Prospective phase II trial of extended treatment with rituximab in patients with B-cell post-transplant lymphoproliferative disease

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Acknowledgments: the authors thank Dr. Pilar Sabin, Dr. Carlos Panizo, Dr. Miguel Canales and Dr. Pascual Fernández Abellan for the inclusion of patients in the trial and collection of clinical data.

Manuscript received February 8, 2007.
Manuscript accepted August 8, 2007.

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ABSTRACT

Background and Objectives

The elective treatment of patients with post-transplant lymphoproliferative disorders is controversial. The purpose of this trial was to evaluate the efficacy of treatment with extended doses of rituximab adapted to the response in patients with post-transplant lymphoproliferative disorders after solid organ transplantation.

Design and Methods

This was a prospective, multicenter, phase II trial. Patients were treated with reduction of immunosuppression and four weekly infusions of rituximab. Those patients who did not achieve complete remission (CR) received a second course of four rituximab infusions. The primary end-point of the study was the CR rate.

Results

Thirty-eight patients were assesable. One episode of grade 4 neutropenia was the only severe adverse event observed. After the first course of rituximab, 13 (34.2%) patients achieved CR, 8 patients did not respond, and 17 patients achieved partial remission. Among those 17 patients, 12 could be treated with a second course of rituximab, and 10 (83.3%) achieved CR, yielding an intention-to-treat CR rate of 60.5%. Eight patients excluded from the trial because of absence of CR were treated with rituximab combined with chemotherapy, and six (75%) achieved CR. Event-free survival was 42% and overall survival was 47% at 27.5 months. Fourteen patients died, ten of progression of their post-transplant lymphoproliferative disorder.

Interpretation and Conclusions

These results confirm that extended treatment with rituximab can obtain a high rate of CR in patients with post-transplant lymphoproliferative disorders after solid organ transplantation without increasing toxicity, and should be recommended as initial therapy for these patients.

Key words: post-transplant lymphoproliferative disorders, rituximab, prognostic factors.

Haematologica 2007; 92:1489-1494. DOI: 10.3324/haematol.11360

Post-transplant lymphoproliferative disorders are a serious complication of prolonged immunosuppression in recipients of solid organ transplants. The reported incidence varies from 1% to 5%.[1,2] Risk factors for the development of post-transplant lymphoproliferative disorders include intense immunosuppressive therapy[2] and primary Epstein-Barr virus (EBV) infection.[3,4] The most common pathological finding is EBV-driven B-cell proliferation, ranging from B-cell hyperplasia to overt B-cell lymphoma.[5,6] These malignancies tend to behave more aggressively and, in general, to have poorer outcomes than lymphomas occurring in non-immunocompromised patients. Post-transplant lymphoproliferative disorder remains a major cause of morbidity and mortality and about 50% of patients with this disorder die within a short period after its diagnosis.[7]

Reduction of immunosuppression remains the standard front-line therapy, with response rates ranging from 20% to 85%, with localized or polymorphic disease more likely to respond.[8,9] The elective treatment of patients in whom reduction of immunosuppression fails is controversial. The different therapeutic approaches have often been based on clinical outcome of limited series of patients. The therapeutic efficacy of antiviral therapy has not been proven.[10] Surgery and radiotherapy may be efficacious in some cases of localized post-transplant lymphoproliferative disorders.[11] Different chemotherapy regimens have been used, but have usually been associated with high toxicity, especially in patients with poor performance status at diagnosis, and the response rate has been poor, ranging from 25% to 35%.[12,13] As a result of the poor response to conventional therapies, alternative treatment options have been tried in recent years. Ongoing clinical trials on the infusion of expanded HLA-identical EBV-specific cytotoxic T-cells have given promising, but still preliminary, results.[14] Therapy with monoclonal antibodies has been used for several years. Monoclonal anti-CD21 and anti-CD24 B-cell antibodies were studied in open label trials, yielding a response rate of 60%, but these antibodies are no longer produced.[15,16] The chimeric anti-CD20 monoclonal antibody rituximab has been demonstrated to be an effective therapy for B-cell non-Hodgkin's lymphomas, and has also been used in post-transplant lymphoproliferative disorders. Many case reports and some retrospective analyses have shown that rituximab is effective in the treatment of CD20-positve post-transplant lymphoproliferative disorders.[17,18] The first large prospective phase II study was recently published. This trial included 43 patients assessable for efficacy who were treated with four standard doses of rituximab.[19]

We conducted a prospective, multicenter, phase II trial in 41 patients with B-cell post-transplant lymphoproliferative disorders after solid organ transplantation, examining the effect of treatment with reduction of immunosuppression and extended doses of rituximab according to the early response.

Design and Methods

All patients were treated in compliance with regulations and guidelines of the Institutional Review Boards of the participating centers. Between November 2000 and August 2005, 41 consecutive adult patients diagnosed with B-cell post-transplant lymphoproliferative disorders after solid organ transplantation were included in this prospective trial. The study was conducted in 12 Spanish centers. Three patients were excluded from the analyses. One was an 11-year-old boy, another patient died before starting treatment, and one patient had a B-cell post-transplant lymphoproliferative disorder after peripheral blood stem cell transplantation. Therefore, 38 patients were assessable.

Study eligibility

Patients were eligible for inclusion in this study if they were adults older than 18 years of age, had signed informed consent and had an untreated B-cell post-transplant lymphoproliferative disorder with CD20 expression in neoplastic tissue. Another inclusion criteria was the absence of response within 2 weeks after discontinuation or reduction of immunosuppressive drug therapy; however, patients who had a poor performance status at diagnosis in whom it was clinically unfeasible to wait for the effect of reduction of immunosuppression were also included. A poor performance status was not an exclusion criterion. The local transplant teams decided changes of immunosuppressive therapy. Patients with central nervous system disease or any serious concomitant disease were not eligible. All patients underwent evaluation for disease extent before entry into the study. The evaluation included an assessment of clinical symptoms, a physical examination, computed tomography scan of chest, abdomen and pelvis, and bone marrow biopsy. In some patients a gallium scintigraphy was performed.

Treatment

Treatment consisted of four rituximab infusions, each of 375 mg/m^2, on days 1, 8, 15, and 22. Response was evaluated 4 to 8 weeks after the end of treatment. If patients achieved CR, they were followed without further treatment. Patients who achieved a partial remission (PR) were treated again with another four weekly rituximab infusions at the same doses, and response was again evaluated 4 to 8 weeks later. Premedication consisting of paracetamol and dipheniramine was administered before each rituximab infusion. Patients without a response and patients with progression were excluded from the study and were able to receive other treatments, although a short course of 3-4 cycles of rituximab combined with CHOP-like chemotherapy regimens was recommended. Treatment was stopped if there was no response, if the lymphoma progressed, if the patient refused to continue, or if the investigator considered it necessary because of concomitant illness or adverse events.

Study end-point

The primary end-point was the CR rate 4 to 8 weeks after the end of therapy. Tumor response was assessed by computed tomography scan, gallium scintigraphy in some cases and bone marrow biopsy if there was initial involvement of the marrow. The efficacy of treatment was classified as: CR, defined as no evidence of disease in terms of clinical symptoms, biopsy or imaging findings; 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. The overall response rate was defined as the sum of the CR and PR rates.

Statistical methods

All analyses were carried out on an intention-to-treat basis. Results of the descriptive analysis are expressed as medians and limits for continuous data and number of cases with their proportions for qualitative data. Odds ratios (OR) were calculated using unconditional logistic regression techniques. All logistic regression models were fitted using the maximum likelihood estimation of parameters. All variables were entered into the regression analysis as categorical variables with two categories coded 0 (absent) or 1 (present). Statistical significance was established at an α value of 0.05, and, accordingly, 95% confidence intervals (CI) around the OR are presented. Survival analysis was performed by means of Kaplan-Meier techniques. The Cox proportional hazard regression model was used to identify factors predictive of survival. Overall survival was measured from the first dose of rituximab until death or last contact, and event-free survival from the first dose of rituximab to the date of relapse, progression, death or last contact.

Results

Patients

A total of 38 patients with B-cell post-transplant lymphoproliferative disorders were assessable. Immunosuppressive drug therapy was reduced in all patients. Twenty-six (68%) patients were male. The median age was 55 years (range 19-69).

Histopathological findings

Histopathological findings are shown in Table 1. A lymph node was obtained for diagnosis from 18 patients (in 13 cases, a peripheral node and in 5, a node from the abdomen by laparotomy). The diagnosis was made by gastric biopsy in six cases, bone marrow biopsy in three patients, and hepatic ileum biopsy in two patients. Six cases were diagnosed from biopsies of other extra-nodal tissue (small bowel in 2, breast in 1, lung in 1, paravertebral mass in 1, and ascitic effusion in 1), and in three cases the origin of the biopsy tissue was not reported. Seven (18%) cases were considered to have polymorphic B-cell post-transplant lymphoproliferative disorders. All samples were CD20 positive.

Table 1. Characteristics of the 38 patients included in the study.

	No. of patients	*%*
Age ≤60 years	25	66
Male sex	26	68
Transplanted organ		
Kidney	22	58
Liver	13	34
Heart	2	5
Lung	1	3
Histology of PTLD		
Polymorphic	7	18
Monomorphic	31	82
DLBCL	28	
MZL	2	
Burkitt's	1	
EBV in tissue	14/20	68

PTLD: post-transplant lymphoproliferative disease; DLBCL: diffuse large B-cell lymphoma; MZL: marginal zone lymphoma; EBV: Epstein Barr virus.

Twenty tissue samples were assessed for EBV expression at diagnosis. LPM-1 and EBER were studied simultaneously in seven samples (4 were positive), only LPM-1 in five (4 were positive) and only EBER in eight (6 were positive). Overall, 14 (70%) samples were positive for any type of EBV expression.

Clinical presentation

Data on the clinical presentation of the B-cell post-transplant lymphoproliferative disorders are shown in Table 2. The median time from transplant to the lymphoproliferative disorder was 66.2 months (limits 2.2-202); eight (21%) patients developed the disorder within 12 months after organ transplantation (early post-transplant lymphoproliferative disorder). Twenty-two (61%) out of 36 patients had Ann Arbor stage III-IV disease. Twenty-three (61%) had extranodal disease, six (15%) of them with graft involvement. Seventeen (49%) out of 35 patients had an International Prognostic Index (IPI) ≥3.

Safety and efficacy

One episode of grade 4 neutropenia was the only acute severe adverse event observed, and treatment was not discontinued after recovery. Figure 1 shows the main results of the study. After the first course of rituximab therapy, 13 (34.2%) patients achieved CR, 17 PR and eight did not respond (five patients who did not respond did not complete the first four cycles of rituximab because they progressed during treatment).

Among the eight patients who did not respond, five died of progressive disease and three were treated with chemotherapy combined with rituximab and are alive

Table 2. Disease characteristics at the time of study entry (n=38).

	No. of patients	*%*
Time between transplant and PTLD ≤1 year	8	21
Ann Arbor Stage		
I	6/36	17
II	8/36	22
III	6/36	17
IV	16/36	44
Bulky disease	8/34	24
Graft involvement	6	16
Patients with extranodal sites of disease	23	61
Liver	8	
Bone marrow	6	
Gastrointestinal	4	
Ears, nose and throat	2	
Others	10	
Number of extranodal sites of disease		
0	15	
1	19	
2	1	
3	3	
B symptoms	17/30	57
ECOG 2-4	15/36	42
Elevated LDH	16/31	52
Elevated β2microglobulin	17/25	68
IPI		
Low	11/35	31
Intermediate/low	7/35	20
Intermediate/high	10/35	29
High	7/35	20

PTLD: post-transplant lymphoproliferative disease; ECOG: performance status; LDH: lactate dehydrogenase; IPI: International Prognostic Index.

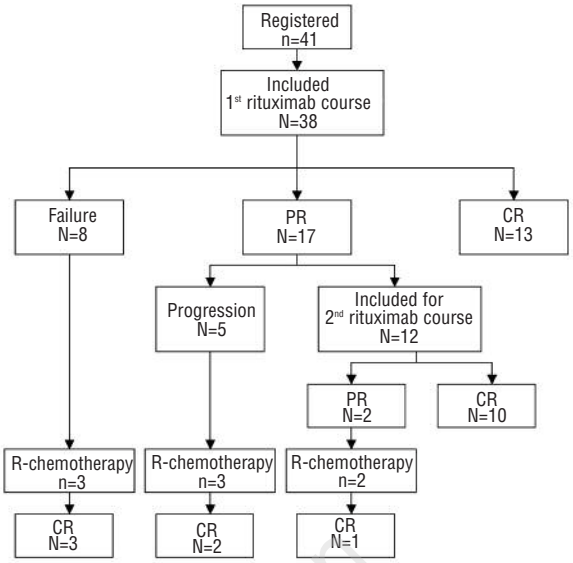

Figure 1. Treatment and outcome of the study group. CR: complete remission; PR: partial remission; R-chemotherapy: rituximab combined with chemotherapy.

Table 3. Response of the 38 patients at the end of treatment with rituximab and follow-up.

	No. of patients	*%*
Best response at the end of treatment		
Complete remission	23	60
Partial remission	7	19
Failure	8	21
Follow-up (median time 27.5 months)		
Relapses	2	5
Deaths	14	37
Causes of death		
Progression	10	26
Infection	3	8
Cardiac arrest	1	3

without evidence of lymphoma.

Among the 17 patients in PR, five progressed before the second course of rituximab could be administered, two died of progressive disease and three were treated with chemotherapy combined with rituximab (1 died of progression, 1 died of infection during chemotherapy and 1 is alive and free of lymphoma). The other 12 patients in PR were treated with additional doses of rituximab, and ten (83,3%) achieved CR. Two of these patients did not complete the four additional cycles by protocol: one died after six cycles due to hepatic abscesses without evidence of lymphoma at autopsy and one patient was evaluated after six cycles and treatment was stopped because he had achieved CR. The two patients who did not achieve CR after the second course of rituximab were treated with chemotherapy combined with rituximab: one died of progression and one is alive and free of disease. In an intention-to-treat analysis, 23 (60.5%) patients achieved CR with rituximab therapy (Table 3). Among the eight patients excluded from the trial because of absence of CR who were treated with chemotherapy, seven were treated with R-CHOP (two to eight cycles) and one with R-EPOCH. Overall, six (75%) of these patients achieved CR.

With a median follow-up of 27.5 months, two patients relapsed at 6.5 and 7 months after CR. One of them was treated with chemotherapy and is alive and free of disease, and the other died of disease progression. During this time period, 14 (36.8%) patients died. Ten (26.3%) patients died of disease progression, three patients of infection without evidence of post-transplant lymphoproliferative disease (1 of pneumonia, 1 of septic shock, and 1 of hepatic abscesses) and one patient suffered a cardiac arrest of unknown cause. Figure 2 shows the overall survival curve.

Prognostic factors

We studied different factors that could be predictive of CR: age, sex, organ transplanted, type of immunosuppression, monomorphic versus polymorphic B-cell post-transplant lymphoproliferative disorder, EBV expression in tissue, time between transplant and post-transplant lymphoproliferative disease (early versus late), Ann Arbour stage, bulky disease, graft involvement, extranodal disease, number of extranodal sites of disease, B symptoms, ECOG score, lactate dehydrogenase (LDH) and β_2-microglobulin levels, IPI, hemoglobin concentration, leukocyte count, platelet count, albumin level, and gammaglobulin level. None of the variables analyzed showed a clinically relevant prognostic significance, either for response or for survival.

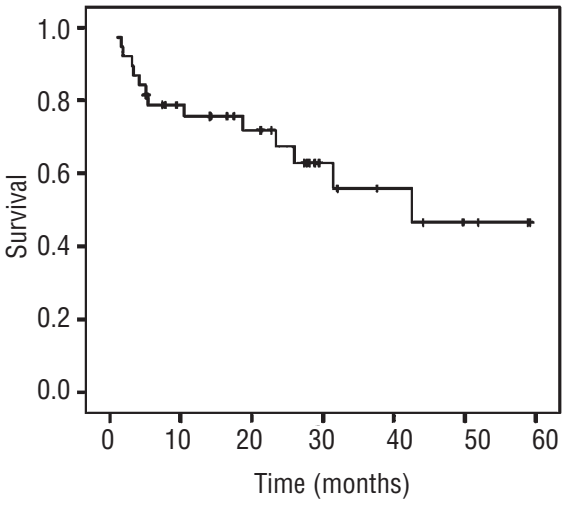

Figure 2. Overall survival probability of the 38 patients included in the study.

Discussion

The aim of this prospective clinical trial was to analyze the CR rate after treatment with extended doses of rituximab in patients with B-cell post-transplant lymphoproliferative disorders following solid organ transplantation. Patients with disseminated post-transplant lymphoproliferative disorders who do not respond to reduction of immunosuppression have been treated with conventional cytotoxic chemotherapy, but the associated toxicity has been significant and included treatment-related deaths in about 25% of patients,[12,13] mainly due to organ dysfunction and infections resulting from the immunosuppressive therapy. Several retrospective analyses have been conducted to demonstrate the benefit of rituximab in patients with B-cell post-transplant lymphoproliferative disorders.[17,18] There are only, however, two prospective studies of therapy with rituximab in patients with B-cell post-transplant lymphoproliferative disorders after failure of reduction of immunosuppression. The first one was carried out in Germany and included 17 patients,[20] and the other was recently published by a French group and included 43 patients.[19] In both studies therapy consisted of four infusions of rituximab at a standard dose. In our prospective study we treated 38 patients with extended doses of rituximab adapted to the previous response, to a maximum of eight infusions. Over 34% of patients achieved CR after four cycles of rituximab, and 26.3% more responded after two to four additional cycles of rituximab for a delayed CR rate of 60.5%. It is remarkable that ten (83%) out of 12 patients who received a second course of rituximab therapy achieved CR. In the trial published by the French group, the CR rate after four doses of rituximab was 28% at day 80 and 30% at day 360. This is similar to our results, but in our trial, a large number of patients in PR after the first four cycles achieved CR with additional doses of rituximab. In our trial, eight patients were treated with chemotherapy after rituximab therapy, and six (75%) achieved CR with lower toxicity than that usually described in the literature,[12,13] probably because they were in fitter and had less tumor disease than at diagnosis.

Only two patients relapsed after CR. This is also in accordance with the results of the French trial and indicates that the main aim of the treatment for patients with post-transplant lymphoproliferative disorders is to reach CR. There are still patients who cannot complete the first course of rituximab because their disease progresses very quickly, and who cannot be treated with either more rituximab or chemotherapy. Pre-emptive treatment would be the only way to manage these high-risk patients.

The selection of patients who could benefit from initial rituximab therapy is important. We did not find any variable significantly related to prognosis. In the French series,[19] an elevated LDH level was the only factor predictive of a poor overall response. For the German group,[20] the presence of EBV in tissue and a shorter time between transplantation and diagnosis of the lymphoproliferative disorder were associated with better response. Other prognostic factors for a better response found in retrospective analyses were a good performance status and detection of EBV in tumor tissue.[22] However, in our study, neither LDH nor other variables classically related with prognosis in immunocompetent patients, such as those included in the IPI or the EBV status, were of prognostic significance.

The toxicity of rituximab therapy has been found to be very low. We did not observe any graft rejection. Only three patients died of infections, which is comparable with outcomes in other trials and expected in this type of immunocompromised population.[21] One episode of grade 4 neutropenia was the only severe adverse event observed. Neutropenia has been described in immunocompetent patients treated with rituximab.[23] It is usually transitory and does not require suspension of treatment.

These results confirm that extended treatment with rituximab can obtain a high rate of CR in patients with B-cell post-transplant lymphoproliferative disorders after solid organ transplantation without increasing toxicity, and should be recommended as initial therapy. There is still a subgroup of patients who do not respond. Pre-emptive treatment for these high-risk patients should be investigated.

Authors' Contributions

EGB: conception and design of the study, inclusion of patients, collection of data, data interpretation, manuscript writing; EDD, FJC, JG-C, AS, AB, JMR, AI, JB, PS, CP, PF-A, MC: inclusion of patients, collection of data, final approval of manuscript; ME: data analysis and interpretation; AFdS: conception and design of the study, final approval of manuscript.

Conflicts of Interest

The authors reported no potential conflicts of interest. Some of the data of this study were presented in part at the 45th Annual Meeting of the American Society of Hematology, San Diego, CA, December 6-9, 2003, and at the 45th Annual Meeting of the Asociación Española de Hematología y Hemoterapia, Santiago de Compostela, October 23-25, 2003.

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