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ORIGINAL ARTICLE

Long-term follow-up of rituximab in treatment of chronic graft-versus-host disease—single center experience

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Abstract

Rituximab was recently described also as first-line therapy of chronic graft-versus-host disease (cGvHD). We retrospectively analyzed the efficacy and safety of all patients receiving rituximab for treatment of cGvHD between 2005 and 2016 at the Regensburg University transplant center with a median follow-up after rituximab therapy of 2.8 years. Responses of 29 allogeneic stem cell-transplanted patients (median age 49) with previous failure of response to steroids including one patient after donor lymphocyte infusion were assessed. Three months after rituximab application, the overall response rate was 31% (7% complete ($n = 2$) and 24% partial remission ($n = 7$)). At 12 months, overall survival was 72% ($n = 21$) and failure-free survival was 24% ($n = 7$). We further analyzed associations of rituximab response with clinical characteristics showing a higher response rate in steroid-dependent cGvHD patients (89% of 9 responding compared to steroid refractory patients (11% responding)). However, this difference was not statistically significant. Seven patients (24%) (including four lethal infectious complications) developed serious infections requiring hospitalization within 1–9 months after rituximab therapy exclusively in patients failing to respond to rituximab. In conclusion, rituximab appears to be an effective treatment of cGvHD especially in steroid dependent patients, but identification of biomarker predicting response will be crucial to avoid long-term infectious morbidity and mortality in non-responders.

Keywords Allogeneic stem cell transplantation · Chronic graft-versus-host disease · Rituximab

Introduction

Chronic graft-versus-host disease (cGvHD) is still one of the major complications in patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT). cGvHD essentially contributes to non-relapse mortality and substantially influences quality of life [1]. Although a number of trials evaluated new treatment options in initial treatment of cGvHD, steroids and cyclosporine remain the established first-line standard, but more than 50% of patients require subsequent additional treatment due to failure of sustained response [2].

In recent years, increasing evidence accumulated on the role of B cells in the pathogenesis of cGvHD [1, 3]. This is supported by the observation of high levels of B cell activating factor (BAFF) promoting an aberrant B cell homeostasis in patients with active cGvHD [4, 5] and emerging evidence for antibody-mediated damage of host tissues [6]. Therefore, B cell targeting therapies seem to be an interesting strategy in second-line treatment of cGvHD. The anti-CD20 monoclonal and B cell depleting antibody rituximab was reported to be an efficient second-line therapy [7–11]. Rituximab was also described in the setting of cGvHD prophylaxis and showed a reduced rate of cGvHD [12, 13]. More recently, rituximab was used in first-line therapy and also showed significant cGvHD reduction [14, 15]. Additional B cell-directed treatments like ibrutinib have been introduced further supporting the role of B cells in cGvHD [16].

Beside those positive reports on rituximab therapy, patient numbers reported remain low and there are also studies with adverse outcomes after rituximab application [17]. In addition, B cells seem to play a role also in graft-versus-leukemia effect [18, 19].

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Therefore, we retrospectively analyzed the efficacy and safety of all patients receiving rituximab for treatment of cGvHD between 2005 and 2016 at University Hospital of Regensburg with a median follow-up after rituximab of 2.8 years.

Patients and methods

Patients

All patients treated with rituximab for cGvHD were analyzed from the transplant center of the University Hospital of Regensburg between 2005 and 2016 ($n = 29$). Diagnosis and response assessment was performed according to the criteria of the National Institute of Health (NIH) consensus criteria [20]. Patients treated with rituximab for EBV reactivation or isolated immune cytopenia were excluded from the analysis. Two patients treated with rituximab because cGvHD received a prior course of rituximab for treatment of immune-mediated cytopenia before onset of cGvHD 1 and 2 years prior to application for cGvHD, respectively. Patients received four doses of weekly rituximab intravenously at a dose of 375 mg/m^2.

Definition of rituximab response

Response was assessed at 3, 6, and 12 months after first infusion of rituximab. In case of starting an additional new immunosuppression, response assessment was performed separately for those patients, and last response assessment for rituximab was performed at onset of new treatment. Last day of follow-up was in July 2017.

Complete remission (CR) was defined as resolution of all organ manifestations and symptoms of cGvHD [21]. An improvement by at least one organ grade without progression at other sides was defined as partial response (PR). cGvHD patients with progressive manifestations were classified as progressive disease (PD). Mixed response was defined as CR or PR in one organ in combination of progression in another organ. Patients without CR, PR, or PD were classified as 'no change' (NC). Steroid dose, B and CD4$^+$ T cells in peripheral blood, and gamma-globulin level in serum were assessed at baseline and at response assessment time points.

Results

Patient characteristics

Between 2005 and 2016, 29 patients were treated with rituximab for cGvHD. Detailed characteristics of the patients including gender, age, diagnosis, donor type, stem cell source conditioning regimen, GvHD prophylaxis, and history of acute GvHD are illustrated in Table 1.

Table 2 shows characteristics before start of rituximab. The median follow-up after rituximab application was 1015 days (range: 36–3520). Patients received a median of four doses (3–11) of rituximab. All patients had at least one prior line of immunosuppressive therapy; most patients (22 out of 29) had two or more prior therapy lines. All patients received further immunosuppressive medication already applied before start of rituximab, but no new immunosuppressive agent was

Table 1 Detailed characteristics of the patients including gender, age, diagnosis, donor type, stem cell source conditioning regimen, GvHD prophylaxis, and history of acute GvHD

Characteristics	Value
Patients	29
Male, *n* (%)	18 (62)
Female, *n* (%)	11 (38)
Age, median (range)[a]	49 (21–65)
Diagnosis	
AML, *n* (%)	15 (51)
MDS, *n* (%)	2 (7)
Multiple myeloma, *n* (%)	4 (14)
NHL, *n* (%)	4 (14)
Others, *n* (%)	4 (14)
Donor type	
HLA-matched unrelated, *n* (%)	16 (55)
HLA-mismatched unrelated, *n* (%)	0
HLA-matched related, *n* (%)	12 (41)
HLA-mismatched related, *n* (%)	1 (4)
Haploidentical related, *n* (%)	0
Sex mismatch	
Yes, *n* (%)	10 (34)
No, *n* (%)	19 (66)
Stem cell source	
Peripheral blood stem cells, *n* (%)	26 (90)
Bone marrow, *n* (%)	3 (10)
GvHD prophylaxis	
ATG/CSA/MTX, *n* (%)	7 (24)
ATG/CSA/MMF, *n* (%)	9 (31)
CSA/MTX, *n* (%)	5 (17)
CSA/MMF, *n* (%)	6 (21)
Others, *n* (%)	2 (7)
History of aGvHD	
Grades 0–I, *n* (%)	23 (79)
Grades II–IV, *n* (%)	6 (21)

[a] Age at first R treatment

aGvHD acute graft-versus-host-disease, *AML* acute myeloid leukemia, *ATG* anti-thymocyte globulin, *CSA* cyclosporine, *MDS* myelodysplastic syndrome, *MMF* mycophenolate mofetil, *MTX* methotrexate, *NHL* non-hodgkin lymphoma, *R* rituximab

Table 2 Characteristics before start of rituximab

Characteristics	Value
Onset of cGvHD after allo-SCT, median days,(range)	321 (82–1337)
Time point of rituximab treatment after allo-SCT, median days,(range)	784 (181–2885)
Time point of rituximab treatment after cGvHD onset, median days,(range)	349 (45–2129)
Median follow-up after rituximab application	1015 (36–3520)
Number of rituximab cycles, median (range)	4 (3–11)
cGvHD, *n* (%)	
Mild	0
Moderate	11 (38)
Severe	18 (62)
Steroid response of cGvHD	
Sterois resistance	6 (21)
Steroid dependence	23 (79)
Number of organ involvement of cGvHD, *n* (%)	
One	1 (3)
Two	10 (34.5)
Three	8 (28)
Four or more	10 (34.5)
Type of cGvHD organ involvement, *n* (%)	
Skin	27 (93)
Oral	17 (59)
Eyes	14 (48)
Liver	3 (10)
Gut	3 (10)
Lung	3 (10)
Musculoskeletal	19 (66)
Genital	3 (10)
ISM at the beginning of rituximab, *n* (%)	
No ISM	0
One ISM	6 (21)
Two ISM	13 (45)
Three ISM	10 (34)
Number of prior therapies before rituximab, *n* (%)	
One	7 (24)
Two	15 (52)
Three	4 (14)
Four or more prior therapies	3 (10)

allo-SCT allogeneic hematopoietic stem cell transplantation, *cGvHD* chronic graft-versus-host-disease, *ISM* immunosuppressive medication

started in parallel to rituximab. Most patients (23 out of 29) had two or three concomitant immunosuppressants.

Almost all patients ($n = 27$, 93%) had skin involvement of cGvHD. Importantly, three patients also had liver (10%), lung ($n = 3$, 10%), or genital ($n = 3$, 10%). Eleven (38%) patients had moderate and 18 (62%) severe cGvHD. Most patients ($n = 23$, 79%) had steroid-dependent cGvHD, compared to six (21%) patients with steroid-resistant cGvHD. Seven patients had thrombocytes lower than 100/nl at the time of rituximab therapy, compared to 22 patients with more than 100 thrombocytes/nl. At time of cGvHD diagnosis, five patients had thrombocytes lower than 100/nl and 24 patients more than 100/nl.

The median number of circulating B cells was 147.5/μl (range 0–1468/μl) and median gamma-globulin level was 3.9 g/l (range 1.8–11.3 g/l) at the time of rituximab start. The median number of circulating $CD4^+$ T cells was 281/μl (range 32–964/μl).

Response to rituximab after 3 months

Three months after first application of rituximab, two (7%) and seven (24%) patients achieved a CR or PR, respectively (Table 3). One patient had a mixed response. In contrast, ten (34.5%) patients showed no response and two (7%) patients had PD. In addition, start of additional immunosuppressants was necessary in five (17%) patients. Of those, three had at the day of new immunosuppression NR and two patients PD. One patient died 40 days after rituximab application due to pulmonary embolism and another patient died 36 days after rituximab treatment due to bacterial sepsis. Together, the overall response rate at 3 months after rituximab therapy was 31% and failure-free survival (FFS), defined as absence of an additional systemic therapy, relapse, or non-relapse mortality, was 66% ($n = 19$).

At start of rituximab, median steroid dose was 0.42 mg/kg body weight compared to 3 months after rituximab application where median steroid dose was 0.15 mg/kg body weight (Table 3). We also analyzed steroid dose for responding and non-responding patients separately. Here, responder had a median dose of 0.39 mg/kg body weight at the beginning, which was reduced at 3 months to 0.13 mg/kg body weight. Non-responder had a median of 0.42 mg/kg body weight at rituximab application and 0.2 mg/kg body weight at 3 months afterward.

Response to rituximab after 6 and 12 months

As shown in Table 3, at 6 months after rituximab treatment, two (7%) and seven (24%) patients still showed a CR or PR, respectively. Six (21%) patients remained unresponsive. Four additional patients were treated with new immunosuppressants, two patients because of PD and two patients with stable cGvHD. Four patients died due to progression of cGvHD ($n = 1$) or bacterial sepsis ($n = 3$). FFS at 6 months was 52% ($n = 15$).

At 12 months, additionally, seven patients received new immunosuppressive medication, with three patients having PD, two patients NR, and one patient PR. Eight (28%) patients were dead. Only four (14%) patients were still in PR and another three (10%) patients had no response. FFS was 24% ($n = 7$).

Association to response of rituximab treatment

We next analyzed associations between responder and non-responder to rituximab therapy. At 3 months after rituximab, nine patients (31%) responded compared to 20 non-responders (69%). The median number of pretreatments was comparable between both groups (median 2 previous lines of therapy). Only one patient (3%) with steroid refractory cGvHD showed a PR after 3 and 6 months after rituximab treatment, whereas eight patients (28%) with a PR or CR had steroid-dependent cGvHD. In the non-responder group, 5 patients (17%) had steroid refractory and 15 patients (52%) steroid-dependent disease. In addition, seven responding patients (24%) had quiescent cGvHD, compared to two responding patients (7%) with de novo and progressive cGvHD, respectively. Non-responding patients could be subdivided as follows: 4 patients (14%) with de novo, 13 patients (45%) with quiescent, and 3 patients (10%) with progressive cGvHD. However, due to limited patient numbers in each group, differences were not statistically significant and

Table 3 Responses after first application of rituximab

Response to rituximab at 3 months after application						
CR, *n* (%)	PR, *n* (%)	NC, *n* (%)	Mixed, *n* (%)	PD, *n* (%)	Start of additional ISM, *n* (%)	Death, *n* (%)
2 (7)	7 (24)	10 (34.5)	1 (3.5)	2 (7)	5 (17)	2 (7)
Response to rituximab at 6 months after application						
CR, *n* (%)	PR, *n* (%)	NC, *n* (%)	Mixed, *n* (%)	PD, *n* (%)	Start of additional ISM, *n* (%)	Death, *n* (%)
2 (7)	7 (24)	6 (21)	1 (3)	1 (3)	6 (21)	6 (21)
Response to rituximab 12 months after application						
CR, *n* (%)	PR, *n* (%)	NC, *n* (%)	Mixed, *n* (%)	PD, *n* (%)	Start of additional ISM, *n* (%)	Death, *n* (%)
0 (0)	4 (14)	3 (10)	0 (0)	1 (3)	13 (45)	8 (28)
					Dose	Number of patients
Steroids (mg/kg body weight) at start of rituximab, median (range)					0.42 (0.19–1.05)	29
Responder					0.39 (0.19–1)	9
Non-responder					0.42 (0.19-1.05)	20
Steroids (mg/kg body weight) after 3 months, median (range)					0.15 (0–0.31)	21
Responder					0.13 (0–0.27)	9
Non-responder					0.2 (0.1–0.31)	12

CR complete remission, *ISM* immunosuppressive medication, *NC* no change, *PD* progressive disease, *PR* partial response

the low number of patients with steroid refractory cGvHD compared to steroid-dependent patients precludes any valid conclusion with regard to the association with response.

The median number of B cells in peripheral blood before rituximab in patients showing any response within 1 year after treatment was 244/μl, whereas non-responding patients had 69/μl B cells, which was not statistically significant. $CD4^+$ T cells were higher in non-responding patients compared to responding patients (median 363 and 256/μl, respectively), but also not statistically significant. Patients with quiescent cGvHD had a median of 147.5/μl B cells in peripheral blood, compared to de novo cGvHD patients with a median of 244/μl.

Infectious complications after rituximab

Infectious complications were divided into the following WHO categories: hospital admission, intensive care unit, and death. Non-serious infections were not included into the analysis. We observed serious infections in seven patients with a median of 5 (1–9) months after rituximab infusion. Three patients required hospital admission and four patients died due to infections. Infectious causes were viral ($n = 1$), fungal ($n = 1$), bacterial ($n = 4$), and unknown ($n = 1$).

Next, we analyzed association between infections and response in those patients. Notably, five of seven patients had progressive cGvHD after rituximab therapy, and the other two patients showed only a non-durable PR. Although patient numbers are low, it appears that patients non-responding to treatment showed infectious complications which may be also due to intensified immunosuppression following rituximab treatment since in four patients developing serious infections, immunosuppressive regimen was changed (e.g., tocilizumab, total nodal irradiation, imatinib, and everolimus) in the period between rituximab application and infection.

We also analyzed median time of recovery of immunoglobulin levels > 4 g/l without substitution after rituximab application. Multiple myeloma patients with active disease were excluded from the analysis. Eight of the remaining 25 patients reached an immunoglobulin serum level above 4 g/l with a median time of 991 days (range 343–2386) after rituximab treatment. Three patients are still dependent for immunoglobulin substitution, with a follow-up of 3813, 1657, and 1015 days, respectively. Thirteen patients died before regeneration of immunoglobulins due to GvHD progression ($n = 6$), infections ($n = 5$), secondary malignancy patient ($n = 1$), and pulmonary embolism ($n = 1$).

Discussion

In this retrospective, single-center analysis of rituximab in treatment of cGvHD, we observed an overall response rate of 31% at 3 months after first application. This response rate is lower compared to prior published trials [7, 9, 10, 22], where overall response rates ranged from 55 to 70%. This difference might be due to center-specific patient population and the heterogeneous lines of prior therapy. Additionally, response rates of all therapies decline with better defined end points and higher numbers of patients [23]. Moreover, our cohort included all patients treated with rituximab, also patients with DLI-induced cGvHD and high-risk AML patients with active disease at time of transplantation who are usually excluded in clinical trials.

Despite the limited patient number, the retrospective character of the analysis, and the single-center study, our data demonstrate a moderate efficacy of rituximab after failure of first-line treatment of cGvHD. In addition, the results demonstrate a significant infectious morbidity and in part mortality following rituximab mainly occurring in patients failing to respond. Therefore, the identification of biomarker or patient characteristics predicting subsequent response to rituximab might be beneficial. One specific characteristic of rituximab is the relatively long biological half live resulting in prolonged depletion of B cells which persists for months even after termination of treatment impairing response to new antigens [13]. Moreover, the optimal dose for treatment of cGvHD has not been evaluated so far and a retrospective analysis published by Bonin et al. showed comparable response rates with lower doses [24]. In addition to rituximab, other B cell active agents have been evaluated in treatment of cGvHD. Ibrutinib was previously shown to be effective in murine and also human cGvHD [16, 25]. Miklos et al. treated patients with inadequate response to steroid-containing immunosuppression with ibrutinib. They observed a best overall response rate of 67% with a high rate of sustained response. Based on this study, ibrutinib was approved in treatment of cGvHD in the USA. Ibrutinib might be beneficial compared to rituximab due to the only transient inhibition of B cells and loss of effects after discontinuation of the drug and activity on $CD21^-CD20^-$ plasmablasts. The results demonstrate the need for analyses of unselected patient populations complementary to clinical trials.

Compliance with ethical standards

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Conflict of interest Daniel Wolff received honoraria from Mallinckrodt, Novartis, Shire and Neovii. All other authors declare no conflict of interest.

Ethical approval Because our study was a retrospective analysis, no additional ethical approval of the institutional committee was necessary.

Informed consent Informed consent to receive rituximab was obtained from all individual participants included in the study.

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