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Letter

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Obinutuzumab in Allogeneic Transplantation for CLL and Richter's Transformation in the Age of Targeted Therapies

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The introduction of B-cell receptor inhibitors including Bruton tyrosine kinase inhibitors (ibrutinib and acalabrutinib) and phosphoinositide 3-kinase inhibitors (idelalisib and duvelisib), as well as the BCL2 inhibitor venetoclax has dramatically improved management options for patients with high-risk chronic lymphocytic leukemia (HR-CLL). These fortunate developments have downscaled the role of allogeneic stem cell transplantation (alloHCT) in this patient population and shifted research activities from alloHCT to newer therapeutic approaches. Nonetheless, despite the effectiveness of targeted novel agents (NAs), drug intolerance, primary resistance, progression, and Richter's transformation (RT) remain serious limitations for many patients. For patients who experience progression or toxicity on all of the available NAs, outcomes remain poor.[1,2]

For young, fit patients, in whom NAs are not expected to provide long-term disease control or with high-grade transformation, alloHCT is still a viable option.[3] AlloHCT harbors the potential for long-term disease control,[4] but is associated with severe risks like chronic graft-versus-host disease (GVHD), a significant percentage of non-relapse mortality and last but not least (early) relapse. Against this background, strategies to improve the outcome of alloHCT in HR-CLL and RT are needed, but scarce.

We report the course of 3 intensively pretreated HR-CLL patients (including one with RT) who received peritransplant obinutuzumab within the prospective CLL-TX1 trial, a single-arm, phase-II study for patients with HR-CLL or RT of the German CLL Study Group (NCT03153514) (for Consort diagram, please refer to Suppplemental Digital Content 1, http://links.lww.com/HS/A212). Obinutuzumab is a humanized type-II CD20 antibody, which has shown superior efficacy in comparison to rituximab by inducing direct cell death as well as enhanced antibody dependant cellular cytotoxicity.[5] Unfortunately, the trial coincided with a multitude of trials testing NAs for the respective patient population and with approvals of NAs for CLL, so that the decision was made to discontinue enrollment due to slow recruitment.

Patients were enrolled between November 2017 and April 2018. The competent review boards approved the study and written informed consent was obtained from all patients.

Patients were eligible for inclusion, if they had

1. Documented CLL according to International Workshop on CLL (iwCLL) criteria,[6] requiring alloHCT consistent with the consensus statement of the European Research Initiative on CLL (ERIC) and the European Society for Blood and Marrow Transplantation (EBMT)[7]:
   a. Nonresponse or early relapse within 24 months after purine analogue combination therapy or treatment of similar efficacy plus TP53 mutation, deletion (del)17p and/or del11 plus response to NAs or
   b. Nonresponse or early relapse within 24 months after purine analog combination therapy or treatment of similar efficacy and refractory to or nontolerating NAs.
2. Transformation of CLL to aggressive non-Hodgkin lymphoma (RT).

Both fully HLA-matched (HLA-A, -B, -C, -DRB, and -DQB1) related and unrelated donors were allowed.

The conditioning regimen was fludarabine 30 mg/m^2 i.v. day (d) −6 to −2 and busulphan 3.2 mg/kg i.v. from d −5 (or −4, based on the patient's general condition) to d −3. Patients received obinutuzumab 100 mg i.v. on d −8, 900 mg on d −7 followed by

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1000 mg on d −1, +7, and +14. A second cycle obinutuzumab (1000 mg i.v. once per week for 4 wks) was allowed in case of active disease and/or minimal residual disease (MRD) positivity around d+60, +90, +180 or +270 posttransplant. GVHD prophylaxis included cyclosporine A and mycophenolate mofetil.

Pretransplant characteristics of patients are summarized in Table 1. Patient 1 was diagnosed with RT and patients 2 and 3 with HR-CLL. All patients had received multiple lines of previous therapies including at least 1 (patient with RT) or 3 (patients with HR-CLL) NAs (see Table 1). All 3 patients achieved a partial response, but with significant residual disease activity, before alloHCT (see Table 1). Patient 1 had a sibling donor, whereas patients 2 and 3 had unrelated donors. Cycle 1 of obinutuzumab was completed as per protocol in all three patients. Patient 1 and patient 3 received a second cycle of obinutuzumab: Patient 1 due to MRD positivity (ie, 1 CLL cell in 100 leukocytes or less) in the peripheral blood and bone marrow on d+61 and patient 3 due to an intermediate MRD status (ie, 1 CLL cell in 10,000 to more than 100 leukocytes) in the peripheral blood on d+195. Of note patient 1 achieved MRD reduction to intermediate MRD status on d+106 and to MRD negativity (flow-cytometric with a cut-off of 10–4 [ie, <1 cell in 10,000 leukocytes]) on d+180, despite elevation of immunosuppressive therapy during this period in the context of a GVHD episode. In patient 3, the start of the second cycle obinutuzumab was delayed for logistical reasons until d+257. Subsequently, a negative MRD status was measured with a time delay at this point. The administered immunosuppressive therapy was stable between d+195 and d+257.

Neutrophil engraftment (absolute neutrophil count > 0.5×10^8/L) was achieved on d + 25 (patient 1), d +11 (patient 2), and d +15 (patient 3). Platelet engraftment (platelets > 20×10^8/L) occurred in patient 2 on d +10. Platelets did not drop below this threshold in patients 1 and 3. Complete lymphohematopoietic donor chimerism was achieved on d +180 (patient 1), d +171 (patient 2), and d +151 (patient 3).

Nonhematopoietic toxicity was modest and lay within the expected range. In total, 9 serious adverse events (SAEs) and one serious adverse reaction (pyrexia, CTC [Common Terminology Criteria] grade 1) that were assessed as possibly related to the study drug occurred during the 2-year trial phase. Reported SAEs were all related to infections including three cases of pneumonia, one *Escherichia coli* sepsis, one *Cytomegalovirus* (CMV) gastritis, one *Herpes simplex* infection, one Parainfluenza virus infection, and one infection not otherwise specified.

All 3 patients developed acute GVHD (≤grade 2), no severe acute GVHD (≥grade 3) was reported. Clinically relevant chronic GVHD occurred in 2 patients: mild ocular chronic GVHD was diagnosed on d +526 in patient 1, and in patient 2, an episode of pulmonal chronic GVHD was suspected in the context of a CMV-pneumonia on d +169. Respiratory symptoms were fully reversible after adequate antiviral treatment and steroid administration.

Table 1.

Baseline Characteristics of Patients Included in the CLL-TX1 Trial

	Patient 1	Patient 2	Patient 3
Age at alloHCT (y)	57	57	66
Gender	Male	Male	Male
Diagnosis	RT (DLBCL)	CLL	CLL
Years from diagnosis to alloHCT	5	12	12
Prior treatments	1. FC	1. Chlorambucil	1. FCR
	2. BR	2. FC	2. Ofatumumuab
	3. Ibrutinib	3. R	3. Venetoclax
	4. R-CHOP	4. BR	4. Ibrutinib + obinutuzumab
	5. R-DHAP	5. R-idelalisib	
		6. Ibrutinib	5. Ibrutinib
		7. Venetoclax	6. Idelalisib + obinutuzumab
No. prior NAs	1	3	3
Disease status before conditioning	PR (lymphadenopathy, hepatosplenomegaly and 30% BM infiltration)	PR (residual lymphadenopathy, 20%–30% BM infiltration)	PR (lymphadenopathy up to 4.3 cm, 0.01% CLL cells in BM)
Cytogenetics			
Del (17p)	No	No	Yes
Del(11q)	No	No	No
Trisomy 12	Yes	Yes	No
Del (13q)	No	Yes	No
Complex karyotype ≥ 3	Yes	No	No
Complex karyotype ≥ 5	No	No	No
Molecular genetics			
Unmutated IGHV	Yes	No	Yes
Mutated TP53	No	No	Yes
After failure of ibrutinib			
BTK mutation	No	n.d.	No
PLCgamma mutation	n.d.	n.d.	No
Donor type	Related; fully HLA-matched	Unrelated; fully HLA-matched	Unrelated; fully HLA-matched
HCT-CI	5	0	6
Conditioning regimen	FluBu 2	FluBu 3	FluBu 2
CD34+ cells transplanted	13.59×10^6/kg	6.27×10^6/kg	8.07×10^6/kg
Bulky disease (Lymph node size ≥ 5 cm)	No	No	No

alloHCT = allogeneic stem cell transplantation; BM = bone marrow; BR = bendamustine + rituximab; CLL = chronic lymphocytic leukemia; del = deletion; DLBCL = diffuse large B-cell lymphoma; FC(R) = fludarabine + cyclophosphamide (+ rituximab); FluBu 2 = fludarabine 30 mg/m2 day −6 to −2 + busulphan 3.2 mg/kg i.v. day −4 and −3; FluBu 3 = fludarabine 30 mg/m2 day −6 to −2 + busulphan 3.2 mg/kg i.v. day −5 to −3; HCT-CI = hematopoietic cell transplantation- specific comorbidity index; HLA = human leukocyte antigen system; IGHV = immunoglobulin heavy chain variable region; NA = targeted novel agents (including ibrutinib, idelalisib, and venetoclax); n.d. = not done; PR = partial response; R = rituximab; R-CHOP = rituximab + cyclophosphamide + hydroxydaunorubicin + vincristine + prednisone; R-DHAP = rituximab + dexamethasone + cytarabine + cisplatin; RT = Richter's transformation.

All 3 patients were free of systemic immunosuppression 1 year after alloHCT.

At 2 years after alloHCT, MRD negativity in peripheral blood and bone marrow was achieved in all three patients (see Fig. 1 for individual levels of MRD at certain times after alloHCT). Patient 1 was assessed with a partial response according to IWCLL guidelines[6] due to a borderline enlarged spleen. Patients 2 and 3 both had a complete response (CR). With database closure for follow-up on September 30, 2021 (46, 42, and 41 mo after alloHCT, respectively, for patients 1, 2. and 3) all three patients are alive without signs of relapse.

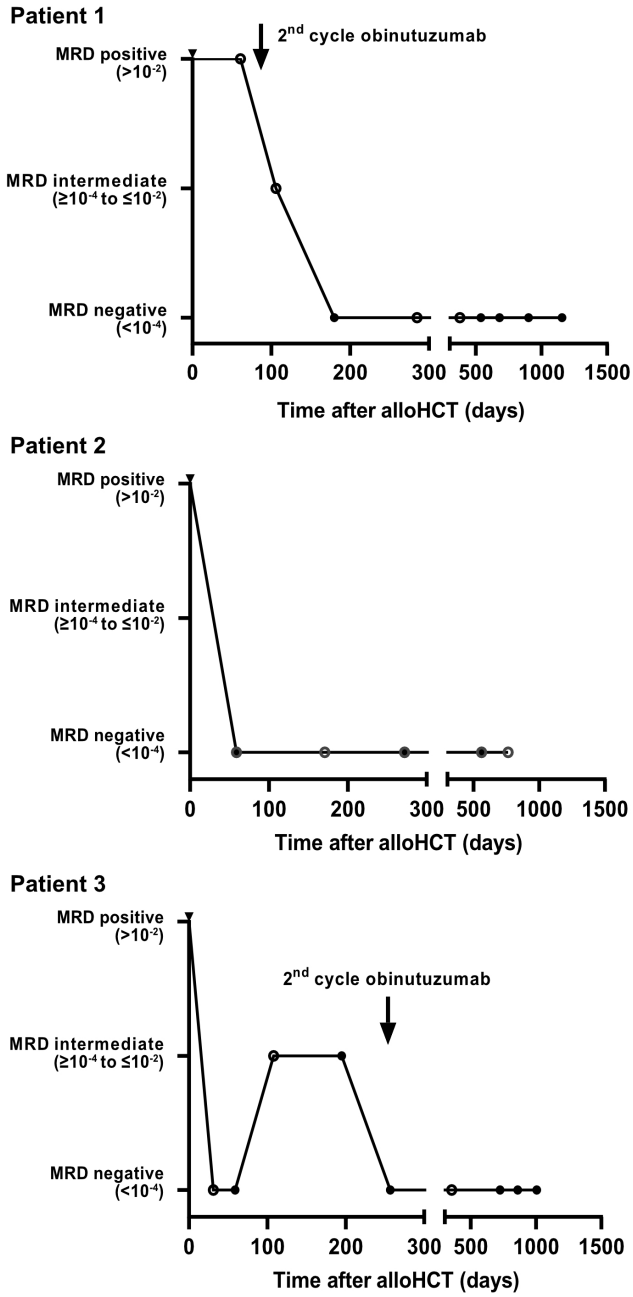

Figure 1. Course of MRD after alloHCT for patient 1, 2, and 3 assessed in bone marrow (open circles) and peripheral blood (filled circles). The first measuring point (reverted triangle) indicates the MRD status in the bone marrow before start of conditioning regimen for alloHCT. alloHCT = allogeneic stem cell transplantation; MRD = minimal residual disease.

A number of publications have described different approaches in transplantation for Richter[8,9] and CLL patients,[3,8,10–12] including the addition of the CD20 antibodies rituximab[13,14] and ofatumomab.[15,16] To our knowledge, however, this is the first report of the addition of the CD20-antibody obinutuzumab peritransplant for patients with HR-CLL or RT. Adding obinutuzumab to low-intensity conditioning in the setting of HR-CLL and RT was feasible and safe.

In this prospectively followed cohort of 3 patients, all heavily pretreated and with active disease before transplant, complete donor chimerism as well as MRD negativity in peripheral blood and bone marrow was achieved in all cases and all were free of systemic immunosuppressants 1 year after transplantation latest. Posttransplant GVHD and infectious complications could be well managed in all 3 patients. Still the addition of B-cell depletion to alloHCT conditioning certainly harbors the risk of increased infectious complications and a close monitoring is warranted. Of note, to date >3 years after transplantation, none of the patients died or experienced relapse.

Even though the broad availability of NAs has cut back the role of alloHCT in CLL, we now increasingly see patients who progress through multiple lines of NAs or develop RT and for whom alloHCT is a feasible option; therefore, strategies to reduce risks of alloHCT are needed.

Against this backdrop and given the favorable course of all 3 patients followed in our trial, the addition of obinutuzumab to reduced-intensity conditioning alloHCT for patients with HR-CLL and RT is something to consider, but further evaluation is warranted.

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