



Universiteit
Leiden
The Netherlands

Allogeneic hematopoietic cell transplantation for patients with TP53 mutant or deleted chronic lymphocytic leukemia: results of a prospective observational study

Schetelig, J.; Hoek, J.; Stilgenbauer, S.; Middeke, J.M.; Andersen, N.S.; Fox, C.P.; ... ; Dreger, P.

Citation

Schetelig, J., Hoek, J., Stilgenbauer, S., Middeke, J. M., Andersen, N. S., Fox, C. P., ... Dreger, P. (2020). Allogeneic hematopoietic cell transplantation for patients with TP53 mutant or deleted chronic lymphocytic leukemia: results of a prospective observational study. *Bone Marrow Transplantation*, 56, 692-695. doi:10.1038/s41409-020-01013-y

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](https://creativecommons.org/licenses/by/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3182209>

Note: To cite this publication please use the final published version (if applicable).



Allogeneic hematopoietic cell transplantation for patients with *TP53* mutant or deleted chronic lymphocytic leukemia: Results of a prospective observational study

Johannes Schetelig ^{1,2,3,4} · Jennifer Hoek^{3,5} · Stephan Stilgenbauer^{4,6} · Jan Moritz Middeke ¹ · Niels Smedegaard Andersen^{3,4,7} · Christopher P. Fox ^{3,8} · Stig Lenhoff^{3,9} · Liisa Volin^{3,4,10} · Avichai Shimoni^{3,11} · Wilfried Schroyens^{3,12} · Michel van Gelder^{3,4,13} · Donald Bunjes^{3,6} · Anja van Biezen^{3,5} · Henning Baldauf² · Liesbeth C. de Wreede^{2,14} · Olivier Tournilhac^{3,4,15} · Nicolaus Kröger ^{3,16} · Ibrahim Yakoub-Agha^{3,17} · Peter Dreger ^{3,4,18}

Received: 17 December 2019 / Accepted: 24 July 2020 / Published online: 16 August 2020
© The Author(s) 2020. This article is published with open access, corrected publication 2021

To the Editor,

Patients with chronic lymphocytic leukemia (CLL) with a deleted or mutated *TP53* gene (*TP53*_{mut/del}) have the worst prognosis among genetically defined CLL subgroups. Disruption of *TP53* function confers resistance to chemotherapy and leads to less sustained disease control on pathway inhibitor treatment [1, 2]. In contrast, in several studies of patients who received alloHCT, presence of *TP53*_{mut/del} was

no significant risk factor [3–7]. Progression-free 5-year survival rates after alloHCT ranged between 33% and 45% and many long-term survivors were MRD-negative [5, 6, 8]. In order to evaluate alloHCT for patients with *TP53*_{mut/del} CLL in first or second remission prior to transplantation, a prospective observational study enrolled patients between 2010 and 2012. Here, we report long-term outcomes.

The study was conducted as a registry-based prospective observational study by the Chronic Malignancies Working Party of EBMT. Eligibility criteria were as follows: Patients had to be scheduled to receive HLA-compatible related or unrelated alloHCT for 17p-*TP53*-mutated CLL. Patients had to be in first or second complete (CR) or partial remission (PR) at the time of alloHCT. Patients with >1 mismatch at HLA-A, HLA-B, HLA-C, or HLA-DRB1, ≥70 years of age, ex vivo T-cell depletion of the graft or intended in vivo T-cell depletion with alemtuzumab were

Previous presentations: Annual Meeting of the European Society for Blood and Marrow Transplantation at London in 2013 and at Istanbul in 2015.

Supplementary information The online version of this article (<https://doi.org/10.1038/s41409-020-01013-y>) contains supplementary material, which is available to authorized users.

✉ Johannes Schetelig
johannes.schetelig@uniklinikum-dresden.de

- ¹ University Hospital, Dresden, Germany
- ² DKMS Clinical Trials Office, Dresden, Germany
- ³ European Society for Blood and Marrow Transplantation (EBMT), Leiden, Netherlands
- ⁴ European Research Initiative on Chronic Lymphocytic Leukemia (ERIC), Barcelona, Spain
- ⁵ EBMT Data Office, Leiden, The Netherlands
- ⁶ Ulm University, Ulm, Germany
- ⁷ Rigshospitalet, Copenhagen, Denmark
- ⁸ Nottingham University Hospitals NHS Trust, Nottingham, UK
- ⁹ University Hospital Lund, Lund, Sweden

- ¹⁰ Helsinki University Central Hospital, Helsinki, Finland
- ¹¹ Chaim Sheba Medical Center, Tel-Hashomer, Israel
- ¹² Antwerp University Hospital, Edegem, Belgium
- ¹³ University Medical Center Maastricht, Maastricht, The Netherlands
- ¹⁴ Medical Statistics, Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands
- ¹⁵ Service Therapie Cellulaire & Hematologie Clinique, Centre Hospitalier Universitaire, Clermont Ferrand, France
- ¹⁶ University Hamburg Eppendorf, Hamburg, Germany
- ¹⁷ Centre Hospitalier Universitaire de Lille, LIRIS, INSERM U995, Université de Lille, Lille, France
- ¹⁸ Department of Medicine V, University of Heidelberg, Heidelberg, Germany

Table 1 Univariable analysis of overall-free and relapse-free survival, relapse incidence and non-relapse mortality.

Variables	<i>N</i>	5-yr OS (95% CI)	<i>p</i> -value	5-yr RFS (95% CI)	<i>p</i> -value	5-yr CIR (95% CI)	<i>p</i> -value	5-yr NRM (95% CI)	<i>p</i> -value
Total cohort	39	49 (35–68)		29 (17–48)		42 (26–58)		29 (14–44)	
<i>Patient age at HCT</i>									
<60 years	26	46 (29–72)	0.85	25 (12–50)	0.34	51 (31–72)	0.10	24 (6–42)	0.58
≥60 years	13	54 (33–89)		38 (19–76)		23 (0–48)		38 (11–66)	
<i>HCT-CI, score</i>									
<3	28	54 (38–77)	0.11	31 (17–54)	0.47	44 (24–63)	0.94	26 (9–43)	0.28
≥3	11	36 (17–79)		27 (10–72)		36 (6–67)		36 (5–68)	
<i>Detection of deletion(17p)/TP53_{mut}</i>									
During Course CLL	14	38 (18–79)	0.84	18 (5–60)	0.32	52 (22–81)	0.26	30 (3–58)	0.84
At diagnosis	25	54 (38–78)		36 (21–61)		36 (17–55)		28 (10–46)	
<i>Disease stage</i>									
First remission	13	69 (48–99)	0.12	54 (33–89)	0.04	23 (0–47)	0.050	23 (0–47)	0.40
Advanced stage	26	39 (23–64)		18 (8–42)		51 (30–71)		31 (12–50)	
<i>Remission status before conditioning</i>									
Complete remission	8	47 (21–100)	0.92	33 (12–96)	0.51	42 (0–84)	0.56	25 (0–57)	0.76
Partial remission	31	49 (34–71)		28 (15–50)		42 (24–60)		30 (13–48)	
<i>Alemtuzumab last line prior to HCT</i>									
No	10	34 (14–85)	0.11	20 (6–69)	0.02	40 (7–73)	0.17	40 (6–74)	0.06
Yes	29	53 (37–76)		32 (18–56)		43 (23–62)		26 (8–44)	
<i>Donor type</i>									
HLA-identical sibling	11	36 (17–79)	0.29	27 (10–72)	0.46	45 (13–78)	0.50	27 (0–56)	0.73
Alternative donor	28	53 (37–77)		30 (16–54)		40 (21–59)		30 (12–48)	

p-values are based on the log-rank test (OS and PFS) and the Gray test (CIR and NRM), they compare the outcomes of the groups during the whole follow-up.

OS overall survival, RFS relapse-free survival, RI relapse incidence, NRM non-relapse mortality, CI confidence interval, HCT hematopoietic stem cell transplantation, HCT-CI hematopoietic cell transplantation-comorbidity index

excluded. All patients signed informed consent. The trial complied with the declaration of Helsinki and was registered with clinicaltrials.gov (NCT01675102).

Patients who achieved a CR were tested for minimal residual disease (MRD) in peripheral blood and bone marrow. Testing for MRD was done locally using flow cytometry or molecular analyses. The primary endpoint of the study was to analyse relapse-free survival (RFS) at one year after alloHCT with a null hypothesis of ≤50% RFS at that time point. Details on data management and the statistical analysis are provided in the supplement. Data were analyzed as of August 31, 2019.

A total of 41 patients were enrolled at 11 centres between June 2010 and September 2012. One patient with Richter's Syndrome and one patient aged >70 years at alloHCT did not meet the eligibility criteria, and were excluded from the study after review of the data. The final analysis set therefore included data from 39 patients, 28 male and 11 female patients. Median age was 59 years (range, 28–69 years). All patients had a Karnofsky Performance Score ≥80%. The median hematopoietic cell transplantation-comorbidity

index (HCT-CI) was 0 with a range from 0 to 9. Thirty-five patients (90%) had a deletion 17p confirmed by FISH with or without a *TP53*-mutation. Four patients (10%) had a *TP53*-mutation only. The deletion (17p)/*TP53*-mutation was diagnosed during the course of the disease after first treatment in 14 patients (36%).

Patients had a median number of 2 (range, 1–6) prior lines of therapy prior to alloHCT. Thirteen patients (33%) with *TP53*_{mut/del} diagnosis had received only one line of treatment for remission induction prior to transplantation. Ten of these patients had received alemtuzumab for remission induction.

Altogether 16 patients (41%) had been exposed to purine-analogues (PA), of whom 44% had PA-refractory CLL or experienced relapse within 2 years after PA-containing chemotherapy. Thirty patients (77%) had received alemtuzumab for remission induction prior to transplantation. Alemtuzumab was the last line of treatment in 29 of these 30 patients (97%). At the time of alloHCT, 8 patients (21%) were in CR and 31 patients (79%) were in PR. The majority of patients (62%) received reduced-intensity conditioning. Eleven patients

(28%) had HLA-identical sibling donors and 28 patients (82%) had HLA-compatible unrelated donors, including 5 donors with a single mismatch at HLA-A, HLA-B, HLA-C, or HLA-DRB1. Further patient and transplant characteristics are provided in Table S1.

All patients engrafted, and no secondary graft failure was reported. The cumulative incidence of acute GVHD grades II–IV at 100 days was 36% (95% CI, 21–51%). The cumulative incidence of limited or extensive chronic GVHD at 1 year after alloHCT was 63% (95% CI, 48–79%).

Eleven out of 29 patients (38%) with PR prior to transplantation achieved a CR as best response. In the subset of 22 patients who were already MRD-negative at alloHCT or became MRD-negative after alloHCT, 8 relapses were observed and 5 patients died without relapse. The 5-year RFS from first MRD-negative test was 35% (95% CI, 13–58%).

At last follow up, 19 patients were alive with a median follow-up time of 6 years (range, 1–8 years). Eleven patients were alive and MRD-negative at last assessment. One-year RFS was 62% (95% CI, 46–77%). Altogether 17 patients relapsed after HCT. Eleven patients died without relapse after alloHCT. Causes of death were GVHD-related with or without concomitant infection in 7 patients. Estimates for survival, RFS, NRM and relapse incidence and the impact of risk factors are provided in Table 1 and Fig. S1.

Patients who had experienced acute GVHD grades II–IV or chronic GVHD had a significantly lower risk of relapse, indicated by a hazard ratio of 0.2 (95% CI, 0.05–0.7, $p = 0.01$) for GVHD modelled as a time-dependent covariate in an extended Cox regression model. Among 11 patients without relapse after transplantation, nine patients (81%) had experienced chronic GVHD which had resolved completely in 5 patients (56%) at last follow-up.

Results for the whole cohort were mixed but showed significant differences for two major subgroups (see Fig. S2). Patients who were referred for alloHCT at advanced disease stages of $TP53_{mut/del}$ CLL had disappointing results. Their 5-year incidence of relapse was 51% (95% CI, 30–71%). Most of these patients had acquired $TP53_{mut/del}$ as a secondary event after one or more lines of chemoimmunotherapy. Good outcomes were observed among 13 patients who received alloHCT in first remission whose RFS at 5 years was 54% (95% CI, 33–89%) owing to a much lower risk of relapse. Notably, the best subgroup consisted of 10 patients who had received alemtuzumab with or without high-dose corticosteroids for remission induction and proceeded to alloHCT in first remission.

Although the sequence of alemtuzumab-based remission induction and alloHCT in first remission turned out to be most promising in this study, this treatment approach is outdated in the light of today's treatment options for

patients with $TP53_{mut/del}$ CLL. For example, in a phase II trial performed by the NIH, the overall response rate (ORR) of patients with $TP53_{mut/del}$ CLL on ibrutinib was 96% and treatment naive patients had a 5-year PFS of ~80% [9]. With a fixed-duration treatment with venetoclax and obinutuzumab, mostly elderly patients with $TP53_{mut/del}$ CLL and coexisting conditions achieved ORR rates of 85% and 2-year PFS was ~75% [1]. Owing to the more favourable risk-benefit ratio of both oral pathway-inhibitors compared to alloHCT, transplantation in first remission of $TP53_{mut/del}$ CLL is no longer recommended [10]. Current guidelines suggest that patients with $TP53_{mut/del}$ CLL who failed one pathway-inhibitor or who were intolerant to either BTKi or BCL2i should be referred to a transplant centre [10–12]. Our data indicate that remission induction with alemtuzumab prior to alloHCT should not be excluded for patients with relapsed/refractory $TP53_{mut/del}$ CLL who lack better options. Finally, in patients with relapsed $TP53_{mut/del}$ CLL, who failed on pathway-inhibitor treatment and have no access to new targeted drugs or CAR-T cells, conventional chemotherapy should be avoided and alloHCT should be considered.

Acknowledgements We wish to thank the patients and their families, the local data managers, and physicians and the staff at the EBMT Data Office in Leiden, who made this study possible.

Participating centers not acknowledged by coauthorship Belgium: Cliniques Universitaires St. Luc, Brussels (A. Ferrant); Czech Republic: Institute of Hematology and Blood Transfusion, Prague (A. Vitek); Finland: Helsinki University Central Hospital, Helsinki (R. Niittyvuopio), Central Hospital, Turku (M. Itala); France: Hopital La Miletrie, Poitiers (F. Guillhot); Germany: Charité, University Hospital Benjamin Franklin, Berlin (L. Uharek), University Hospital, Göttingen (B. Glass), AK St. Georg, Hamburg (N. Schmitz), University Hospital, Hannover (A. Ganser), Department of Medicine II, University Hospital, Kiel (M. Kneba), University Hospital, Münster (M. Stelljes), Deutsche Klinik für Diagnostik, Wiesbaden (R. Schwerdtfeger); Italy: Ospedale Maggiore di Milano, Milano (F. Onida), Istituto Nazionale dei Tumori (P. Corradini); Spain: Hospital St. Creu I St. Pau, Barcelona (R. Martino), Clinica Puerta de Hierro, Madrid (J.A. García-Marco), Hospital Clínico, Salamanca (D. Caballero), Hospital Universitario La Fe, Valencia (M.A. Sanz).

Funding Open Access funding enabled and organized by Projekt DEAL.

Compliance with ethical standards

Conflict of interest JS—consultancy honoraria from AstraZeneca, Janssen, Roche, Gilead, Abbvie, Sanofi, Molmed; lecture fees from AstraZeneca, Janssen, Roche, Gilead, Abbvie, Sanofi, Novartis; research support from Genzyme, Sanofi, GSK, Novartis, Abbvie. CPF—Speaker/consultancy honoraria and travel support from Janssen. SS—Honoraria for consultancy, Advisory board member, Speaker honoraria, Research grants, Travel support from AbbVie, Amgen, AstraZeneca, Celgene, Gilead, GSK, Hoffmann La-Roche, Janssen, Novartis. PD—consultancy for AbbVie, AstraZeneca, Gilead, Janssen, Novartis, Riemser, Roche; speakers bureau for

AbbVie, Gilead, Novartis, Riemsler, Roche; research support from Neovii and Riemsler. The remaining authors declared no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Fischer K, Al-Sawaf O, Bahlo J, Fink AM, Tandon M, Dixon M, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380:2225–36.
- O'Brien S, Furman RR, Coutre S, Flinn IW, Burger JA, Blum K, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. *Blood* 2018;131:1910–9.
- Sorror ML, Storer BE, Sandmaier BM, Maris M, Shizuru J, Maziarz R, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *J Clin Oncol*. 2008;26:4912–20.
- Brown JR, Kim HT, Armand P, Cutler C, Fisher DC, Ho V, et al. Long-term follow-up of reduced-intensity allogeneic stem cell transplantation for chronic lymphocytic leukemia: prognostic model to predict outcome. *Leukemia* 2013;27:362–9.
- Kramer I, Stilgenbauer S, Dietrich S, Bottcher S, Zeis M, Stadler M, et al. Allogeneic hematopoietic cell transplantation for high-risk CLL: 10-year follow-up of the GCLLSG CLL3X trial. *Blood* 2017;130:1477–80.
- van Gelder M, Ziagkos D, de Wreede L, van Biezen A, Dreger P, Gramatzki M, et al. Baseline characteristics predicting very good outcome of allogeneic hematopoietic cell transplantation in young patients with high cytogenetic risk chronic lymphocytic leukemia—a retrospective analysis from the Chronic Malignancies Working Party of the EBMT. *Clin Lymphoma Myeloma Leuk*. 2017;17:667–75 e2.
- Schetelig J, de Wreede LC, van Gelder M, Andersen NS, Moreno C, Vitek A, et al. Risk factors for treatment failure after allogeneic transplantation of patients with CLL: a report from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transpl*. 2017;52:552–60.
- Schetelig J, de Wreede LC, Andersen NS, Moreno C, van Gelder M, Vitek A, et al. Centre characteristics and procedure-related factors have an impact on outcomes of allogeneic transplantation for patients with CLL: a retrospective analysis from the European Society for Blood and Marrow Transplantation (EBMT). *Br J Haematol*. 2017;178:521–33.
- Ahn IE, Farooqui MZH, Tian X, Valdez J, Sun C, Soto S, et al. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. *Blood* 2018;131:2357–66.
- Dreger P, Ghia P, Schetelig J, van Gelder M, Kimby E, Michallet M, et al. High-risk chronic lymphocytic leukemia in the era of pathway inhibitors: integrating molecular and cellular therapies. *Blood* 2018;132:892–902.
- Stilgenbauer S, Eichhorst B, Schetelig J, Hillmen P, Seymour JF, Coutre S, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: results from the full population of a Phase II Pivotal trial. *J Clin Oncol*. 2018;36:1973–80.
- Hoffmann A, Dietrich S, Hain S, Rieger M, Hegenbart U, Sellner L, et al. Allogeneic transplantation in high-risk chronic lymphocytic leukemia: a single-center, intent-to-treat analysis. *Haematologica* 2019;104:e304–e6.