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Brief Article

# Refractory and 17p-deleted chronic lymphocytic leukemia: improving survival with pathway inhibitors and allogeneic stem cell transplantation

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A B S T R A C T

Refractory/early relapsed and 17p deletion/p53 mutation (del(17p)/TP53mut)-positive chronic lymphocytic leukemia (CLL) has been conventionally considered a high-risk disease, potentially eligible for treatment with allogeneic stem cell transplantation (alloSCT). In this multicenter retrospective analysis of 157 patients, we compared the outcomes of patients with high-risk CLL treated with alloSCT, a B-cell receptor pathway inhibitor (BCRi), and both. Seventy-one patients were treated with BCRis, 67 patients underwent reduced-intensity conditioning alloSCT, and 19 received alloSCT with a BCRi before and/or after transplantation. Inverse probability of treatment weighting analyses were performed to compare the alloSCT and no-alloSCT groups; in the 2 groups, 5-year OS, PFS, and cumulative incidence of nonrelapse mortality (NRM) and relapse were 40% versus 60% ($P = .096$), 34% versus 17% ($P = .638$), 28% versus 5% ($P = .016$), and 38% versus 83% ($P = .005$), respectively. Patients treated with alloSCT plus BCRi had a 3-year OS of 83%. The 3-year OS and NRM by year of alloSCT, including patients treated with BCRi, were 53% and 17% in 2000 to 2007, 55% and 30% in 2008 to 2012, and 72% and 18% in 2013 to 2018. In conclusion, the combination of pathway inhibitors and alloSCT is feasible and may further improve the outcome of high-risk CLL patients.



## INTRODUCTION

Chronic lymphocytic leukemia (CLL) is generally considered an indolent disease of the elderly, but more aggressive subtypes have been identified based on clinical and biological features [1]. In particular, patients who are refractory or early relapsing (R/R) after chemoimmunotherapy (CIT) and patients carrying a 17p deletion (del17p) and/or a p53 mutation (TP53mut) have shown poor survival, ranging from 12 to 24 months after CIT [2]. For these reasons, young patients have

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been conventionally considered good candidates for allogeneic stem cell transplantation (alloSCT), with the first recommendations formally defined in 2007 by the European Group for Blood and Marrow Transplantation (EBMT) [3]. Reduced-intensity conditioning (RIC) alloSCT has shown to be equally effective across all subgroups of patients with a plateau in survival curves, suggesting that the negative impact of del(17p)/TP53mut and/or refractoriness was abrogated by the graft-versus-leukemia (GVL) effect [4]. However, long-term follow-up of RIC alloSCT in CLL revealed late toxicities, such as chronic graft-versus-host disease (GVHD), infections, and secondary tumors [5].

The introduction of B cell receptor (BCR) and bcl-2 pathway inhibitors (PIs) has radically changed the therapeutic landscape for patients with CLL. The opportunity to have oral drugs devoid of significant toxicities decreased the number of alloSCT performed in CLL patients over the last few years, also because PIs showed high efficacy in del(17p)/TP53mut and R/R patients [6-9]. Indications for alloSCT in CLL are continuously evolving, and the question of whether PIs will replace transplantation or will be combined with it, is a matter of debate.

To explore this question, we performed a retrospective study in a population of young high-risk CLL patients to assess the impact of PIs on survival outcomes. Patients were selected based on criteria of eligibility for transplantation published in 2007 to identify high-risk patients. The more recent 2018 EBMT/European Research Initiative on CLL (ERIC) criteria that split R/R CLL into 2 categories were also applied: CLL high-risk 1 (HR1), comprising patients who failed CIT and harbor TP53 abnormalities but respond to a first PI, and CLL high-risk 2 (HR2), comprising patients who had failed both CIT and first PI, independent of TP53 status [10]. Our aim was to describe the evolving outcomes of high-risk CLL patients, performing a balanced comparison of the effect of different therapeutic strategies emerging from the advent of PIs on poor prognosis CLL patients.

## METHODS

Consecutive patients with R/R and/or del(17p)/TP53mut CLL were retrospectively identified from 11 Northern Italian referral centers. The study population was selected based on the following criteria: age <70 years; no significant comorbidity that would hamper the transplantation procedure; presence of de novo or acquired del(17p)/TP53mut CLL necessitating therapy; or relapse within 2 years after CIT or autologous stem cell transplantation (ASCT) or refractory to CIT (absence of response or relapse within 6 months from the end of CIT). Between November 2000 and February 2018, data on 157 patients were collected, including 71 treated with a BCR pathway inhibitor (BCRi) as a first PI without alloSCT (no-alloSCT group), 67 underwent alloSCT (alloSCT group), and 19 underwent alloSCT and received BCRi therapy before and/or after transplantation (BCRi-alloSCT group). In the no-alloSCT group, patients did not undergo transplantation because of donor unavailability or patient and/or physician decisions. Patients were also classified in terms of eligibility transplantation based on the 2018 EBMT/ERIC criteria [10].

The clinical protocol was approved by the Ethics Committee of the participating centers, and informed consent was obtained from all living patients.

### Statistical Analysis

The primary objectives of the study were progression-free survival (PFS) and overall survival (OS). The secondary objectives were nonrelapse mortality (NRM), crude cumulative incidence (CCI) of relapse, event-free survival (EFS) in the no-alloSCT group, and graft-versus-host disease- and relapse-free survival (GRFS) [11] in the alloSCT group. Survival and incidence times were started at the alloSCT and BCRi treatment start date in the alloSCT and no-alloSCT groups, respectively. Patients receiving BCRi before and/or after alloSCT (BCRi-alloSCT group) were analyzed separately, with the analysis starting from the date of transplantation. A comparison based on the year of transplantation was done, with different time periods defined on the evolution of eligibility criteria for alloSCT in CLL and the introduction of BCRi (2000 to 2007 versus 2008 to 2012 versus 2013 to 2018).

PFS was defined as the time to recurrence or death, whichever occurred first. OS was defined as the time to death from any cause. EFS was defined as the time to disease progression, treatment withdrawal due to toxicity, second-line treatment, or death, whichever occurred first. GVHD-free, relapse-free survival (GRFS) was defined as the time to grade III-IV acute GVHD or chronic GVHD necessitating systemic immunosuppressive treatment at any time, disease progression, or death from any cause. NRM was defined as the time to death without previous disease relapse. For all the endpoints, time was censored after a 3- and 5-year follow-up for living patients who were free from the relevant event. PFS, OS, EFS, and GRFS curves were estimated using the Kaplan-Meier method, and the curves were compared using the weighted log-rank test. The CCI of NRM and relapse were estimated in a competing-risk setting using cumulative incidence estimates, and the curves were compared using the weighted Gray test. To estimate the CCI of relapse, death without relapse was evaluated as a competing event. In the estimation of NRM, death not directly attributable to disease progression, and death attributable to disease progression were evaluated as competing events.

We compared the outcome of patients in the alloSCT and no-alloSCT groups by performing a balanced comparison using weighted Kaplan-Meier and incidence curves and weighted log-rank and Gray tests. We estimated a propensity score (PS) as a balancing score to account for the bias consistent with a nonrandom assignment of treatment (alloSCT or no-alloSCT) in the study groups [12]. This technique allowed us to mimic the random distribution of the variables compared between the study groups as can be achieved only in a randomized clinical trial, without the need to remove patients from the analysis. Treatment PS was estimated using a multivariable logistic model with binary response (alloSCT or no-alloSCT) and covariates, including age (continuous), del(17p)/TP53mut (yes, no, unknown), and number of chemotherapy lines ($\leq 2$, $>2$). Patient age was modeled as a continuous variable using 3-knot restricted cubic splines to obtain a flexible fit [13]. All other variables were modeled as categorical variables using dummy variables. We used the method of stabilized weights, which has been proposed as a more advantageous analog to one-to-one pair matching without replacement of the PS with a caliper to estimate the inverse probability of treatment weight (IPTW) [14]. Differences in median (numerical variables) and proportions (categorical variables) between baseline patient characteristics of the study groups were compared using the standardized mean difference (SMD) [15]. The SMD expresses the size of the difference between study groups relative to the variability observed in groups. An SMD $<.1$ was considered indicative of a very well-balanced distribution, an SMD $\geq .3$ was considered indicative of a relevant between-group imbalance, increasing with increasing SMD. The minimum SMD value is 0 (identical distributions) but its maximum is not limited to 1, so it cannot be interpreted as "percentage of imbalance". SMD was calculated before and after IPTW adjustment, when it is expected to be $<.3$ for the variables included in the multivariable logistic model used to estimate the PSs.

Statistical analyses were performed using SAS version 9.4 (TS1M3)(SAS Institute, Cary, NC) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Patient Characteristics

Patient characteristics in alloSCT and no-alloSCT groups are summarized in Table 1. In the alloSCT group, 65% of 49 tested patients were positive for del(17p)/TP53mut, and 75% of 36 evaluable patients had an unmutated immunoglobulin gene heavy chain variable region (IGHV). Thirteen patients had 11q deletion. Overall, according to the Barcelona/Brno prognostic model [16], 22 of 35 (63%) evaluable patients were at high risk, 10 were at intermediate risk, and 3 were at low risk. Of 32 patients with del17p/TP53MUT assessed, 4 underwent alloSCT after 1 line of chemotherapy, which was based on high-dose sequential chemotherapy, and the remaining 28 were treated for R/R disease. Transplantation was performed in 29 patients between 2000 and 2007, in 29 patients between 2008 and 2012, and in 9 patients between 2013 and 2018 and were included in the analysis by year of transplantation. The median (interquartile range extreme [IQRE]) time from diagnosis to alloSCT in these 3 groups was 59 months (IQRE, 25 to 96 months), 51 months (IQRE, 28 to 107 months), and 62 months (IQRE, 10 to 87 months), respectively (Supplementary Table 1). Patients who underwent transplantation before 2012 were more chemorefractory, had more progressive disease, and received stem cells more often from a sibling donor, either haploidentical or HLA-identical. Patients who underwent transplantation after 2012 more often did so while in complete or partial response after fewer than 3 lines of chemotherapy.

Seventy-one patients treated with BCRis without alloSCT were available for analysis starting in May 2013. The median

**Table 1**
Baseline Characteristics of 67 Allografted Patients and 71 Patients Treated with BCRis without AlloSCT

| Characteristic | AlloSCT Group | | BCRi Group | | SMD | |
|---|---|---|---|---|---|---|
| | Observed | IPTW Adjusted | Observed | IPTW Adjusted | Observed | IPTW Adjusted |
| Sex, n (%) | | | | | 0.125 | 0.134 |
| Male | 50 (74.6) | 27.8 (71.7) | 49 (69.0) | 30.6 (77.6) | | |
| Female | 17 (25.4) | 10.9 (28.3) | 22 (31.0) | 8.9 (22.4) | | |
| Age, yr, median (IQRE) | 56.0 (52.0-59.5) | 55 (52-59) | 61.0 (54.0-67.0) | 57.0 (48.0-60.0) | 0.473 | 0.006 |
| del17p/p53mut , n (%) | | | | | 0.877 | 0.105 |
| Yes | 32 (47.8) | 25.3 (65.3) | 52 (73.2) | 26.7 (67.6) | | |
| No | 17 (25.4) | 13.2 (34.2) | 19 (26.8) | 12.8 (32.4) | | |
| Unknown | 18 (26.9) | 0.2 (0.5) | 0 (0.0) | 0 (0.0) | | |
| IGHV mutated, n (%) | | | | | 0.786 | 0.357 |
| Yes | 9 (13.4) | 6.5 (16.7) | 9 (12.7) | 5.8 (14.6) | | |
| No | 27 (40.3) | 20.7 (53.5) | 52 (73.2) | 27.3 (69.2) | | |
| Unknown | 31 (46.3) | 11.5 (29.8) | 10 (14.1) | 6.4 (16.2) | | |
| Line number, n (%) | | | | | 0.288 | 0.002 |
| ≤2 | 33 (49.3) | 24.1 (62.4) | 45 (63.4) | 24.6 (62.2) | | |
| >2 | 34 (50.7) | 14.6 (37.6) | 26 (36.6) | 14.9 (37.8) | | |
| Binet stage at relapse, n (%) | | | | | 0.723 | 0.801 |
| A | 3 (4.5) | 3.0 (7.8) | 3 (4.2) | 2.5 (6.4) | | |
| B | 34 (50.7) | 20.9 (53.9) | 24 (33.8) | 12.3 (31.1) | | |
| C | 18 (26.9) | 7.7 (19.9) | 41 (57.7) | 21.8 (55.2) | | |
| Unknown | 12 (17.9) | 7.1 (18.4) | 3 (4.2) | 2.9 (7.3) | | |
| Chemorefractory/early relapse, n (%) | | | | | 0.793 | 1.042 |
| Yes | 32 (47.8) | 15.1 (39.0) | 41 (57.7) | 24.2 (61.2) | | |
| No | 35 (52.2) | 23.6 (61.0) | 18 (24.4) | 8.2 (20.8) | | |
| Not applicable | 0 (0) | 0 (0) | 12 (16.9) | 7.1 (18.0) | | |
| Bulky, n (%) | | | | | 0.838 | 1.014 |
| ≤5 cm | 49 (73.1) | 31.6 (81.8) | 32 (45.1) | 17.1 (43.2) | | |
| >5 cm | 10 (14.9) | 3.4 (8.7) | 36 (50.7) | 19.6 (49.5) | | |
| Unknown | 8 (11.9) | 3.7 (9.6) | 3 (4.2) | 2.9 (7.3) | | |
| Disease response at transplantation, n (%) | | | | | – | – |
| Complete response | 20 (29.9) | 14.3 (36.9) | – | – | | |
| Partial response | 25 (37.3) | 14.1 (36.5) | – | – | | |
| Stable/progressive disease | 22 (32.8) | 10.3 (26.6) | – | – | | |
| Donor, n (%) | | | | | – | – |
| Identical sibling | 28 (41.8) | 13.7 (35.5) | – | – | | |
| Matched unrelated | 32 (47.8) | 20.5 (53.0) | – | – | | |
| Haploidentical | 7 (10.4) | 4.5 (11.6) | – | – | | |

time from diagnosis to the start of BCRi therapy was 77 months (IQRE, 37 to 124 months). Forty-six of these patients (65%) received ibrutinib, and they remained longer on therapy than the other 31 patients, who were treated with idelalisib (data not shown). The results of del(17p)/TP53mut were available for all patients, showing positivity in 73% of them, whereas unmutated IGHV was observed in 85% of the 61 evaluable patients. Fourteen patients had 11q deletion. Overall, according to the Barcelona/Brno prognostic model, 45 out of 61 evaluable patients (74%) were at high risk, 13 were at intermediate risk, and 3 were at low risk. Fifty-four patients (76%) experienced BCRi withdrawal due to disease progression (n = 34) or toxicity (n = 20). Forty-five patients (63%) received a second-line treatment after BCRi; 12 patients switched to another BCRi, 19 patients received venetoclax, 7 received a second BCRi followed by venetoclax, 6 patients switched to a second PI not specified, and 1 patient received chemotherapy. Fourteen of 52 del17p/TP53MUT patients had de novo del17p, whereas 38 patients were R/R and could belong to the HR1 risk group. Of 57 patients treated with BCRis for R/R disease, 44 relapsed and could potentially identify the HR2 group.

The median follow-up was 108 months (IQRE, 94 to 149 months) in the alloSCT group and 55 months (IQRE, 45 to 66 months) in the no-alloSCT group. After IPTW adjustment, age, del17p/TP53MUT, and number of previous chemotherapy lines were balanced among the study groups (Table 1).

Nineteen patients received both alloSCT and BCRi and were included in the BCRi-alloSCT group (Table 2). Transplantation was performed in 1 patient between 2000 and 2007, in 4 patients between 2008 and 2012, and in 14 patients between 2013 and 2018 (Supplementary Table 2). Seven patients received BCRi as a bridge to alloSCT, 7 after transplantation to treat relapse and 5 before and after alloSCT. Twelve out of 19 patients (63%) were positive for del(17p)/TP53mut, and 82% of 17 evaluable patients had unmutated IGHV. All patients with del17p/TP53MUT were treated for R/R disease. Seventy-nine percent of the patients were chemorefractory. Four patients had 11q deletion. Overall, according to the Barcelona/Brno prognostic model, 10 of 17 (59%) evaluable patients were at high risk, and 7 were at intermediate risk. The median duration of follow-up in the BCRi-alloSCT group was 53 months (IQRE, 27 to 130 months).

**Table 2**
Baseline Characteristics of 19 Allografted Patients Treated with BCRis before and/or after AlloSCT

| Characteristic | Value |
|---|---|
| Sex, n (%) | |
| Male | 16 (84.2) |
| Female | 3 (15.8) |
| Age, yr, median (IQRE) | 53 (49.5-59.0) |
| del17p/p53mut, n (%) | |
| Yes | 12 (63.2) |
| No | 7 (36.8) |
| IGHV mutated, n (%) | |
| Yes | 3 (15.8) |
| No | 14 (73.7) |
| Unknown | 2 (10.5) |
| Line number, n (%) | |
| ≤2 | 8 (42.1) |
| >2 | 11 (57.9) |
| Binet stage at relapse, n (%) | |
| B | 5 (26.3) |
| C | 11 (57.9) |
| Unknown | 3 (15.8) |
| Chemorefractory/early relapse, n (%) | |
| Yes | 15 (78.9) |
| No | 4 (21.1) |
| Bulky, n (%) | |
| ≤5 cm | 13 (68.4) |
| >5 cm | 6 (31.6) |
| Disease response at transplantation, n (%) | |
| Complete response | 5 (26.3) |
| Partial response | 10 (52.6) |
| Stable/progressive disease | 4 (21.1) |
| Donor, n (%) | |
| Identical sibling | 6 (31.6) |
| Matched unrelated | 12 (63.2) |
| Haploidentical | 1 (5.3) |

Twelve out of 19 patients (63%) received a BCRi before alloSCT, including 6 patients with ibrutinib, 4 patients with ibrutinib followed by venetoclax, 1 patient with rituximab-venetoclax followed by ibrutinib, and 1 patient with ibrutinib, followed by idelalisib and venetoclax. All these patients had previously received chemotherapy. After alloSCT, 9 patients received ibrutinib due to relapse, of whom 2 also received venetoclax; 1 received ibrutinib, idelalisib and venetoclax; and 1 received only venetoclax after alloSCT. Based on 2018 EBMT/ERIC criteria, 5 of 12 patients treated with BCRis before alloSCT belonged to the HR1 group, 5 belonged to the HR2 group, and 2 were not classified (1 patient who received ibrutinib followed by alloSCT without having del(17p)/TP53mut and 1 patient who received 3 PIs before alloSCT). The stem cell source was an HLA-identical sibling donor in 3 patients, a MUD donor in 8 patients, and a haploidentical donor in 1 patient. Disease stage before alloSCT was as follows: CR in 5 patients, PR in 6 patients, and PD in 1 patient. The median duration of follow-up in this subgroup of patients was 27 months (IQRE, 19 to 41 months).

### *Survival Outcomes in AlloSCT and No-AlloSCT Recipients*

*AlloSCT group*

In the alloSCT group, the 3-year and 5-year OS, PFS, NRM, and CCI of relapse were 52%/38%, 37%/31%, 24%/28%, and 39%/40%, respectively. The CCI of extensive chronic GVHD was 22% at 3 and 5 years. The 3- and 5-year GRFS rates were 22% and 19%, respectively. Thirty-two patients who were R/R and del (17p)/TP53mut had 3- and 5-year OS, PFS, NRM, and CCI of relapse of 50%/28%, 28%/19%, 25%/31%, and 47%/50%, respectively. In 27 patients without IGHV mutation had a 3- and 5-year OS, PFS, NRM, and CCI of relapse of 56%/41%, 37%/33%, 18%/22%, and 44%/44%, respectively, not significantly different compared with results obtained in IGHV-mutated patients except for NRM (11% at both 3 and 5 years).

Patients were analyzed based on year of transplantation (excluding those patients receiving PI before and/or after alloSCT). In patients undergoing alloSCT between 2000 and 2007, between 2008 and 2012, and after 2012, the 3-year OS, PFS, and CCI of NRM and relapse were 52%/48%/67%, 31%/35%/67%, 17%/34%/11%, and 52%/31%/22%, respectively. The 5-year OS, PFS, and CCI of NRM and relapse were 41%/31%/53%, 24%/31%/53%, 21%/38%/24%, and 55%/31%/22%, respectively.

The 3-year CCI of extensive chronic GVHD was 17% in 2000 to 2007, 28% in 2008 to 2012, and 22% in 2013 to 2018. The 3-year GRFS in the 3 time periods was 18%, 19%, and 47%, respectively.

*No-alloSCT group*

In the no-alloSCT group, the 3- and 5-year OS, PFS, and CCI of NRM and relapse were 71%/55%, 47%/13%, 9%/13%, and 50%/83%, respectively. Three and 5-year EFS for all patients were 43% and 9%, respectively. The 3-year EFS in ibrutinib-treated patients was 58%. In 38 patients who were R/R and del(17p)/TP53mut, the 3- and 5-year OS, PFS, and CCI of NRM and relapse of 61%/45%, 47%/10%, 13%/13%, and 47%/85%, respectively. In the 52 patients without IGHV mutation, the 3- and 5-year OS, PFS, and CCI of NRM and relapse were 67%/48%, 46%/11%, 10%/15%, and 52%/85%, respectively, and were not significantly different than results obtained in IGHV-mutated patients. The 3-year OS of 45 patients who started a second BCRi was 41%.

*Propensity score results in the alloSCT and no-alloSCT groups*

The IPTW-weighted curves of the alloSCT and no-alloSCT groups had a 3- and 5-year OS, PFS, and CCI of NRM and relapse of 58%/40%, 39%/34%, 24%/28%, 37%/38% respectively for the alloSCT group and 73%/60% ($P$= .097), 43%/17% ($P$= .638), 4%/5% ($P$= .016), and 54%/83% ($P$= .005), respectively, for the no-alloSCT group (Figure 1).

### *AlloSCT Combined with BCRi*

The 3-year and 5-year OS of patients who received BCRi either before and/or after alloSCT was 83% and 74%, respectively (Figure 2A). The analysis was then limited to 12 patients who received BCRi before alloSCT. Two-year OS, PFS, and CCI of NRM and relapse were 83%, 47%, 17%, and 37% (Figure 2B). At the last follow-up, 3 patients had died of progressive disease and 3 patients had died of NRM (1 from GVHD and 2 from infection). Three of 12 patients experienced grade II-IV acute GVHD; 2 of them received ibrutinib before alloSCT and 1 received ibrutinib followed by venetoclax. Four of 12 patients had extensive chronic GVHD, 1 during post-alloSCT venetoclax therapy. At the time of analysis, among the 5 HR1 patients, 4 were alive, 2 were receiving therapy because of relapse at the last follow-up, and 1 had died of GVHD, and among the 5 HR2 patients, 4 were alive, 2 were receiving therapy, and 1 had died of infection after undergoing haploidentical transplantation.

The 3-year and 5-year OS by year of alloSCT, including patients who did and did not receive PIs, were 53%/43% in

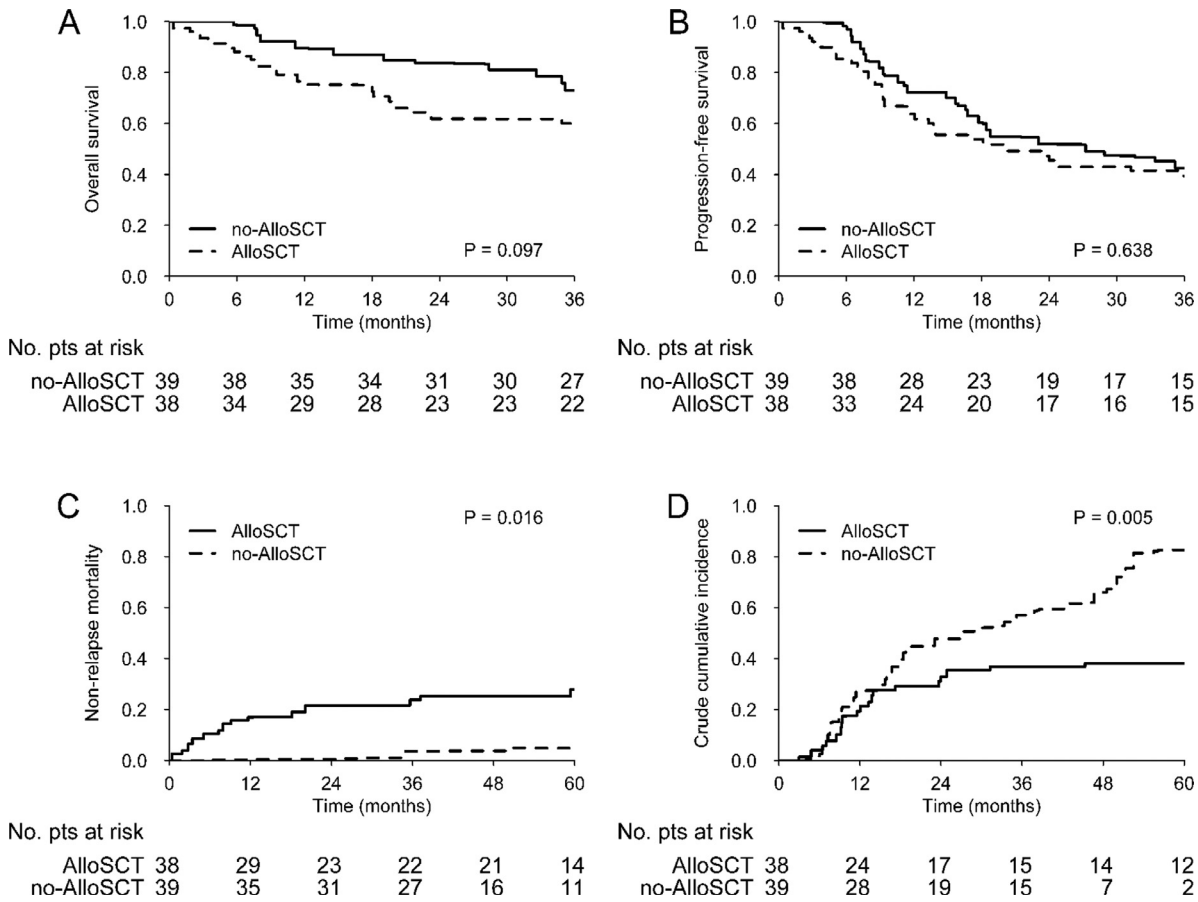


**Figure 1.** Inverse-probability treatment-weighted OS (A) and PFS (B) curves, and CCI of NRM (C) and relapse (D) according to alloSCT.

2000 to 2007, 55%/39% in 2008 to 2012, and 72%/56% in 2013 to 2018 (Figure 3A). The 3-year and 5-year NRM by year of alloSCT were 17%/20% in 2000 to 2007, 30%/33% in 2008 to 2012, and 18%/28% in 2013 to 2018 (Figure 3B).

## DISCUSSION

This retrospective analysis in high-risk CLL patients evaluated the role of alloSCT in the PI era. Our patients were selected based on the EBMT criteria published in 2007 identifying a high-risk CLL population, at least in the "pre-BCRi" era. In fact, most of the patients were del(17p)-positive and chemorefractory. Survival curves of the BCRi group are similar to those reported in previously published studies of ibrutinib in del(17p)/TP53mut R/R CLL patients [17,18]. The high incidence of relapse and low PFS at 5 years might be related to the fact that 25 of 71 patients were treated with idelalisib, which was less well tolerated. With regard to allografted patients, the 3-year OS probability of 52% is in agreement with follow-up data published by the EBMT group [5,19].

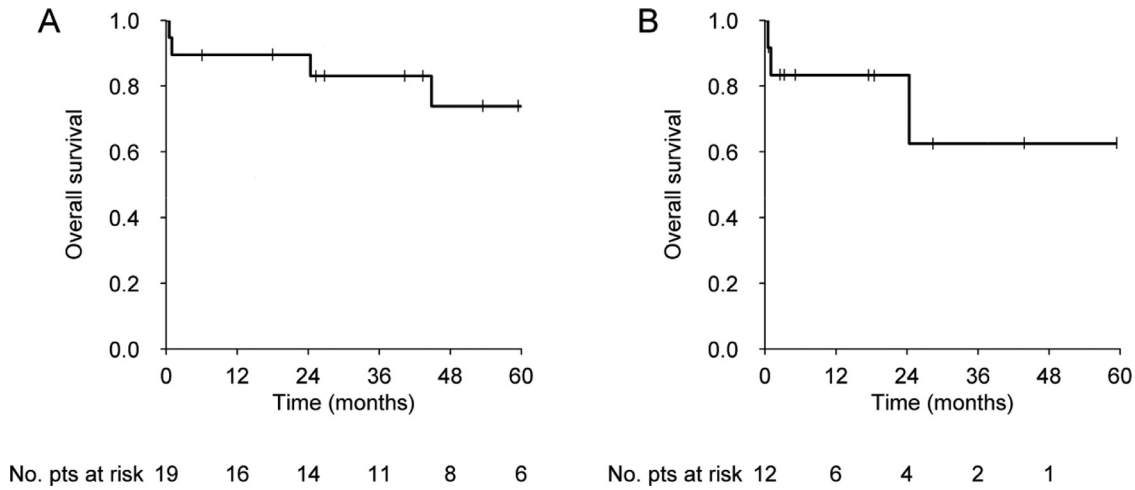


**Figure 2.** OS curve of patients who underwent alloSCT combined with pre- and/or post-BCRi (A) and OS curve of the subgroup of patients who received BCRi pre-alloSCT (B).

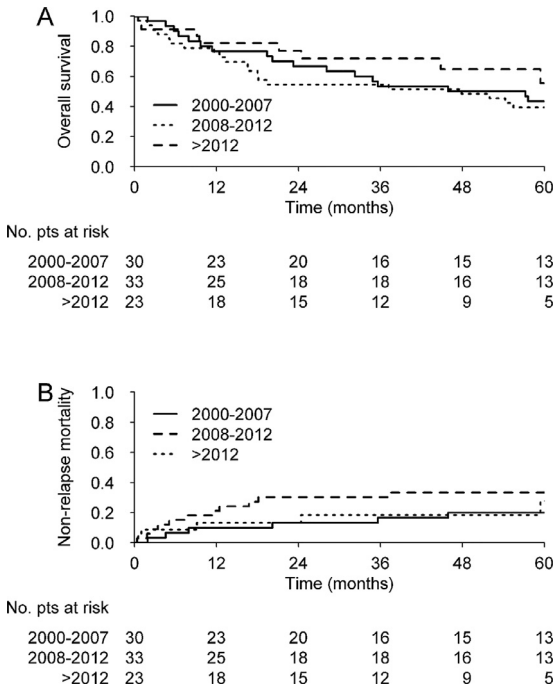


**Figure 3.** OS (A) and NRM (B) in patients who underwent alloSCT between 2000 and 2007, between 2008 and 2012, and after 2012, including patients treated with BCRis.

Even though patients who received only BCRis were selected in the more recent years of the study, we were able to collect data for a median follow-up of almost 5 years, which can be considered an informative span of time in del(17p)/TP53mut R/R CLL [19-21]. In the weighted analysis at 5 years, we observed significant differences in NRM in favor of BCRi therapy and in the CCI of relapse in favor of alloSCT. On the other hand, we did not find any statistical difference in OS and PFS between patients treated with BCRis and those who could undergo an alloSCT. It is important to note that all consecutive allografted patients were included, independent of donor type and disease status. In particular, we included 12% of weighted patients with a haploidentical donor and 27% of patients with stable and progressive disease. The cumulative incidence of relapse and NRM after alloSCT reached a plateau after 2 years, in accordance with previously published data [19-21]. Moreover, after 2012, the NRM decreased, likely due to improved supportive care measures and better patient selection. On the other hand, despite a shorter follow-up, the incidence of relapse of patients treated with BCRi did not indicate a plateau. The fact that BCRi therapy was not able to induce durable CR implies the need for continuous treatment of the patients, the potential risk of selecting more aggressive tumor clones, and/or the onset of late side effects [22]. In addition, as known, patients who failed ibrutinib and venetoclax had very poor outcomes, and therapies to achieve remission before alloSCT are limited in these patients [23-25]. We chose 2 parameters that reflect the impact of toxicity and the need for continuous medication. For the alloSCT group, we chose GRFS, which is an important endpoint of transplantation studies and identifies patients who survived without CLL and GVHD; therefore, those who may have a good quality of life with no long-term medication. For patients who received BCRi, we estimated EFS, which assesses patients without CLL progression or toxicities causing drug withdrawal or therapy change. At 3 and 5 years, GRFS was 22%/19% and EFS probability was 43%/9%, respectively, with no evident plateau in the EFS curve.

Data are accumulating on the combined approach of alloSCT and BCRi [26-29]. Ryan et al [28] first described the feasibility of ibrutinib in 27 CLL patients who relapsed after alloSCT. Most of the patients experienced a response, which was complete in 7 patients without GVHD. Moreover, 4 patients achieved minimal residual disease negativity, which persisted even after ibrutinib withdrawal. Considering that most of the responses after ibrutinib in R/R patients were partial and transient after therapy withdrawal, that study suggested a possible additive effect of alloSCT and BCRis. More recently, the EBMT registry data demonstrated the feasibility of treating patients with BCRis before and after alloSCT [28,29]. Finally, a multicenter phase 2 study reported a response rate of 67% in chronic GVHD patients treated with ibrutinib, suggesting a dual role of this BCRi in the context of alloSCT [30].

To assess the impact of a combined alloSCT and BCRi approach, we selected 19 allografted patients who were treated with BCRis as a bridge to alloSCT and/or for relapse and analyzed outcomes in terms of OS. The 5-year OS probability of 74% may suggest a role for PIs in increasing survival of allografted patients. In addition, the inclusion of these patients in the analysis by year of transplantation revealed a further improvement in survival after 2012. The fact that alloSCT performed in more recent years was associated with improved outcomes likely reflects improvements in transplantation procedures and patient selection, but with a contribution of the combined strategy with BCRis as well. These data, combined with the continuous relapse seen in these high-risk patients treated without alloSCT, justifies the ongoing effort to pursue alloSCT in appropriate patients together with PIs before and after alloSCT.

The latest recommendation for alloSCT in CLL patients published in 2014 and updated in 2018 suggests performing alloSCT in R/R patients with del(17p)/TP53mut who exhibit a response after treatment with PIs [10]. This is supported by data showing a median PFS of 19 months in patients with R/R disease progressing after ibrutinib and 24 months in patients with del(17p) who did not achieve minimal residual disease negativity after venetoclax [31,32]. To reduce NRM, patients should be age <65 years, without comorbidities, and with a well-matched donor. Recently, Dreger et al [33] published an intention-to-treat analysis based on the EBMT/ERIC criteria showing no survival disadvantage for patients meeting the transplantation eligibility criteria. In particular, 2-year PFS and OS were 68% and 95% for the HR1 group and 56% and 65% for the HR2 group [33]. Unfortunately, in our study, only 12 patients received PIs before alloSCT, making the analysis based on the HR1 and HR2 categories infeasible. Overall, these patients had a 2-year PFS and OS of 47% and 83%, respectively, including patients treated with more than 2 PIs before alloSCT and with alternative donors. The available duration of follow-up does not allow for definitive conclusions on the long-term outcome.

We acknowledge the limitations of this study owing to its retrospective nature. Our patients likely do not reflect those considered for transplantation today, who would be less chemotherapy-treated and more inhibitor-treated. Venetoclax has been used in most BCRi-treated patients after disease progression and likely will further modify the approach to alloSCT, because the bcl-2 inhibitor is able to produce complete and durable responses. Finally, new perspectives have been opened by chimeric antigen receptor T cells for immunotherapy in CLL,

which may provide an alternative to alloSCT in the future [34]. Based on our results, we can conclude that (1) although BCRis offer a less toxic therapeutic approach, high-risk CLL patients experience a continuous pattern of relapse; (2) alloSCT offers long-term disease control in at least one-third of transplant recipient, but the advantage is offset by a high NRM; (3) as supported by recent results, a combined strategy of PI pre- and post-alloSCT and better selection of patients could be more appropriate to increase long-term survival.

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