Rapid #: -22039775

CROSS REF ID: **49293482760002321**

LENDER: **WEL (Wellesley College) :: Main Library**

BORROWER: **ZXY (University of Liege) :: Main Library**

TYPE:	Article CC:CCG
JOURNAL TITLE:	Bone marrow transplantation
USER JOURNAL TITLE:	Bone marrow transplantation.
ARTICLE TITLE:	Allogeneic hematopoietic stem cell transplantation for adults with therapy-related acute myeloid leukaemia: a retrospective multicentre study on behalf of the SFGM-TC
ARTICLE AUTHOR:	Gaëlle Rey
VOLUME:	58
ISSUE:	12
MONTH:	
YEAR:	2023
PAGES:	1331-1338
ISSN:	0268-3369
OCLC #:	

Processed by RapidX: 2/12/2024 7:41:02 AM

ARTICLE

Check for updates

Allogeneic hematopoietic stem cell transplantation for adults with therapy-related acute myeloid leukaemia: a retrospective multicentre study on behalf of the SFGM-TC

Gaëlle Rey[1], Elisabeth Daguenet[2], Paul Bonjean[3], Raynier Devillier[4], Nathalie Fegueux[5], Edouard Forcade[6], Micha Srour[7], Patrice Chevallier[8], Marie Robin[9], Felipe Suarez[10], Jean-Baptiste Micol[11], Hélène Labussière-Wallet[12], Karin Bilger[13], Etienne Daguindau[14], Jacques-Olivier Bay[15], Amandine Fayard[15], Claude-Eric Bulabois[16], Stéphanie Nguyen-Quoc[17], Alexis Genthon[18], Corentin Orvain[19], Pascal Turlure[20], Michael Loschi[21], Xavier Poiré[22], Gaëlle Guillerm[23], Yves Beguin[24], Natacha Maillard[25], Jean-Baptiste Mear[26], Emilie Chalayer[1], Jérôme Cornillon[1] and Emmanuelle Tavernier[1]✉

We report the results from a multicentre retrospective study of 220 adult patients who underwent allogeneic hematopoietic stem cell transplantation (alloHSCT) for therapy-related acute myeloid leukaemia (t-AML). Median age at t-AML diagnosis was 56 years, with a prior history of haematological (45%) or breast (34%). Median time from cytotoxic exposure to t-AML diagnosis was 54.7 months. At transplant, around 20% of patients had measurable residual disease and 3% of patients were not in complete remission. The median follow-up was 21.4 months (Q1–Q3, 5.9–52.8). At 12 months, overall survival (OS), event-free survival (EFS), and graft-versus-host-disease (GVHD)-free-relapse-free survival (GRFS) were 60.7% (95% CI 54.6–67.5), 52.8% (95% CI 46.5–68.4), and 44.1% (95% CI 37.6–51.8), respectively. At 5 years, OS, EFS, and GRFS were 44.1% (95% CI 37.4–52.1), 40.4% (95% CI 33.9–48.1), and 35.3% (95% CI 28.8–43.3), respectively. At last follow-up, 44% of patients were in complete remission ($n = 96$) and transplant-related mortality accounted for 21% of all deaths ($n = 119$). Multivariable analysis revealed that uncontrolled t-AML at transplant was associated with lower EFS (HR 1.94, 95% CI 1.0–3.7, $p = 0.041$). In conclusion, alloHSCT for t-AML shows encouraging results and offers additional opportunity with the emergence of novel pre-graft therapies.

Bone Marrow Transplantation (2023) 58:1331–1338; https://doi.org/10.1038/s41409-023-02082-5

INTRODUCTION

Therapy-related acute myeloid leukaemia (t-AML) is defined as a clonal proliferation and expansion of abnormal differentiated myeloid blasts, as a consequence of exposure to cytotoxic therapy [1]. It results from mutational events induced by radiotherapy or chemotherapy. Indeed, cytotoxic therapies have the ability to induce mutagenic and clastogenic DNA damage, thus leading to genomic instability. Moreover, hematopoietic stem/progenitors cells that acquired heterozygous TP53 mutations upon aging are resistant to chemotherapy and preferentially expand after treatment [2]. Given that the bone marrow is highly sensitive to mutagenic effects, there are 4.7 times greater risk to develop leukaemia after therapy [3–5]. Among chemotherapies, the best known agents are alkylating agents and topoisomerase II inhibitors, and immunosuppressive therapies, methylating agents and thiopurines are also proven to be in cause [3, 4].

In recent years, the incidence of t-AML increased due to the improvement of survival and greater life expectancy in patients treated for cancer [6–9]. Based on a Swedish study, the incidence of t-AML almost doubled between 1997 and 2015, from a mean of 0.39 cases per 100,000 adult inhabitants between 1997 and 2006 to 0.63 between 2007 and 2015 [10]. In adults, t-AML accounts for approximately 5–10% of all AMLs [11, 12]. Despite recent advances, t-AMLs remain of poor prognosis. The median survival for t-AML patients treated with standard chemotherapy is about 8–14 months [4, 13]. In this context, allogeneic hematopoietic stem cell transplantation

[1]Département d'hématologie clinique, Centre Hospitalier Universitaire de Saint-Étienne, Saint-Priest-en-Jarez, France. [2]Département Universitaire de Recherche et d'Enseignement, Centre Hospitalier Universitaire de Saint-Étienne, Saint-Priest-en-Jarez, France. [3]Unité de Recherche Clinique Innovation Pharmacologique, Centre Hospitalier Universitaire de Saint-Étienne, Saint-Priest-en-Jarez, France. [4]Institut Paoli Calmette, Marseille, France. [5]Hôpital Saint Eloi, Centre Hospitalier Universitaire de Montpellier, Montpellier, France. [6]Centre Hospitalier Universitaire Haut-Lévêque Magellan, Bordeaux, France. [7]Hôpital Claude Hurriez, Centre Hospitalier Universitaire de Lille, Lille, France. [8]Centre Hospitalier Universitaire Hôtel-Dieu, Nantes, France. [9]Hôpital Saint-Louis, APHP, Université de Paris Cité, Paris, France. [10]Hôpital Necker, Paris, France. [11]Institut Gustave Roussy, Villejuif, France. [12]Hôpital Lyon Sud, Centre Hospitalier Universitaire de Lyon, Lyon, France. [13]Centre Hospitalier Universitaire Hautepierre, Strasbourg, France. [14]Centre Hospitalier Universitaire Jean Minjoz, Besançon, France. [15]Hôpital Estaing, Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France. [16]Centre Hospitalier Universitaire de Grenoble, Grenoble, France. [17]Hôpital Pitié-Salpêtrière, Paris, France. [18]Hôpital Saint-Antoine, Paris, France. [19]Centre Hospitalier Universitaire d'Angers, Angers, France. [20]Centre Hospitalier Universitaire Dupuytren, Limoges, France. [21]Hôpital de l'Archet, Centre Hospitalier Universitaire de Nice, Nice, France. [22]Cliniques Universitaires St. Luc, Brussels, Belgium. [23]Centre Hospitalier Universitaire Augustin Morvan, Brest, France. [24]CHU of Liège and University of Liège, Liège, Belgium. [25]Hôpital Jean Bernard, Poitiers, France. [26]Centre Hospitalier Universitaire de Rennes, Rennes, France. ✉email: emmanuelle.tavernier@chu-st-etienne.fr

Received: 24 February 2023 Revised: 20 July 2023 Accepted: 3 August 2023
Published online: 31 August 2023

(alloHSCT) provides a curative approach for these patients. Unfortunately, little data are available in literature on alloHSCT in t-AML patients, mainly because these patients were excluded from clinical trials. Moreover, the existing literature on t-AML is often confounded by the inclusion of therapy-related myelodysplastic syndromes (t-MDS) and/or secondary AML (transformed from MDS or myeloproliferative neoplasms, s-AML) [14]. While allograft could be thought not to be beneficial to t-AML patients, due to unfavourable AML prognosis and a high transplant-related mortality, we conducted this analysis to describe clinical outcomes of t-AML patients who underwent alloHSCT and to demonstrate the impact of this procedure in this fragile and heavily treated population.

METHODS

Data sources

This study was approved by the scientific committee of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC). Data were collected from the SFGM-TC transplant registry, the ProMISe database, from 24 transplantation centres in France and Belgium. Centres contributed detailed clinical, pathological, and outcome data to the registry as well as additional characteristics on primary tumour. All patients were included in the registry and gave their written informed consent for data acquisition and analysis.

Patient selection and procedures

Patients with t-AML who were ≥18 year old and underwent alloHSCT between 2013 and 2019 were studied. Patients with prior malignancy but without exposure to cytotoxic agents or radiotherapy were excluded, as well as secondary AML (occurring after a myeloid disease, e.g. myelodysplastic syndrome or myeloproliferative disorder) with no cytotoxic therapy exposure. Based on the cytogenetic and molecular results, patients were stratified into favourable, intermediate, and poor risk categories following the MRC classification [15] and ELN-2017 risk stratification system [16]. GVHD prophylaxis consisted of a combination between antilymphocyte serum, an anticalcineurin and methotrexate in MAC patients with HLA allele-matched donor. In RIC patients with HLA allele-matched donor, thymoglobulin and an anticalcineurin were administered. Finally, for patients with mismatched donor, high-dose cyclophosphamide was added to an anticalcineurin and mycophenolate mofetil, except for cord blood unit in which an anticalcineurin was combined to mycophenolate mofetil.

Study endpoints

Clinical outcomes included overall survival (OS), event-free survival (EFS), therapy-related mortality (TRM), and survival free from grade III-IV acute graft - versus - host disease (GVHD), chronic GVHD, and relapse (GRFS). OS was defined as the time from alloHSCT to death from any cause. EFS was defined as the time to t-AML relapse or death from any cause and surviving patients in continuous complete response (CR) were censored at the time of last contact. Relapse was defined as detection of the disease from any biological evidence, including cytology, flow cytometry, cytogenetic and molecular data. TRM was defined as death in remission from specific cause: infection, GVHD and other causes related to alloHSCT (including organ dysfunction). GRFS was defined as survival without grade III-IV acute GVHD, systemic therapy-requiring chronic GVHD, or relapse.

Statistical analyses

Patient characteristics were described using numbers and proportions for categorical variables and using mean, standard deviation, median and interquartile range for continuous variables. OS, EFS and GRFS were estimated with the Kaplan–Meier method. Univariate and multivariate analyses with Cox regression models were conducted to assess the association of baseline characteristics with OS and EFS. Patients with missing data on at least one variable of interest were excluded from the multivariable model and their characteristics were compared with those included in the models to detect potential attrition bias. All results were expressed as hazard ratios (HR) with 95% confidence intervals (95% CI) and all tests were performed with a two-sided alpha risk of 5%. Statistical analyses were performed with R software version 3.6.2.

Table 1. Patient and tumour characteristics at baseline ($n = 220$)[a].

Characteristics	
Median age, y (range), $N = 220$	56 (18–74)
Sex, female no. (%), $N = 220$	133 (61)
Prior tumour	
Organ system, no. (%), $N = 219$	
Haematological	98 (45)
Lymphoid neoplasia	67 (31)
Acute leukaemia	13 (6)
Myeloproliferative neoplasia	8 (4)
Myeloma	5 (2)
Other	5 (2)
Breast	74 (34)
Urological	13 (6)
Digestive	11 (5)
Others	23 (10)
Cytotoxic agent, no. (%)[b]	
Alkylating agents, $N = 207$	147 (71)
Nitrogen mustard	113 (55)
Platins	35 (17)
Others	33 (16)
Antimetabolite, $N = 207$	95 (46)
Purine analogue	16 (7)
Antifolate	13 (6)
Pyrimidine analogue	77 (37)
Topoisomerase inhibitors, $N = 207$	127 (61)
Topoisomerase inhibitor type I	30 (15)
Topoisomerase inhibitor type II	122 (59)
Spindle poison, $N = 207$	102 (49)
Vinca alkaloids	63 (30)
Taxanes	40 (19)
Other drugs, $N = 210$	65 (31)
Radiotherapy, no. (%), $N = 217$	102 (47)
t-AML	
Median time between cytotoxic exposure and diagnosis of t-AML, months (range), $N = 217$	54.7 (2.3–441.8)
Cytogenetics – MRC classification, no. (%), $N = 213$	
Favourable	13 (6)
Intermediate	109 (51)
Adverse	91 (42.7)
ELN 2017 risk category, no. (%), $N = 197$	
Favourable	27 (14)
Intermediate	70 (35)
Adverse	100 (51)

no. number, *t-AML* therapy-related acute myeloid leukaemia, *y* years.
[a]Percentages are calculated out of the amount of data available.
[b]Most patients received several drugs from the same antineoplastic class.

RESULTS

Baseline patient, disease, and treatment characteristics

A total of 220 t-AML patients who underwent alloHSCT between 2013 and 2019 were included. Patient and prior tumour characteristics are detailed in Table 1. Median age at diagnosis of AML was 56 years [range, 18–74], with a majority of women (61%). Patients mainly presented history of haematological (45%)

and breast (34%) neoplasia. Most patients received multiple drug chemotherapy and radiotherapy. There was a predominance of alkylating agents (71%) followed by topo-isomerase inhibitors (61%), spindle poison agents (49%), radiotherapy (47%) and anti-metabolites (46%). Median time from cytotoxic exposure to t-AML diagnosis was 54.7 months. Cytogenetic scores showed that 51% had intermediate risk or 43% had poor risk. Of note, 41 patients had monosomic and/or complex karyotype, including 19 patients with abnormality of the short arm of chromosome 17. At the molecular level, 14% had favourable profile, 36% had intermediate risk and 51% had adverse risk genetic profile. All patients received at least one induction therapy.

Transplant characteristics

Median time from t-AML diagnosis to alloHSCT was 5.5 months. Transplant characteristics are summarised in Table 2. At the time of transplant, 3.1% of patients had uncontrolled disease. For 18% of patients, disease was still detectable on the pre-graft bone marrow evaluation. The Karnofsky score at diagnosis was ≥90 in 62% of patients. Preparative regimen was either myeloablative (MAC) (30%), non-myeloablative/reduced intensity (NMA/RIC) (62%) or sequential (9%) (Supplementary Table 1). Most patients received a 10/10 HLA-matched graft (58%). Mobilised peripheral blood was the stem cell source in 85% of patients and umbilical cord blood (UCB) for 5% of them. Median time of engraftment was 17 days.

Clinical outcomes

Median follow-up time of the cohort was 21.4 months (IQ [5.9–52.8]). At day 100, 88% of evaluated patients were in CR ($n = 84$) and 74% of evaluated patients had a full donor chimerism ($n = 83$). Acute GVHD occurred in 47% of patients, including mostly grade I-II (76%) and cGVHD occurred in 32% of patients with 49% of them having limited cGVHD. Relapse of t-AML was detected in 38% of patients at a median onset of 4 months. Among them, 7% also had a progressive prior tumour after transplantation. Post-graft treatments were introduced for 35% patients, i.e. for t-AML relapse (27%) and as a pre-emptive therapy (5%) (Supplementary Table 2). Palliative care was provided for 2% of patients.

At last follow-up, 44% patients were in CR ($n = 96$), 2% were alive with t-AML relapse, 1% were alive with relapse of prior tumour and 54% died. The main cause of death was t-AML relapse (52%), followed by infectious complications (22%), GVHD (9%), other HSCT-related toxicities (8%), and relapse of prior tumour (4%). Of note, three patients died from another neoplasia following transplantation. The causes of TRM were infections (55%, $n = 27$), GVHD (20%, $n = 10$), multiple organ failure (10%, $n = 5$), post-transplant neoplasia (4%, $n = 2$), allergy (2.0%, $n = 1$), graft failure (2%, $n = 1$) and non-specified (6%, $n = 3$). TRM was non-significantly lower in the RIC/NMA group (33%) compared to MAC (47%) and sequential conditioning (53%) ($p = 0.157$).

Survival endpoints

Overall survival. Median OS was 31 months (95% CI 8.1-NR). One-year and 5-year OS post-transplant were respectively 60.7% (95% CI 54.6–67.5) and 44.1% (95% CI 37.4–52.1) (Fig. 1). Univariate analysis showed a significant association between adverse cytogenetics (HR 1.70, 95% CI 1.2–2.5, $p = 0.005$), molecular risk categories (HR 1.90, 95% CI 1.0–3.6, $p = 0.049$), uncontrolled t-AML at transplantation (HR 1.78, 95% CI 1.2–2.7, $p = 0.007$), sequential conditioning regimen (HR 2.03, 95% CI 1.2–3.9, $p = 0.009$) and OS (Table 3). A pre-transplantation Karnofsky score at diagnosis ≥90 was associated with better OS (HR 0.59, 95% CI 0.4–0.9, $p = 0.011$). However, in multivariable analysis, no variable was independently associated with OS (Table 4).

Table 2. Transplant-related characteristics and AlloHSCT outcomes[a].

AlloHSCT characteristics	
Prior tumour status at transplantation, no. (%), $N = 193$	
Complete response	178 (92)
Stable/untreated	8 (4)
Uncontrolled	6 (3)
Partial response	1 (1)
t-AML status at the time of transplant, no. (%), $N = 218$	
CR	178 (82)
Not in CR	40 (18)
Karnofsky at transplantation, no. (%), $N = 181$	
≥90%	113 (62)
<90%	68 (38)
Stem cells source, no. (%), $N = 207$	
Peripheral blood	176 (85)
Bone marrow	20 (10)
Cord blood	11 (5)
HLA match, no. (%), $N = 207$	
Matched sibling (10/10)	64 (31)
Matched unrelated (10/10)	56 (27)
Mismatched unrelated (9/10, CBU)	54 (26)
Mismatched sibling (5/10)	33 (16)
Conditioning therapy, no. (%), $N = 220$	
RIC/NMA	136 (62)
MAC	65 (30)
Sequential	19 (9)
Median time of hematopoietic recovery, day (range), N = 208	17 (0–37)
Acute GVHD, no. (%), $N = 213$	101 (47)
Grade I	34 (34)
Grade II	43 (43)
Grade III-IV	20 (20)
UK	4 (4)
Chronic GVHD, no. (%), $N = 205$	67 (32)
Limited	33 (49)
Extensive	30 (45)
UK	4 (6)
Response at D100, no. (%), $N = 95$	
CR	84 (88)
Cytological relapse	10 (11)
Molecular relapse	1 (1)
Chimerism at D100, no. (%), $N = 113$	
Full donor	83 (74)
Partial	26 (23)
Failure	4 (4)
Post-graft treatments, no. (%), $N = 215$	
None	137 (64)
Anti-leukaemic treatments	60 (27)
Pre-emptive treatment	10 (5)
Palliative care	5 (2)
UK	2 (1)
Second alloHSCT, no. (%), $N = 220$	17 (8)

CBU cord blood unit, *CR* complete response, *D100* Day 100 after transplant, *GVHD* graft-versus-host disease, *MAC* myeloablative conditioning, *NMA* non-myeloablative conditioning, *no.* number, *RIC* reduced-intensity conditioning, *t-AML* therapy-related acute myeloid leukaemia, *UK* unknown.

[a]Percentages are calculated out of the amount of data available.

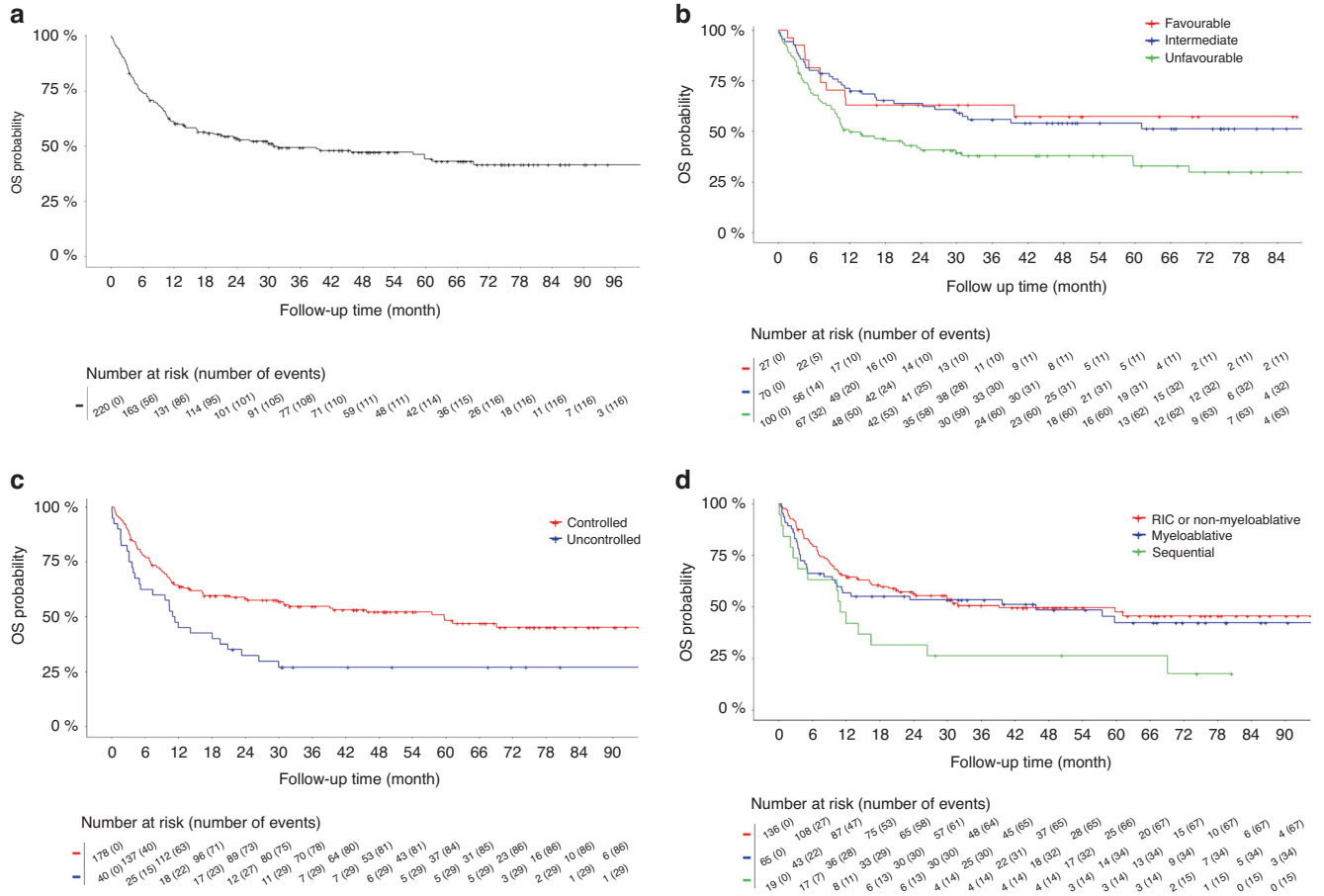

Fig. 1 Overall survival after transplant within the entire cohort and subgroups of patients. a Entire cohort ($N = 220$). **b** Subgroup analysis by molecular risk category. **c** Subgroup analysis by AML status at transplantation. **d** Subgroup analysis by graft conditioning.

Event-free survival. Median EFS was 16.3 months (95% CI 9.9–40.8). One-year and 5-year EFS were respectively estimated at 52.8% (95% CI 46.5–68.4) and 40.4% (95% CI 33.9–48.1), with most relapse events occurring in the first 2 years (Fig. 2). Univariate analysis showed a significant association between adverse cytogenetics (HR 1.60, 95% CI 1.1–2.3, $p = 0.009$), uncontrolled t-AML at transplantation (HR 1.97, 95% CI 1.3–3.0, $p = 0.001$), sequential conditioning regimen (HR 2.39, 95% CI 1.4–4.1, $p = 0.001$), and EFS (Table 3). In multivariable analysis, uncontrolled t-AML at transplantation was the only independent variable associated with lower EFS (HR 1.94, 95% CI 1.0–3.7, $p = 0.041$) (Table 4). Furthermore, myeloablative conditioning regimen was non-significantly associated with EFS (HR 0.59, 95% CI 0.3–1.0, $p = 0.066$) in multivariable analysis.

Graft-versus-host disease-free relapse-free survival. Median GRFS was 6.3 months (95% CI 4.7–13.4). One-year and 5-year GRFS were respectively estimated at 44.1% (95% CI 37.6–51.8) and 35.3% (95% CI 28.8–43.3), with most events occurring during the first two years (Fig. 3).

DISCUSSION

AML is a highly heterogeneous disease, requiring individualised treatment approaches. Of note, t-AML has a unique pathogenesis and clinical course, and its prognosis is usually poor. AlloHSCT offers a potentially curative treatment for t-AML patients. However, the subsequent toxicities of this procedure and the difficulty to obtain CR often prevent from choosing this therapeutic option. Although outcomes after alloHSCT have improved [17], it remains poor for t-AML patients due to their neoplasia history, comorbidities and poor prognosis of t-AML per se. This manuscript describes the outcomes for alloHSCT in t-AML patients after retrospective analysis from a large representative cooperating group.

In this cohort, 5-year OS and 5-year EFS were respectively of 44.1% and 40.4%. These results are promising. In a CIBMTR study analysing data of t-AML patients who underwent alloHSCT between 2000 and 2014, Metheny et al. reported a 5-year OS and 5-year EFS of 25% and 23%, respectively [18]. The CIBMTR population was overall similar to our cohort, with comparable median age and prognostic groups, as well as a majority of women. Differences in outcomes between these two studies might be explained by the fact that CIBMTR patients were treated 5 years earlier, while novel therapies and post-engraftment treatments have since emerged, thus improving OS and EFS [19]. Substantive progresses have been made during the last decade. In the CIBMTR study, there was no data about pre-emptive treatment in post-graft period, probably because these strategies were not available. Here, about 5% of patients received a pre-emptive post-graft treatment, with further expected improvement. For instance, only five patients received donor lymphocyte infusion (DLI) in this cohort. Considering the high risk of relapse, the use of DLI, alone or in association with other pre-emptive treatment, should be systematically considered for t-AML patients. Moreover, there is a noticeable difference in the use of MAC conditioning. Indeed, the CIBMTR study reported 61% of MAC conditioning, whereas there was only 29.5% of patients in the present study. We therefore suggest that MAC might not be the most appropriate conditioning therapy for t-AML patients,

Table 3. Univariate analysis of OS and EFS.

Variable	OS			EFS		
	N	HR (95% CI)	*p* value	*N*	HR (95% CI)	*p* value
Prior tumour						
Haematological	98			96		
Gynaecological & breast neoplasia	82	1.14 (0.76–1.69)	0.529	80	1.08 (0.73–1.60)	0.683
Urological	13	1.00 (0.43–2.34)	0.995	13	1.50 (0.76–2.94)	0.243
Digestive	11	0.83 (0.33–2.07)	0.683	11	0.69 (0.28–1.73)	0.432
Others	15	1.08 (0.53–2.19)	0.833	15	1.00 (0.49–2.01)	0.990
Cytotoxic agent						
Alkylating agents	147	0.95 (0.63–1.43)	0.804	145	0.95 (0.64–1.41)	0.789
Antimetabolites	95	1.10 (0.76–1.59)	0.615	94	0.93 (0.65–1.33)	0.706
Topoisomerase inhibitors	127	1.08 (0.69–1.69)	0.728	125	1.11 (0.77–1.61)	0.571
Spindle poison	102	1.33 (0.92–1.93)	0.130	101	1.35 (0.95–1.93)	0.098
Radiotherapy	102	1.03 (0.71–1.47)	0.895	99	0.85 (0.60–1.21)	0.373
Time between cytotoxic exposure and diagnosis of t-AML	217	0.99 (0.99–1.01)	0.552	213	0.99 (0.99–1.01)	0.867
Age at diagnosis						
< 60 years	127			126		
≥ 60 years	93	0.89 (0.61–1.29)	0.544	90	0.76 (0.53–1.10)	0.149
Karyotype risk category						
Favourable/intermediate	122			120		
Adverse	91	1.70 (1.18–2.45)	0.005	89	1.60 (1.12–2.28)	0.009
Molecular risk category						
Favourable	27			27		
Intermediate	70	1.11 (0.56–2.20)	0.763	68	1.08 (0.57–2.04)	0.809
Adverse	100	1.90 (1.00–3.61)	0.0496	98	1.79 (0.99–3.25)	0.055
Karnofsky score at transplantation						
<90%	68			65		
≥90%	113	0.59 (0.39–0.88)	0.011	113	0.70 (0.47–1.05)	0.082
t-AML status at the time of transplant						
CR	178			175		
Not in CR	40	1.58 (0.9–2.9)	0.007	39	1.97 (1.30–3.00)	0.001
Stem cell source						
Peripheral blood	176			173		
Bone marrow	20	1.19 (0.63–2.22)	0.593	20	0.95 (0.51–1.78)	0.876
Cord blood	11	0.93 (0.38–2.29)	0.875	11	0.82 (0.34–2.03)	0.673
HLA match						
10/10	87			85		
Haplo-identical and others	120	0.97 (0.66–1.43)	0.882	119	0.96 (0.66–1.39)	0.833
Conditioning regimen						
RIC/NMA	136			132		
MAC	65	1.18 (0.79–1.77)	0.425	65	1.07 (0.72–1.59)	0.728
Sequential	19	2.03 (1.16–3.56)	0.013	19	2.39 (1.41–4.07)	0.001

given their comorbidities and previous treatments. Besides, clinical practices are also differing, especially regarding HLA matching. In the CIBMTR study, only six loci were evaluated to determine HLA matching, whereas 10 loci were explored in the present study. In addition, we also noticed that the graft source was more often peripheral blood in our study (85% vs 70% in the CIBMTR study), maybe favouring a better graft versus leukaemia activity. Therefore, these parameters might explain differences in terms of OS and EFS, including eligibility criteria for alloHSCT and graft management that vary between centres. Finally, the present study was conducted on the threshold of novel therapies, such as CPX-351 and venetoclax, reflecting the most recent outcomes to be observed and to be further expected with the use of these strategies.

Whereas the main cause of death was relapse of t-AML, we report a TRM of 21%, which is better than other studies about t-AML [18, 20] and may be more comparable to studies including de novo AML [21–23]. The leading cause of TRM was infectious complications.

Moreover, the 1-year and 5-year GRFS were 44.1% and 35.3%. This result suggests that benefit from alloHSCT is not only gain in survival but also from the standpoint of quality of life. It is interesting to note that GRFS curve was not modified after 18–24 months, suggesting a stable outcome from the second year

Table 4. Multivariable analysis of OS and EFS[a].

Variable	OS			EFS		
	N	HR (95% CI)	*p* value	*N*	HR (95% CI)	*p* value
Age at diagnosis						
<60 years	–			126		
≥60 years	–	–	–	90	0.69 (0.42–1.13)	0.137
Karyotype risk category						
Favourable/intermediate	122			120		
Adverse	91	2.08 (0.60–7.26)	0.251	89	1.53 (0.55–4.25)	0.412
Molecular risk category						
Favourable	27			27		
Intermediate	70	1.01 (0.43–2.37)	0.984	68	0.81 (0.37–1.77)	0.601
Adverse	100	1.02 (0.26–4.04)	0.975	98	1.00 (0.32–3.12)	0.996
Karnofsky score at transplantation						
<90%	68			65		
≥90%	113	0.73 (0.47–1.15)	0.173	113	0.83 (0.53–1.29)	0.408
t-AML status at the time of transplant						
CR	178			175		
Not in CR	40	1.58 (0.95–2.60)	0.082	39	1.94 (1.03–3.67)	0.041
Conditioning regimen						
RIC/NMA	136			132		
MAC	65	0.71 (0.40–1.25)	0.230	65	0.59 (0.34–1.03)	0.066
Sequential	19	1.39 (0.65–2.99)	0.394	19	1.30 (0.60–2.84)	0.500

[a]Only variables with univariate *p*-value < 0.2 were included in the multivariable analysis.

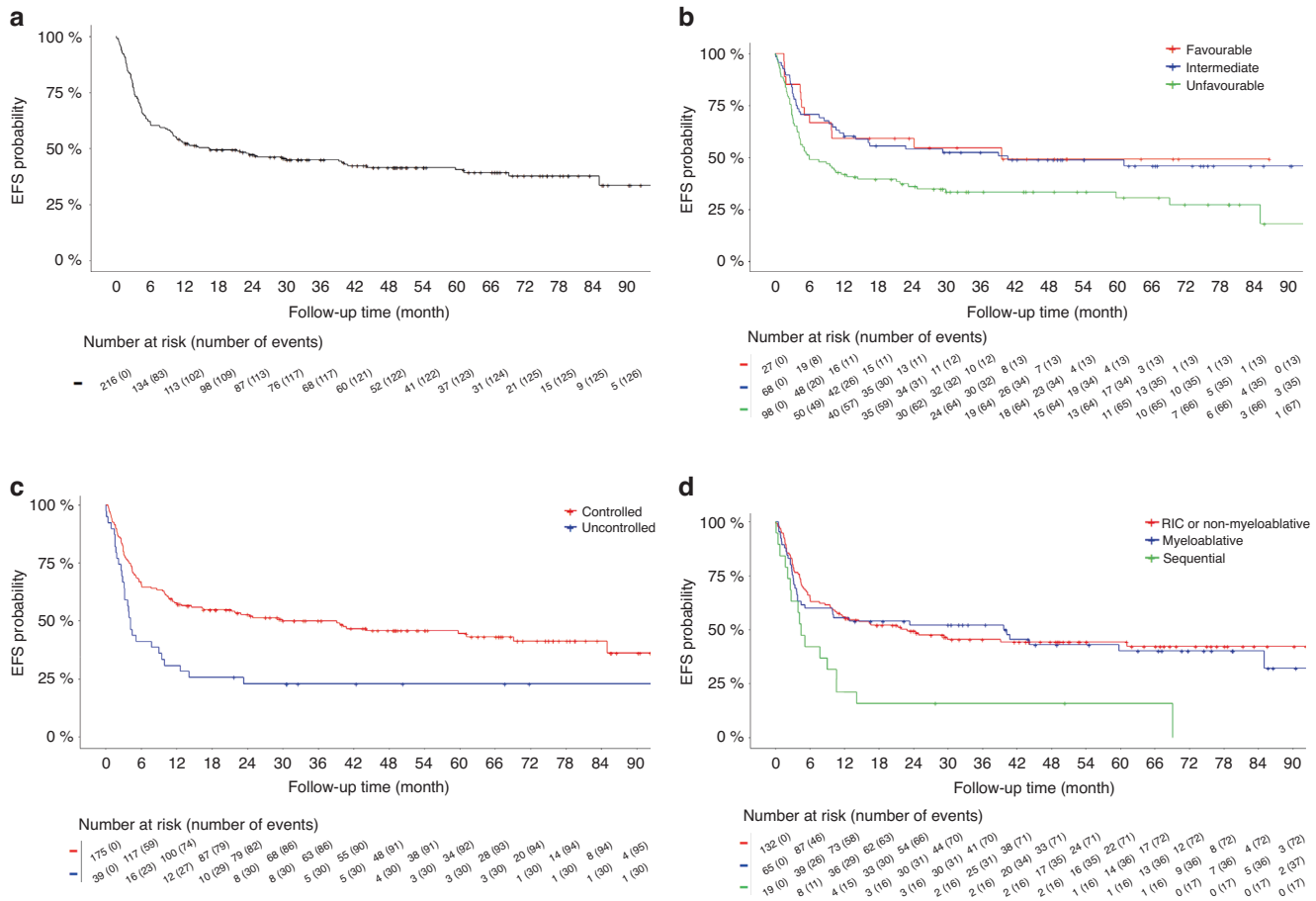

Fig. 2 Event-free survival after transplant within the entire cohort and subgroups of patients. a Entire cohort ($N = 216$). **b** Subgroup analysis by molecular risk category. **c** Subgroup analysis by AML status at transplantation. **d** Subgroup analysis by graft conditioning.

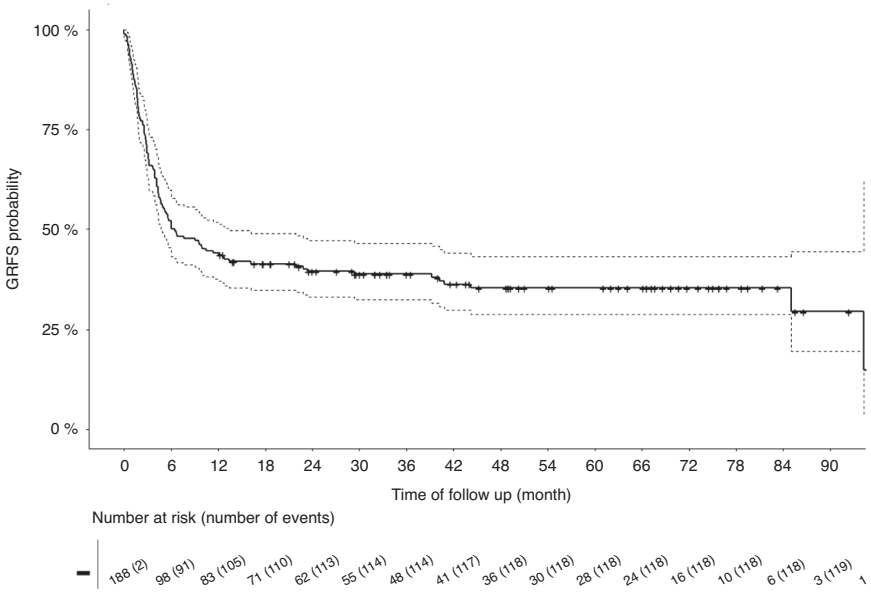

Fig. 3 Graft-versus-host disease-free relapse-free survival within the entire cohort. $N = 188$.

after transplant. This result is comparable with GRFS of de novo AML [24–26] and is better than GRFS of s-AML patients (including t-AML and AML following other myeloid neoplasm, treated or not) who underwent alloHSCT before 2016 [25, 27, 28]. An EBMT study about outcomes in t-AML patients transplanted between 2000 and 2016 found a 2-year GRFS of 23%, with no information about HLA matching and stem cell source [20].

Eligibility for alloHSCT partially relies on scoring systems to assess pre-transplant comorbidity, such as the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) [29, 30]. Based on HCT-CI, a prior history of solid tumour (excluding non-melanoma skin cancer) should be scored with 3 points. Indeed, HCT-CI score ≥ 3 was associated with a two-year OS of 39%. However, in this cohort, we observed a 5-year OS of 44.1%. Since the evaluation of this score, several changes in clinical practices and patient management may explain this difference. Moreover, HCT-CI was not applicable to alternative graft source [31, 32]. More recently, another study showed that cancer comorbidity did not impair 2-year OS [33]. These data suggest that this comorbidity score may not be applicable to all AML patients, especially t-AML patients for whom alloHSCT is the only therapeutic option. Indeed, we can assume that 35% of high-risk patients in our cohort were alive with a good quality of life and leukaemia-free at five years. These observations are encouraging results, even if there was a bias as only most fit patients and in remission received alloHSCT. However, considering recent advances in pre-graft therapy, such as CPX-351 [34–36] and the association of azacytidine and venetoclax [37, 38], there are still opportunities that more t-AML patients will be able to achieve complete response and to benefit from alloHSCT.

In conclusion, we reported data of 220 t-AML patients who underwent alloHSCT between 2013 and 2019. This study spanned a six-year period and included patients from 22 French centres and 2 Belgian centres, which gives a broad perspective on the management and outcomes of alloHSCT in t-AML patients. It showed an improvement in the management and the outcome of these patients, although alloHSCT was undertaken in older patients. However, t-AML prognosis remains poorer compared to de novo AML. With future pre-emptive anti-leukaemic targeted therapies following alloHSCT, such as FLT3 or IDH inhibitors, and a better understanding of physiopathology, there are further options to improve the survival of t-AML patients.

DATA AVAILABILITY

All data supporting this article are provided in the manuscript (Tables 1–4; Figs. 1, 2 and 3; Supplementary Data 1 and 2).

REFERENCES

1. McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. Nat Rev Cancer. 2017;17:513–27.
2. Wong TN, Ramsingh G, Young AL, Miller CA, Touma W, Welch JS, et al. The role of TP53 mutations in the origin and evolution of therapy-related AML. Nature. 2015;518:552–5.
3. Allan JM, Travis LB. Mechanisms of therapy-related carcinogenesis. Nat Rev Cancer. 2005;5:943–55.
4. Larson RA. Etiology and management of therapy-related myeloid leukemia. Hematology. 2007;2007:453–9.
5. Nenova I, Grudeva-Popova J. Carcinogenic potential of antitumor therapies - is the risk predictable? J BUON. 2017;22:1378–84.
6. Morton LM, Dores GM, Tucker MA, Kim CJ, Onel K, Gilbert ES, et al. Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. Blood. 2013;121:2996–3004.
7. Borthakur G, Estey EE. Therapy-related acute myelogenous leukemia and myelodysplastic syndrome. Curr Oncol Rep. 2007;9:373–7.
8. Cancer Survivorship --- United States, 1971–2001. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5324a3.htm (accessed 20 Sep2021).
9. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019;69:363–85.
10. Nilsson C, Linde F, Hulegårdh E, Garelius H, Lazarevic V, Antunovic P, et al. Characterization of therapy-related acute myeloid leukemia: increasing incidence and prognostic implications. Haematologica. 2022. https://doi.org/10.3324/haematol.2022.281233.
11. Granfeldt Østgård LS, Medeiros BC, Sengeløv H, Nørgaard M, Andersen MK, Dufva IH, et al. Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a national population-based cohort study. JCO. 2015;33:3641–9.
12. Churpek JE, Larson RA. The evolving challenge of therapy-related myeloid neoplasms. Best Pract Res Clin Haematol. 2013;26:309–17.
13. Hulegårdh E, Nilsson C, Lazarevic V, Garelius H, Antunovic P, Derolf ÅR, et al. Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish Acute Leukemia Registry. Am J Hematol. 2015;90:208–14.
14. Nampoothiri RV, Law AD, Lam W, Chen C, Al-Shaibani Z, Loach D, et al. Predictors of outcomes of therapy-related acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation. Hematol Oncol Stem Cell Ther. 2022;15:27–35.
15. Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH, 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;116:354–65.
16. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129:424–47.
17. McDonald GB, Sandmaier BM, Mielcarek M, Sorror M, Pergam SA, Cheng G-S, et al. Survival, nonrelapse mortality, and relapse-related mortality after allogeneic hematopoietic cell transplantation: comparing 2003–2007 versus 2013–2017 cohorts. Ann Intern Med. 2020;172:229.
18. Metheny L, Callander NS, Hall AC, Zhang M-J, Bo-Subait K, Wang H-L, et al. Allogeneic transplantation to treat therapy-related myelodysplastic syndrome and acute myelogenous leukemia in adults. Transplant Cell Ther. 2021;27:923.e1–923.e12.
19. Döhner H, Wei AH, Löwenberg B. Towards precision medicine for AML. Nat Rev Clin Oncol. 2021;18:577–90.
20. Lee CJ, Labopin M, Beelen D, Finke J, Blaise D, Ganser A, et al. Comparative outcomes of myeloablative and reduced-intensity conditioning allogeneic hematopoietic cell transplantation for therapy-related acute myeloid leukemia with prior solid tumor: a report from the acute leukemia working party of the European society for blood and bone marrow transplantation. Am J Hematol. 2019;94:431–8.
21. Bastida JM, Cabrero M, Lopez-Godino O, Lopez-Parra M, Sanchez-Guijo F, Lopez-Corral L, et al. Influence of donor age in allogeneic stem cell transplant outcome in acute myeloid leukemia and myelodisplastic syndrome. Leuk Res. 2015;39:828–34.
22. Tomizawa D, Tanaka S, Kondo T, Hashii Y, Arai Y, Kudo K, et al. Allogeneic hematopoietic stem cell transplantation for adolescents and young adults with acute myeloid leukemia. Biol Blood Marrow Transplant. 2017;23:1515–22.
23. Goyal SD, Zhang M-J, Wang H-L, Akpek G, Copelan EA, Freytes C, et al. Allogeneic hematopoietic cell transplant for AML: no impact of pre-transplant extramedullary disease on outcome. Bone Marrow Transpl. 2015;50:1057–62.
24. Yokohama Cooperative Study Group for Hematology (YACHT), Ando T, Fujisawa S, Teshigawara H, Ogusa E, Ishii Y, et al. Impact of treatment-related weight changes from diagnosis to hematopoietic stem-cell transplantation on clinical outcome of acute myeloid leukemia. Int J Hematol. 2019;109:673–83.
25. Schmaelter A-K, Labopin M, Socié G, Itälä-Remes M, Blaise D, Yakoub-Agha I, et al. Inferior outcome of allogeneic stem cell transplantation for secondary acute myeloid leukemia in first complete remission as compared to de novo acute myeloid leukemia. Blood Cancer J. 2020;10:26.
26. Salas MQ, Chen S, Lam W, Pasic I, Gerbitz A, Michelis FV, et al. Less is more: superior graft-versus-host disease-free/relapse-free survival with reduced-intensity conditioning and dual T cell depletion in acute myelogenous leukemia. Biol Blood Marrow Transplant. 2020;26:1511–9.
27. Gatwood KS, Labopin M, Savani BN, Finke J, Socie G, Beelen D, et al. Transplant outcomes for patients with therapy-related acute myeloid leukemia with prior lymphoid malignancy: an ALWP of EBMT study. Bone Marrow Transpl. 2020;55:224–32.
28. Sengsayadeth S, Labopin M, Boumendil A, Finke J, Ganser A, Stelljes M, et al. Transplant outcomes for secondary acute myeloid leukemia: acute leukemia working party of the European Society for blood and bone marrow transplantation study. Biol Blood Marrow Transplant. 2018;24:1406–14.
29. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106:2912–9.
30. ElSawy M, Storer BE, Pulsipher MA, Maziarz RT, Bhatia S, Maris MB, et al. Multicentre validation of the prognostic value of the haematopoietic cell transplantation- specific comorbidity index among recipient of allogeneic haematopoietic cell transplantation. Br J Haematol. 2015;170:574–83.
31. Jullien M, Orvain C, Berceanu A, Couturier M, Guillaume T, Peterlin P, et al. Impact of allogeneic stem cell transplantation comorbidity indexes after haplotransplant using post-transplant cyclophosphamide. Cancer Med. 2021;10:7194–202.
32. Elsawy M, Storer BE, Milano F, Sandmaier BM, Delaney C, Salit RB, et al. Prognostic performance of the augmented hematopoietic cell transplantation-specific comorbidity/age index in recipients of allogeneic hematopoietic stem cell transplantation from alternative graft sources. Biol Blood Marrow Transplant. 2019;25:1045–52.
33. D'Angelo CR, Novitsky B, Mee Lee S, Godley LA, Kline J, Larson RA, et al. Characterization of cancer comorbidity prior to allogeneic hematopoietic cell transplantation. Leuk Lymphoma. 2019;60:629–38.
34. Alfayez M, Kantarjian H, Kadia T, Ravandi-Kashani F, Daver N. CPX-351 (vyxeos) in AML. Leuk Lymphoma. 2020;61:288–97.
35. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid. Leuk JCO. 2018;36:2684–92.
36. Lancet JE, Uy GL, Newell LF, Lin TL, Ritchie EK, Stuart RK, et al. CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial. Lancet Haematol. 2021;8:e481–e491.
37. Cherry EM, Abbott D, Amaya M, McMahon C, Schwartz M, Rosser J, et al. Venetoclax and azacitidine compared with induction chemotherapy for newly diagnosed patients with acute myeloid leukemia. Blood Adv. 2021;5:5565–73.
38. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383:617–29.

AUTHOR CONTRIBUTIONS

Conceptualisation, ET; Methodology, GR, ED, ET; Patients care, GR, RD, NF, EF, MS, PC, MR, FS, JBM, HLW, KB, ED, JOB, AF, CEB, SNQ, AG, CO, PT, ML, XP, GG, YB, NM, JBM, EC, JC, ET; Collected the data, GR, ED, RD, NF, EF, MS, PC, MR, FS, JBM, HLW, KB, ED, JOB, AF, CEB, SNQ, AG, CO, PT, ML, XP, GG, YB, NM, JBM, EC, JC, ET; Analysed data, GR, ED, PB, ET; Writing – original draft, GR, ED, ET; Review and editing, all the authors.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-023-02082-5.

Correspondence and requests for materials should be addressed to Emmanuelle Tavernier.

Reprints and permission information is available at http://www.nature.com/reprints

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