999, the leading causes of death were sepsis (10 of 17), acute liver failure (2 of 17) and disease progression after initial failure of treatment (6 of 17). Between 2000 and 2010, 5 of the 9 patients died of sepsis and 4 patients relapsed within 2 years after achieving CR (3, 3, 7 and 20 months after CR, respectively); all relapsing patients died of disease progression. In univariate analysis, IPI was not significantly associated with OS (hazard ratio = 1.3 [0.99–1.75], P = 0.054). CNS localizations (P = 0.22), B or T phenotype (P = 0.6) and EBV status (P = 0.54) were not significantly associated with OS.

Renal graft prognosis and long-term complications

Median creatinine was 1.3 mg/dL [1–1.9] before PTLDs and 1.6 mg/dL [1.1–2.3] at the end of the follow-up (P = 0.22). Seventy per cent of the patients still had a functional graft. Eight patients were required to resume dialysis after graft loss. Deterioration of kidney function occurred in the first year of treatment for two patients. One case was attributed to the toxicity of chemotherapy, and the other was due to recurrent BK virus nephropathy. For other patients, the median time from PTLD treatment to graft loss was 8 years [5–11 years]. Three patients received second kidney transplantations (6–11 years after PTLD treatment) and resumed immunosuppressive therapy (follow-up 1, 60 and 101 months). In both cohorts, 11 patients (42%) resumed immunosuppressive therapy after treatment for lymphoma. No PTLD relapse was observed. Other patients were maintained under corticosteroid alone.

Table 2. Clinical characteristics of patients at diagnosis

<table>
<thead>
<tr>
<th>Organ localization, n (%)</th>
<th>1980–1999 (n = 21)</th>
<th>2000–2010 (n = 31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>1 (5)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>2 (9)</td>
<td>3 (10)</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>3 (14)</td>
<td>10 (32)</td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>4 (19)</td>
<td>5 (24)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>2 (9)</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>Organ localization, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal Only</td>
<td>16 (76)</td>
<td>10 (33)</td>
<td>0.004</td>
</tr>
<tr>
<td>Elevated</td>
<td>5 (24)</td>
<td>20 (67)</td>
<td></td>
</tr>
<tr>
<td>LDH, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4 (19)</td>
<td>4 (14)</td>
<td>0.93</td>
</tr>
<tr>
<td>Elevated</td>
<td>5 (24)</td>
<td>20 (67)</td>
<td></td>
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<tr>
<td>IPI, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (28)</td>
<td>8 (28)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (24)</td>
<td>6 (21)</td>
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<tr>
<td>2</td>
<td>4 (19)</td>
<td>3 (10)</td>
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<td>3</td>
<td>2 (10)</td>
<td>4 (14)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Ann Arbor stage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (5)</td>
<td>8 (28)</td>
<td>0.042</td>
</tr>
<tr>
<td>1</td>
<td>10 (47)</td>
<td>13 (45)</td>
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</tr>
<tr>
<td>2</td>
<td>4 (19)</td>
<td>7 (24)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5 (24)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase; IPI, international prognosis index.

*aSome patients had multiple organ localizations and are reported in different rows in this table.

undetectable EBV in their blood sample had a detectable EBV genome in the tumour in 53% of cases (P = 0.6 by \( \chi^2 \) test). Four patients still had positive EBV viral load after complete remission.

Treatment

All but six patients had an RI: calcineurin inhibitors and anti-metabolites were withdrawn, whereas corticosteroids were increased from 0.2 to 1 mg/kg. None of the evaluable patients showed favourable outcomes after RI. In the first cohort, haematologists were asked for therapeutic advice, but management was performed in the kidney transplantation unit. At the time of diagnosis, 38% of patients underwent surgical resection of lesions. After surgery, three patients died of immediate complications. Chemotherapy was administered in 76% of patients, and 31% received additional radiotherapy (three for upper respiratory tract, one for CNS and one for gastric localization). In the second cohort, all therapeutic decisions were discussed in multidisciplinary committees involving haematologists and transplant physicians. Patients were systematically transferred to the haematology department. Surgery was used only in the case of vital emergency and most of the patients were treated according to the chemotherapy protocols used for immunocompetent patients.
monomorphic PTLD, \( n = 3 \)

- **Diffuse Large B Cell Lymphoma**
  - \( n = 12 \)
  - \( n = 17 \)
  - \( n = 29 \)
  - \( n = 15 \)

- **Burkitt’s Lymphoma**
  - \( n = 0 \)
  - \( n = 2 \)
  - \( n = 2 \)
  - \( n = 0 \)

- **Plasmacytoma-like lesion**
  - \( n = 2 \)
  - \( n = 1 \)
  - \( n = 3 \)
  - \( n = 1 \)

- **T-cell lymphoma**
  - \( n = 4 \)
  - \( n = 3 \)
  - \( n = 7 \)
  - \( n = 2 \)

- **Peripheral T-cell lymphoma**
  - \( n = 1 \)
  - \( n = 3 \)
  - \( n = 2 \)
  - \( n = 1 \)

- **Other T-cell lymphoma**
  - \( n = 2 \)
  - \( n = 7 \)
  - \( n = 4 \)
  - \( n = 0 \)

**Table 4. Chemotherapy regimens used according to histological classification of late-onset PTLDs**

<table>
<thead>
<tr>
<th>Histology and localizations</th>
<th>1980–1999 (n = 21)</th>
<th>2000–2010 (n = 31)</th>
<th>Total (n = 52)</th>
<th>EBV-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical Hodgkin’s lymphoma (n = 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Polymorphic PTLD (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS (n = 4)</td>
<td>HD MTX + HD ARA (n = 1)</td>
<td>R-HD MTX + R-HD ARA (n = 1)</td>
<td>HD MTX + HD ARA (n = 1)</td>
<td>R-CHOP + HD MTX (n = 1)</td>
</tr>
<tr>
<td>Other (n = 3)</td>
<td>Deceased before treatment (n = 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monomorphic PTLD (n = 42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-cell lymphoma (n = 34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma (n = 24)</td>
<td>CHOP (n = 8)</td>
<td>R-CHOP (n = 11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmacytoma-like (n = 3)</td>
<td>CHOP (n = 2)</td>
<td>R-CHOP (n = 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkitt’s lymphoma (n = 2)</td>
<td></td>
<td>R-HD MTX (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS (n = 5)</td>
<td>CHOP (n = 1)</td>
<td>High dose corticosteroids (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-cell lymphoma (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatosplenic T lymphoma (n = 1)</td>
<td>CHOP (n = 1)</td>
<td>Deceased before treatment (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaplastic T lymphoma (n = 2)</td>
<td></td>
<td>CHEP + HD MTX (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral T lymphoma (n = 2)</td>
<td></td>
<td>VP16-DHAX (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS (n = 2)</td>
<td>HD MTX + HD ARA (n = 1)</td>
<td>COPADM / CYVE / HD MTX /</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>BEAM ASCT (n = 1)</td>
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</tr>
</tbody>
</table>

R-ABVD, rituximab, adriamycin, bleomycin, vinblastin, dacarbazine; R-CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone; HD MTX, high-dose methotrexate; HD ARA, high-dose aracryn; COPADM, cyclophosphamide, oncovin, prednisolone, adriamycin, methotrexate; CYVE, cytarabin etoposide; C of the follow-up. No other type of cancer was diagnosed.

Only one patient had an acute graft rejection episode and was subsequently treated with high-dose corticosteroids.

Infectious diseases were the most common complication after treatment. Recurrent bacterial infections were associated with hypogammaglobulinemia in seven patients (27%), three of whom were substituted with intravenous immunoglobulin. Viral reactivations were observed with hepatitis C virus (n = 4), hepatitis B virus (n = 3) and BK virus (n = 2). Skin cancers were diagnosed in 19.2% of the surviving patients at the end of the follow-up. No other type of cancer was diagnosed.

**Discussion**

This study is a monocentric comparison of two longitudinal cohorts of patients with late-onset PTLD after renal transplantation. We show that complete remission and survival improved during the last decade, with low toxicity and good renal prognosis. This change in prognosis may be due to the use of rituximab in combination with chemotherapy and to a more standardized treatment strategy. Our cohort represents a homogeneous set of patients. Our two groups of patients were comparable. The only
statistically significant difference was the use of induction treatment in the second group, which could have increased the rate of PTLDs. In the French Registry study, a decreased use of T-cell-depleting induction was associated with a decrease in lymphoma incidence [26]. All patients had kidney transplantation to prevent biases caused by co-morbidities and differences in the degree of immunosuppression that could be observed with other organ transplantations. We excluded early-onset PTLDs because they have a good response to RI most of the time. On the other hand, we think that the late-onset PTLD best treatment is an important question. Although our conclusions are limited because our study is retrospective, we show that the changes in our practice have modified the outcome over the past 10 years.

After 1999, rituximab was introduced for lymphoma treatment [27–30]. After the first successful treatment of PTLD with rituximab [31–33], four prospective studies were conducted to evaluate the rituximab monotherapy on B-cell PTLD [19–22]. CR was achieved in 29–60.5% of the cases. OS was 67% at 1 year [20], 47% at 2 years [21] and 56% at 3 years [22]. Long-term follow-up showed a high progression rate with rituximab alone [34]. In the case of refractory or relapse after rituximab monotherapy, salvage anthracyclin-based chemotherapy in second-line therapy achieved a 70% overall response rate [35]. Although these studies demonstrate the efficiency and safety of rituximab, rituximab alone was insufficient to improve the results obtained with chemotherapy alone [24, 36–38]; however, combining rituximab with chemotherapy showed interesting results [39, 40]. In a recent multicentre analysis, patients with rituximab-based treatment had improved outcomes (73% 3-year OS) over outcomes from patients with chemotherapy alone (33% 3-year OS) [41]. This difference could be explained by the presence of early-onset PTLDs in this study, which have very good response to rituximab. In contrast, patients treated with chemotherapy alone had T-cell lymphoma or CNS lymphoma, each of which carries a poor prognosis and could bias the differences observed. Recently, a prospective phase 2 study showed that sequential treatment with four courses of rituximab followed by four courses of CHOP-based chemotherapy provides good results on CD20-expressing PTLDs [23]. In this study, 68% of the patients achieved CR after sequential treatment and 5-year OS was 55%. Only age and time from transplantation to PTLDs was a predictive factor for OS. However, there are still few data about the comparison of rituximab in monotherapy, chemotherapy alone and combination of rituximab with chemotherapy. After 1999, most of the patients at our hospital with CD20-expressing PTLDs were treated with rituximab in combination with chemotherapy as a first-line therapy. Four patients were treated with rituximab in the ongoing protocol [20]. Other patients received chemotherapy alone. Many differences between the two periods could explain prognosis improvement: less reliance on surgery, a better management of treatment toxicity and infectious complications in haematology unit and the use of rituximab in combination with chemotherapy. Moreover, despite immunosuppression and significant comorbidities related to medical history, rituximab was not associated with an increase in infectious complications. Because we compared two retrospective historical cohorts, our study does not allow the comparison of chemotherapy with or without rituximab. Moreover, the number of patients does not allow the performance of subgroup analysis according to each histological subtype. However, these results are coherent with the recent prospective trial on sequential treatment [23] and suggest that the combination of rituximab and chemotherapy could be a safe and efficient treatment for late-onset PTLDs.

Due to a limited number of patients, we could not identify a significant prognosis factor, although IPI was close to significance. Multiple prognosis factors were
previously identified: the time between graft and PTLD diagnosis, the number of localizations, graft involvement [42], CNS involvement, EBV status [41, 43], clonality [43] and hypoalbuminaemia [41] could all predict OS. As these studies do not distinguish between early- and late-onset PTLDs, these factors could reflect the heterogeneity of PTLDs. IPI is used to predict outcomes for immuno-competent patients with aggressive NHL [44, 45]. The IPI score was identified as a prognostic factor in some series of PTLDs [12, 46], whereas in other series it was not prognostic [34, 43]. Predictive factors of favourable response to rituximab monotherapy were age, normal LDH, good PS and EBV-related PTLD. Rituximab monotherapy led to improved response rates in early-onset PTLDs compared with late-onset PTLDs [22, 34]. Patients with early-onset PTLDs or non-bulky disease could still benefit of rituximab monotherapy as a first-line treatment. It could also represent an acceptable alternative for patients unfit to receive chemotherapy. Most of the patients received chemotherapy in this cohort. These regimens were decided with a team of haematologists according to age, comorbidity and graft function. Recently, Parker et al. [47] published guidelines to help in the choice of treatment for PTLDs. In addition to age and graft function, basic tests were recommended to evaluate cardiac and hepatic functions. Patients older than 65 years or with organ dysfunction may not benefit from chemotherapy because of increased treatment-related toxicity. The majority of patients in our cohort were under 60 years. However, age is a risk factor for late-onset PTLDs [3, 26] and has been identified as an important prognostic factor [43]. The use of chemotherapy in older patients could be associated with increased toxicity and should be discussed accordingly. These difficult decisions are still debated in non-transplanted patients [48]. Elderly patients may benefit from reduced-dose chemotherapy or rituximab monotherapy, which could prevent toxicity associated with overtreatment.

It should be noted that infectious complications are the main cause of mortality in our cohort. Despite an improvement in the management of this complication in the last decade, chemotherapy is a major risk factor for severe sepsis. Trappe et al. [23] showed similar complications and proposed the use of systematic supportive treatment with granulocyte-colony stimulating factor for patients treated with chemotherapy. The risk of acute graft rejection is increased after RI, but is likely counterbalanced by the use of increased doses of corticosteroids, rituximab and chemotherapy [49]. In our cohort, only one patient had acute graft rejection. Furthermore, chemotherapy was not responsible for severe toxicity following renal transplant, despite the use of high-dose nephrotoxic drugs such as methotrexate. Because of the theoretical risk of relapse, an important question is the attitude towards anti-rejection prophylaxis. At the end of the follow-up, no relapse was observed for patients who resumed immunosuppressive treatment. A report from the Organ Procurement and Transplant Network/United Network for Organ Sharing database (OPTN/UNOS) indicated that a second transplantation after PTLD was acceptable, with 85.5% OS and no relapse [50]. The same result was reported in a smaller series of second kidney transplantations after PTLD [51]. It suggests that the relapse risk after PTLD treatment is not increased by immunosuppressive treatment resumption. Even if the optimal delay between remission and second transplantation is unknown, a period of at least 1 year is now recommended [47].

In summary, we showed that the prognosis of late-onset PTLDs after kidney transplantation improved dramatically over the last three decades. This result could be explained by multiple changes in our practice: improved management of toxicity and infectious complications or the use of rituximab in combination with chemotherapy as a first-line treatment for CD20-expressing lymphoma. During the last decade, it enabled an improvement in response, OS and DFS, with low toxicity and low graft impairment.

Conflict of interest statement. None declared.

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