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ORIGINAL ARTICLE

Long-term follow-up of a prospective phase 2 clinical trial of extended treatment with rituximab in patients with B cell post-transplant lymphoproliferative disease and validation in real world patients

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Abstract

The purpose of this report is to provide long-term follow-up of 38 patients diagnosed of post-transplant lymphoproliferative disease (PTLD) included in a phase 2 clinical trial of first line therapy with rituximab and to evaluate the same therapy in a real world cohort of 21 consecutive patients treated once the trial was closed. Eligible patients were ≥ 18 years of age with a biopsy-proven CD20 positive B cell PTLD and treatment naive except for reduction of immunosuppression. Treatment consisted in four weekly infusions of rituximab at the standard dose of 375 mg/m^2. Patients in complete remission (CR) were followed without further treatment, and those in partial remission (PR) were treated with another four cycles of weekly rituximab. Median follow-up in the clinical trial was 13.0 years. Disease-specific survival (DSS) at 10 years was 64.7% [95% confidence interval (CI) 48.2–81.2%]. For those patients who achieved CR (61%), DSS at 5 and 10 years was 94.4% (95% CI 83.8–100%) and 88.1% (95% CI 72.6–100%), respectively, and only 1 patient progressed beyond 5 years. The median follow-up of the real world patients was 6.5 years. DSS at 5 years was 75.2% (95% CI 56.4–94.0%). DSS at 5 years of patients who achieved CR (38%) was 87.5% (95% CI 64.6–100%). In conclusion, PTLD patients in CR after rituximab have an excellent long-term outcome. These results not only apply in the clinical trial setting but are also reproducible in the real world. However, those patients who do not respond represent an unmet clinical need and should be included in prospective clinical trials.

Keywords Post-transplant lymphoproliferative disease · Rituximab · Long-term follow-up · Clinical trial · Lymphoma

Introduction

Post-transplant lymphoproliferative disease (PTLD) has become a serious complication of both solid organ (SOT) and hematopoietic stem cell transplantation. The most common pathological finding is Epstein-Barr virus (EBV)-driven B cell proliferation, ranging from early and polymorphic lesions to monomorphic lymphomas [1]. The higher incidence of newly

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diagnosed PTLD in the last years is related to growing numbers of transplants, the older age of donors and recipients, and the use of new immunosuppressive agents and regimens [2, 3]. Among adults, kidney transplants have the lowest incidence, followed by liver, heart, and lung transplants. PTLD is associated with significant morbidity and mortality, and therefore, it is mandatory to choose the optimal first line therapy for the patients [4].

Reduction of immunosuppression remains the standard frontline therapy, and response rates have been reported, especially in early lesions and polymorphic PTLD [5, 6]. PTLD patients who did not respond were historically treated with standard chemotherapy regimens used in other lymphomas, with a good disease control but with a high treatment-related mortality of around 30% [7, 8]. The introduction of rituximab monotherapy, four weekly infusions at standard dose, improved the overall remission rates (ORR, range from 44 to 60%) and especially reduced toxicity-related mortality [9, 10]. Nowadays, rituximab has become the standard therapy in patients who do not respond to reduction of the immunosuppression, but there are scarce data about the long-term outcome of these patients as well as how this therapy works in the real world.

We conducted a prospective phase 2 clinical trial of extended treatment with rituximab, which included 38 patients with PTLD who received treatment with four weekly infusions of rituximab at standard doses as first line therapy after failure to the reduction of immunosuppression. Those patients who did not achieve complete remission (CR) received a second course of four rituximab infusions. The CR rate was 34% after the first four doses of rituximab and 61% at the end of the therapeutic plan, without any relevant acute toxicity or treatment-related mortality. The purpose of this report is to provide a longer follow-up of the phase 2 trial, in which extended doses of rituximab were used in patients with PTLD after SOT [11], and to validate these results in a cohort of consecutive patients diagnosed of PTLD after the closure of the trial and treated in the real world with the same therapeutic regimen.

Patients and methods

Patients

The phase 2 trial was approved by all relevant institutional review boards or ethics committees, and all patients were provided written informed consent prior to enrolling. The study was conducted in accordance with the Declaration of Helsinki.

Previously published results of the trial of extended doses of rituximab in patients with PTLD after SOT, treated between November 2000 and August 2005, provide detailed patient eligibility criteria [11]. In brief, eligible patients were ≥ 18 years of age with a biopsy-proven CD20 positive B cell PTLD and treatment naive except for reduction of immunosuppression. Of note, poor performance status was not an exclusion criterion.

A cohort of all consecutive patients diagnosed of PTLD between December 2006 and August 2016 (once the clinical trial closed), from 2 academic Spanish centers, and treated with the same regimen, was used to validate the results in the real world.

Table 1 Clinical characteristics of PTLD patients at diagnosis

	Clinical trial $n = 38$ n (%)	Real world $n = 21$ n (%)
Median age at PTLD (range), years	55 (19–69)	63 (36–72)
Age ≤ 60 years	25 (66)	9 (43)
Male gender	26 (68)	17 (85)
Transplanted organ		
Kidney	22 (58)	5 (24)
Liver	13 (34)	11 (53)
Heart	2 (5)	3 (14)
Lung	1	1
Others		1
Monomorphic lymphoma	31 (82)	16 (76)
DLBCL	28 (74)	14 (67)
MZL	2	2
Burkitt's	1	0
Time from transplant to PTLD<1 year	8 (21)	1 (5)
Ann Arbor stage III–IV	22/36 (61)	13 (62)
Graft involvement	6/32 (19)	3/16 (19)
Bulky disease	8/34 (24)	5 (24)
Extranodal involvement	23 (61)	14/20 (70.0)
B symptoms	17/30 (57)	4/20 (20)
ECOG PS 2-4	15/36 (42)	6 (29)
Elevated LDH	16/31 (52)	11/19 (58)
IPI ≥ 3	17/35 (49)	12/20 (60)
EBV in tissue	14/20 (68)	3/14 (21)

PTLD, post-transplant lymphoproliferative disease; DLBCL, diffuse large B cell lymphoma; MZL, marginal zone B cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; IPI, international prognostic index; EBV, Epstein-Barr virus

Comparison between patients included in the clinical trial and patients treated in the real world

Study design

The phase 2 trial included 38 patients diagnosed of PTLD who were treated with reduction of immunosuppression and four weekly infusions of rituximab at standard doses (375 mg/m^2). Patients in CR were followed without further treatment. Patients in partial remission (PR) were treated with another 4

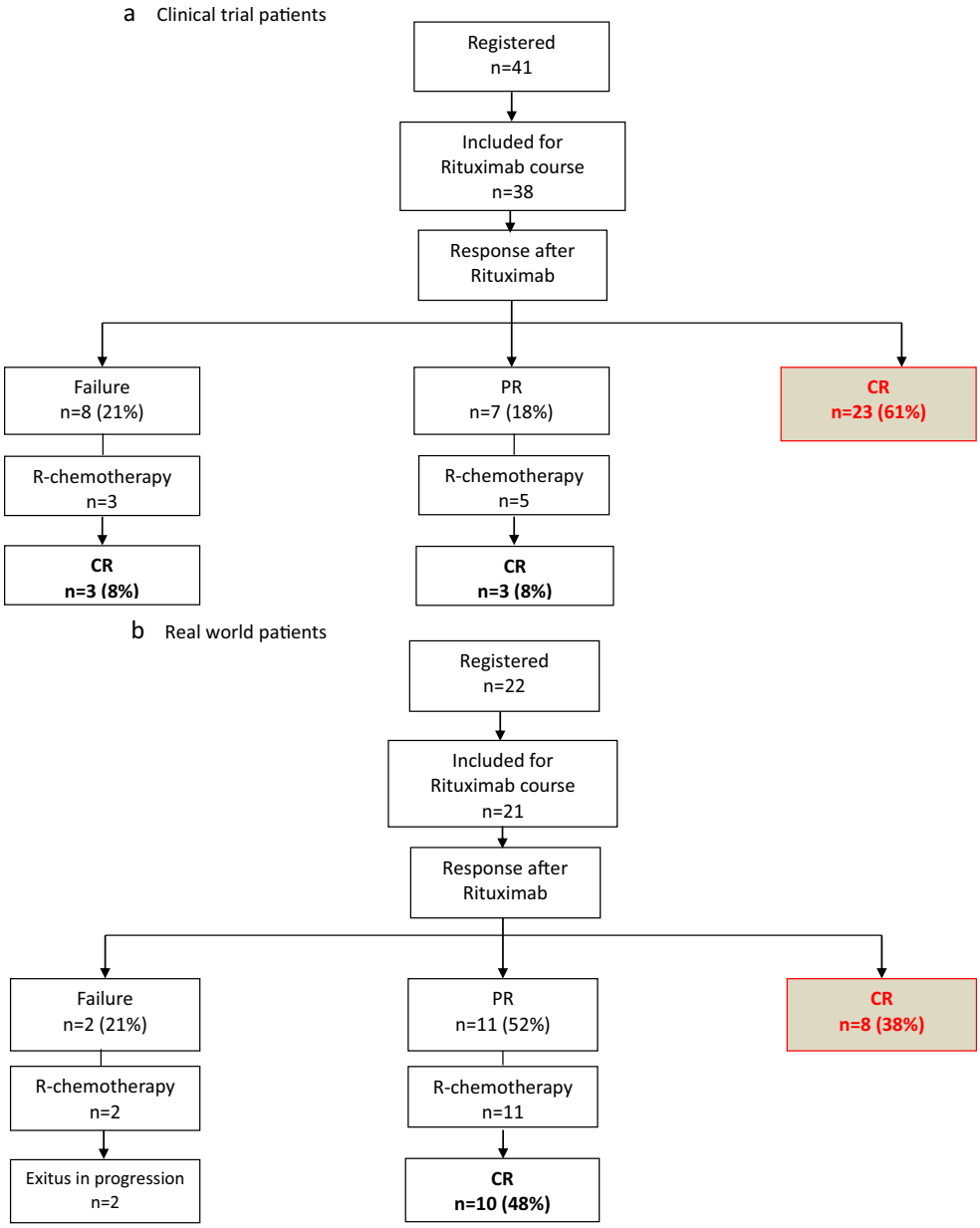

Fig. 1 Treatment and outcome of the two cohorts: clinical trial patients (**a**) and real world patients (**b**). CR, complete remission; PR, partial remission; R-chemotherapy, rituximab combined with chemotherapy

cycles of weekly rituximab infusions at the same doses. Patients without CR after 4–8 cycles of rituximab or with progressive disease were allowed to receive a short course of 3–4 cycles of R-CHOP (rituximab 375 mg/m^2 [day 1], cyclophosphamide 750 mg/m^2 [day 1], doxorubicin 50 mg/m^2 [day 1], vincristine 1.4 mg/m^2 [day 1, capped at a maximum of 2 mg,] and prednisone 60 mg/m^2 [days 1–5]) or R-CHOP-like chemotherapy. Twenty-one consecutive patients were treated with the same regimen in the clinic off-trial.

Diagnosis was based on local pathological review. Patients were staged according to the Ann Arbor system. Response after therapy was classified as complete remission (CR), defined as no evidence of disease in terms of clinical symptoms, biopsy, or imaging findings; partial remission (PR), defined as a reduction of more than 50% of the tumor mass, with disappearance of the initial symptoms; and failure, defined as a less than 50% reduction of the tumor mass or disease progression. Disease status was assessed by each investigator with computerized tomography (CT) in patients included in the clinical trial and with ^{18}F-fluorodeoxyglucose positron emission tomography/computerized tomography (FDG-PET/CT) in 18 (86%) real world patients.

Statistical methods

Survival curves were plotted by the Kaplan-Meier method. Due to the long follow-up period, some patients died from causes not related to PTLD; therefore, disease-specific

Table 2 Causes of death

	Clinical trial *n* = 38 Median follow-up 13 years Deaths 21 (55%) *n* (%)	Real life patients *n* = 21 Median follow-up 6.5 years Deaths 7 (33%) *n* (%)
Progression	13 (62)	4 (57)
Infection without lymphoma	3 (14)	2 (29)
Septic shock	1	1
Respiratory	1	
Hepatic abscesses	1	
Colonic perforation (diverticula)		1
Others	5 (24)	1 (14)
Secondary malignancy (Hodgkin Lymphoma)	1	
Cardiac arrest after cardiac surgery	1	
Intracranial hemorrhage	1	
Traffic accident	1	
Unknown	1	
Suicide		1

survival (DSS) was used to evaluate the real impact of the therapy with rituximab in survival. DSS was calculated from the time of diagnosis of PTLD to the time of progression/relapse or death due to PTLD, and deaths from other causes were censored. Overall survival (OS) was calculated from the time of diagnosis of PTLD to the time of death, regardless of the cause.

Predictive factors for CR to rituximab were analyzed with a binary logistic regression model. Univariate analysis for survival was performed with the log-rank test and multivariate analysis with a Cox regression model. Factors included in the analyses were age, gender, Ann Arbor stage, graft involvement, bulky disease, extra nodal involvement, B symptoms, Eastern Cooperative Oncology Group (ECOG) performance status (PS), serum lactate dehydrogenase (LDH) levels, and time from transplant to PTLD.

All analyses were performed at a 95% confidence interval, and differences were considered statistically significant when the p value was less than *0.05*.

Results

Clinical characteristics of the patients are shown in Table 1. There were some differences at diagnosis between patients treated in the real world and those treated in the clinical trial: real world patients were older (median age 63 vs 55 years), fewer had B symptoms (20% vs 57%), and the transplanted organ was more frequently the liver or heart instead of kidney.

The flowchart of the patients treated in the clinical trial is shown in Fig. 1a. Twenty-six (68%) patients received 1 to 4 rituximab infusions and 12 (32%) between 5 and 8 infusions. Twenty-three (61%) patients achieved CR after monotherapy with rituximab. Eight (21%) patients were treated with R-CHOP/R-CHOP-like after failure of rituximab. With a median follow-up for the alive patients of 13.0 years, 21 (55%) died, 13 (34%) due to progression. Causes of death are shown in Table 2. DSS at 5 and 10 years was 68.6% [95% confidence interval (CI) 52.9–84.3%] and 64.7% (95% CI 48.2–81.2%), respectively (Fig. 2a). OS at 10 years was 49.5% (95% CI 32.8–66.2%) (Fig. 2b). For those patients who achieved CR after rituximab monotherapy, DSS at 5 and 10 years was 94.4% (95% CI 83.8–100%) and 88.1% (95% CI 72.6–100%), respectively. Only 1 patient progressed beyond 5 years of follow-up.

Among the 21 real world patients, 10 (48%) were treated with 1 to 4 rituximab infusions, and 11 (52%) received between 5 and 8 infusions. Eight (38%) patients achieved CR with rituximab (Fig. 1b). Thirteen (62%) patients were treated with R-CHOP/R-CHOP-like after failure to rituximab. With a median follow-up for the alive patients of 6.5 years, 7 (33%) patients died, 4 (19%) due to progression (Table 2). DSS and OS at 5 years were 75.2% (95% CI 56.4–94.0%) and 62.7% (95% CI 40.4–85.0%), respectively (Fig. 2c and d). DSS at 5 years in patients who achieved CR with rituximab monotherapy was 87.5% (95% CI 64.6–100%).

Taking into account all the patients (those treated in the clinical trial and those treated in real world), predictive factors for response to rituximab were not found. On the other hand, the only significant independent prognostic factor for DSS was poor ECOG PS 2-4 [hazard ratio (HR) 3.2; 95% CI 1.05–9.3].

Discussion

The aim of this study is to analyze long-term survival, after a median follow-up of 13 years, of patients diagnosed of PTLD after SOT and treated with rituximab monotherapy in first line in a clinical trial, and to evaluate this therapy in a cohort of consecutive patients treated in the real world, once the clinical trial was closed. As the incidence of PTLD is low, the main limitation of our study is the relatively low number of patients analyzed.

Patients who achieve CR after rituximab monotherapy (4 to 8 cycles) have an excellent long-term outcome, both in the clinical trial and in the real world, with a 5-year DSS of 94.4% and 87.5%, respectively. Moreover, patients in CR have a very low risk of progression after 5 years and can be considered cured. These results are in concordance with

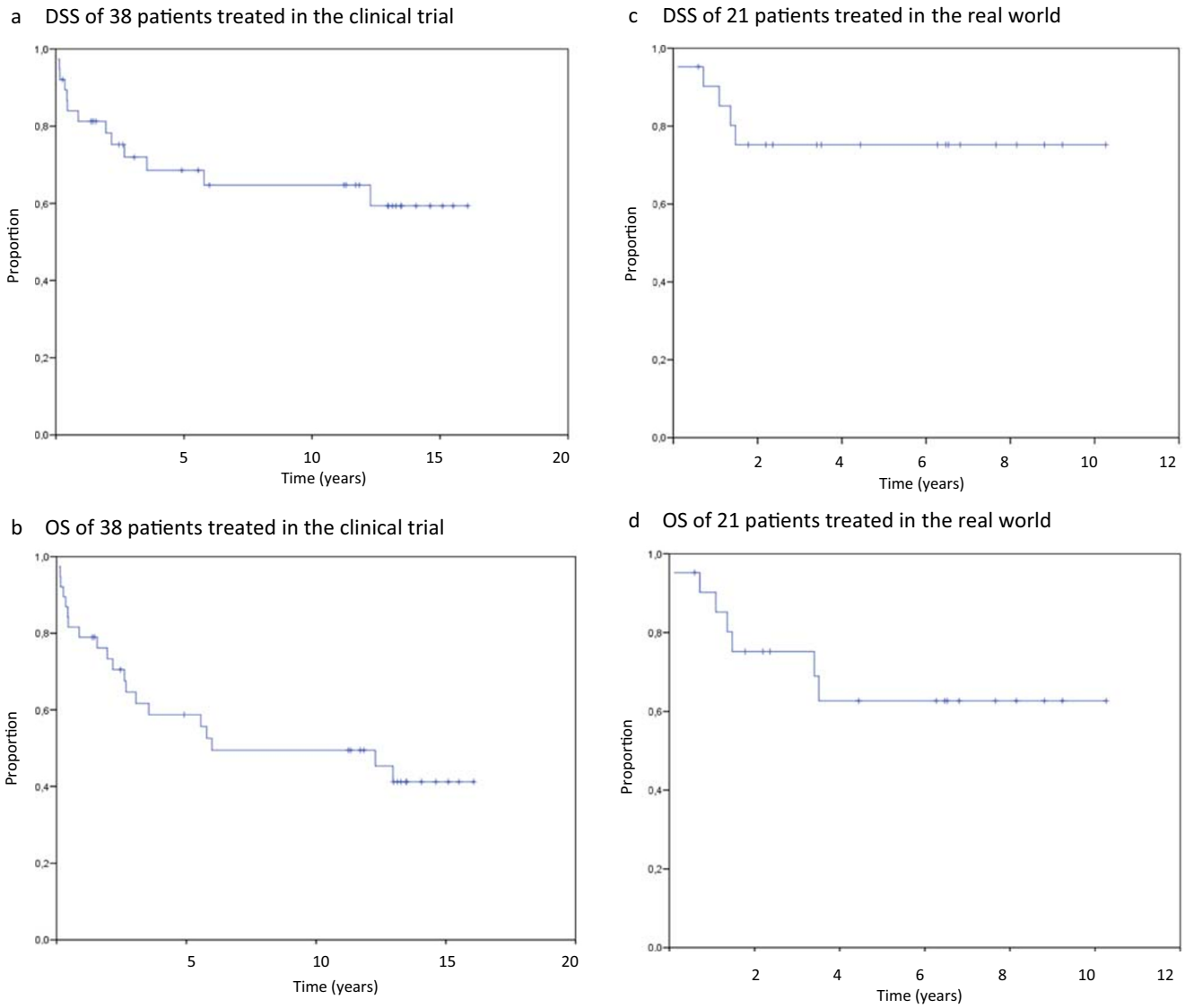

Fig. 2 DSS (**a**) and OS (**b**) of 38 patients treated in the clinical trial, with a median follow-up of 13 years. DSS (**c**) and OS (**d**) of 21 patients treated in the real world, with a median follow-up of 6.5 years

Trappe et al [12]. They reported the results of 152 patients treated with 4 doses of rituximab, those in CR received a consolidation with another 4 courses of rituximab, and all the others, even those in PR, received treatment with R-CHOP. Twenty-five percent of the patients achieved CR with rituximab monotherapy, which was a highly significant predictor of survival. The design of our trial was different, since patients in PR after the first 4 doses of rituximab could receive another 4 doses, and those who achieved CR after this second course did not require chemotherapy. With this strategy, more patients could benefit of rituximab monotherapy, as their survival has also been excellent without need of chemotherapy.

Unfortunately, factors at diagnosis that predict response to rituximab were not found, and therefore, patients who respond to rituximab monotherapy could not be identified at the time of diagnosis. In the French trial, 43 patients were treated with just 4 courses of rituximab, and they found that an elevated serum LDH was the only predictive factor for survival after rituximab therapy [10]. In the first trial published by Trappe et al [13], all patients received chemotherapy after the 4 rituximab doses. They observed that late onset of PTLD and EBV positivity predicted a good outcome, although factors related to response to rituximab were neither found.

There were some differences between patients treated in the real world and those treated in the clinical trial. Real world patients were older, and the transplanted organs were more frequently the liver and heart instead of kidney. These differences probably represent the different time in which patients were treated. Patients were included in the clinical trial between 2000 and 2005, and patients from the real world were treated between 2006 and 2016. Nowadays, patients are transplanted at older age, and, with the improvement of the surgical procedures, other

organs are transplanted more frequently. Moreover, among adults, kidney transplants have the lowest incidence of PTLD, followed by liver, heart, and lung transplants [3]. The CR rate of 38% after rituximab monotherapy is lower than the 61% achieved in the patients treated in the clinical trial, and more patients received chemotherapy in the real world cohort. These differences could be explained by multiple factors. On one side, the evaluation of response was done with CT in the clinical trial, while FDG-PET/CT was the standard procedure used in the majority of the patients treated in the real world, which is more sensitive to detect active disease, but can also result in the identification of more false positive lesions [14]. On the other hand, the time point to evaluate response was not standardized in the real world setting, and there could have been a trend to treat more intensively these patients, due to clinical doubts on the quality of the response. Nevertheless, in spite of these differences, patients from the real world in CR after rituximab monotherapy had also an excellent long-term outcome, demonstrating that these results not only apply in the clinical trial setting.

However, in our series, around 30% of patients still die due to progressive disease. These results are similar in other trials [12, 13]. Therefore, patients who do not achieve CR with rituximab monotherapy do poorly, and ideally, should be included in prospective clinical trials with new drugs.

Other immunotherapies are being tested in these patients. Tabelecleucel is a cell product with EBV-cytotoxic T lymphocytes (CTLs) derived from volunteer donors. Several trials are now ongoing using tabelecleucel in PTLD patients with promising results [15]. Immune checkpoints regulate T cell responses to maintain self-tolerance. PD-L1 (programed death-ligand 1), mainly expressed by antigen presenting cells, engages its receptor PD1 on T cells, to provide a growth inhibitory signal. A high proportion of monomorphic PTLD in children expresses PD-L1 to evade immune recognition [16]. A good response has been reported using a checkpoint inhibitor in a case of PTLD after an allogeneic stem cell transplant [17]. Nevertheless, they have to be used carefully, because they could increase the risk of graft rejection due to the non-specific T cell immunity enhancement. The anti-CD30 monoclonal antibody brentuximab vedotin (BV) has been used in PTLD patients, due to the expression of CD30 in a high proportion of cases [18]. In a phase 1/2 trial, BV combined with rituximab is used as frontline therapy in CD30+ lymphomas arising in patients with immunodeficiency [19]. In another trial, BV is used in relapsed/refractory NHL, and some of the cases included are PTLD (NCT 01421667), but no results have been reported yet.

Conclusions

In conclusion, patients with PTLD who achieve CR with rituximab monotherapy have an excellent long-term outcome, but unfortunately, factors at diagnosis that could predict response to rituximab were not found. Nevertheless, a high proportion of patients still die due to progressive disease. Those patients who do not respond to rituximab should be included in prospective clinical trials with new drugs.

Authors' contributions EGB designed the study, coordinated the trial, interpreted the data, and wrote the article. AFS was the study coordinator, participated in the study design, interpreted the data, and edited the article. ME helped with the design and was responsible for statistical analysis. FJC, JG, CP, AS, JMS, AL, JB, AM, SM, and EDD reported updated patient data and read and commented on the article. All the authors proofread the article and agreed on the data presented.

Compliance with ethical standards

Conflict of interest Eva González-Barca: Consultant and/or honoraria for Roche, Gilead, Janssen, Celgene, AbbVie, Sandoz, Kyowa Kirin, Celltrion, and Takeda.

Francisco Javier Capote: Consultant and/or honoraria for Celgene, Janssen, Amgen, Roche, Gilead, and Takeda.

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Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of informed consent Informed consent was obtained from all patients for being included in the study.

References

1. Swerdlow SH, Webber SA, Chadburn A, Ferry JA (2008) Post-transplant lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris NL et al (eds) Classification of tumours of hematopoietic and lymphoid tissues, 4th edn. IARC, Lyon, pp 343–350

2. Domingo-Domènech E, de Sanjosé S, González-Barca E, Romagosa V, Domingo-Clarós A, Gil-Vernet S, Figueras J, Manito N, Otón B, Petit J, Grañena A, Fernández de Sevilla A (2001) Post-transplant lymphomas: a 20- year epidemiologic, clinical and pathologic study in a single center. Haematologica 86:715–721
3. Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ, Wolfe RA, Goodrich NP, Bayakly AR, Clarke CA, Copeland G, Finch JL, Fleissner ML, Goodman MT, Kahn A, Koch L, Lynch CF, Madeleine MM, Pawlish K, Rao C, Williams MA, Castenson D, Curry M, Parsons R, Fant G, Lin M (2011) Spectrum of cancer risk among US solid organ transplant recipients. JAMA 306:1891–1901
4. Petrara MR, Giunco S, Serraino D, Dolcetti R, De Rossi A (2015) Post-transplant lymphoproliferative disorders: from epidemiology to pathogenesis driven treatment. Cancer Lett 369:37–44
5. Reshef R, Vardhanabhuti S, Luskin MR, Heitjan DF, Hadjiliadis D, Goral S, Krok KL, Goldberg LR, Porter DL, Stadtmauer EA, Tsai DE (2011) Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder. Am J Transplant 11:336–347
6. Tsai DE, Hardy CL, Tomaszewski JE, Kotloff RM, Oltoff KM, Somer BG, Schuster SJ, Porter DL, Montone KT, Stadtmauer EA (2001) Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. Transplantation 71:1076–1088
7. Choquet S, Trappe R, Leblond V, JagerU DF, Oertel S (2007) CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. Haematologica 92:273–274
8. Gonzalez-Barca E, Domingo-Domenech E, Gomez Codina J, Capote F, Flores E, Briones J, Salar A, Panizo C, Montalban C, Ribera JM, Caballero D, Muñoz A, Gallur L, Canales MA, Fernandez P, Encuentra M, Fernandez de Sevilla A (2004) First-line treatment with rituximab improves survival of patients with post-transplant lymphoproliferative disease (PTLD). Blood 104: 1406
9. Oertel SH, Verschuuren E, Reinke P, Zeidler K, Papp-Váry M, Babel N, Trappe RU, Jonas S, Hummel M, Anagnostopoulos I, Dörken B, Riess HB (2005) Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). Am J Transplant 5:2901–2906
10. Choquet S, Leblond V, Herbrecht R, Socié G, Stoppa AM, Vandenberghe P, Fischer A, Morschhauser F, Salles G, Feremans W, Vilmer E, Peraldi MN, Lang P, Lebranchu Y, Oksenhendler E, Garnier JL, Lamy T, Jaccard A, Ferrant A, Offner F, Hermine O, Moreau A, Fafi-Kremer S, Morand P, Chatenoud L, Berriot-Varoqueaux N, Bergougnoux L, Milpied N (2006) Efficacy and safety of rituximab in B-cell post-transplant lymphoproliferative disorders: results of a prospective multicentre phase II study. Blood 107:3053–3057
11. González-Barca E, Domingo-Domenech E, Capote FJ, Gómez-Codina J, Salar A, Bailen A, Ribera JM, López A, Briones J, Muñoz A, Encuentra M, de Sevilla AF (2007) Prospective phase II trial of extended treatment with rituximab in patients with B-cell post-transplant lymphoproliferative disease. Haematologica 92: 1489–1494
12. Trappe RU, Dierickx D, Zimmermann H, Morschhauser F, Mollee P, Zaucha JM, Dreyling MH, Dührsen U, Reinke P, Verhoef G, Subklewe M, Hüttmann A, Tousseyn T, Salles G, Kliem V, Hauser IA, Tarella C, Van Den Neste E, Gheysens O, Anagnostopoulos I, Leblond V, Riess H, Choquet S (2017) Response to rituximab induction is a predictive marker in B-cell post-transplant lymphoproliferative disorder and allows successful stratification into rituximab or R-CHOP consolidation in an international, prospective, multicenter phase II trial. J Clin Oncol 35: 536–543
13. Trappe R, Oertel S, Leblond V, Mollee P, Sender M, Reinke P, Neuhaus R, Lehmkuhl H, Horst HA, Salles G, Morschhauser F, Jaccard A, Lamy T, Leithäuser M, Zimmermann H, Anagnostopoulos I, Raphael M, Riess H, Choquet S, German PTLD Study Group; European PTLD Network (2012) Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 13:196–206
14. Montes de Jesus FM, Kwee TC, Nijland M, Kahle XU, Huls G, Dierckx RAJO, van Meerten T, Gheysens O, Dierickx D, Vergote V, Noordzij W, Glaudemans AWJM (2018) Performance of advanced imaging modalities at diagnosis and treatment response evaluation of patients with post-transplant lymphoproliferative disorder: a systematic review and meta-analysis. Crit Rev Oncol Hematol 132:27–38
15. Prockop S, Li A, Baiocchi RA, Bunin N, Mahadeo KM, Nemecek ER, Nikiforow S, Reshef R, Tsai DE, Navarro WH, O'Reilly RJ (2017) Efficacy and safety of ATA129 partially matched allogeneic third party epstein-barr virus-targeted cytotoxic T lymphocytes in a multicenter study for post transplant lymphoproliferative disorder. Blood 130:4520
16. Schiefer AI, Salzer E, Füreder A, Szepfalusi Z, Müller-Sacherer T, Huber WD, Michel-Behnke I, Lawitschka A, Pichler H, Mann G, Hutter C, Simonitsch-Klupp I, Attarbaschi A (2019) PD-L1 and PD1 expression in post-transplantation lymphoproliferative disease (PTLD) of childhood and adolescence: an inter and intra-individual descriptive study covering the whole spectrum of PTLD categories. Cancer Med 8:4656–4668
17. Kassa C, Remenyi P, Sinko J, Kallay K, Kertesz G, Krivan G (2018) Successful nivolumab therapy in an allogeneic stem cell transplant child with post-transplant lymphoproliferative disorder. Pediatric Transpl 22:e13302
18. Vase MØ, Maksten EF, Bendix K, Hamilton-Dutoit S, Andersen C, Møller MB, Sørensen SS, Jespersen B, Kampmann J, Søndergård E, Nielsen PS, D'amore F (2015) Occurrence and prognostic relevance of CD30 expression in post-transplant lymphoproliferative disorders. Leuk Lymphoma 56:1677–1685
19. Gandhi M, Ma S, Smith SM, Nabhan C, Evens AM, Winter JN, Gordon LI, Petrich AM (2014) Brentuximab vedotin (BV) plus rituximab as front line therapy for patients with Epstein Barr virus (EBV) + and/or CD30+ lymphoma: phase I results of an ongoing phase I-II study. Blood 124:3096