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REVIEW

Management of patients with post-transplant lymphoproliferative disorder: the role of rituximab

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Summary

Post-transplant lymphoproliferative disorder (PTLD) is a serious complication of solid organ and bone marrow transplantations. Rituximab (Rituxan, Mabthera), a chimeric monoclonal antibody to the CD20 antigen on the surface of B-cell lymphocytes, has been used increasingly in the treatment of PTLD. Rituximab was initially approved for the treatment of low-grade non-Hodgkin lymphomas, but multiple case studies, retrospective analyses, and phase II trials demonstrate the benefit of rituximab in PTLD. This paper reviews the current data on rituximab and its promising role in the management of PTLD.

Introduction to PTLD

Post-transplant lymphoproliferative disorder (PTLD) has been broadly defined as a lymphoid proliferation or lymphoma that develops as a consequence of pharmacological immunosuppression following the solid organ or bone marrow transplantation [1]. The histologic subtypes of PTLD range from the early Epstein–Bar virus (EBV)-associated polymorphic lymphoid proliferations to EBV-positive or -negative monomorphic lymphomas of B-cell or less often T-cell origin (Table 1). The majority of cases are EBV-associated, of B-cell origin, and express CD20 antigen [2].

The pathogenesis of EBV-associated PTLD is linked to T-cell dysfunction. The suppressed EBV-specific immune response results in uncontrolled EBV reactivation in adults or primary EBV infection in children [2]. The etiology of EBV-negative PTLD, which is much less common, has not been well defined. It usually occurs later after transplant and has a worse prognosis [3].

The highest risk of developing PTLD is during the first year after transplant [4,5]. In solid organ transplant recipients, the median time of onset of PTLD is about 6 months [5,6]. In bone marrow transplant recipients, the median time of onset is about 2 months and the patients tend to have widespread disease and rapidly progressive course [5,6].

The frequency of PTLD varies depending on the type of transplant and level of immunosuppression. An analysis of 3796 solid organ transplant patients revealed that the highest frequency of PTLD was in lung transplant patients (8.2%) while renal transplant patients had the lowest frequency (1.3%) [5]. Within a group of 2030 patients after renal transplantation, higher level of immunosuppression was associated with an increased risk of developing PTLD [7]. About 30% of pediatric patients

Table 1. World Health Organization classification of post-transplant lymphoproliferative disease (PTLD) [1].

1. Early lesions
Reactive plasmacytic hyperplasia
Infectious mononucleosis-like
2. Polymorphic PTLD
3. Monomorphic PTLD
B-cell neoplasms
Diffuse large B-cell lymphoma
Burkitt/Burkitt-like lymphoma
Plasma cell myeloma
Plasmacytoma-like lesions
T-cell neoplasms
Peripheral T-cell lymphoma
Other types
4. Hodgkin-like PTLD

after small intestinal transplantation can develop PTLD [8].

Overall, the mortality rate for PTLD is high and has been estimated at about 60% after solid organ transplants and 80% after the bone marrow transplantation [1]. A multivariable model for survival using three adverse factors including poor performance status, monomorphic disease, and graft organ involvement was developed recently [9].

Conventional PTLD treatment

There are no large, prospective, randomized trials that would provide clear guidelines for PTLD treatment. It is challenging to conduct clinical trials in a disease like PTLD because of its heterogeneity and relatively low frequency. Most of the available data on PTLD treatment comes from retrospective analyses. Three basic concepts of PTLD management include enhancement of the immune system, destruction of the lymphoma cells, and the elimination of EBV.

Reduction in immunosuppression

Reduction in immunosuppression (RI) is considered the first line therapy for PTLD [5,10]. The concept is to reconstitute the immune system by reducing the patient's immunosuppressive regimen. The technique is usually tailored to the individual patient based on their organ transplant type. In general, RI would involve deletion of azathioprine or mycophenolate mofetil and minimization of calcineurin inhibitors and steroids. The magnitude of RI is patient-specific and may be limited in those with history of organ rejection or when the graft is indispensable for survival. In kidney transplant patients, when graft rejection is compatible with life, RI can be very aggressive and one can consider complete cessation of immunosuppression.

The time to response for RI is not well defined. In one series, median time to documentation of response was found to be 3.6 weeks [5]. Patients, however, might show signs of clinical improvement within 1–2 weeks. The strategy of RI alone can result in high response rates (RR) ranging from 0% to 89% depending upon the prognostic factors such as elevated lactate dehydrogenase (LDH), multi-organ involvement by PTLD, and organ failure at the time of diagnosis [5]. At the time of PTLD diagnosis, each patient should be assessed for the likelihood of response to RI, the ability to reduce immunosuppressive medications and whether there is time for RI to take effect. Other treatments might need to be used in conjunction with RI if the patient is not a candidate for RI alone.

Chemotherapy

Conventional cytotoxic chemotherapy which has been shown to be curative for many lymphomas in non-PTLD setting can be administered to PTLD patients who fail or are not amenable to RI. In certain aggressive PTLD subtypes (i.e. Burkitt lymphoma-like disease), conventional cytotoxic chemotherapy is used as the first line treatment as less aggressive approaches appear ineffective [11,12].

Various multi-drug regimens such as CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) have been used in PTLD patients [13–19]. In spite of the high RR up to 70%, the associated toxicity is significant and includes treatment-related deaths in about 25% of patients [15,16,20]. The high mortality of the standard chemotherapy regimens in the PTLD population might occur because of various factors including baseline pharmacologic immunosuppression, graft dysfunction, and colonization with resistant or hospital acquired infectious organisms.

Attempts have been made to reduce the toxicity of conventional chemotherapy by decreasing the intensity of chemotherapy doses and by empiric use of colony-stimulating growth factors (G-CSF) to prevent neutropenia [21,22].

Antiviral agents

Targeting EBV by antiviral agents such as ganciclovir or acyclovir has been attempted for prophylaxis and treatment of PTLD [23–25]. In order to prevent development of PTLD, 18 high-risk pediatric patients after liver transplant received 100 days of i.v. ganciclovir at 6–10 mg/kg/day [25]. None developed PTLD as opposed to the 10% PTLD in historical controls [25]. In 198 adult patients who received either ganciclovir or acyclovir during immunosuppressive therapy with antilymphocyte globulin, only 0.5% developed PTLD as opposed to 7% in

historical controls [26]. It is difficult to make conclusions based on the limited number of these non-randomized studies as the definition of 'high-risk' patients and the dosing are inconsistent.

It is unlikely that antiviral agents would be effective as a monotherapy for treatment of PTLD [27]. The latent EBV-infected B-cells which carry EBV genome and express a limited number of viral proteins are not eliminated by the use of antiviral agents. However, arginine butyrate, which selectively activates the EBV thymidine kinase gene in latently EBV-infected human lymphoid cells and tumor cells, was used in combination with ganciclovir in six patients with PTLD, who were resistant to conventional radiation and/or chemotherapy [28]. The combination produced complete responses (CR) in four of six patients, with a partial response (PR) occurring in the fifth patient [28]. Infusion of patient-derived EBV-specific T-cells is being developed for management of patient with EBV-associated PTLD [29,30].

Other PTLD therapies

Non-specific immune stimulants such as interferon-alpha can enhance immune system in patients with PTLD [13]. However, interferon use has the unfortunate side effect of inducing frequent concurrent allograft rejection and is not widely employed. Other treatment modalities such as external beam radiation and surgery can be used in settings of localized PTLD [5,13].

Monoclonal antibodies

Monoclonal antibodies have an important role in management of hematological malignancies. In PTLD, these agents are attractive because of their low immunosuppressive properties, targeting of lymphocyte and potential activation of the immune system. Successful monoclonal antibody therapy for the treatment of PTLD was first reported with the use of two murine monoclonal antibodies against B-cell antigens (CD21 and CD24) [31,32]. The treatment was tolerated well in all 58 patients enrolled in the multicenter study and 36 (61%) patients achieved CR [32]. With median follow-up of 61 months, the overall survival (OS) was 46% [32]. While the anti-CD21 and anti-CD24 antibodies were not developed commercially, they set the ground work for the monoclonal antibodies in use today.

Rituximab

Structure and mechanims of action

Rituximab is a chimeric anti-CD20 IgG monoclonal antibody consisting of human constant regions linked to murine variable domains [33]. The murine Fab domain of rituximab binds the CD20 antigen, which is a transmembrane protein located on the surface of mature B-cells, but not on hematopoietic stem cells or plasma cells. The CD20 antigen is involved in the regulation of transmembrane calcium conductance and cell-cycle progression during human B-cell activation [34].

Rituximab has three potential mechanisms of action including apoptosis, complement activation, and antibody-dependent cell-mediated cytotoxicity (Fig. 1). *In vitro*, the binding of rituximab to the CD20 antigen initiates direct signaling leading to apoptosis of the targeted lymphocyte [35,36]. Immune-mediated mechanisms might also play a role. The importance of complement-mediated cytotoxicity was suggested by an experiment with knockout mice lacking the intact complement pathway (C1q–/–). After injection with human CD20-positive tumor cells, the knockout animals failed to respond to rituximab as opposed to the wild-type animals that were cured of the disease [37]. Antibody-dependent cell-mediated cytotoxicity is the third potential mechanism of action. The Fc portion of rituximab binds the Fc receptor of effector cells such as macrophages. As rituximab is also bound to the lymphocyte by the Fab portion, it brings the effector cells to the contact with the lymphocyte. The effector cells are then activated, which result in cellular killing of the lymphoma cells. This theory is supported by data from an animal model with Fc receptor-deficient mouse, in which rituximab had significantly diminished activity [38]. Also, it has been demonstrated that Fcγ receptor polymorphisms affect the affinity for the Fc portion of rituximab and can have an impact on the time to progression in patients with follicular lymphoma who were treated with rituximab [39–41]. New anti-CD20 antibodies are being developed with re-engineered Fc portions to enhance the efficacy of rituximab by increasing the binding affinity to the Fcγ receptor [42].

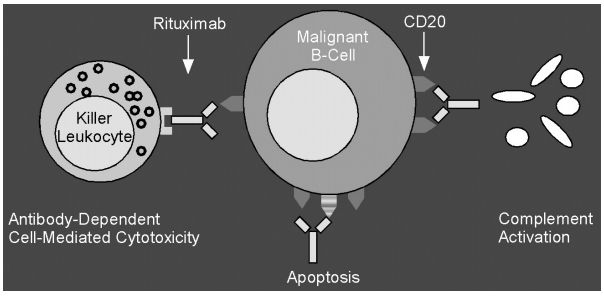

Figure 1 Rituximab: three potential mechanisms of action include apoptosis, complement activation and antibody-dependent cell-mediated cytotoxicity.

Indications and administration

Rituximab was first approved for the treatment of relapsed low-grade CD20-positive non-Hodgkin lymphomas with reported overall RR up to 50% and CR rates of 5% [43]. However, duration of response in patients with low-grade lymphoma is limited with medium time to progression of 13 months [43]. Since the initial approval, it has been widely used as a single agent or in combination with chemotherapy regimens for the treatment of various CD20-positive hematological malignancies [44–48].

Rituximab also has an expanding role in management of various non-malignant diseases, especially autoimmune conditions including rheumatoid arthritis [49], Sjögren's syndrome [50], systemic lupus erythematosus [51], myasthenia gravis [52,53], autoimmune hemolytic anemia [54,55], and idiopathic thrombocytopenic purpura [56]. In these diseases, it is assumed that B cells play a critical role in the autoimmune process. In transplant patients, several small, non-controlled studies and case reports demonstrated the benefit of rituximab in management of humoral allograft rejection [57–59].

Rituximab is usually administered as a slow i.v. infusion weekly for four doses. As opposed to many chemotherapy agents, it does not require adjustments for lung, kidney, liver, or heart dysfunction. It is recommended to premedicate patients with acetaminophen and antihistamine before each infusion to prevent infusional reactions. If the patient experiences adverse reactions related to rituximab, they usually occur during the first administration. In subsequent infusions, reactions are milder in intensity or do not arise at all [43].

Mild reactions during the infusion (flu-like symptoms, fever, chills, rigors, nausea, headache, and rash) can be treated symptomatically. Rarely, more serious reactions such as angioedema, hypotension, bronchospasm, and hypoxia can occur, usually within 30–120 min of beginning the first infusion. At that time, rituximab should be stopped and supportive care initiated. After resolution of all symptoms, the infusion can be restarted at slower rate.

As of 2004, over 540,000 patients received rituximab world-wide [60]. In a few lymphoma patients, rituximab therapy resulted in major complications including tumor lysis syndrome, infusion-related death, mucocutaneous reactions, delayed neutropenia, and lung injury, but none of these exceeded 0.5% in post-marketing safety data analysis [60]. As rituximab affects both the malignant and non-malignant CD20-positive B cells, there are concerns about infectious complications from the therapy. Despite B-cell depletion for approximately 6 months, immunoglobulin levels remain stable after one cycle of treatment with rituximab in lymphoma patients [45]. Extended use of the drug may result in some decrease of IgM levels [61]. However, patients receiving maintenance rituximab for non-Hodgkin lymphoma were not reported to have an increased infection rate after 2 years of continuous B-cell suppression [47].

There have been case reports of hepatitis B virus (HBV) reactivation resulting in liver failure [62], fatal varicella-zoster infection [63], and pure red cell aplasia because of parvovirus B19 [64] in follicular lymphoma patients treated with rituximab. These events, however, are rare.

Data on safety of rituximab in PTLD patients are limited. Based on the multiple case reports and several phase II trials, patients with PTLD appear to tolerate rituximab as well as *de novo* lymphoma patients. Of note, reactivation of cytomegalovirus infection resulted in death of a PTLD patient after treatment with rituximab [65]. Those PTLD patients who have an increased risk of HBV infection should be considered for HBV screening test prior rituximab.

Rituximab in management of PTLD

In 1998, Fay *et al.* reported the first use of rituximab in a pediatric patient with Fanconi disease who developed PTLD 6 months after the matched unrelated donor transplant [66]. The patient developed a tonsillar mass and cervical lymphadenopathy while off immunosuppression. The biopsy was consistent with polymorphic CD20-positive B-cell PTLD. Nearly all B-cell nuclei contained EBV RNA and high levels of EBV DNA were found in peripheral blood. The patient received rituximab in the standard dosing (375 mg/m^2 for 4 weekly doses) and experienced tumor regression only 3 days after the first infusion. He achieved CR without relapse at 6 months [66].

Many more case reports and case series of using rituximab in PTLD in various settings appeared in the literature in the next several years [67–86]. The cases include pediatric and adult PTLD patients who underwent solid organ or bone marrow transplantations and achieved excellent results with rituximab. Most of the patients also underwent concurrent RI and some had concurrent antiviral therapy [82]. Many patients experienced clinical improvement within a few days of the first infusion [74,75,77], but in some the benefit was not seen until a few months later [76].

Most patients in the case reports were treated with the standard dose of rituximab at 375 mg/m^2 once a week for four consecutive weeks. There were some exceptions to the dosing of rituximab. Five PTLD patients after intestinal transplants were treated by rituximab weekly until CR was achieved (range 3–6 months). Afterwards, the treatment intervals were extended to periods ranging from

every other week to every 3 months [87]. With median follow-up of 8 months (range 3–30 months), all of these patients remained in CR and did not have major infections or complications from the 'rituximab maintenance' dosing [87].

The majority of the case reports describe the use of rituximab in the early onset PTLD, but it might be effective for patients with late onset PTLD. Dotti *et al.* presented a case series of five patients who had late onset CD20-positive PTLD (at least 2 years after a solid organ transplant) and were treated with rituximab [71]. Two patients with advanced disease had only PR, but three patients who underwent successful debulking with surgery or radiotherapy prior to rituximab had excellent clinical outcome [71].

Several larger retrospective analyses have been conducted to demonstrate the benefit of rituximab in patients with PTLD [20,87–94]. Milpied *et al.* reviewed 32 adult PTLD patients, after both solid transplant and bone marrow transplant, who received rituximab [94]. The majority of patients had an early onset (median time of onset 5 months) and an EBV-associated disease. In addition to RI, rituximab was used as the first line treatment in 30 patients and as a salvage treatment in two patients who failed chemotherapy. Most patients received standard 4 weekly doses of rituximab with the median time from diagnosis of PTLD to treatment of 14 days (range 1–110 days). Rituximab treatment was well tolerated and resulted in RR 69% (20 patients achieved CR). There was a better RR for early onset (76%) than late onset (47%) disease. With a median follow-up of 8 months (range 1–16 months), 24 (75%) were alive, with 15 (68%) of the rituximab responders in CR. The 1-year projected survival was 73% [94].

Gonzalez-Barca *et al.* [93] reviewed data on 108 adult solid organ transplant patients with PTLD including 36 patients who received rituximab. With medium follow-up of 15 months, the OS of patients treated with rituximab was significantly better than for the whole group (76% vs. 21%) [93]. In another retrospective analysis with median follow-up of 41 months, 26 PTLD pediatric patients treated with rituximab were evaluated [88]. The RR was 85% with 18 (69%) patients achieving CR [88]. The four non-responders comprised two EBV-negative cases, Burkitts-like disease, and a fulminant PTLD case at 2 months post-transplant [88]. With the mean follow-up of 41 months, the OS was 73% with one graft loss [88]. An analysis of 33 PTLD patients after allogeneic bone marrow transplant revealed that 26 patients received rituximab [92]. The results were quite striking in favor of rituximab with OS at day 180 for patients treated with rituximab at 46% as opposed to 0% for those who did not receive it. In the group of patients treated with rituximab, the mortality rates of patients with advanced disease were significantly higher (82% vs. 7%) [92].

Phase II trials confirmed the clinical benefit of rituximab in PTLD in prospective manner [88,95–98]. The RR to single agent rituximab in PTLD patients ranged from 44% to 75% with CR rate ranging from 28% to 75%. The duration of CR varied depending on the trial, but there were clearly some patients with prolonged disease-free survival after single agent rituximab. In the largest prospective trial, response assessment by computed tomography was performed at about 3 months after starting the treatment [98]. The major differences in the results of the phase II trials are likely secondary to the heterogeneity of patients enrolled, small sample sizes, and short time of follow-up.

In a multicenter, prospective phase II study, Oertel *et al.* [97] treated 17 adult patients with standard dose of rituximab for PTLD. The mean follow-up time was 24 months [97]. Overall, 12 (71%) patients responded. Nine patients (53%) achieved CR, with a mean duration of 17.8 months. Two patients relapsed, at intervals three and 5 months after obtaining CR. The mean OS was 37 months with 11 (65%) patients alive at the end of the study. Adverse events were rare and of low grade [97].

In a pediatric population, Webber *et al.* [88] studied prospectively 14 pediatric patients with refractory disease, defined as those who had relapsed disease, no response to RI, or had concomitant allograft rejection. The patients were given standard dose of rituximab at 375 mg/m^2 weekly for 4 weeks with no further treatment for those with CR or for those with no response. Patients with PR received four further doses (weeks 5–8) [88]. The mean follow-up was 18 months. Out of the 12 evaluable patients in the ongoing trial, 75% achieved CR and 10 patients were alive with one graft loss. Two deaths were because of fungal pneumonia and complications from elective surgery in a patient with CR [88].

The largest prospective trial of using rituximab in PTLD was recently published by Choquet *et al.* [98]. This multicenter, open label, European phase II trial enrolled 46 patients with PTLD after solid organ transplantation who did not improve after RI [98]. The study included both pediatric and adult patients who were treated with standard dose of 375 mg/m^2 weekly for 4 weeks. Most of the PTLD cases were of relatively late onset with only 14 (35%) patients with PTLD diagnosis <1 year after their transplantation. At day 80, the RR was 44% including 12 (28%) patients with CR. Normal LDH was a significant predictor for response. At day 360, the responses were maintained in 68% of patients. The OS rate at 1 year was 67%. Rituximab was well tolerated with only two grades three to four adverse events related to the treatment [98].

Single agent rituximab might be effective in prevention of fulminant PTLD. In a group of 49 patients after allogeneic bone marrow transplant, 17 experienced EBV reactivation as detected by positive quantitative polymerase chain reaction (more than or equal to 1000 genome equivalents per milliliter). As reactivation of the virus is thought to correlate with an increased risk of developing PTLD, these patients received 'pre-emptive' rituximab [99]. When compared with historical cohort with the same risk profile, this strategy showed a significant reduction in PTLD incidence and eliminated any PTLD-associated mortality [99]. In a study of 56 patients after allogeneic stem cell transplant, monitoring of EBV reactivation and CD8 positive T-cell immune response helped determine when to use rituximab before the immune response was overwhelmed by the viral burden [100].

Apart from its use as a single agent, rituximab has been reported to have chemosensitizing effect on several lymphoma cell lines, possibly by augmenting apoptosis [36,101]. Clinically, patients with CD20-positive non-Hodgkin lymphomas who receive combination treatment of rituximab with cytotoxic chemotherapy have superior outcomes when compared with cytotoxic chemotherapy alone [102]. In PTLD, a pilot trial of rituximab in addition to cyclophosphamide and prednisone was conducted in six patients with history of solid organ transplantation

Table 2. Efficacy of rituximab in the treatment of PTLD in various settings.

Reference	Publication	Transplant type (population)	*n*	Response
Elstrom *et al.* [20]	Article/retrospective analysis	Solid organ and bone marrow (adults)	22	Response rate (RR) was 68% and 13 (59%) patients had CR; when compared with patients who received chemotherapy, the RR was similar with less toxicity
Webber *et al.* [88]	Abstract/retrospective analysis	Solid organ (pediatrics)	26	Response rate was 75% and 18 (69%) patients had CR; four non-responders included two Epstein–Bar virus negative cases, one fulminant disease, and one Burkitts-like disease
Ferry *et al.* [92]	Abstract/retrospective analysis	Bone marrow (pediatric and adult)	26	Overall survival (OS) at 180 days of 26 patients who received rituximab was 46% (vs. 0% for seven patients who did not received rituximab); patients with less advanced disease and low viral load had better response rate
Milpied *et al.* [94]	Article/retrospective analysis	Solid organ and bone marrow (adults)	32	Response rate was 69% and 20 (63%) patients had complete responses (CR); projected OS was 73% at 1 year; four patients relapsed and three died while in remission
Gonzalez-Barca *et al.* [93]	Abstract/retrospective analysis	Solid organ (adult)	36	The 36 patients who received rituximab had improved OS when compared with the total 108 PTLD patients (76% vs. overall 21% with median follow-up 15 months)
Morrison *et al*. [95]	Abstract/phase II trial	Solid organ (adults)	8	Response rate was 75% with three CRs, three PRs, one progressive disease, and one death
Horwitz *et al.* [96]	Abstract/phase II trial	Solid organ (pediatrics and adults)	14	Response rate was 62% (three with CRs, five with PRs); one patient had stable disease at 1 month; four patients progressed on therapy and went on to receive chemotherapy, resulting in two septic deaths
Webber *et al.* [88]	Abstract/phase II trial	Solid organ (pediatric)	12	Nine (75%) patients had CR, OS was 83% with median follow-up 18 months
Oertel *et al.* [97]	Article/phase II trial	Solid organ (adult)	17	Nine (53%) patients achieved CR, one with PR, one with progressive disease; mean OS 37 months, no severe adverse events
Choquet *et al.* [98]	Article/phase II trial	Solid (pediatric and adult)	43	At day 80, RR was 44% with 12 patients in CR; at day 360, responses were maintained in 68%; the treatment was well tolerated

[18]. They received two to six courses of cyclophosphamide (600 mg/m^2, on day 1 of each course) and prednisone (1 mg/kg, every 12 h for 10 doses), given every 3 weeks. The first two courses were given in combination with 4–6 weekly doses of rituximab (375 mg/m^2). With median follow-up of 12.5 months (range 4–29 months), all patients responded including five patients with CR [18]. The one patient who did not achieve CR had PR, but eventually progressed and died of fulminant disease. There were no infectious complications and all allografts in surviving patients were functional [18]. Preliminary data from an ongoing phase II trial of sequential rituximab followed by CHOP chemotherapy with granulocyte colony-stimulating growth factor (G-CSF) were presented recently [22]. In the 25 evaluable PTLD patients, nine (36%) had severe infections and three (12%) died of treatment-related causes [22].

Rituximab versus chemotherapy

Until recently, patients with PTLD who failed RI were treated with cytotoxic chemotherapy [15,16]. There are no prospective, randomized trials comparing chemotherapy to rituximab for patients who do not respond to RI. However, a recent retrospective study analyzed data on 35 PTLD patients who underwent treatment with rituximab, chemotherapy, or both [20]. The findings confirmed that both single agent rituximab and chemotherapy can be highly effective in patients who failed RI [20]. Both types of therapies resulted in prolonged disease-free survival and cure in a number of PTLD patients. The 22 patients who received rituximab had RR 68% with 13 (59%) patients in CR. Their median OS was 31 months. The 23 patients who received cytotoxic chemotherapy had RR 72% with 13 (57%) patients in CR and the median OS of 42 months. While rituximab was well tolerated, 26% of patients who received chemotherapy died from treatment-related toxicities [20]. An important observation in this study was that patients who failed treatment with rituximab were able to receive salvage chemotherapy later [20]. These results suggest that, when possible, rituximab should be considered first in EBV-related, CD-20-positive cases of PTLD.

Conclusion

Many case reports, retrospective analyses, and several prospective trials have demonstrated that rituximab is effective for CD20-positive PTLD in various settings (Table 2). PTLD patients can achieve long-term CR and potential cure after single agent rituximab treatment. When compared with cytotoxic chemotherapy, rituximab has comparable RR, but significantly reduced toxicity and treatment-associated mortality. Limited data suggest that patients with fulminant, advanced disease, EBV-negative or late-onset tumors are less likely to respond to single agent rituximab [20,71,92,94,98,103]. For these patients, cytotoxic chemotherapy might be necessary early in the treatment course.

However, for the majority of EBV-associated CD20-positive PTLD patients, we favor rituximab as the second line of treatment right after RI. Given the significant toxicity, chemotherapy is best reserved for use in patients who are ineligible or fail rituximab. In the future, trials with combination therapies involving rituximab and other immune-based treatments will hopefully improve the clinical outcome of patients with PTLD.

References

1. Harris NL, Swerdlow SH, Frizzera G, Knowles DM. Post-transplant lymphoproliferative disorders In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press, 2001: 264 pp.
2. Gottschalk S, Rooney CM, Heslop HE. Post-transplant lymphoproliferative disorders. *Annu Rev Med* 2005; **56**: 29.
3. Nelson BP, Nalesnik MA, Bahler DW, Locker J, Fung JJ, Swerdlow SH. Epstein-Barr virus-negative post-transplant lymphoproliferative disorders: a distinct entity? *Am J Surg Pathol* 2000; **24**: 375.
4. Trofe J, Buell JF, Beebe TM, *et al.* Analysis of factors that influence survival with post-transplant lymphoproliferative disorder in renal transplant recipients: the Israel Penn International Transplant Tumor Registry experience. *Am J Transplant* 2005; **5**: 775.
5. Tsai DE, Hardy CL, Tomaszewski JE, *et al.* Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. *Transplantation* 2001; **71**: 1076.
6. Nalesnik MA. Posttransplantation lymphoproliferative disorders (PTLD): current perspectives. *Semin Thorac Cardiovasc Surg* 1996; **8**: 139.
7. Herzig KA, Juffs HG, Norris D, *et al.* A single-centre experience of post-renal transplant lymphoproliferative disorder. *Transpl Int* 2003; **16**: 529.
8. Finn L, Reyes J, Bueno J, Yunis E. Epstein-Barr virus infections in children after transplantation of the small intestine. *Am J Surg Pathol* 1998; **22**: 299.
9. Ghobrial IM, Habermann TM, Maurer MJ, *et al.* Prognostic analysis for survival in adult solid organ transplant recipients with post-transplantation lymphoproliferative disorders. *J Clin Oncol* 2005; **23**: 7574.
10. Starzl TE, Nalesnik MA, Porter KA, *et al.* Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. *Lancet* 1984; **1**: 583.

11. Pasquale MA, Weppler D, Smith J, *et al.* Burkitt's lymphoma variant of post-transplant lymphoproliferative disease (PTLD). *Pathol Oncol Res* 2002; **8**: 105.
12. Sekiguchi N, Nishimoto J, Tanosaki R, *et al.* EBV-positive Burkitt lymphoma as a late-onset posttransplantation lymphoproliferative disorder after allogeneic stem cell transplantation. *Int J Hematol* 2004; **79**: 387.
13. Davis CL, Wood BL, Sabath DE, Joseph JS, Stehman-Breen C, Broudy VC. Interferon-alpha treatment of post-transplant lymphoproliferative disorder in recipients of solid organ transplants. *Transplantation* 1998; **66**: 1770.
14. Buell JF, Gross TG, Hanaway MJ, *et al.* Chemotherapy for posttransplant lymphoproliferative disorder: the Israel Penn International Transplant Tumor Registry experience. *Transplant Proc* 2005; **37**: 956.
15. Mamzer-Bruneel MF, Lome C, Morelon E, *et al.* Durable remission after aggressive chemotherapy for very late post-kidney transplant lymphoproliferation: a report of 16 cases observed in a single center. *J Clin Oncol* 2000; **18**: 3622.
16. Swinnen LJ, Mullen GM, Carr TJ, Costanzo MR, Fisher RI. Aggressive treatment for postcardiac transplant lymphoproliferation. *Blood* 1995; **86**: 3333.
17. Komrokji RS, Oliva JL, Zand M, Felgar R, Abboud CN. Mini-BEAM and autologous hematopoietic stem-cell transplant for treatment of post-transplant lymphoproliferative disorders. *Am J Hematol* 2005; **79**: 211.
18. Orjuela M, Gross TG, Cheung YK, Alobeid B, Morris E, Cairo MS. A pilot study of chemoimmunotherapy (cyclophosphamide, prednisone, and rituximab) in patients with post-transplant lymphoproliferative disorder following solid organ transplantation. *Clin Cancer Res* 2003; **9**: 3945S.
19. Dharnidharka VR, Douglas VK, Hunger SP, Fennell RS. Hodgkin's lymphoma after post-transplant lymphoproliferative disease in a renal transplant recipient. *Pediatr Transplant* 2004; **8**: 87.
20. Elstrom RL, Andreadis C, Aqui NA, Tsai DE. Treatment of post-transplant lymphoproliferative disorder (PTLD) with rituximab or chemotherapy: the University of Pennsylvania experience. *Blood* 2005; **106**: Abstract No: 936.
21. Gross TG, Bucuvalas JC, Park JR, *et al.* Low-dose chemotherapy for Epstein-Barr virus-positive post-transplantation lymphoproliferative disease in children after solid organ transplantation. *J Clin Oncol* 2005; **23**: 6481.
22. Trappe R, Oertel S, Choquet S, LeBlond V, Papp-Vary M, Riess H. Sequential treatment with the anti-CD 20 antibody rituximab and CHOP + GCSF chemotherapy in patients with post-transplant lymphoproliferative disorder (PTLD): first interim analysis of a multicenter phase II study. *Blood* 2005; **106**: Abstract No: 932.
23. Shapiro RS, McClain K, Frizzera G, *et al.* Epstein-Barr virus associated B cell lymphoproliferative disorders following bone marrow transplantation. *Blood* 1988; **71**: 1234.
24. Faller DV, Mentzer SJ, Perrine SP. Induction of the Epstein-Barr virus thymidine kinase gene with concomitant nucleoside antivirals as a therapeutic strategy for Epstein-Barr virus-associated malignancies. *Curr Opin Oncol* 2001; **13**: 360.
25. McDiarmid SV, Jordan S, Kim GS, *et al.* Prevention and preemptive therapy of posttransplant lymphoproliferative disease in pediatric liver recipients. *Transplantation* 1998; **66**: 1604.
26. Darenkov IA, Marcarelli MA, Basadonna GP, *et al.* Reduced incidence of Epstein-Barr virus-associated post-transplant lymphoproliferative disorder using preemptive antiviral therapy. *Transplantation* 1997; **64**: 848.
27. Crumpacker CS. Ganciclovir. *N Engl J Med* 1996; **335**: 721.
28. Mentzer SJ, Perrine SP, Faller DV. Epstein–Barr virus post-transplant lymphoproliferative disease and virus-specific therapy: pharmacological re-activation of viral target genes with arginine butyrate. *Transpl Infect Dis* 2001; **3**: 177.
29. Comoli P, Maccario R, Locatelli F, *et al.* Treatment of EBV-related post-renal transplant lymphoproliferative disease with a tailored regimen including EBV-specific T cells. *Am J Transplant* 2005; **5**: 1415.
30. Gustafsson A, Levitsky V, Zou JZ, *et al.* Epstein-Barr virus (EBV) load in bone marrow transplant recipients at risk to develop posttransplant lymphoproliferative disease: prophylactic infusion of EBV-specific cytotoxic T cells. *Blood* 2000; **95**: 807.
31. Fischer A, Blanche S, Le Bidois J, *et al.* Anti-B-cell monoclonal antibodies in the treatment of severe B-cell lymphoproliferative syndrome following bone marrow and organ transplantation. *N Engl J Med* 1991; **324**: 1451.
32. Benkerrou M, Jais JP, Leblond V, *et al.* Anti-B-cell monoclonal antibody treatment of severe posttransplant B-lymphoproliferative disorder: prognostic factors and long-term outcome. *Blood* 1998; **92**: 3137.
33. Reff ME, Carner K, Chambers KS, *et al.* Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood* 1994; **83**: 435.
34. Tedder TF, Engel P. CD20: a regulator of cell-cycle progression of B lymphocytes. *Immunol Today* 1994; **15**: 450.
35. Shan D, Ledbetter JA, Press OW. Apoptosis of malignant human B cells by ligation of CD20 with monoclonal antibodies. *Blood* 1998; **91**: 1644.
36. Demidem A, Lam T, Alas S, Hariharan K, Hanna N, Bonavida B. Chimeric anti-CD20 (IDEC-C2B8) monoclonal antibody sensitizes a B cell lymphoma cell line to cell killing by cytotoxic drugs. *Cancer Biother Radiopharm* 1997; **12**: 177.
37. Di Gaetano N, Cittera E, Nota R, *et al.* Complement activation determines the therapeutic activity of rituximab in vivo. *J Immunol* 2003; **171**: 1581.
38. Clynes RA, Towers TL, Presta LG, Ravetch JV. Inhibitory Fc receptors modulate in vivo cytoxicity against tumor targets. *Nat Med* 2000; **6**: 443.

39. Koene HR, Kleijer M, Algra J, Roos D, von dem Borne AE, de Haas M. Fc gammaRIIIa-158V/F polymorphism influences the binding of IgG by natural killer cell Fc gammaRIIIa, independently of the Fc gammaRIIIa-48L/R/H phenotype. *Blood* 1997; **90**: 1109.
40. Cartron G, Dacheux L, Salles G, *et al.* Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcgammaRIIIa gene. *Blood* 2002; **99**: 754.
41. Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. *J Clin Oncol* 2003; **21**: 3940.
42. Weng WK, Stavenhagen J, Koenig S, Levy R. Rituximab variants with re-engineered Fc with higher affinity to activating FcγR eliminate the functional difference between FcγR genotypes. *Blood* 2005; **106**: Abstract No: 347.
43. McLaughlin P, Grillo-Lopez AJ, Link BK, *et al.* Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998; **16**: 2825.
44. Witzig TE, Vukov AM, Habermann TM, *et al.* Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma: a phase II trial in the North Central Cancer Treatment Group. *J Clin Oncol* 2005; **23**: 1103.
45. Davis TA, White CA, Grillo-Lopez AJ, *et al.* Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: results of a phase II trial of rituximab. *J Clin Oncol* 1999; **17**: 1851.
46. Chong EA, Svoboda J, Cherian S, *et al.* Regression of pulmonary MALT lymphoma after treatment with rituximab. *Leuk Lymphoma* 2005; **46**: 1383.
47. Hainsworth JD, Litchy S, Shaffer DW, Lackey VL, Grimaldi M, Greco FA. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma – a randomized phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol* 2005; **23**: 1088.
48. Feugier P, Van Hoof A, Sebban C, *et al.* Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 2005; **23**: 4117.
49. Edwards JC, Szczepanski L, Szechinski J, *et al.* Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004; **350**: 2572.
50. Ahmadi-Simab K, Lamprecht P, Nolle B, Ai M, Gross WL. Successful treatment of refractory anterior scleritis in primary Sjogren's syndrome with rituximab. *Ann Rheum Dis* 2005; **64**: 1087.
51. Looney RJ, Anolik JH, Campbell D, *et al.* B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. *Arthritis Rheum* 2004; **50**: 2580.
52. Zaja F, Russo D, Fuga G, Perella G, Baccarani M. Rituximab for myasthenia gravis developing after bone marrow transplant. *Neurology* 2000; **55**: 1062.
53. Wylam ME, Anderson PM, Kuntz NL, Rodriguez V. Successful treatment of refractory myasthenia gravis using rituximab: a pediatric case report. *J Pediatr* 2003; **143**: 674.
54. Quartier P, Brethon B, Philippet P, Landman-Parker J, Le Deist F, Fischer A. Treatment of childhood autoimmune haemolytic anaemia with rituximab. *Lancet* 2001; **358**: 1511.
55. Ramanathan S, Koutts J, Hertzberg MS. Two cases of refractory warm autoimmune hemolytic anemia treated with rituximab. *Am J Hematol* 2005; **78**: 123.
56. Stasi R, Provan D. Management of immune thrombocytopenic purpura in adults. *Mayo Clin Proc* 2004; **79**: 504.
57. Usuda M, Fujimori K, Koyamada N, *et al.* Successful use of anti-CD20 monoclonal antibody (rituximab) for ABO-incompatible living-related liver transplantation. *Transplantation* 2005; **79**: 12.
58. Alausa M, Almagro U, Siddiqi N, Zuiderweg R, Medipalli R, Hariharan S. Refractory acute kidney transplant rejection with CD20 graft infiltrates and successful therapy with rituximab. *Clin Transplant* 2005; **19**: 137.
59. Aranda Jr JM, Scornik JC, Normann SJ, *et al.* Anti-CD20 monoclonal antibody (rituximab) therapy for acute cardiac humoral rejection: a case report. *Transplantation* 2002; **73**: 907.
60. Kimby E. Tolerability and safety of rituximab (MabThera((R))). *Cancer Treat Rev* 2005; **31**: 456.
61. Piro LD, White CA, Grillo-Lopez AJ, *et al.* Extended rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. *Ann Oncol* 1999; **10**: 655.
62. Dervite I, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. *N Engl J Med* 2001; **344**: 68.
63. Bermudez A, Marco F, Conde E, Mazo E, Recio M, Zubizarreta A. Fatal visceral varicella-zoster infection following rituximab and chemotherapy treatment in a patient with follicular lymphoma. *Haematologica* 2000; **85**: 894.
64. Sharma VR, Fleming DR, Slone SP. Pure red cell aplasia due to parvovirus B19 in a patient treated with rituximab. *Blood* 2000; **96**: 1184.
65. Suzan F, Ammor M, Ribrag V. Fatal reactivation of cytomegalovirus infection after use of rituximab for a post-transplantation lymphoproliferative disorder. *N Engl J Med* 2001; **345**: 1000.
66. Faye A, Van Den Abeele T, Peuchmaur M, Mathieu-Boue A, Vilmer E. Anti-CD20 monoclonal antibody for post-transplant lymphoproliferative disorders. *Lancet* 1998; **352**: 1285.
67. Faye A, Quartier P, Reguerre Y, *et al.* Chimaeric anti-CD20 monoclonal antibody (rituximab) in post-transplant

B-lymphoproliferative disorder following stem cell transplantation in children. *Br J Haematol* 2001; **115**: 112.
68. Ganne V, Siddiqi N, Kamaplath B, *et al.* Humanized anti-CD20 monoclonal antibody (Rituximab) treatment for post-transplant lymphoproliferative disorder. *Clin Transplant* 2003; **17**: 417.
69. Savoldo B, Rooney CM, Quiros-Tejeira RE, *et al.* Cellular immunity to Epstein-Barr virus in liver transplant recipients treated with rituximab for post-transplant lymphoproliferative disease. *Am J Transplant* 2005; **5**: 566.
70. Serinet MO, Jacquemin E, Habes D, Debray D, Fabre M, Bernard O. Anti-CD20 monoclonal antibody (Rituximab) treatment for Epstein-Barr virus-associated, B-cell lymphoproliferative disease in pediatric liver transplant recipients. *J Pediatr Gastroenterol Nutr* 2002; **34**: 389.
71. Dotti G, Rambaldi A, Fiocchi R, *et al.* Anti-CD20 antibody (rituximab) administration in patients with late occurring lymphomas after solid organ transplant. *Haematologica* 2001; **86**: 618.
72. Zompi S, Tulliez M, Conti F, *et al.* Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with clonal lymphoproliferative disorders after orthotopic liver transplantation: a report of three cases. *J Hepatol* 2000; **32**: 521.
73. Garcia VD, Bonamigo Filho JL, Neumann J, *et al.* Rituximab in association with rapamycin for post-transplant lymphoproliferative disease treatment. *Transpl Int* 2003; **16**: 202.
74. Bueno J, Ramil C, Somoza I, *et al.* Treatment of monomorphic B-cell lymphoma with rituximab after liver transplantation in a child. *Pediatr Transplant* 2003; **7**: 153.
75. Herman J, Vandenberghe P, van den Heuvel I, Van Cleemput J, Winnepenninckx V, Van Damme-Lombaerts R. Successful treatment with rituximab of lymphoproliferative disorder in a child after cardiac transplantation. *J Heart Lung Transplant* 2002; **21**: 1304.
76. Zilz ND, Olson LJ, McGregor CG. Treatment of post-transplant lymphoproliferative disorder with monoclonal CD20 antibody (rituximab) after heart transplantation. *J Heart Lung Transplant* 2001; **20**: 770.
77. Al-Akash SI, Al Makadma AS, Al Omari MG. Rapid response to rituximab in a pediatric liver transplant recipient with post-transplant lymphoproliferative disease and maintenance with sirolimus monotherapy. *Pediatr Transplant* 2005; **9**: 249.
78. Abderrahim E, Karoui C, Smaoui W, *et al.* Anti-CD20 antibodies to treat lymphoproliferative syndromes following renal transplantation. *Transplant Proc* 2003; **35**: 2708.
79. Jenkins D, DiFrancesco L, Chaudhry A, *et al.* Successful treatment of post-transplant lymphoproliferative disorder in autologous blood stem cell transplant recipients. *Bone Marrow Transplant* 2002; **30**: 321.
80. Skoda-Smith S, Douglas VK, Mehta P, Graham-Pole J, Wingard JR. Treatment of post-transplant lymphoproliferative disease with induction chemotherapy followed by haploidentical peripheral blood stem cell transplantation and Rituximab. *Bone Marrow Transplant* 2001; **27**: 329.
81. Stachel DK, Schmid I, Schuster F, Stehr M, Baumeister FA, Muller-Hocker J. Lymphoproliferative syndrome in an infant after stem cell transplantation: successful therapy with T-lymphocytes and anti-CD20 monoclonal antibodies. *Med Pediatr Oncol* 2000; **35**: 503.
82. Hanel M, Fiedler F, Thorns C. Anti-CD20 monoclonal antibody (Rituximab) and Cidofovir as successful treatment of an EBV-associated lymphoma with CNS involvement. *Onkologie* 2001; **24**: 491.
83. Yedibela S, Reck T, Niedobitek G, *et al.* Anti-CD20 monoclonal antibody treatment of Epstein-Barr virus-induced intrahepatic lymphoproliferative disorder following liver transplantation. *Transpl Int* 2003; **16**: 197.
84. Garcia VD, Bonamigo-Filho JS, Neumann J, *et al.* Rituximab and rapamycin for posttransplant lymphoproliferative disease treatment: report of three cases. *Transplant Proc* 2002; **34**: 2993.
85. Verschuuren EA, Stevens SJ, van Imhoff GW, *et al.* Treatment of posttransplant lymphoproliferative disease with rituximab: the remission, the relapse, and the complication. *Transplantation* 2002; **73**: 100.
86. Kuehnle I, Huls MH, Liu Z, *et al.* CD20 monoclonal antibody (rituximab) for therapy of Epstein-Barr virus lymphoma after hemopoietic stem-cell transplantation. *Blood* 2000; **95**: 1502.
87. Berney T, Delis S, Kato T, *et al.* Successful treatment of posttransplant lymphoproliferative disease with prolonged rituximab treatment in intestinal transplant recipients. *Transplantation* 2002; **74**: 1000.
88. Webber S, Harmon W, Faro A, *et al.* Anti-CD20 monoclonal antibody (rituximab) for refractory PTLD after pediatric solid organ transplantation: multicenter experience from a registry and from a prospective clinical trial. *Blood* 2004; **104**: Abstract No: 746.
89. Muti G, Cantoni S, Oreste P, *et al.* Post-transplant lymphoproliferative disorders: improved outcome after clinico-pathologically tailored treatment. *Haematologica* 2002; **87**: 67.
90. Reams BD, McAdams HP, Howell DN, Steele MP, Davis RD, Palmer SM. Posttransplant lymphoproliferative disorder: incidence, presentation, and response to treatment in lung transplant recipients. *Chest* 2003; **124**: 1242.
91. Ghobrial IM, Habermann TM, Ristow K, Ansell SM, McGregor CG, ONeill BP. Post-transplant lymphoproliferative disorders involving the central nervous system (CNS-PTLD): therapy with rituximab. *Blood* 2003; **102**: Abstract No: 4913.
92. Ferry CK, Maillard A, Agbalika F, *et al.* Treatment of B-lymphoproliferative disorder after hematopoietic stem cell transplantation. Role and immunological follow-up of Rituximab®. *Blood* 2002; **100**: Abstract No: 420.
93. Gonzalez-Barca E, Domingo-Domenech E, Gomez-Codina J, *et al.* First-line treatment with rituximab improves

survival of patients with post-transplant lymphoproliferative disease (PTLD). *Blood* 2004; **104**: Abstract No: 1406.
94. Milpied N, Vasseur B, Parquet N, *et al.* Humanized anti-CD20 monoclonal antibody (Rituximab) in post transplant B-lymphoproliferative disorder: a retrospective analysis on 32 patients. *Ann Oncol* 2000; **11** (Suppl. 1): 113.
95. Morrison VA, Bartlett N, Dunn DL, Peterson BA. Rituximab therapy for post-transplant lymphoproliferative disorders (PTLD): preliminary outcome results. *Proc of ASCO Ann Meet* 2001; Abstract No: 1177.
96. Horwitz SM, Tsai DE, Twist C, *et al.* Rituximab is effective therapy for post-transplant lymphoproliferative disorder (PTLD) not responding to reduction in immunosuppression: a prospective trial in adults and children. *Proc of ASCO Ann Meet* 2001; Abstract No: 1134.
97. Oertel SH, Verschuuren E, Reinke P, *et al.* Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). *Am J Transplant* 2005; **5**: 2901.
98. Choquet S, Leblond V, Herbrecht R, *et al.* Efficacy and safety of rituximab in B-cell post-transplant lymphoproliferative disorders: results of a prospective multicentre phase II study. *Blood* 2005 [prepublished online 27 October 2005].
99. van Esser JW, Niesters HG, van der Holt B, *et al.* Prevention of Epstein-Barr virus-lymphoproliferative disease by molecular monitoring and preemptive rituximab in high-risk patients after allogeneic stem cell transplantation. *Blood* 2002; **99**: 4364.
100. Clave E, Agbalika F, Bajzik V, *et al.* Epstein-Barr virus (EBV) reactivation in allogeneic stem-cell transplantation: relationship between viral load, EBV-specific T-cell reconstitution and rituximab therapy. *Transplantation* 2004; **77**: 76.
101. Polito L, Bolognesi A, Tazzari PL, *et al.* The conjugate rituximab/saporin-S6 completely inhibits clonogenic growth of CD20-expressing cells and produces a synergistic toxic effect with Fludarabine. *Leukemia* 2004; **18**: 1215.
102. Hiddemann W, Kneba M, Dreyling M, *et al.* Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2005; **106**: 3725.
103. Ghobrial IM, Habermann TM, Ristow KM, *et al.* Prognostic factors in patients with post-transplant lymphoproliferative disorders (PTLD) in the rituximab era. *Leuk Lymphoma* 2005; **46**: 191.

