Prognostic impact of number of induction courses to attain complete remission in patients with acute myeloid leukemia transplanted with either a matched sibling or human leucocyte antigen 10/10 or 9/10 unrelated donor: An Acute Leukemia Working Party European Society for Blood and Marrow Transplantation study.

Justin Loke, Myriam Labopin, Charles Craddock, Gérard Socié, Tobias Gedde-Dahl, Didier Blaise, Edouard Forcade, Urpu Salmenniemi, Anne Huynh, Jurjen Versluis, et al.

Received: 21 December 2023 | Revised: 14 February 2024 | Accepted: 16 February 2024

DOI: 10.1002/cncr.35308

ORIGINAL ARTICLE

Prognostic impact of number of induction courses to attain complete remission in patients with acute myeloid leukemia transplanted with either a matched sibling or human leucocyte antigen 10/10 or 9/10 unrelated donor: An Acute Leukemia Working Party European Society for Blood and Marrow Transplantation study

Justin Loke MD, PhD[1,2] | Myriam Labopin MD[3,4] | Charles Craddock MD, PhD[5,6] | Gérard Socié MD[7] | Tobias Gedde-Dahl MD[8] | Didier Blaise MD, PhD[9] | Edouard Forcade MD, PhD[10] | Urpu Salmenniemi MD[11] | Anne Huynh MD[12] | Jurjen Versluis MD, PhD[13] | Ibrahim Yakoub-Agha MD, PhD[14] | Hélène Labussière-Wallet MD[15] | Johan Maertens MD[16] | Jakob Passweg MD[17] | Claude Eric Bulabois MD[18] | Ludovic Gabellier MD, PhD[19] | Stephan Mielke MD, PhD[20] | Cristina Castilla-Llorente MD[21] | Eric Deconinck MD[22,23] | Eolia Brissot MD, PhD[4] | Arnon Nagler MD[24] | Fabio Ciceri MD, PhD[25] | Mohamad Mohty MD, PhD[4]

Correspondence
Mohamad Mohty.
Email: mohamad.mohty@inserm.fr

Abstract

Introduction: For the majority of patients with acute myeloid leukemia (AML) an allogeneic stem cell transplant (SCT) in first complete remission (CR) is preferred. However, whether the number of courses required to achieve CR has a prognostic impact is unclear. It is unknown which factors remain important in patients requiring more than one course of induction to attain remission.

Methods: This Acute Leukaemia Working Party study from the European Society for Blood and Marrow Transplantation identified adults who received an allograft in first CR from either a fully matched sibling or 10/10 or 9/10 human leucocyte antigen (HLA)-matched unrelated donor (HLA-A, HLA-B, HLA-C, HLA-DR, or HLA-DQ). Univariate and multivariate analyses were undertaken to identify the prognostic impact of one or two courses of induction to attain CR.

Results: A total of 4995 patients were included with 3839 (77%) patients attaining a CR following one course of induction chemotherapy (IND1), and 1116 patients requiring two courses (IND2) to attain CR. IND2 as compared to IND1 was a poor

prognostic factor in a univariate analysis and remained so in a multivariate Cox model, resulting in an increased hazard ratio of relapse (1.38; 95% confidence interval [CI], 1.16–1.64; $p = .0003$) and of death (1.27; 95% CI, 1.09–1.47; $p = .002$). Adverse prognostic factors in a multivariate analysis of the outcomes of patients requiring IND2 included age, *FLT3*-ITD, adverse cytogenetics, and performance status. Pretransplant measurable residual disease retained a prognostic impact regardless of IND1 or IND2.

Conclusion: Initial response to chemotherapy as determined by number of courses to attain CR, retained prognostic relevance even following SCT in CR.

KEYWORDS
AML, induction chemotherapy, MRD, stem cell transplant

INTRODUCTION

Allogeneic stem cell transplantation (SCT) plays a critical role in the management of acute myeloid leukemia (AML) in reducing the risk of disease relapse through cytotoxicity from the conditioning regimen, as well as through the graft-versus-leukemia (GVL) effect.[1–3] To ensure time for this to develop, transplant strategies are premised on allografting patients in complete remission (CR). A significant proportion of patients who do not attain a CR following the first course of induction chemotherapy (IND1), achieve CR following the second course (IND2).[4] As such, the standard definition of primary refractory disease is defined as failure to achieve a CR following two courses of induction chemotherapy.[5] Although it is well accepted that transplantation of patients with primary refractory disease[6] results in poor overall survival (OS), it is unclear whether outcomes of patients are equivalent if they required one or two courses of chemotherapy to achieve a CR. For example, UK Medical Research Council/National Cancer Research Institute data emphasize the prognostic benefit of attaining a CR following the first course of induction chemotherapy. Nevertheless, for patients who only attain a PR post course 1 but subsequently attained a CR, there was no difference in relapse rates[7] as compared to patients who achieved a CR upfront. This is consistent with data from the Eastern Cooperative Oncology Group that demonstrated no significant difference in OS or disease-free survival (DFS) for patients who required one as compared to two cycles of induction treatment to attain CR.[4] In contrast, in patients who receive a SCT, more recent data suggest patients[8,9] requiring two courses of induction to achieve a CR may have a poorer posttransplant outcome, as compared to those who only require one course.

For patients in CR, pretransplant measurable residual disease (MRD) has been shown to be an important independent discriminant of outcomes following SCT,[10] especially for those in receipt of a reduced-intensity conditioning (RIC)[11] regimen. Retrospective data had suggested outcomes for patients with detectable MRD pretransplant are similar to those with active disease.[12] Therefore, to accurately estimate the prognostic impact of number of cycles of induction to attain CR, it is critical to understand how the presence or absence of detectable pretransplant MRD interacts with this factor.

The aim of this Acute Leukemia Working Party (ALWP) study from the European Society for Blood and Marrow Transplantation (EBMT), was to first identify the prognostic value of the number of cycles of induction required for attainment of CR in patients with AML in first complete remission (CR1) before a SCT, and second, to identify which prognostic factors (including pretransplant MRD) influence the outcomes of patients requiring more than one course of chemotherapy to attain CR.

MATERIALS AND METHODS

Study design

Adults aged 18 years or over with a diagnosis of AML who received a SCT in CR1 from 2010 to 2020 were included in this study. All patients received either a fully human leucocyte antigen (HLA) matched sibling donor, or an HLA 10/10 or 9/10 (HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ) matched unrelated donor. Cord or haploidentical stem cell donor SCTs were excluded from this study. All patients had to have information on the number of cycles of induction required to reach CR1. Cytogenetic risk was classified as previously described.[13] Contributing centers provided pretransplant MRD data (taken before transplant and following pretransplant therapy), which was performed as previously described.[14]

EBMT centers commit to obtain informed consent according to the local regulations applicable at the time of transplantation to report pseudonymized data to the EBMT. The review committee of the ALWP of the EBMT registry approved this study. The EBMT is a voluntary group of more than 600 transplant centers that report consecutive SCT and follow-ups annually (Supporting Table 1).

Statistical analysis

Patient-, disease-, and transplant-related characteristics for the two cohorts (IND1 to CR vs. IND2 required for CR) were compared by using the χ^2 statistic for categorical variables and the Mann-Whitney

test for continuous variables. Acute and chronic graft-versus-host disease (GVHD) was graded as per previous definitions.[15,16] Relapse was defined as an increase of 5% blasts or more in the bone marrow. Nonrelapse mortality (NRM) was defined as death without relapse. OS and leukemia-free survival (LFS) were defined from time of transplant to the event. NRM, cumulative incidence of relapse (CIR), and acute and chronic GVHD were estimated using cumulative incidence to accommodate for competing risks. In the study of acute and chronic GVHD, relapse and death were defined as competing events. The Kaplan–Meier method was used to estimate the probabilities of LFS and OS.[17,18] Gray's test for cumulative incidence functions and the log-rank test for OS and LFS were used in univariate analyses. Multivariate analysis was performed on data from complete cases using a Cox proportional hazards model that included variables differing significantly ($p < .05$) between the groups, factors known to be associated with outcomes, plus a center frailty effect to take into account the heterogeneity across centers. A second multivariate model was performed using data from patients who received two inductions for identification of prognostic factors in this cohort. Acute and chronic GVHD were included in the Cox model as time-dependent variables. Results were expressed as the hazard ratio (HR) with a 95% confidence interval (CI). Two-sided tests were used. To determine factors associated with time-to-event outcomes, a type 1 error rate was fixed at 0.05. Analyses were performed using R 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

RESULTS

Patient and transplant characteristics

A total of 4995 patients were included in this study with 3839 (77%) patients attaining a CR following IND1, and 1116 requiring IND2 to attain CR. The median follow-up period was 43.5 months, and the median age of the whole cohort was 54.2 years. The characteristics of the cohort according to total number of induction courses are listed in Table 1. IND2 patients were marginally younger and had less nucleophosmin 1 (NPM1) mutant disease. Notably, although there was a shorter duration of time from CR1 to SCT in IND2 patients, there was no overall difference in time from diagnosis to SCT. Despite the extra cycle of induction chemotherapy, Karnofsky performance score at time of transplant was not significantly worse in the IND2 group of patients. IND2 patients were more likely to be transplanted with a myeloablative conditioning (MAC) regimen. Finally, there was no significant difference in frequency of detectable pretransplant MRD between the two groups.

Patients requiring two cycles of induction to attain CR1 had a poorer OS and increased risk of relapse as compared to patients who only required one

IND2 patients had an inferior OS, LFS, and increased risk of relapse as compared to IND1 patients (Figure 1; Supporting Table 2). Patients in IND2 had a CIR of 39.8% (95% CI, 36.5–43.1) as compared to IND1 patients who had a CIR of 29.1% (95% CI, 27.4–30.7; $p = .001$) at 5 years post SCT. This resulted in an impaired OS (at 5 years following an allograft) of 50.7% (95% CI, 47.2–54.1) in IND2 patients versus 58.5% (95% CI, 56.6–60.4; $p = .001$) in IND1 patients. There was no significant difference in incidences of either acute or chronic GVHD.

To ascertain whether this was due to underlying biological factors, we included in a Cox multivariate analysis variables including cytogenetic risk and *FLT3*-ITD and *NPM1* mutational status. This data was available for 2847 patients (IND1: $n = 2254$, IND2: $n = 593$) (Table 2). This analysis confirmed the detrimental effect of adverse cytogenetics, *FLT3*-ITD, and lack of *NPM1* mutation on CIR, LFS, and OS. The presence of adverse cytogenetics resulted in an increased risk of relapse (HR, 1.69; 95% CI, 1.41–2.01; $p < .0001$) and death (HR for OS: 1.7; 95% CI, 1.47–1.98; $p < .0001$). Independent of these known adverse prognostic factors, IND2 remained an adverse prognostic factor, resulting in an increased HR of relapse of 1.38 (95% CI, 1.16–1.64; $p = .0003$) and for death (HR, 1.27; 95% CI, 1.09–1.47; $p = .002$).

Presence of *FLT3*-ITD and adverse cytogenetics resulted in increased relapse risk and reduced OS in patients who require IND2

Having identified the poorer outcomes of patients who require IND2, we sought to understand which factors influenced the outcomes of this cohort (Supporting Table 3). We performed a multivariate analysis that included patients with information on *FLT3*-ITD and *NPM1* mutation information ($n = 574$) (Table 3). Increased age, presence of a *FLT3*-ITD mutation or adverse cytogenetics, and reduced performance status all independently resulted in an increased risk of death. Presence of adverse karyotype at diagnosis was a particularly adverse prognostic factor (OS HR, 2.06; 95% CI, 1.5–2.82; $p < .0001$).

A factor associated with improved OS when included as a time-dependent variable, was the presence of chronic GVHD. It was associated with a reduction in relapse risk (HR, 0.64; 95% CI, 0.42–0.98; $p = .039$) and an improved OS (HR, 0.60; 95% CI, 0.43–0.85; $p = .004$) (Supporting Table 4). However, any benefit is restricted to those who have limited chronic GVHD. This is because patients with extensive chronic GVHD were at high risk of NRM (HR, 1.93; 95% CI, 1–3.72; $p = .049$), resulting in no benefit to OS. In contrast, in patients with limited chronic GVHD, there was a trend to benefit for OS (HR, 0.61; 95% CI, 0.37–1; $p = .052$) (Table 3). The presence of acute GVHD (grade II–IV), when analyzed as a time-dependent variable was associated with an increased risk of NRM (HR, 2.13; 95% CI, 1.32–3.45; $p = .002$) resulting in an impaired OS (HR, 1.43; 95% CI, 1.06–1.92; $p = .019$).

Intensification of the conditioning regimen (RIC vs. MAC) resulted in no significant improvement in OS in IND2 group of patients (OS, RIC vs. MAC HR, 1.08; 95% CI, 0.79–1.48; $p = .64$), although there was a trend for a reduction in CIR for patients who were

TABLE 1 Patient characteristics according to whether one or two cycles are required to attain complete remission.

	No. of cycles required to attain CR1		
	One (n = 3839)	Two (n = 1116)	p
Patient age (years)			
Median (min–max)	54.6 (18.1–76.9)	52.8 (18–75.6)	.0004
Patient sex			
Male	2067 (53.9%)	613 (55%)	.51
Female	1771 (46.1%)	502 (45%)	
Missing	1	1	
Type of AML			
Primary	3597 (93.7%)	1061 (95.1%)	.088
Secondary	242 (6.3%)	55 (4.9%)	
MRC karyotype classification			
Intermediate	2799 (72.9%)	813 (72.8%)	.97
Adverse	1040 (27.1%)	303 (27.2%)	
FLT3-ITD			
Absent	1676 (62.6%)	476 (64.9%)	.24
Present	1002 (37.4%)	257 (35.1%)	
Missing	1161	383	
NPM1 mutation			
Absent	1679 (65.2%)	535 (78.6%)	<.0001
Present	896 (34.8%)	146 (21.4%)	
Missing	1264	435	
Time diagnosis to CR1 (days)			
Median [IQR]	42 [34–56]	72 [57–95]	<.0001
Missing	1844	454	
Time CR1 to SCT (days)			
Median [IQR]	101 [71–135]	77 [43.2–116]	<.0001
Missing	1844	454	
Time diagnosis to SCT (months)			
Median (min–max) [IQR]	4.86 (0.6–17.6) [3.9–5.9]	4.93 (1.9–16.7) [3.9–6.2]	.017
MRD pretransplant			
MRD neg	1026 (67.6%)	279 (67.9%)	.92
MRD pos	491 (32.4%)	132 (32.1%)	
Missing	2322	705	
Type of donor			
Fully matched sibling	1575 (41%)	427 (38.3%)	.066
Unrelated (HLA 10/10 matched)	1878 (48.9%)	553 (49.6%)	
Unrelated (HLA 9/10 matched)	386 (10.1%)	136 (12.2%)	
Conditioning intensity			
MAC	1670 (43.5%)	549 (49.2%)	.0007
RIC	2168 (56.5%)	566 (50.8%)	
Unknown	1	1	
Karnofsky score			
<90	895 (25.1%)	290 (28%)	.056
≥90	2675 (74.9%)	745 (72%)	
Unknown	269	81	
In vivo T-cell depletion			
Absent	1249 (32.6%)	376 (33.7%)	.49
Present	2581 (67.4%)	739 (66.3%)	
Unknown	9	1	

Note: Cytogenetic risk by karyotyping as previously defined.[13]
Abbreviations: AML, acute myeloid leukemia; CR1, first complete remission; HLA, human leucocyte antigen; IQR, interquartile range; MAC, myeloablative conditioning; max, maximum; min, minimum; MRC, Medical Research Council; MRD, measurable residual disease; neg, negative; pos, positive; RIC, reduced intensity conditioning; SCT, stem cell transplant.

treated with a MAC (RIC vs. MAC HR, 1.44; 95% CI, 1–2.07; p = .05) (Table 3).

Detectable MRD before transplant remained a prognostic factor regardless of whether patients required one or two courses of induction to attain CR

Pretransplant MRD was available in 1517 of 3839 patients and 411 of 1116 patients for IND1 and IND2, respectively. By univariate analysis, detectable MRD before transplant remained a prognostic factor for relapse and OS regardless of whether patients were in the IND1 or IND2 group (Table 4). For example, OS at 2 years for IND1 patients, with detectable pretransplant MRD was 63.7% versus 73.4% for those with no detectable MRD (p = .001). For IND2 patients, OS at 2 years for those with detectable MRD was 56.7% versus those with no detectable MRD, 67.4% (p = .001).

DISCUSSION

In this study from the ALWP of the EBMT of patients with AML who received an allograft in first CR, patients requiring two courses of induction chemotherapy to attain CR were at an increased risk of

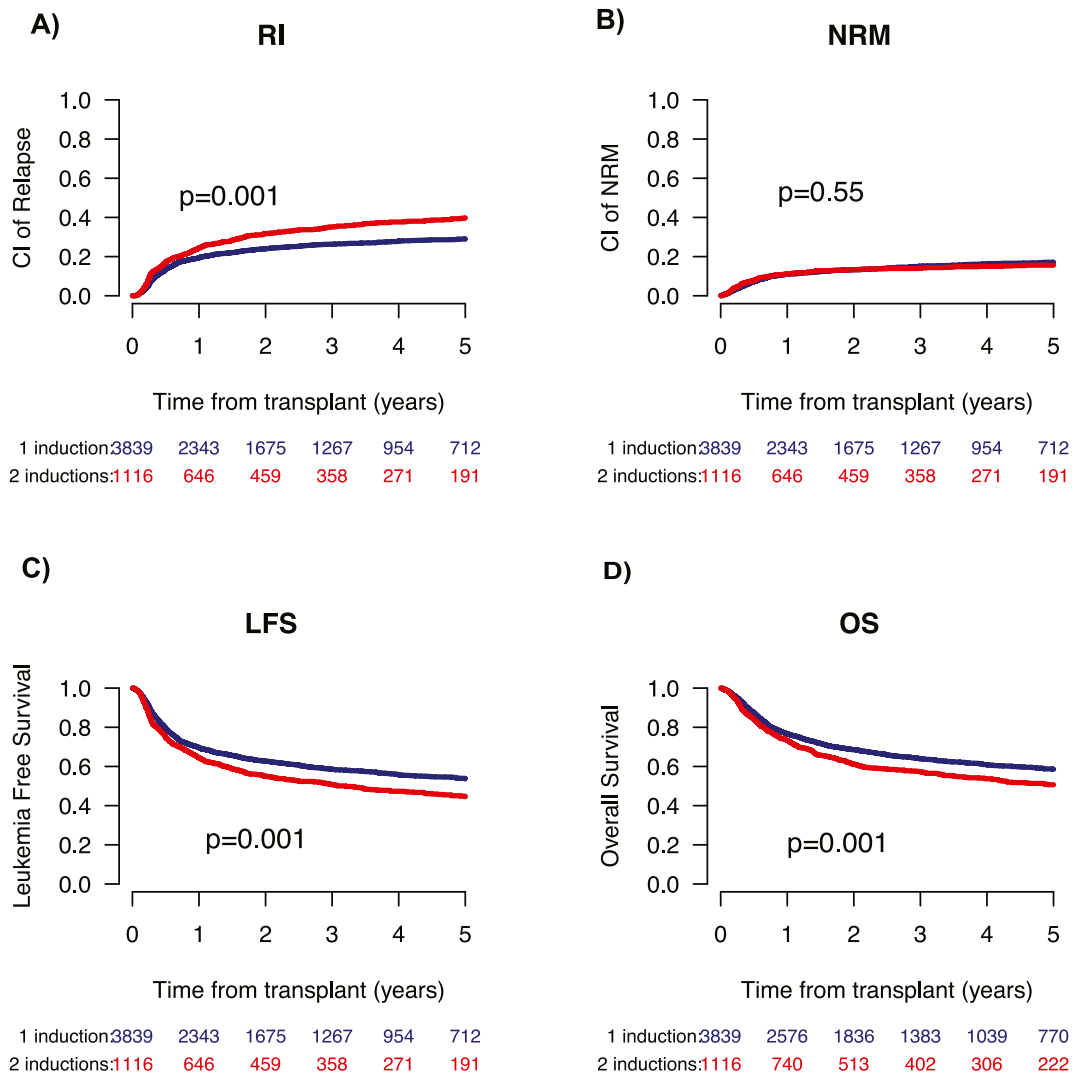

FIGURE 1 (A) Relapse incidence (RI), (B) nonrelapse mortality (NRM), (C) leukemia-free survival (LFS), and (D) overall survival (OS) from time of transplant for patients with acute myeloid leukemia who require either one or two courses of induction to achieve complete remission.

death but not of NRM, as compared to those who only required one course of induction chemotherapy. The lack of impact of a second course of induction on NRM suggests that the major mechanism by which these patients have inferior outcomes remains that of chemo-resistant disease, rather than patient deconditioning as a result of a further course of induction chemotherapy. Consistent with this is the observation that the major factor influencing the outcomes of IND2 patients is adverse cytogenetics, which is associated with chemo-resistance. However, further cytotoxic therapy, via myeloablative conditioning, had no additional benefit in terms of survival but a potential benefit in incidence of relapse. There is a trend to benefit in OS from the occurrence of limited chronic GVHD in this cohort, potentially implicating a GVL effect in this context. This has particular importance in the context of the current debate surrounding the optimal management of high risk AML patients before an allograft,[19] as to whether further chemotherapy treatment[10] may be of benefit. Here, the data reinforce the importance of SCT in the management of these patients through delivery of both GVL, alongside maximal cytotoxic therapy in terms of conditioning intensity.[11] This is supported by the recent results of the ASAP trial[20] where patients who were refractory to a first course of induction chemotherapy were randomized to either a second course of induction or directly to a RIC allo-SCT. This resulted in comparable rates of survival and remission attainment in both randomization arms.

Our data corroborate a recent Center for International Blood and Marrow Transplant Research (CIBMTR) study that demonstrates largely similar overall findings[9]—relapse risk was increased in IND2 patients, regardless of conditioning intensity, however, differences in OS were detected only in MAC patients. A recent ALWP EBMT study examining the outcomes of patients with AML who received an allograft from haploidentical donors also demonstrated an inferior OS due to increased incidences of relapse in those who required two courses of induction to achieve CR, as compared to

TABLE 2 Cox multivariate analysis of requirement for IND1 to CR versus IND2 and other patient- and transplant-related variables post allo-SCT.

	Relapse		NRM		LFS		OS		Acute GVHD II-IV		Chronic GVHD	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
IND2 versus IND1	1.38 (1.16–1.64)	.0003	1.01 (0.79–1.29)	.95	1.24 (1.08–1.43)	.003	1.27 (1.09–1.47)	.002	1.03 (0.85–1.23)	.79	0.92 (0.78–1.07)	.28
Age (HR per 10 years)	1.07 (1–1.14)	.063	1.38 (1.24–1.52)	<.0001	1.16 (1.1–1.23)	<.0001	1.21 (1.14–1.29)	<.0001	1.01 (0.94–1.08)	.8	1 (0.94–1.05)	.9
Year of SCT	1 (0.97–1.03)	.96	1 (0.96–1.04)	.97	1 (0.98–1.02)	.89	1 (0.98–1.02)	.97	0.99 (0.96–1.02)	.48	0.99 (0.97–1.02)	.64
Secondary AML	1.12 (0.8–1.57)	.52	1.1 (0.72–1.67)	.66	1.12 (0.86–1.46)	.4	1.18 (0.89–1.55)	.25	1.07 (0.77–1.48)	.68	1.12 (0.84–1.48)	.45
Adverse cytogenetics (intermediate as reference)	1.69 (1.41–2.01)	<.0001	1.44 (1.14–1.83)	.002	1.59 (1.38–1.84)	<.0001	1.7 (1.47–1.98)	<.0001	1.13 (0.94–1.36)	.19	0.98 (0.84–1.16)	.83
UD 10/10	0.83 (0.71–0.99)	.034	1.64 (1.3–2.08)	<.0001	1.07 (0.93–1.22)	.34	1.17 (1.01–1.35)	.041	2.06 (1.71–2.48)	<.0001	1.25 (1.08–1.45)	.003
UD 9/10	0.87 (0.67–1.13)	.3	1.61 (1.14–2.29)	.008	1.09 (0.88–1.34)	.43	1.19 (0.95–1.49)	.14	2.24 (1.73–2.9)	<.0001	1.33 (1.06–1.66)	.012
Female donor to male recipient	0.77 (0.62–0.96)	.018	1.34 (1.05–1.72)	.02	0.95 (0.81–1.12)	.54	0.99 (0.83–1.18)	.91	1.37 (1.13–1.66)	.001	1.29 (1.1–1.52)	.002
Diagnosis to SCT (month)	0.95 (0.9–0.99)	.019	1.02 (0.97–1.08)	.38	0.97 (0.94–1.01)	.15	0.99 (0.95–1.03)	.62	0.97 (0.93–1.02)	.2	1.02 (0.98–1.05)	.37
RIC versus MAC	1.04 (0.87–1.25)	.63	0.93 (0.73–1.19)	.57	1.01 (0.87–1.17)	.89	1.03 (0.88–1.21)	.7	0.95 (0.78–1.14)	.57	1.04 (0.89–1.22)	.6
PBSC versus BM	0.96 (0.76–1.21)	.75	0.89 (0.66–1.21)	.46	0.92 (0.76–1.11)	.39	0.98 (0.8–1.2)	.86	1.21 (0.94–1.55)	.13	1.24 (1.02–1.52)	.035
Recipient CMV-positive	1.01 (0.86–1.19)	.9	1.22 (0.98–1.51)	.077	1.09 (0.96–1.24)	.19	1.19 (1.03–1.37)	.017	0.95 (0.81–1.11)	.5	1.09 (0.95–1.25)	.23
Donor CMV-positive	0.98 (0.84–1.14)	.78	1.04 (0.84–1.28)	.72	1 (0.88–1.13)	.96	0.98 (0.86–1.12)	.77	1.04 (0.89–1.22)	.62	0.96 (0.84–1.1)	.55
In vivo TCD	1.24 (1.03–1.49)	.022	0.8 (0.64–1)	.052	1.06 (0.91–1.22)	.48	0.95 (0.81–1.11)	.53	0.74 (0.6–0.89)	.002	0.56 (0.48–0.65)	<.0001
KPS ≥90	0.99 (0.83–1.18)	.9	0.64 (0.51–0.79)	<.0001	0.84 (0.73–0.97)	.014	0.79 (0.68–0.91)	.001	0.89 (0.74–1.06)	.18	0.95 (0.81–1.11)	.49
FLT3-ITD present	1.75 (1.46–2.1)	<.0001	1.25 (0.97–1.62)	.089	1.58 (1.36–1.83)	<.0001	1.56 (1.33–1.84)	<.0001	1.2 (1–1.45)	.053	1.11 (0.95–1.31)	.2
NPM1-positive	0.74 (0.61–0.91)	.004	0.82 (0.62–1.08)	.15	0.76 (0.65–0.89)	.0009	0.77 (0.65–0.92)	.004	0.87 (0.71–1.06)	.16	0.95 (0.8–1.12)	.53

Note: Cytogenetic risk as previously defined.[13]

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; CI, confidence interval; CMV, cytomegalovirus; CR, complete remission; GVHD, graft-versus-host disease; HR, hazard ratio; IND1, one cycle of induction; IND2, two cycles of induction; KPS, Karnofsky performance score; LFS, leukemia-free survival; MAC, myeloablative conditioning; NMR, nonrelapse mortality; OS, overall survival; PBSC, peripheral blood stem cell; RIC, reduced intensity conditioning; SCT, stem cell transplant; TCD, T-cell depletion; UD, unrelated donor (matched sibling as reference).

TABLE 3 Cox multivariate analysis of factors that influence the outcomes of patients who require two courses of induction chemotherapy to attain a CR.

	Relapse		NRM		LFS		OS	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Acute GVHD	1.18 (0.84–1.67)	.34	2.13 (1.32–3.45)	.002	1.42 (1.08–1.87)	.013	1.43 (1.06–1.92)	.019
Chronic GVHD								
Limited	1.08 (0.64–1.81)	.78	0.53 (0.19–1.52)	.24	0.9 (0.57–1.42)	.65	0.61 (0.37–1)	.052
Extensive	0.67 (0.38–1.18)	.17	1.93 (1–3.72)	.049	1.07 (0.71–1.63)	.74	0.88 (0.58–1.35)	.57
Age (HR per 10 years)	0.99 (0.87–1.13)	.92	1.35 (1.09–1.68)	.006	1.09 (0.98–1.22)	.13	1.17 (1.04–1.32)	.01
Year of SCT	1.04 (0.99–1.1)	.13	0.97 (0.9–1.06)	.52	1.02 (0.98–1.07)	.36	1.03 (0.98–1.08)	.29
Secondary AML	0.99 (0.45–2.19)	.98	1.08 (0.32–3.57)	.9	1.01 (0.52–1.94)	.99	1.04 (0.52–2.08)	.91
Adverse cytogenetics	1.89 (1.32–2.71)	.0005	2.06 (1.19–3.56)	.01	1.89 (1.4–2.54)	<.0001	2.06 (1.5–2.82)	<.0001
UD 10/10	0.75 (0.53–1.07)	.11	1.67 (0.97–2.88)	.064	0.95 (0.71–1.27)	.73	1.08 (0.79–1.47)	.63
UD 9/10	1.02 (0.61–1.69)	.95	1.53 (0.7–3.37)	.29	1.1 (0.72–1.68)	.64	1.25 (0.79–1.98)	.34
Female donor to male recipient	1.02 (0.67–1.55)	.92	1.03 (0.55–1.94)	.92	1.02 (0.72–1.43)	.93	0.92 (0.63–1.35)	.68
Diagnosis to SCT (months)	0.94 (0.85–1.03)	.19	1.06 (0.96–1.18)	.26	0.98 (0.92–1.05)	.64	1.01 (0.94–1.08)	.85
RIC versus MAC	1.44 (1–2.07)	.05	0.69 (0.4–1.17)	.17	1.11 (0.83–1.49)	.48	1.08 (0.79–1.48)	.64
PBSC versus BM	0.64 (0.39–1.04)	.072	0.85 (0.42–1.73)	.65	0.69 (0.46–1.03)	.068	0.78 (0.5–1.21)	.27
Recipient CMV+	0.97 (0.69–1.36)	.84	1.19 (0.72–1.96)	.51	1.04 (0.79–1.38)	.77	1.21 (0.9–1.65)	.21
Donor CMV+	0.99 (0.72–1.37)	.96	0.94 (0.58–1.52)	.8	0.98 (0.75–1.28)	.86	1.01 (0.76–1.34)	.96
In vivo TCD	0.87 (0.6–1.28)	.49	0.98 (0.59–1.62)	.92	0.95 (0.71–1.29)	.76	0.87 (0.63–1.21)	.41
KPS ≥90	1.17 (0.81–1.68)	.4	0.44 (0.27–0.72)	.0009	0.83 (0.63–1.1)	.2	0.74 (0.55–1)	.05
FLT3–ITD	2.09 (1.48–2.95)	<.0001	1.25 (0.73–2.14)	.41	1.78 (1.33–2.37)	<.0001	1.89 (1.38–2.57)	<.0001
NPM1 mutation	0.68 (0.44–1.05)	.081	1.25 (0.69–2.25)	.46	0.84 (0.59–1.19)	.34	0.8 (0.55–1.17)	.26

Note: Cytogenetic risk as previously defined.[13] Acute and chronic GVHD as a time-dependent variable.

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; CI, confidence interval; CMV, cytomegalovirus; CR, complete remission; GVHD, graft-versus-host-disease; HR, hazard ratio; KPS, Karnofsky performance score; LFS, leukemia free survival; MAC, myeloablative conditioning; NRM, nonrelapse mortality; OS, overall survival; PBSC, peripheral blood stem cell; RIC, reduced intensity conditioning; TCD, T-cell depletion; UD, unrelated donor (matched sibling as reference).

TABLE 4 Prognostic significance of MRD in patients requiring either one or two cycles of induction chemotherapy to attain CR.

	Relapse	NRM	LFS	OS	Acute GVHD II–IV	Chronic GVHD
One induction						
MRD neg (*n* = 1026)	20% (17.4–22.6)	11.6% (9.6–13.8)	68.5% (65.3–71.4)	73.4% (70.3–76.2)	25% (22.3–27.7)	41.3% (38–44.5)
MRD pos (*n* = 491)	33.9% (29.5–38.5)	11.4% (8.6–14.6)	54.7% (49.8–59.3)	63.7% (58.8–68.2)	28.6% (24.6–32.7)	33.6% (29–38.3)
p value	.001	.88	.001	.001	.14	.004
Two inductions						
MRD neg (*n* = 279)	29.5% (23.9–35.4)	9.6% (6.3–13.8)	60.8% (54.3–66.7)	67.4% (60.9–73)	27.3% (22.1–32.8)	42.6% (36.2–48.9)
MRD pos (*n* = 132)	41.9% (32.5–51)	15.4% (9.6–22.5)	42.6% (33.2–51.7)	56.7% (47–65.3)	24.8% (17.7–32.6)	33% (24.5–41.7)
p value	.005	.1	.001	.001	.6	.1

Abbreviations: CR, complete remission; GVHD, graft-versus-host-disease; LFS, leukemia free survival; MRD, measurable residual disease; neg, negative; NRM, nonrelapse mortality; OS, overall survival; pos, positive.

one.[21] Together, this supports the prognostic significance of requiring two courses of induction to attain a CR in determining posttransplant outcomes.

For IND2 patients who have no MRD detectable before transplant, the risk of relapse and OS was not dissimilar to IND1 patients. In a prior CIBMTR study, MRD was only prognostically significant in

patients who received a RIC allograft.[9] The prognostic importance of pretransplant MRD was relevant in our data set regardless of conditioning intensity (Supporting Table 5). Overall, this suggests that MRD remains important in dynamically reassessing patients' prognosis, even for patients who have already demonstrated a poor response to chemotherapy.

A limitation of this study is that because it is registry-based, information on *FLT3*-ITD, *NPM1* and pretransplant MRD are missing in a proportion of patients. MRD was also not analyzed in a centralized manner. However, there is no evidence of bias in the centers providing these data, and the numbers of patients included in these exploratory analyses remain one of the largest studied. We did not capture the specific details of chemotherapy administered at consolidation following induction courses, however, this study was performed primarily before the era of novel targeted agents. Finally, the prognostic implications of the kinetics of remission achievement with the use of venetoclax-based chemotherapy combinations may be different to that of this study, conducted when anthracycline-based induction regimens predominated.[22]

Finally, a further clinical implication of this study is that choice of induction chemotherapy at diagnosis to increase speed of remission attainment is critical because it may have implications for AML patients post-SCT. This is supported by the current era of advances in therapeutics in AML,[23,24] whose benefits have been extended to patients who have subsequently received an allograft.

AUTHOR CONTRIBUTIONS

Justin Loke: Conceptualization, writing–original draft, and writing–review and editing. **Myriam Labopin:** Conceptualization, methodology, writing–review and editing, formal analysis, data curation, project administration, resources, writing–original draft, and visualization. **Charles Craddock:** Conceptualization, resources, and writing–review and editing. **Gerard Socie:** Writing–review and editing and resources. **Tobias Gedde-Dahl:** Writing–review and editing and resources. **Didier Blaise:** Writing–review and editing and resources. **Edouard Forcade:** Writing–review and editing and resources. **Urpu Salmenniemi:** Writing–review and editing and resources. **Anne Huynh:** Writing–review and editing and resources. **Jurjen Versluis:** Writing–review and editing and resources. **Ibrahim Yakoub-Agha:** Writing–review and editing and resources. **Helene Labussiere-Wallet:** Writing–review and editing and resources. **Johan Maertens:** Writing–review and editing and resources. **Jakob Passweg:** Writing–review and editing and resources. **Claude Eric Bulabois:** Writing–review and editing and resources. **Ludovic Gabellier:** Writing–review and editing and resources. **Stephan Mielke:** Writing–review and editing and resources. **Cristina Castilla-Llorente:** Writing–review and editing and resources. **Eric Deconinck:** Writing–review and editing and resources. **Eolia Brissot:** Writing–review and editing and resources. **Arnon Nagler:** Writing–review and editing and resources. **Fabio Ciceri:** Writing–review and editing and resources. **Mohamad Mohty:** Writing–review and editing, resources, supervision, writing–original draft, conceptualization, and funding acquisition.

AFFILIATIONS

[1]University of Birmingham, Birmingham, UK

[2]Dana-Farber Cancer Institute, Boston, Massachusetts, USA

[3]Acute Leukaemia Working Party, Paris Study Office, European Society for Blood and Marrow Transplantation, Paris, France

[4]Hematology Department, AP-HP, Sorbonne Universités, INSERM, Centre de Recherche Saint-Antoine (CRSA), Saint Antoine Hospital, Paris, France

[5]Birmingham Centre for Cellular Therapy and Transplantation, Centre for Clinical Haematology, Queen Elizabeth Hospital, Birmingham, UK

[6]University of Warwick, Warwick, UK

[7]Department of Hematology-BMT, Hopital St. Louis, Paris, France

[8]Hematology Department, Oslo University Hospital, Rikshospitalet Clinic for Cancer Medicine, Oslo, Norway

[9]Programme de Transplantation & Therapie Cellulaire Centre de Recherche en Cancérologie de Marseille, Marseille, France

[10]CHU Bordeaux Hôpital Haut-leveque, Pessac, France

[11]HUCH Comprehensive Cancer Center, Stem Cell Transplantation Unit, Helsinki, Finland

[12]CHU-Institut Universitaire du Cancer Toulouse, Oncopole, Toulouse, France

[13]Erasmus MC Cancer Institute University Medical Center, Rotterdam, Netherlands

[14]CHU de Lille, INSERM U995, Lille, France

[15]Centre Hospitalier Lyon Sud, Pavillon Marcel Bérard, Lyon, France

[16]Department of Hematology, University Hospital Gasthuisberg, Leuven, Belgium

[17]University Hospital, Hematology, Basel, Switzerland

[18]CHU Grenoble Alpes, Service d`Hématologie, Grenoble, France

[19]Département d`Hématologie Clinique, CHU Lapeyronie, Montpellier, France

[20]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden

[21]Department of Hematology, Gustave Roussy Cancer Campus BMT Service, Villejuif, France

[22]Université de Franche-Comté, EFS, INSERM, UMR RIGHT, Besançon, France

[23]Hématologie, CHU Besançon, Besançon, France

[24]Hematology Division, Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel

[25]Hematology and Bone Marrow Transplantation Unit, Università Vita Salute San Raffaele, Milan, Italy

ACKNOWLEDGMENTS

We acknowledge the data collection from all the centers in the European Society for Blood and Marrow Transplantation (EBMT) for maintaining the registry for this work.

CONFLICT OF INTEREST STATEMENT

Didier Blaise reports fees for professional activities from Institut Paoli Calmettes; and consulting fees from Jazz Pharmaceuticals. Eolia Brissot reports consulting fees from Amgen and Astellas Pharma; and participation on an End Point Review Committee for Jazz Pharmaceuticals. Eric Deconinck reports consulting fees from Stemline Therapeutics Inc. Justin Loke reports fees for professional activities from Aptitude Health; and served on a data and safety monitoring board for the National Institute for Health Research. Stephan Mielke reports fees for professional activities from Celgene/Bristol-Myers

Squibb, Janssen Pharmaceuticals, Kite/Gilead, Novartis Pharma, Pfizer, and SWECARNET; and served on a data and safety monitoring board for Mendes/Immunicum and Miltenyi Biotec. Mohamad Mohty reports consulting fees from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Cilag EMEA, Novartis, Pfizer, Sanofi, and Takeda Oncology. Gerard Socie reports consulting fees from Novartis Pharma; served on a data and safety monitoring board for Incyte Corporation; and reports grant and/or contract funding from Alexion Pharmaceuticals. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

REFERENCES

1. Loke J, Malladi R, Moss P, Craddock C. The role of allogeneic stem cell transplantation in the management of acute myeloid leukaemia: a triumph of hope and experience. *Br J Haematol*. 2020;188(1):129-146. doi:10.1111/bjh.16355
2. Loke J, McCarthy N, Jackson AE, et al. Posttransplant MRD and T-cell chimerism status predict outcomes in patients allografted with AML/MDS. *Blood Adv*. 2023;7(14):3666-3676. doi:10.1182/bloodadvances.2022009493
3. Bacigalupo A, Van Lint MT, Occhini D, et al. Increased risk of leukemia relapse with high-dose cyclosporine A after allogeneic marrow transplantation for acute leukemia. *Blood*. 1991;77(7):1423-1428. doi:10.1182/blood.v77.7.1423.1423
4. Rowe JM, Kim HT, Cassileth PA, et al. Adult patients with acute myeloid leukemia who achieve complete remission after 1 or 2 cycles of induction have a similar prognosis: a report on 1980 patients registered to 6 studies conducted by the Eastern Cooperative Oncology Group. *Cancer*. 2010;116(21):5012-5021. doi:10.1002/cncr.25263
5. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377. doi:10.1182/blood.2022016867
6. Craddock C, Labopin M, Pillai S, et al. Factors predicting outcome after unrelated donor stem cell transplantation in primary refractory acute myeloid leukaemia. *Leukemia*. 2011;25(5):808-813. doi:10.1038/leu.2011.13
7. Wheatley K, Burnett AK, Goldstone AH, et al. A simple, robust, validated and highly predictive index for the determination of risk-directed therapy in acute myeloid leukaemia derived from the MRC AML 10 trial. United Kingdom Medical Research Council's Adult and Childhood Leukaemia Working Parties. *Br J Haematol*. 1999;107(1):69-79. doi:10.1046/j.1365-2141.1999.01684.x
8. Walter RB, Sandmaier BM, Storer BE, et al. Number of courses of induction therapy independently predicts outcome after allogeneic transplantation for acute myeloid leukemia in first morphological remission. *Biol Blood Marrow Transplant*. 2015;21(2):373-378. doi:10.1016/j.bbmt.2014.09.022
9. Boyiadzis M, Zhang M-J, Chen K, et al. Impact of pre-transplant induction and consolidation cycles on AML allogeneic transplant outcomes: a CIBMTR analysis in 3113 AML patients. *Leukemia*. 2023;37(5):1006-1017. doi:10.1038/s41375-022-01738-3
10. Craddock C, Jackson A, Loke J, et al. Augmented reduced-intensity regimen does not improve postallogeneic transplant outcomes in acute myeloid leukemia. *J Clin Oncol*. 2021;39(7):768-778. doi:10.1200/jco.20.02308
11. Hourigan CS, Dillon LW, Gui G, et al. Impact of conditioning intensity of allogeneic transplantation for acute myeloid leukemia with genomic evidence of residual disease. *J Clin Oncol*. 2020;38(12):1273-1283. doi:10.1200/jco.19.03011
12. Araki D, Wood BL, Othus M, et al. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia: time to move toward a minimal residual disease-based definition of complete remission? *J Clin Oncol*. 2016;34(4):329-336. doi:10.1200/jco.2015.63.3826
13. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*. 2010;116(3):354-365. doi:10.1182/blood-2009-11-254441
14. Nagler A, Baron F, Labopin M, et al. Measurable residual disease (MRD) testing for acute leukemia in EBMT transplant centers: a survey on behalf of the ALWP of the EBMT. *Bone Marrow Transplant*. 2021;56(1):218-224. doi:10.1038/s41409-020-01005-y
15. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11(12):945-956. doi:10.1016/j.bbmt.2005.09.004
16. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation*. 1974;18(4):295-304. doi:10.1097/00007890-197410000-00001
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53(282):457-481. doi:10.1080/01621459.1958.10501452
18. Abraham SK, Arnon N, Bipin S. Summary of scientific and statistical methods, study endpoints and definitions for observational and registry-based studies in hematopoietic cell transplantation. *Clin Hematol Int*. 2019;2(1):2. doi:10.2991/chi.d.191207.001
19. Craddock C. Transplant in AML with measurable residual disease: proceed or defer? *Hematology*. 2022;2022(1):528-533. doi:10.1182/hematology.2022000353
20. Stelljes M, Middeke JM, Bug G, et al. Patients with relapsed/refractory AML sequential conditioning and immediate allogeneic stem cell transplantation (allo-HCT) results in similar overall and leukemia-free survival compared to intensive remission induction chemotherapy followed by allo-HCT: results from the randomized phase III ASAP trial. *Blood*. 2022;140(suppl 1):9-11. doi:10.1182/blood-2022-159962
21. Nagler A, Labopin M, Huang XJ, et al. Non-T depleted haploidentical stem cell transplantation in AML patients achieving first complete remission after one versus two induction courses: a study from the ALWP/EBMT. *Bone Marrow Transplant*. 2022;57(4):572-578. doi:10.1038/s41409-021-01537-x
22. Döhner H, Pratz KW, DiNardo CD, et al. ELN risk stratification is not predictive of outcomes for treatment-naïve patients with acute myeloid leukemia treated with venetoclax and azacitidine. *Blood*. 2022;140(suppl 1):1441-1444. doi:10.1182/blood-2022-169509
23. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377(5):454-464. doi:10.1056/NEJMoa1614359
24. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus

daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol*. 2018;36(26):2684-2692. doi:10.1200/jco.2017.77.6112

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Loke J, Labopin M, Craddock C, et al. Prognostic impact of number of induction courses to attain complete remission in patients with acute myeloid leukemia transplanted with either a matched sibling or human leucocyte antigen 10/10 or 9/10 unrelated donor: An Acute Leukemia Working Party European Society for Blood and Marrow Transplantation study. *Cancer*. 2024;130(15):2642-2651. doi:10.1002/cncr.35308