Incidence and outcome of central nervous system relapse after hematopoietic stem cell transplantation in patients suffering from acute myeloid leukemia and acute lymphoblastic leukemia: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Central nervous system (CNS) relapses in acute leukemia (AL) are serious disease recurrences, especially after allogeneic hematopoietic stem cell transplantation (allo-HSCT). The incidence and overall survival (OS) after treatment and best treatment strategies remain largely unknown.

A study on 2,045 patients reports the incidence of CNS relapse after allo-HSCT for acute myeloid leukemia (AML) to be 1.81%.[1] Pre-allo-HSCT CNS involvement was an independent risk factor for CNS relapse post-allo-HSCT, with a lower 3-year OS (60.3 *vs.* 81.5%). In AML, screening for CNS disease is unsystematic and varies: it is sometimes routine, sometimes only in patients with hyperleukocytosis or monoblasts, and irregular for the elderly. The definition of CNS involvement is not clear: most only consider cytologically visible leukemic cells, others consider minor infiltration in flow cytometry. A study on 48 patients (monocytic phenotype, hyperleukocytosis, FLT3-ITD$^+$ or CNS symptoms) demonstrated a CNS involvement in 52%,[2] with unknown incidence of CNS relapse post-allo-HSCT. Another study on 103 patients demonstrated 32% had CNS positivity, screened by either cytology, or flow cytometry.[3] In acute lymphoblastic leukemia (ALL), CNS involvement is an established risk factor and routinely screened for; it is treated therapeutically and prophylactically. CNS relapse is the most important risk factor for relapse and mortality; CNS prophylaxis is integrated into treatment protocols.[4] Around 5% of patients show cytological CNS involvement, but cytology negative CNS infiltration is frequent, demonstrated by animal and post-mortem studies.[5]

Central nervous system relapse after allo-HSCT is life-threatening; however, the exact incidence in a large leukemic cohort is not known. CNS is among the most frequent sites of extramedullary disease progression, especially in ALL.[6] In AML, initial CNS involvement is present in 2-4% of patients.[7-9] The incidence, OS after treatment, and best treatment strategies remain unknown. Literature is scarce and mostly reported as single case reports. One study on CNS relapse in ALL describes 457 patients after first allo-HSCT in first or second complete remission (CR), 15% of whom had a CNS involvement pre-allo-HSCT.[10] Forty-eight percent received post-allo-HSCT CNS prophylaxis. Overall, 18 patients (4%) developed CNS relapse, with pre-allo-HSCT CNS involvement as the only identified risk factor. Fifty percent of these patients had CNS involvement prior to allo-HSCT, regardless of post-allo-HSCT CNS prophylaxis or the conditioning regimen used. A study on allo-HSCT in 71 AML patients with CNS involvement at diagnosis, 52 of whom received intrathecal chemotherapy alone and 19 in combination with irradiation, demonstrated a worse relapse-free survival than a control group without CNS involvement and a disease-free survival and OS benefit from additional irradiation.[11] A study on 1,226 AML, ALL or CML patients described the incidence of CNS relapse after allo-HSCT in a 10-year observation study as 2.3% (29 patients).[12] Risk factors were ALL, non-remission at allo-HSCT, prior CNS disease and prophylactic intrathecal chemotherapy post-allo-HSCT. Three-year OS after CNS relapse was 18% and 1-year OS 42%. Long-term survival was observed only in few patients, and only without systemic disease.

We performed the current retrospective, multicenter analysis based on the registry of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT, more than 600 transplant centers, mainly in Europe) to define the incidence and outcome of CNS relapse after HSCT in patients suffering from AML and ALL.

The study was approved by the ALWP and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Data from allo-HSCT performed between 1996 and 2016 were screened and patients with the following criteria were included: ≥18 years, with AML or ALL, first allo-HSCT in first complete remission (CR), all donor types. We identified patients with and without CNS relapse. We also collected information on type of relapse, relapse site, treatment, and outcome after CNS relapse.

The primary endpoint of this study was OS after CNS relapse. Secondary endpoints were: cumulative incidence of CNS relapse after allo-HSCT, CR after CNS relapse and incidence of acute and chronic graft-*versus*-host disease (GvHD) after CNS relapse.

Univariate comparisons were performed with χ^2 and Fisher's exact tests for categorical variables and Mann-Whitney test for continuous variables. Probability of OS was calculated using the Kaplan-Meier estimator. Probabilities of CNS relapse and GvHD were estimated using cumulative incidence curves. CNS relapse, death and relapse in other sites were competing events. Concerning GvHD, both death and relapse were considered as competing events. Univariate analyses were performed with the log-rank test for OS and Gray's test for cumulative incidence estimates. Results were expressed as estimates with a 95% confidence interval (95% CI). All tests were two-sided with a type 1 error rate fixed at 0.05. Statistical analyses were performed with SPSS 27.0 and R 4.1.1.

Study inclusion criteria were met by 7,991 patients: 5,724 (71.6%) AML, and 2,267 (28.4%) ALL. Patients were transplanted between 1996 and 2016.

Median age was 44 years (interquartile range [IQR]: 31.6-55.4), 6,014 (75.3%) were in first, 1,800 (22.5%) in second, and 177 (2.2%) in third CR. Ninety-one patients of the 7,991 (1.1%) experienced CNS relapse after allo-HSCT; of those, we have information for 88 patients at diagnosis: 4 patients (4.5%) showed initial CNS involvement (see *Online Supplementary Table S1* for patients and transplant characteristics, and patients with and without CNS relapse).

Incidence of CNS relapse was 0.9% (95% CI: 0.7-1.2), 1.2% (95% CI: 1-1.5) and 1.4% (95% CI: 1.1-1.7) at two, five and ten years post allo-HSCT (Figure 1A).

Patients with ALL had higher risk for CNS relapse (1.9% *vs.* 0.9% in AML at 5 years, *P*=0.002) (Figure 1B). The risk of developing a CNS relapse after allo-HSCT was higher after 2010 (median time of transplant, *P*=0.013) (Figure 2A). No other risk factors such as age, donor type, conditioning, use of total body irradiation, patient or donor sex were identified (*Online Supplementary Table S2*).

Median age of patients with CNS relapse was 41 years (IQR: 30.8-50.4). Sixty-one patients (67%) were transplanted in CR1, 27 (29.7%) in CR2, and 3 (3.3%) in CR3. Thirty-six (39.6%) showed an isolated CNS relapse, 30 (33%) a combination of CNS and bone marrow (BM) relapse, 23 (25.3%) suffered a CNS relapse secondary to a hematologic relapse, and 2 (2.2%) after a molecular relapse. Of all CNS relapse patients, 72.5% did not show GvHD before the CNS relapse while 27.5% did. Median time from transplant to CNS relapse was 396 days (IQR: 197-737).

Fifty-two patients had AML (57.1%), 39 ALL (42.9%) (see *Online Supplementary Table S3* for patients' and transplant characteristics). ALL patients with CNS relapse were younger: 33.3 years *versus* 46.1 years in AML (*P*<0.01). Time from transplant to CNS relapse was 401 days in AML (IQR: 247.8-834.2) and 343 days in ALL (IQR: 128.5-665.5) patients (*P*=0.092). The median follow-up after CNS relapse was 88.3 months.

For 66 patients (72.5%), CNS relapse was the first relapse, 25.3% already had a hematologic relapse, and 2.2% already had a molecular relapse. Cumulative incidence of CNS relapse at five years was 4% (95% CI: 2.2-6.5) for AML CBF patients *versus* 0.7% (95% CI: 0.5-1) for patients with intermediate or adverse risk AML (*P*<10-3). All 13 CBF AML patients who relapsed have received cytarabine before transplant; however, we do not have information on exact dosages, neither do we have information on the chemotherapy regimen in CBF AML patients who did not relapse. Thirty-six AML and 30 ALL patients developed CNS relapse as first relapse post HSCT. Thirty-one (48.6%) achieved CR after the CNS relapse (41.2% CR in AML and 56.7% in ALL,

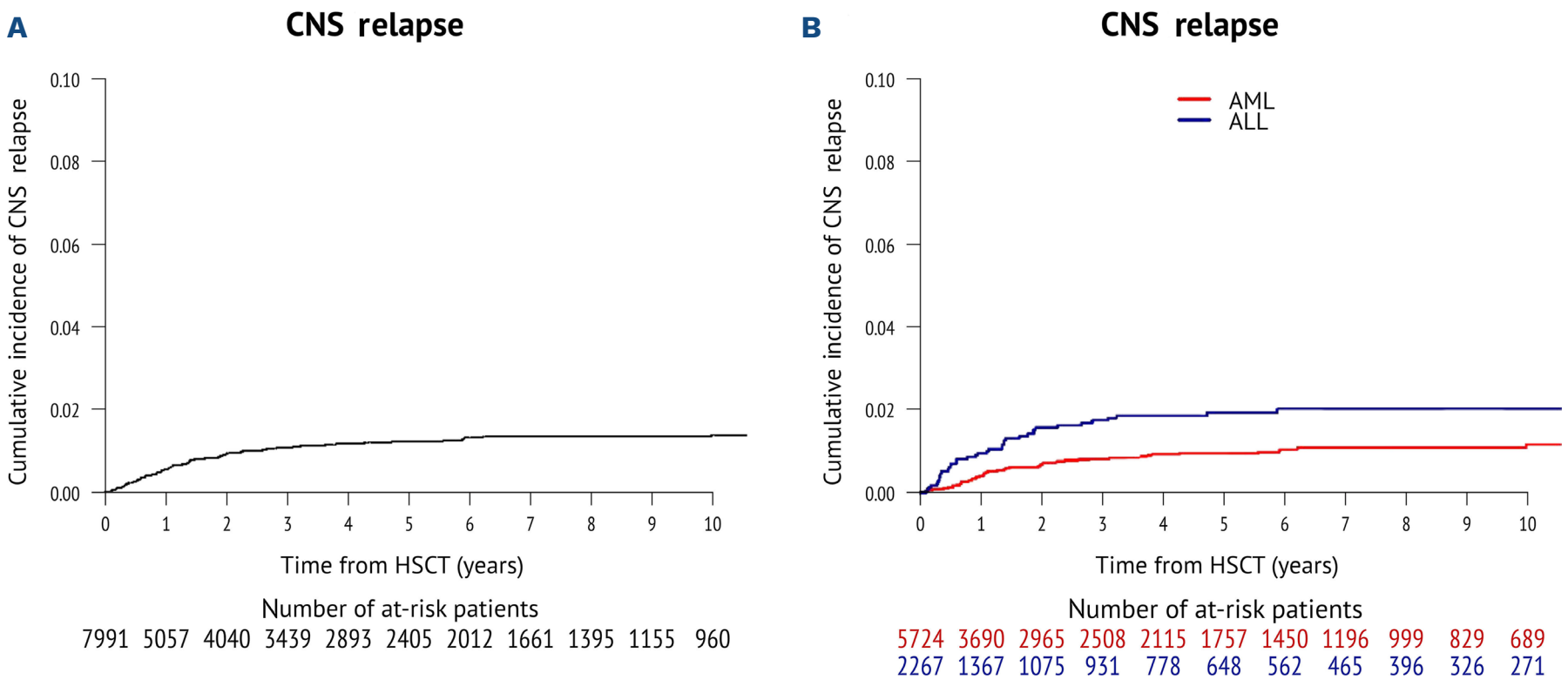

Figure 1. Central nervous system relapse of the population and by diagnosis. (A) Central nervous system (CNS) relapse in the entire population. (B) CNS relapse by diagnosis. HSCT: hematopoietic stem cell transplantation.

P=0.22). Second CNS relapse after the first was detected in 15 (22.7%) of these patients: 5 in AML (13.9%) and 10 (33.3%) in ALL patients.

The OS for the 66 patients was 24% at two years and 12% at five years (Figure 2B). There was no difference in OS between AML and ALL patients (AML: 28.8% and 8.2% at 2 and 5 years; ALL: 19.4% and 15.6% at 2 and 5 years, *P*=0.66) (Figure 3A). The 2-year OS was better in isolated CNS relapse *versus* CNS and concomitant BM relapse (37.5% *vs.* 6.7%, *P*=0.004) (Figure 3B).

This study is the largest multicenter study on CNS relapse in leukemia after allo-HSCT to date. We demonstrate that CNS relapse after allo-HSCT is a rare event (1.1%), but is more frequent in ALL than in AML; the prognosis, however, is dismal. Around half the patients could achieve CR, but the OS remains low (8.2% in AML, 15.5% in ALL at 5 years). OS was better in isolated CNS (37.5% *vs.* 6.7% at 2 years). Only 7 of the 91 patients were alive five years after CNS relapse, 6 patients were censored alive before five years, so only 13 of 91 patients were alive at their last follow-up

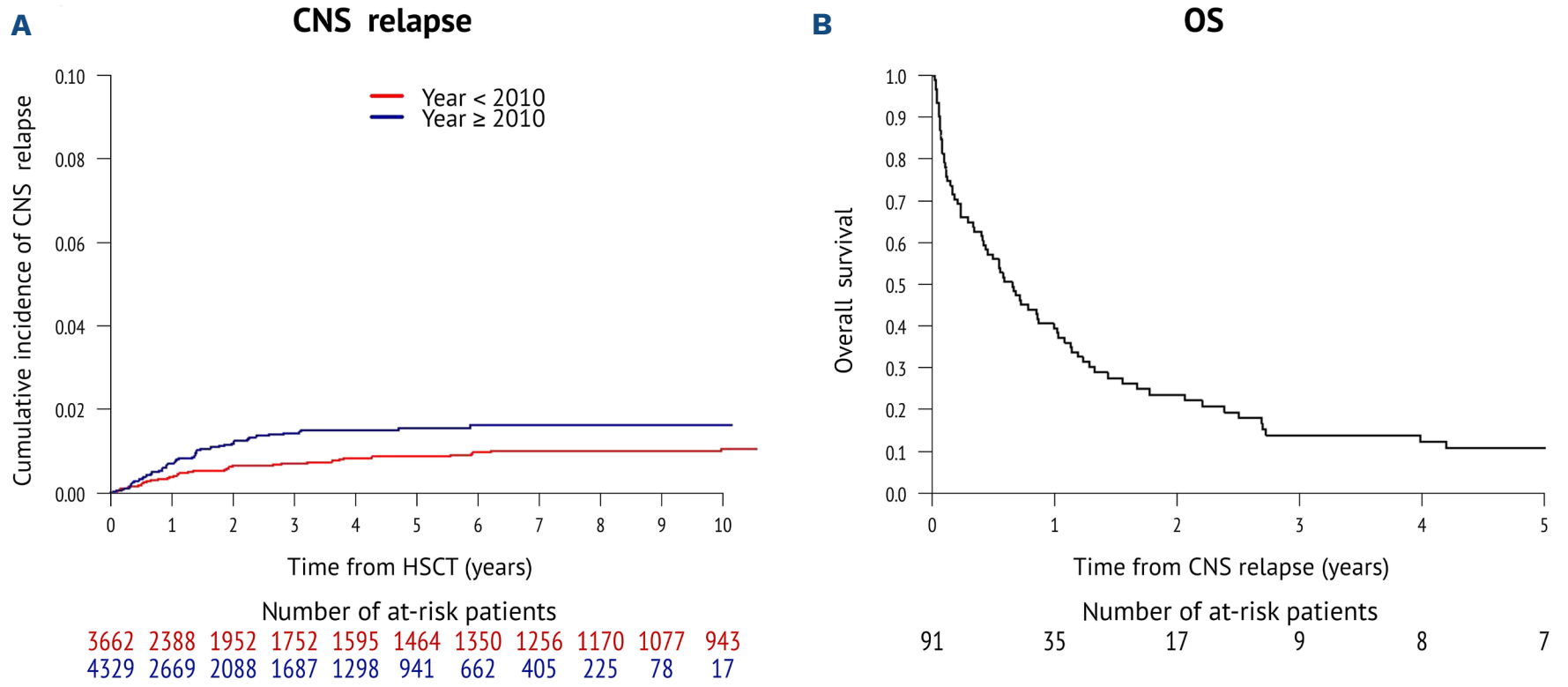

Figure 2. Central nervous system relapse by year and overall survival after relapse. (A) Central nervous system (CNS) relapse by year. (B) Overall survival (OS) after relapse for the entire population. HSCT: hematopoietic stem cell transplantation.

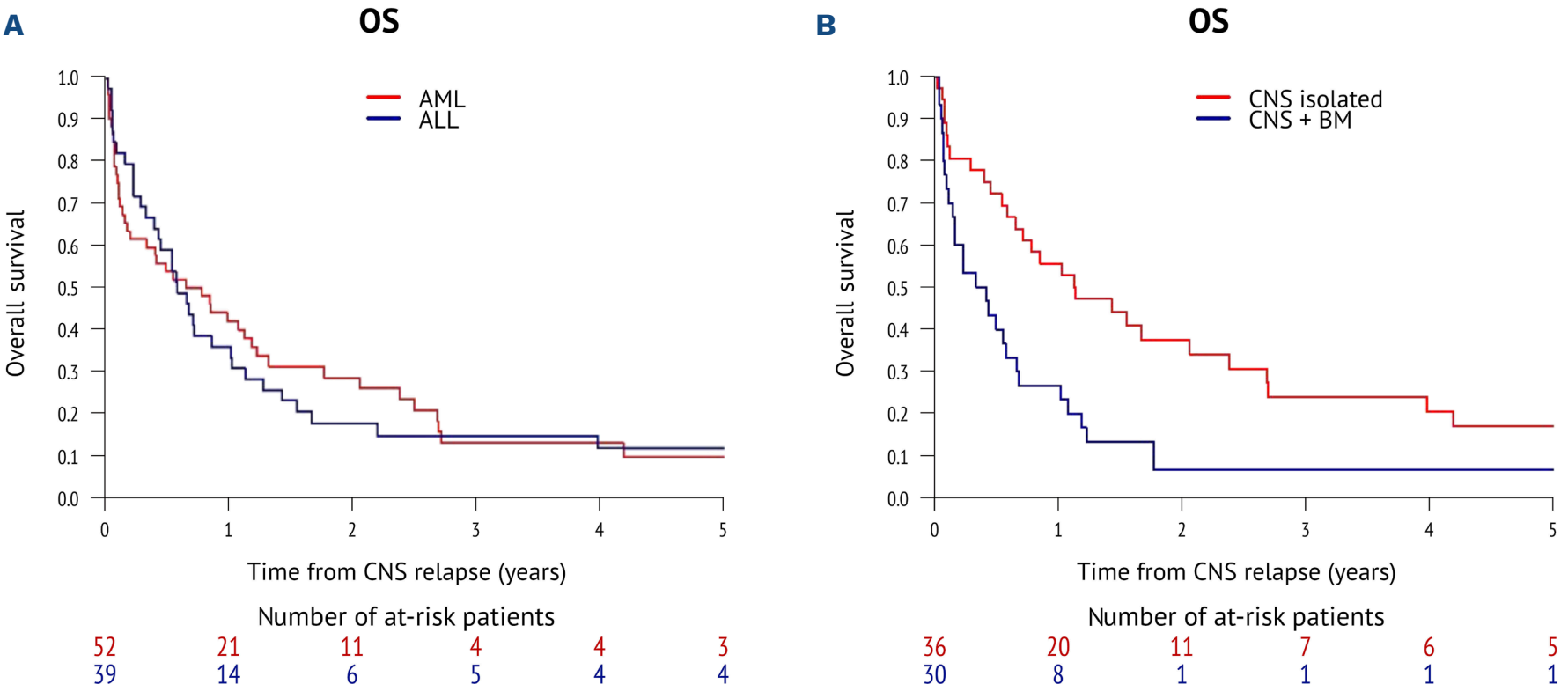

Figure 3. Overall survival by diagnosis and central nervous system isolated *versus* combined with bone marrow. (A) Overall survival (OS) after relapse year of diagnosis. (B) OS after isolated central nervous system (CNS) relapse *versus* bone marrow (BM) and CNS relapse. HSCT: hematopoietic stem cell transplantation.

with a range of 1-22 years after relapse. In conclusion, CNS relapse after allo-HSCT still has a dismal prognosis with few long-term survivors.

Our study has several limitations: no routine screening for CNS disease at diagnosis at all participating centers, and heterogeneous treatment and conditioning for allo-HSCT. The higher incidence in recent years is probably due to better reporting of CNS relapses.

With current treatment protocols with routine intrathecal chemotherapy and/or prophylaxis, it is difficult to lower relapse rates after allo-HSCT in ALL. In AML, screening for concomitant CNS disease at diagnosis is not routinely performed, and future studies are needed to investigate a possible correlation between CNS infiltration at diagnosis and relapse after allo-HSCT. Currently, early detection and treatment of CNS relapse after allo-HSCT seems to be the best and only measure to take for this otherwise dismal complication, as our study demonstrates a better outcome in patients with isolated CNS as compared to a combined CNS and BM relapse. There does not seem to be the need to adapt the approach of screening or adding post-transplant prophylaxis based on leukemia subtypes as no difference was detected. However, due to the retrospective nature of our study, no definite recommendation can be made.

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https://doi.org/10.3324/haematol.2023.284858

Received: December 15, 2023.
Accepted: February 27, 2024.
Early view: March 7, 2024.

Disclosures

YC reports consulting fees from MSD, Novartis, Incyte, BMS, Pfizer, Abbvie, Roche, Jazz, Gilead, Amgen, Astra-Zeneca, and Servier, and travel support from MSD, Roche, Gilead, Amgen, Incyte, Abbvie, Janssen, Astra-Zeneca, and Jazz. GK reports an Advisory Role or Speaker Honoraria from MSD, Pfizer, Amgen, Novartis, Gilead, BMS-Celgene, Abbvie, Biotest, Takeda, Eurocept, and JAZZ, and Financing of Scientific Research from BMS-Celgene, Amgen, Abbvie, Medac and Eurocept. None of the other authors have any conflicts of interest to disclose.

Contributions

SB, YC and ML wrote the manuscript. ML performed statistical analyses. AN and MM revised the manuscript. SB, YC, JF, TGD, TBO, JJC, PJ, HLW, MC, SL, GK, NCG, AN and MM provided patients and patient follow-up. All authors approved the manuscript before submission.

Funding

This study was supported by a grant from the Ministry of Health of the Czech Republic – Conceptual Development of Research Organization (Faculty Hospital in Pilsen – FNPl, 00669806).

Data-sharing statement

Enquiries for data sharing can be made to the EBMT Acute Leukemia Working Party & Lymphoma Working Party.

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