Bone Marrow Transplantation (2017) 52, 372–380

www.nature.com/bmt

ORIGINAL ARTICLE

Long-term survival of patients with CLL after allogeneic transplantation: a report from the European Society for Blood and Marrow Transplantation

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Even with the availability of targeted drugs, allogeneic hematopoietic cell transplantation (allo-HCT) is the only therapy with curative potential for patients with CLL. Cure can be assessed by comparing long-term survival of patients to the matched general population. Using data from 2589 patients who received allo-HCT between 2000 and 2010, we used landmark analyses and methods from relative survival analysis to calculate excess mortality compared with an age-, sex- and calendar year-matched general population. Estimated event-free survival, overall survival and non-relapse mortality (NRM) 10 years after allo-HCT were 28% (95% confidence interval (CI), 25–31), 35% (95% CI, 32–38) and 40% (95% CI, 37–42), respectively. Patients who passed the 5-year landmark event-free survival ($N = 394$) had a 79% probability (95% CI, 73–85) of surviving the subsequent 5 years without an event. Relapse and NRM contributed equally to treatment failure. Five-year mortality for 45- and 65-year-old reference patients who were event-free at the 5-year landmark was 8% and 47% compared with 3% and 14% in the matched general population, respectively. The prospect of long-term disease-free survival remains an argument to consider allo-HCT for young patients with high-risk CLL, and programs to understand and prevent late causes of failure for long-term survivors are warranted, especially for older patients.

Bone Marrow Transplantation (2017) **52,** 372–380; doi:10.1038/bmt.2016.282; published online 12 December 2016

INTRODUCTION

After purine analogs (PAs) were introduced into the treatment of patients with CLL, patients with early relapse or refractory disease after PA-based chemoimmunotherapy were considered high-risk patients. Further high-risk patients are characterized by relapsed CLL harboring del(17p) or *TP53* mutations. In recent years, three new drugs received approval for the treatment of CLL: the Bruton's kinase inhibitor, Ibrutinib, the PI3 kinase inhibitor, Idelalisib and the BCL2 inhibitor, Venetoclax.[1,2] The three drugs have demonstrated significant activity in patients with high-risk CLL and are rather well tolerated, although disease control is transient. The estimated PFS in patients with relapsed or refractory CLL on Ibrutinib was 69% (95% confidence interval (CI), 58–78) at 30 months from the start of treatment. Yet, high-risk genetic abnormalities retain their poor prognostic impact in the context of treatment with Ibrutinib, and PFS of patients with del(17p) at 30 months was only 48% (95% CI, 29–65).[3] On Venetoclax, 72% of patients with del(17p) were in PFS at 12 months.[1]

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is the only treatment to date with curative potential in patients with high-risk CLL. Clearance of minimal residual disease (MRD) by graft-versus-leukemia effects has been described in several independent studies of patients.[4,5] This observation has been interpreted as eradication of the disease. However, cohorts of patients who support this concept of cure by allogeneic transplantation are relatively small.[6–8]

As the median age at first diagnosis of CLL is ~70 years, only a small minority of patients have relapsed/refractory CLL at an age

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Received 18 April 2016; revised 29 July 2016; accepted 2 August 2016; published online 12 December 2016

and in a physical condition that allows allo-HCT to be considered. With the availability of kinase inhibitors and BCL2 inhibitors, decision-making for patients with high-risk CLL who are eligible for allo-HCT has become a challenging task. Patients and physicians must weigh up risks and benefits of allo-HCT compared with well-tolerated oral drugs with the capacity to maintain disease control for a few years.[9,10] Information on combination therapies, cross-resistance of Ibrutinib and Idelalisib and salvage options is just emerging.[11,12] In parallel, second-generation kinase inhibitors are being developed and show very promising results in phase II trials.[13] In this context, it is important to provide information on the curative potential of allo-HCT. Registry data of a large cohort can be used to estimate long-term outcomes. Since cure cannot be assessed on the individual level, excess mortality in long-term survivors compared with the general population can be used as a surrogate marker for cure. Additionally, long-term survivors themselves and their physicians may wish to know of the prospect of cure in relation to certain landmarks that have been passed without relapse or progression.

Here, we report on results from the analysis of long-term survival outcomes and the estimation of excess mortality from a large registry cohort of patients with CLL who received allo-HCT. This information is instrumental for better patient information and improved care for long-term survivors.

MATERIALS AND METHODS

For this study, data were extracted from the registry of the European Society for Blood and Marrow Transplantation. All patients who received a first allo-HCT for CLL between January 2000 and December 2010 were included, with the exception of patients with Richter's transformation or with syngeneic donors.

The primary end point was overall survival (OS), defined as time since either allo-HCT or landmark until death with surviving patients being censored at the time of last follow-up. Landmark time-points were set at 2 and 5 years after allo-HCT. Secondary end points were event-free survival (EFS), cumulative incidence of relapse/progression (CIR) and non-relapse mortality (NRM), all measured either from allo-HCT or from landmark. EFS was defined as time to death or relapse/disease progression (whichever occurred first), with surviving patients being censored at the last time-point reported disease-free. Relapse/progression and NRM were analyzed together in a competing risks framework.[14] At each landmark time-point, the event-free (EF) population consisted of all patients alive without relapse/progression before the landmark.

Next, we compared the mortality of the CLL patients to that of the general population by means of methods from relative survival, thereby assessing which proportion of mortality after allo-HCT could be attributed to CLL and its treatment, and which to background mortality.[15,16] First, the survival outcomes of the landmark populations were analyzed for men and women separately in comparison with the expected survival of a synthetic cohort of the general population in which each patient was matched to an artificial control with the same sex, country and age in the year of allo-HCT. Population tables from the Human Mortality Database were used (www.humanmortality.de). Patients originating from countries for which no mortality data was available through this source were matched to German controls (53 patients in the whole cohort, 16 in the 2-year landmark population). We then studied the impact of age, sex and year of allo-HCT on the excess hazard, defined as the difference between the observed hazard of the CLL patients and the hazard of the matched general population, by means of an additive Cox model for relative survival. Model-based OS estimates with different starting times were always illustrated for the same two reference patient groups: German men, transplanted in 2000 at ages 45 and 65 years. They were chosen because of the distribution of sex and country in the data set. Finally, we assessed the contribution of death with and without prior relapse/progression to all reported deaths in consecutive time intervals since HCT for different age categories, by estimating the relative hazard.[17]

All analyses were performed in SPSS 21 and R 3.1.0 (Armonk, NY, USA), packages 'survival', 'cmprsk', 'relsurv' and 'prodlim'.

RESULTS

Patient characteristics

Data from 2589 patients were analyzed. Patient characteristics are shown in Table 1. At allo-HCT, patients were aged between 12 and 74 years, with a median age of 55 years. The majority of patients (74%) were male. The remission status of patients at the time of transplantation was reported as 16% in CR, 50% in PR and 34% with stable or progressive disease. Fifty-one percent of the patients had an HLA-identical sibling donor. Seventy-seven percent of patients had received reduced-intensity conditioning. The median follow-up time since allo-HCT for patients alive at last follow-up was 3.3 years. The number of patients still under follow-up at the 2- and 5-year landmarks is shown in Figure 1.

Outcomes for the whole cohort of patients

For the whole cohort of patients, OS, EFS, CIR and NRM since allo-HCT are shown in Table 2 and Figure 2. OS decreased from 62% (95% CI, 60–64) at 2 years to 45% (95% CI, 43–48) at 5 years and to 35% (95% CI, 32–38) at 10 years after allo-HCT. The probability of EFS at 2 years was 49% (95% CI, 47–52) and decreased to 28% (95% CI, 25–31) at 10 years. For this registry cohort, NRM was reported as the major cause of treatment failure. The NRM probability was 30% (95% CI, 28–32) at 2 years and 36% (95% CI, 34–38) at 5 years after allo-HCT. Cumulative incidence of relapse was 21% (95% CI, 19–22) at 2 years and 32% (95% CI, 30–35) at 10 years after allo-HCT. The latest relapse in our data was reported as 9 years after allo-HCT. The oldest patient alive was 78 years old at last follow-up.

Outcomes for the landmark populations at 2 and 5 years

OS, EFS, CIR and NRM for patients who passed the 2- and 5-year landmarks after allo-HCT without having experienced relapse or progression are shown in Table 3. In patients who passed the 2-year landmark event-free, relapse/progression and NRM continued to occur. The cumulative incidence of relapse at 8 years after the landmark was 24% (95% CI, 20–28) and NRM was 20% (95% CI, 16–24). The probability of being alive 10 years after allo-HCT (8 years after the landmark) was 65% (95% CI, 60–70). For event-free patients beyond the 5-year landmark, CIR in the next 5 years was 11% (95% CI, 7–16) and NRM was 10% (95% CI, 5–15). The probability of being alive 10 years after allo-HCT was 83% (95% CI, 77–90).

Excess mortality

For male patients who were event-free at the 2-year landmark, 1-year mortality of 8% contrasts with 1% in the matched general population ($P < 0.001$ for a comparison over time). At 10 years after allo-HCT, survival was 63% compared with 92% in the matched general population. One-year mortality for women in the 2-year landmark population was 7% for patients compared with 0.3% in the general population. Survival was 70% at 10 years after allo-HCT compared with 96% in the matched general population, respectively (see Figure 3a).

The Cox model for the excess hazard showed that sex had no impact on the excess hazard (hazard ratio (HR) 1.0 for women versus men, $P = 0.8$), whereas increasing age had a large and significant impact (HR 1.4 for an age difference of 10 years at allo-HCT, $P < 0.001$) and transplantation in more recent years had a slightly adverse impact (HR 1.3 for HCTs performed 5 years apart, $P = 0.1$). The model-based estimate of 1-year mortality of 4% for a man aged 45 years at allo-HCT who passed the 2-year landmark contrasts with 0.4% in the matched general population. In a man aged 65 years at allo-HCT, the corresponding numbers are 9% in 1-year mortality compared with 2% in the matched general

Table 1. Patient characteristics

Parameter	*All patients (%)*	*2-year EF LM population (%)*	*5-year EF LM population (%)*
		Total	
	N = *2589*	N = *1023*	N = *394*
Patient sex			
Male	74	72	73
Female	26	28	27
Age at allo-HCT			
Median (range) (years)	55 (12–74)	54 (12–74)	52 (23–69)
⩽45 years (%)	14	16	20
45–55 years	39	42	43
55–65 years	42	38	34
>65 years	6	4	3
Year of allo-HCT			
⩽2001	9	10	19
2002–2003	14	14	24
2004–2005	16	20	28
2006–2007	21	22	27
2008–2009	26	24	2
2010	14	10	0
Patient nationality			
Belgium	4	3	3
Czech Republic	5	4	4
France	14	16	16
Germany	25	21	21
Great Britain	12	12	11
Italy	11	12	14
Netherlands	6	7	7
Spain	7	6	6
Remaining countries[a]	18	19	19
Remission status at allo-HCT (N = *2439, 94%*)			
CR	16	21	19
PR	50	53	51
Stable/progress	34	27	30
Interval diagnosis CLL-allo-HCT			
Median (range) (months)	55 (2–415)	51 (2–258)	49 (2–258)
⩽4 years	44	47	48
4–8 years	36	35	37
>8 years	20	18	15
Karnofsky status (N = *1424, 55%*)			
90–100%	77	85	84
70–80%	22	14	15
⩽60%	1	1	1
Previous auto-HCT			
No	89	89	89
Yes, >2 years before	9	9	10
Yes, ⩽2 years before	2	2	1
Donor match			
HLA-identical sibling	51	58	66
Other donor	49	42	34
Patient–donor sex constellation			
Male–male	48	47	48
Male–female	26	25	24
Female–male	15	16	15
Female–female	11	13	13
Conditioning			
Reduced intensity	77	79	76
Myeloablative	23	21	24
Source of graft			
Bone marrow	9	9	10
Peripheral blood	89	89	89
Cord blood	2	2	1
Follow-up for patients alive at last follow-up			
Median (range) (years)	3 (0–13)	5 (2–13)	7 (5–13)

Abbreviations: allo-HCT = allogeneic hematopoietic stem cell transplantation; EF = event-free population; LM = landmark. Numbers and percentages provided in the first column indicate number of patients with data for this variable in the full data set, if <95% of data available. [a]Countries contributing <100 patients to the study.

Figure 1. Analysis populations. The number of patients in follow-up at different time-points after allo-HCT. *OS population*: All patients alive and in follow-up at the landmark; *EF population*: All patients in the OS population without relapse/progression before the landmark.

population (Figure 3b, compared with Supplementary Figure S2 for women).

Next, outcomes from the 5-year landmark were investigated. The 5-year mortality of the matched general population was 5% compared with 17% in the landmark population ($P < 0.001$) (Table 3). Male patients who were event-free at the 5-year landmark had a survival of 82% in the next 5 years in contrast with 95% in the matched general population. Five-year survival for the

Table 2. Overall and event-free survival, cumulative incidences of relapse/progression and non-relapse mortality for patients with CLL at 1, 2, 5 and 10 years after allo-HCT

Time from allo-HCT	*Overall survival (%) (95% CI)*	*Event-free survival (%) (95% CI)*	*Incidence of relapse/progression (%) (95% CI)*	*Non-relapse mortality (%) (95% CI)*
1 year	71 (69–73)	62 (60–64)	14 (13–15)	24 (23–26)
2 years	62 (60–64)	49 (47–52)	21 (19–22)	30 (28–32)
5 years	45 (43–48)	35 (33–37)	29 (27–30)	36 (34–38)
10 years	35 (32–38)	28 (25–31)	32 (30–35)	40 (37–42)

Abbreviations: allo-HCT = allogeneic hematopoietic stem cell transplantation; CI = confidence interval.

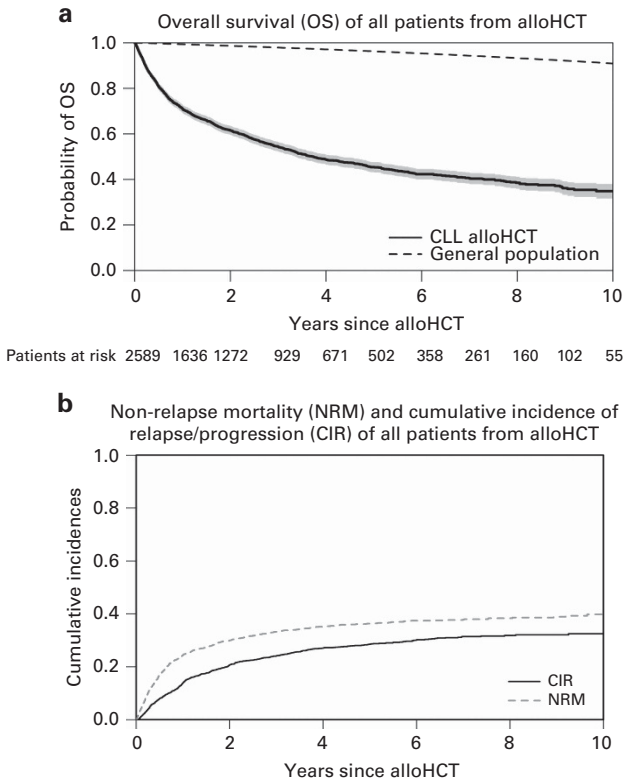

Figure 2. OS, NRM and CIR of all patients from allo-HCT. (**a**) Kaplan–Meier plot for OS of the whole cohort with 95% CIs. The survival probability of the age-, sex-, country- and calendar year-matched general population is shown by the dashed black line. (**b**) CIR and NRM. A full color version of this figure is available at the Bone Marrow Transplantation journal online.

corresponding female patients was 86% compared with 97% in the general population.

A separate Cox model was fitted to assess the excess hazard of this population. Sex still had no significant impact (HR 1.1 for women versus men, $P = 0.9$), whereas the impact of age was increased compared with the 2-year landmark model: HR 2.9 for a 10-year older patient at allo-HCT ($P < 0.001$). Five-year mortality from the 5-year landmark was 8 and 47% in male reference patients aged 45 and 65 years at allo-HCT compared with 3 and 14% in the matched general population (Figure 3c, compared with Supplementary Figure S2 for women).

A further Cox model for the excess hazard of mortality since allo-HCT was fitted. This excess hazard remains above zero until late after allo-HCT, even at 10 years after allo-HCT, implying that excess mortality because of CLL and its treatment does not fully vanish over time (see Supplementary Figure S1, online only). Furthermore, it is larger for patients with increased age at allo-HCT. Patient sex did not influence excess mortality.

Causes of death

We analyzed causes of late NRM. In total, 19 non-relapse deaths beyond the 5-year landmark were reported. The main cause of death was available for 17 of the 19 patients. GVHD was mentioned as main cause of death in 42% of patients, new malignancies in 26% of patients, infections in 11% of patients and miscellaneous causes in 11% of patients. Finally, we compared the relative contribution of NRM versus death after relapse in three time intervals. In the first 2 years after allo-HCT, 79% of deceased patients died from NRM and 21% after having experienced relapse or progression. The corresponding numbers for 2–5 years and after 5 years after allo-HCT were 40 and 32% owing to NRM and 60 and 68% mortality after relapse/progression. Recalculation of these percentages of four age groups ($\leqslant$45, 45–55, 55–65 years and $>$65 years at allo-HCT) showed that after the first 2 years, the contribution of NRM to all deaths was significantly larger for older patients than for younger patients (see Table 4).

DISCUSSION

The aim of this study was to estimate the fraction of cured patients with CLL after allo-HCT. Here, we report on the largest ever published cohort of transplanted patients with CLL, with a large number of patients with follow-up of >5 years. The 5-year EFS of 35% in this large study fits right in the middle of the reported range between 28 and 43% reported from smaller series of patients.[6–8,18,19] When counting from the day of allo-HCT, 28% of patients (95% CI, 25–31) maintained disease control at 10 years. For patients who passed the 2- and 5-year landmark event-free, the fraction of patients who maintained disease control at 10 years from allo-HCT increased to 56% (95% CI, 51–62) and 79% (95% CI, 73–85). These numbers represent a promising perspective for patients with an otherwise life-threatening disease.

The cohort of patients in this study is remarkably different compared with previously published studies on long-term survival after allo-HCT for other diseases. First, the median age at allo-HCT was 55 years as compared with <35 years in cohorts of long-term survivors who were reported so far.[20–23] Second, in our series the percentage of male patients was higher (74%), a feature specific to CLL.

Older age and male sex are linked to higher mortality, and thus, expectedly, the survival probabilities of the landmark populations of CLL patients are not as high as reported from those studies, which analyzed patients whose median age was 20 years lesser at allo-HCT. For example, the 2-year event-free landmark population of CLL patients in our study had a 10-year survival of 65% (95% CI, 60–70) compared with 84% reported by Wingard *et al*.[22] in lymphoma patients with a median age of 34 years at allo-HCT.

Table 3. Overall and event-free survival, cumulative incidences of relapse/progression and non-relapse mortality for the 2- and 5-year LM populations of event-free patients

Time from allo-HCT (years)	*Time from LM (years)*	*Overall survival (%) (95% CI)*	*Event-free survival (%) (95% CI)*	*Incidence of relapse/progression (%) (95% CI)*	*Non-relapse mortality (%) (95% CI)*
2-Year event-free LM population					
3	1	93 (91–94)	86 (84–89)	7 (5–9)	7 (5–8)
5	3	81 (78–84)	71 (68–75)	16 (13–18)	13 (11–15)
10	8	65 (60–70)	56 (51–62)	24 (20–28)	20 (16–24)
5-Year event-free LM population					
6	1	96 (94–98)	92 (89–95)	5 (2–7)	3 (1–5)
10	5	83 (77–90)	79 (73–85)	11 (7–16)	10 (5–15)

Abbreviations: allo-HCT = allogeneic hematopoietic stem cell transplantation; CI = confidence interval; LM = landmark.

To interpret this huge difference, the effect of the disease history and allo-HCT needs to be separated carefully from the expected 'background' mortality in the corresponding general population.

We calculated excess mortality compared with age-, sex-, country- and calendar year-matched controls. The advantage of using an additive Cox model for relative survival compared with the standardized incidence ratio—which is usually used for this purpose—is that the effect of risk factors can be determined and that the changes in excess hazard over time are taken into account. For example, for 65-year-old male patients who passed the 5-year post-allo-HCT landmark event-free, the 5-year mortality was 3.3 times (47% compared with 14%) as high as their matched controls. Reasons for excess mortality are late complications of CLL treatment before allo-HCT, mortality associated with allo-HCT and relapse of CLL. Comorbidity not related to CLL may also have an impact on mortality. The hematopoietic cell transplantation-specific comorbidity index as published in 2005 is a tool for classification of such information.[24] Unfortunately, this index was not reported to the European Society for Blood and Marrow Transplantation registry for patients transplanted between 2000 and 2010. Thus, unfortunately, the degree of measurable comorbidity at allo-HCT cannot be displayed meticulously. Excess mortality was lower for younger patients (see Figure 3c). For example, for a 45-year-old male patient who passed the 5-year landmark, excess mortality was 5% for the next 5 years.

NRM was the main cause of death in the first 2 years following allo-HCT, whereas CLL relapse was the predominant cause of death approximately from this landmark onwards (Table 4). However, NRM also accounted for a substantial fraction of mortality later on as shown by others before.[20,22,23] For example, for the 5-year EF population, the incidence of NRM in the next 5 years was 10% (95% CI, 5–15) compared with 5% mortality of the matched population. This demonstrates that a substantial proportion of late mortality was related to the transplant procedure or the treatment of CLL before allo-HCT.

It has been reported before that mortality remains higher compared with that of matched controls, even for patients who passed the 10-year landmark after allo-HCT.[20,22,23] Interestingly, in our cohort excess mortality increased with age and the impact of age was even more pronounced for late mortality. As this study represents the first report on long-term survivors after allo-HCT in older patients, it is unknown whether this finding is specific for patients with CLL. Several groups have reported on a higher risk of cardiovascular events after allo-HCT.[25–27] In our cohort, GVHD and infections were still the most frequently reported main causes of late NRM. It has been demonstrated before that adjudication of causes of NRM is a complex undertaking and we cannot exclude that causes of death were attributed to GVHD, although other chronic conditions were causal or MRD had reappeared.[28] Thus, detailed information on late causes of mortality is important and therefore our findings provide strong motivation for the implementation of long-term follow-up programs.[29–31]

The cumulative incidence of relapse of 29% at 5 years in this cohort study fits well with previously published data ranging from 17 to 46%.[6–8,18] A common pattern observed in most studies is that reduced-intensity conditioning is associated with higher relapse rates compared with myeloablative regimens. Yet, a consistent effect of conditioning intensity on OS has not been demonstrated for CLL.[18,32] Late relapses occurred in all of these studies. In our registry analysis, very late relapses after allo-HCT remained an important cause of treatment failure. Data on MRD at the landmark time-points were not available and one may speculate that patients with an MRD-negative CR at the landmark time-points have a better prognosis than the EF populations shown in this analysis. Still, the relapse rate was remarkably high. Two lessons can be learned with respect to graft-versus-leukemia effects from this observation. First, immunologic effector mechanisms fail to fully eradicate the disease and rather implement control of growth in a substantial proportion of patients. Second, late immunologic events may release CLL proliferation: this could be explained either by clonal evolution of CLL cells leading to immune escape or by a state of anergy of the donor immune system towards the leukemia.[33]

Which clinical consequences can be delineated from these results? First, monitoring for relapse after allo-HCT remains an important task. Patients with relapse benefit from salvage therapy and still have a relatively good prognosis.[34,35] For example, Ibrutinib represents an appealing treatment option with an attractive risk–benefit profile.[36] In a recently published series, the overall response rate in 16 patients with CLL who experienced relapse after allo-HCT was 88% and the PFS rate at 2 years was 77%.[37] Venetoclax, a BCL2 inhibitor with great activity in patients with relapsed/refractory CLL, has recently been approved by the Food and Drug Administration and may become another option for patients who relapse after allo-HCT.[1] Yet, data on the use of Venetoclax in the post-transplantation setting are still lacking. Owing to the favorable risk–benefit ratio, both Ibrutinib and Venetoclax might even become suitable to treat relapsing CLL at a level of MRD. Second, our findings should provide motivation for improved care for long-term survivors. Elderly patients in particular may need special follow-up programs to counteract the increased hazard of death. Recommendations for the care of long-term survivors have been published in recent years and a variety of tools are available including educational material for patients such as the Transplant Guidelines Application (https://bethematch.org/for-patients-and-families/support-and-resources/).[29,30] It is likely that the implementation of structured follow-up programs and better patient education will be instrumental to further reduce morbidity and mortality after allo-HCT. Finally, the prospect of long-term disease-free survival remains a valid argument for carefully

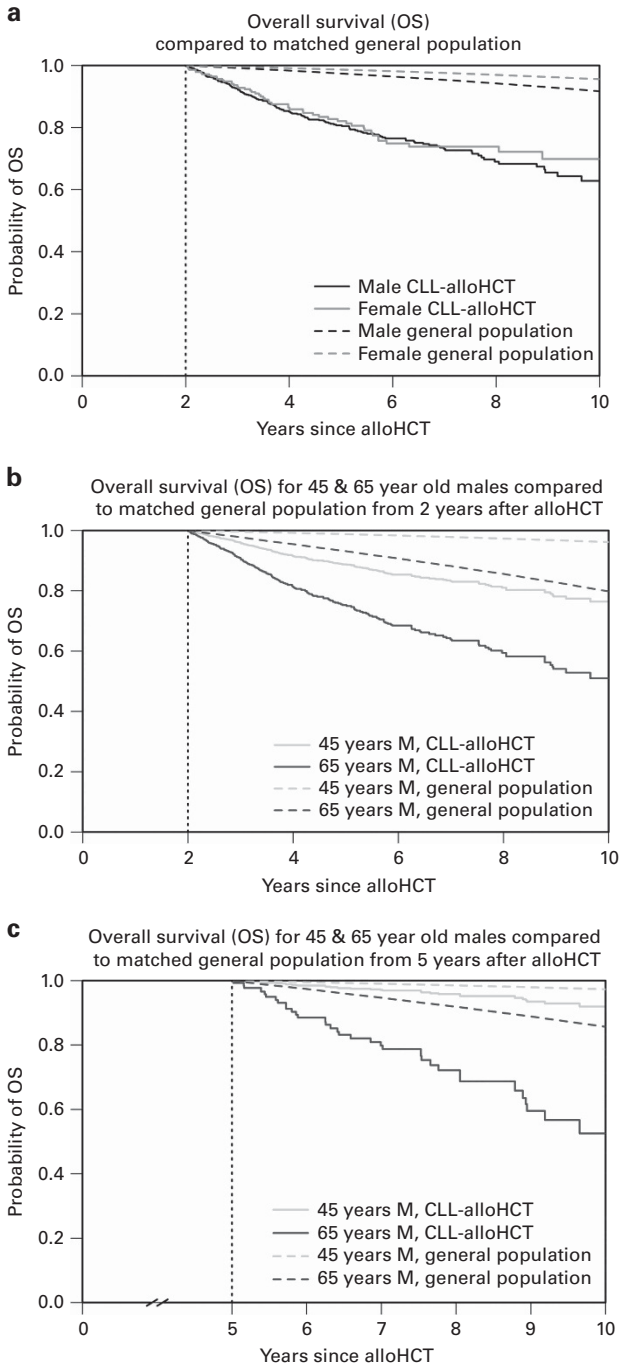

Figure 3. OS compared with matched general population. OS is shown in landmark populations of patients with CLL who were alive and event-free at the 2- and 5-year landmark after hematopoietic cell transplantation (solid lines). This outcome is contrasted with survival of the age-, sex-, country- and calendar year-matched general population (dashed lines). (**a**) OS since the 2-year landmark for male and female patients and the corresponding outcome of the general population. (**b** and **c**) OS since the 2- and 5-year landmark for male reference patients of ages 45 years and 65 years at allo-HCT based on a Cox regression model for relative survival. A full color version of this figure is available at the Bone Marrow Transplantation journal online.

considering allo-HCT in high-risk CLL, balancing individual disease-specific and transplant-related risk factors, options to participate in clinical trials with new drugs, reimbursement of Venetoclax, Ibrutinib and Idelalisib, and the patient's preferences.[9]

Table 4. Contribution of death with and without prior relapse/progression to all deaths in consecutive time intervals since allo-HCT

Time intervals after allo-HCT (years)	*Age at allo-HCT (years)*	*Number of deaths*	*NRM (% of all deaths)*	*P-value*
0–2	⩽45	105	76	
	45–55	325	77	
	55–65	436	81	
	>65	59	81	0.2
2–5	⩽45	37	19	
	45–55	97	42	
	55–65	115	45	
	>65	16	44	0.02
>5	⩽45	6	0	
	45–55	28	21	
	55–65	32	47	
	>65	0	NA[a]	0.006

Abbreviations: allo-HCT = allogeneic hematopoietic stem cell transplantation; NA, not applicable; NRM, non-relapse mortality. [a]Thirteen patients at risk, no dead reported. 'Number of deaths' indicates the reported number of deaths in the data set in the indicated age group and time period. The fourth column gives the proportion of NRM deaths among all observed deaths. The contribution of death after relapse/progression can be calculated as 100 minus this number. The last column contains *P*-values for the χ^2 test for trend in proportions, testing within each time interval the association between age and proportion of NRM.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank Maja Pohar Perme (Institute for Biostatistics and Medical Informatics, University of Ljubljana, Ljubljana, Slovenia) for help with the software. Further, we are very grateful to Emili Montserrat who gave substantial input and critically revised the manuscript.

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Supplementary Information accompanies this paper on Bone Marrow Transplantation website (http://www.nature.com/bmt)