Dexamethasone added to induction and post-remission therapy in older patients with newly diagnosed acute myeloid leukemia: a multicenter, phase II trial (DEXAML-02)

The standard treatment for patients aged over 60 with newly diagnosed acute myeloid leukemia (AML) who are in good overall condition remains intensive chemotherapy.[1] With the exception of one study showing an event-free survival (EFS) benefit after addition of gemtuzumab ozogamycin (GO) to induction chemotherapy, and another one demonstrating the impact of CPX-351 in therapy-related or secondary AML, there has been no recent improvement in outcome for this population.[2,3] The FILO group completed a phase III study showing that the addition of lomustine to intensive chemotherapy significantly increased the complete remission (CR) rate, reduced the incidence of relapse, and improved 2-year EFS.[4]

Recent retrospective studies showed that the addition of dexamethasone to intensive chemotherapy was significantly associated with lower early deaths and better outcome in patients with hyperleukocytosis.[5,6] Moreover, preclinical studies demonstrated that specific oncogenic alterations or therapeutic stress (cytarabine, *FLT3* inhibitors) are associated with upregulation of the inflammatory gene response and expression of the glucocorticoid receptor, which induce sensitization to glucocorticoids in AML models.[7] Therefore, dexamethasone, used as a chemo-sensitizer, may improve treatment response and outcome regardless of leukocytosis. With this rationale, the DEXAML-02 trial evaluated the addition of dexamethasone to induction and post-remission chemotherapy in older AML patients.

This multicenter, phase II, single-arm trial included patients aged 61 years or older, with newly diagnosed AML according to the 2016 WHO classification, favorable or intermediate cytogenetic risk, Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and Hematopoietic Cell Transplantation (HCT)-Comorbidity Index <3 (except history of cancer). AML arising from myelodysplastic syndromes, myeloproliferative neoplasms or chronic myelomonocytic leukemia were not included. This trial was registered at clinicaltrialsregistry.eu (Eudra-CT-2017-004860-36) and clinicaltrials.gov (NCT03609060), and was approved by an Ethics Committee (CPP-IDF1-2018-ND29-cat.1) and the French National Agency for Medicines and Health Products Safety (MEDAECNAT-2018-03-00022). All patients provided written informed consent.

Induction chemotherapy was 8 mg/m² idarubicin on days (d) 1-5, 100 mg/m² cytarabine d1-7, 200 mg/m² lomustine d1, and 10 mg dexamethasone intravenously every 12 hours (hr) d1-3. Patients with no response after the induction cycle were off-study treatment. Patients with CR or CR with incomplete hematologic recovery (CRi) were assigned to consolidation therapy consisting of 6 mini-consolidation courses every 30-45 days with 8 mg/m² idarubicin d1, 50 mg/m² cytarabine subcutaneously every 12 hr d1-5, and 20 mg dexamethasone intravenously d1. Patients with core-binding factor AML could receive up to 3 cycles of cytarabine 1-1.5g/m²/12 hr d1-3 (with the same dose of dexamethasone). Allogeneic hematopoietic stem cell transplantation (HSCT) was recommended in patients with intermediate or adverse risk according to the 2017 European LeukemiaNet (ELN) classification. The addition of midostaurin was authorized in patients with *FLT3* mutations. The primary endpoint was EFS defined according to ELN recommendations. Data analysis was performed using Stata Statistical Software (Release 17.0. Stata Corporation, College Station, TX, USA).

A total of 120 patients were enrolled between August 2018 and February 2020. Six patients were excluded due to exclusion criteria (3 with adverse karyotype, 2 with HCT-Comorbidity Index ≥3, and one with central nervous system involvement) (*Online Supplementary Figure S1*). Characteristics of the 114 patients are shown in Table 1. Next-generation sequencing of 91 myeloid panel genes was centrally performed in 111 patients. The genetic risk according to the 2022 ELN classification was favorable in 33 patients (31%), intermediate in 31 patients (29%), and adverse in 44 patients (40%).

During the induction phase, 2 patients prematurely discontinued dexamethasone. Twenty-three patients with *FLT3* mutation (70%) received midostaurin; 104 patients received anti-fungal prophylaxis, including 87 with an azole agent. Anti-viral and anti-pneumocystis jiroveci prophylaxes were used in 97 and 47 patients, respectively. The most common grade 3-4 adverse events were infection in 57 patients (50%), mucositis in 20 (18%), and hyperglycemia in 12 (11%) (*Online Supplementary Table S1*). Bacterial and fungal infections were observed in 52 and 5 patients, respectively. The median number of days between d1 and an absolute neutrophil count ≥0.5x10^9/L was 26 days (interquartile range [IQR]: 24-30) whereas median duration with platelet counts <10x10^9/L was 10.5 days (IQR: 1.5-19). During post-remission therapy, the frequency of grade 3-4 infections or other adverse events was low (<15%) and stable over the 6 chemotherapy cycles. As a marker of dexamethasone activity, C reactive protein (CRP) levels were measured at inclusion and d8 of induction chemotherapy. Median CRP was 17 mg/L (IQR: 5-53) and 12 mg/L (IQR: 4-27) at inclusion and d8, respectively. Ninety-five patients (83%) achieved CR or CRi by the end of induction (Table 2). Four patients (4%) died at d30 and 9 (8%) at d60.

Table 1. Characteristics of the acute myeloid leukemia patients included in the DEXAML-02 trial.

Characteristics	DEXAML-02 Total=114
Age in years	
Median	70
IQR	66-73
Min;Max	61;80
<70, N (%)	54 (47)
>70, N (%)	60 (53)
Sex, N (%)	
Male	72 (63)
Female	42 (37)
ECOG performance status, N (%)	
0	46 (40)
1	59 (52)
2	9 (8)
HCT-Comorbidity Index	
Median	0
IQR	0-1
Min;Max	0;4
AML status, N (%)	
de novo	108 (95)
Therapy-related	6 (5)
WBC x10^9/L	
Median	4.99
IQR	2-11
Min;Max	0.6;137
Bone marrow blasts, %	
Median	55
IQR	35-83
Min;Max	6;98
Cytogenetic risk, N (%)	
Favorable	5 (4)
Intermediate	108 (96)
2022 ELN risk classification, N (%)	
Favorable	33 (31)
Intermediate	31 (29)
Adverse	44 (40)
Mutations, N (%)	
NPM1	43 (38)
FLT3-ITD	23 (20)
FLT3-TKD	10 (9)
CEBPA bZIP	5 (4)
RUNX1	23 (21)
ASXL1	23 (21)
BCOR	6 (5)
EZH2	5 (5)
SF3B1	3 (3)
SRSF2	27 (24)
STAG2	18 (16)
U2AF1	7 (6)
ZRSR2	3 (3)
TP53	2 (2)

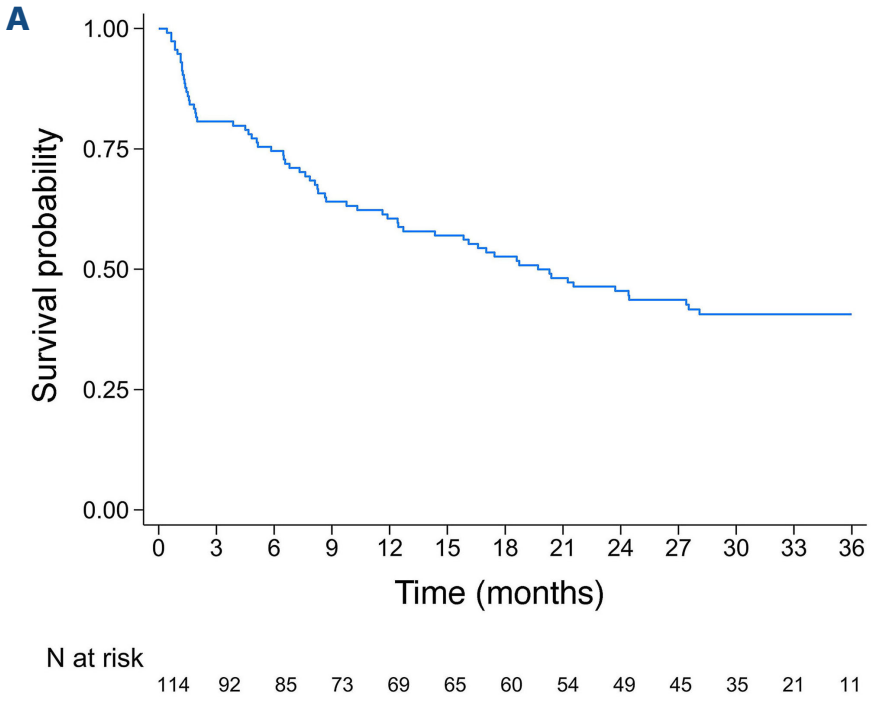
AML: acute myeloid leukemia; ECOG: Eastern Cooperative Oncology Group; ELN: European LeukemiaNet; HCT: hematopoietic cell transplantation; IQR: interquartile range; Min;Max: minimum, maximum; N: number; WBC: white blood cell.

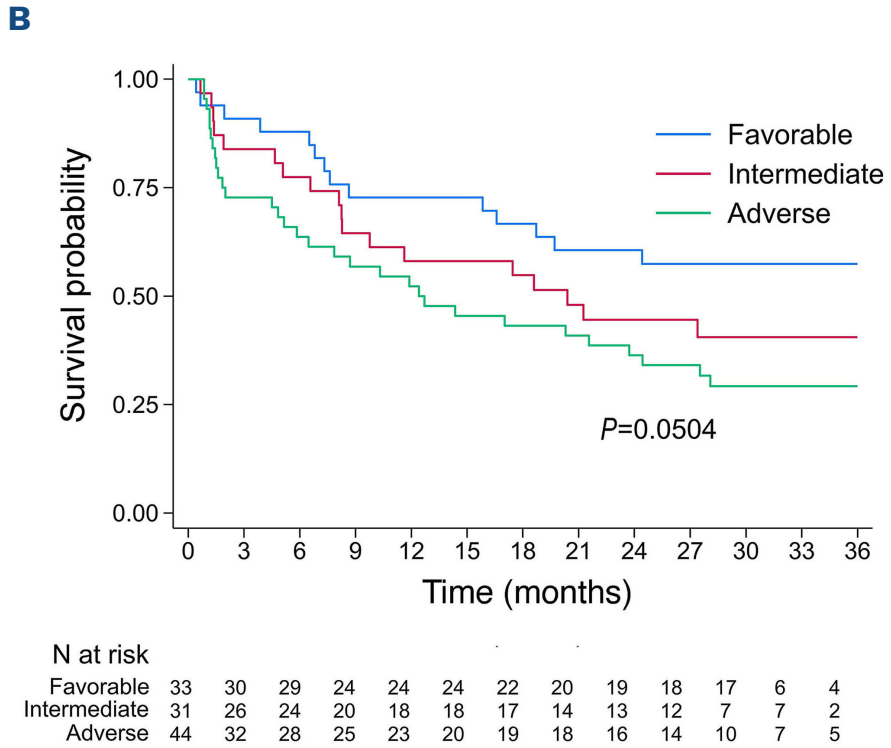
Twenty-three patients (20%) with CR/CRi were allografted after a median duration of 154 days from induction (IQR: 128-188) and after a median of 2 consolidation cycles (IQR: 2-3). All but one patient maintained CR at time of transplant. Donor source was matched-related in 4 subjects,

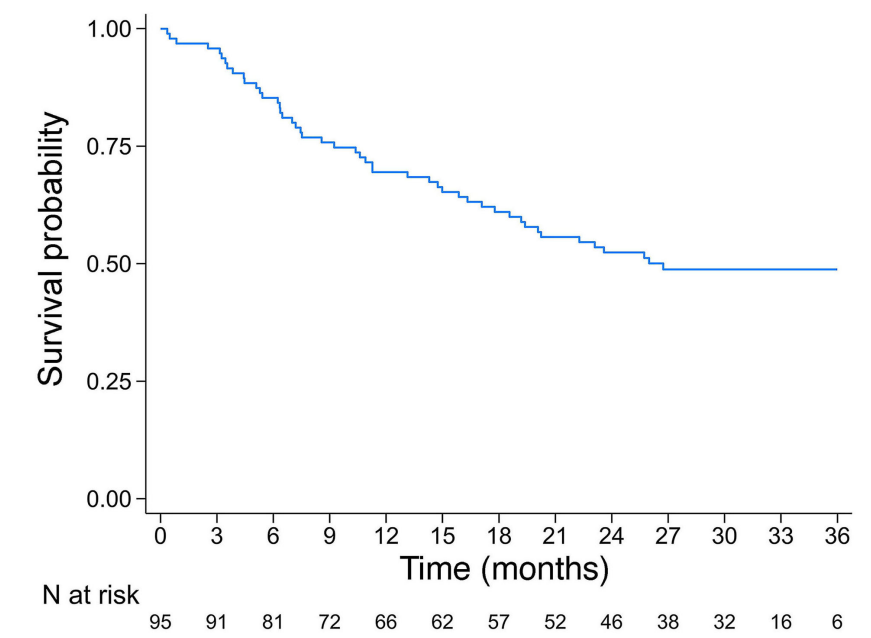
Table 2. Response to induction and outcomes.

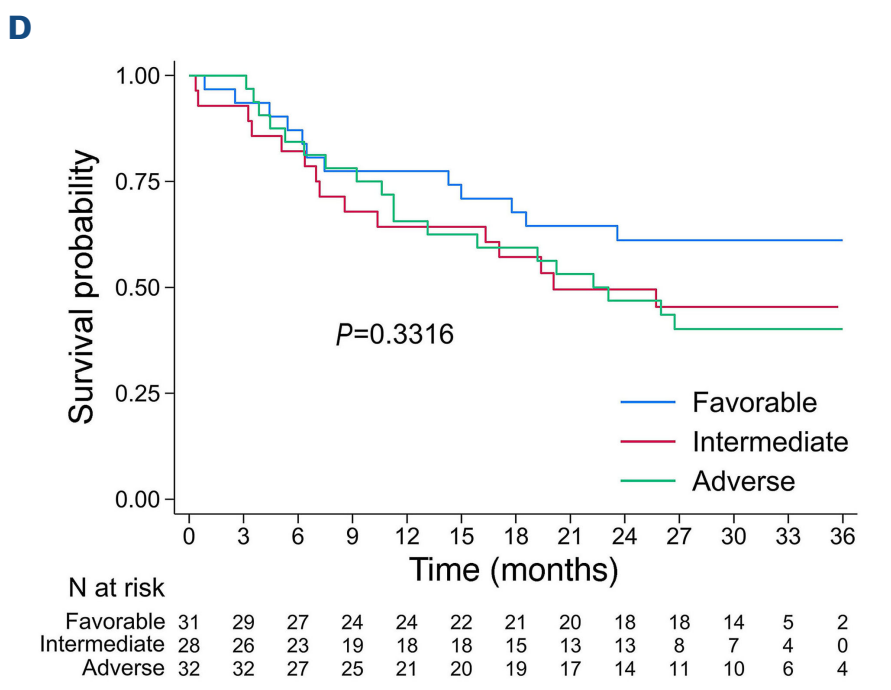
	DEXAML-02 Total=114
Response to induction chemotherapy, N (%)	
CR or CRi	95 (83)
Refractory disease	14 (12)
Day-30 death	4 (4)
Day-60 death	9 (8)
Outcomes	
Median event-free survival in months (IQR)	19.7 (6-NR)
2-year event-free survival, %	46 (95% CI: 36-54)
Median relapse-free survival in months (IQR)	26.7 (9-NR)
2-year relapse-free survival, %	52 (95% CI: 42-62)
Median overall survival in months (IQR)	NR (12-NR)
2-year overall survival, %	63 (95% CI: 54-71)
Outcomes per 2022 ELN risk	
Favorable	**Total=33**
CR or CRi, N (%)	31 (94)
Median event-free survival in months (IQR)	NR (9-NR)
2-year event-free survival, %	61 (95% CI: 42-75)
Median relapse-free survival in months (IQR)	NR (14-NR)
2-year relapse-free survival, %	61 (95% CI: 42-76)
Median overall survival, months (IQR)	NR (24-NR)
2-year overall survival (%)	76 (95% CI: 57-87)
Intermediate	**Total=31**
CR or CRi, N (%)	28 (90)
Median event-free survival in months (IQR)	20.4 (7-NR)
2-year event-free survival, %	45 (95% CI: 27-61)
Median relapse-free survival in months (IQR)	20.1 (7-NR)
2-year relapse-free survival, %	50 (95% CI: 30-66)
Median overall survival in months (IQR)	NR (11-NR)
2-year overall survival, %	58 (95% CI: 39-73)
Adverse	**Total=44**
CR or CRi, N (%)	32 (73)
Median event-free survival in months (IQR)	12.4 (2-NR)
2-year event-free survival, %	36 (95% CI: 23-50)
Median relapse-free survival in months (IQR)	22.3 (9-NR)
2-year relapse-free survival, %	47 (95% CI: 29-63)
Median overall survival in months (IQR)	27.5 (9-NR)
2-year overall survival, %	57 (95% CI: 41-70)

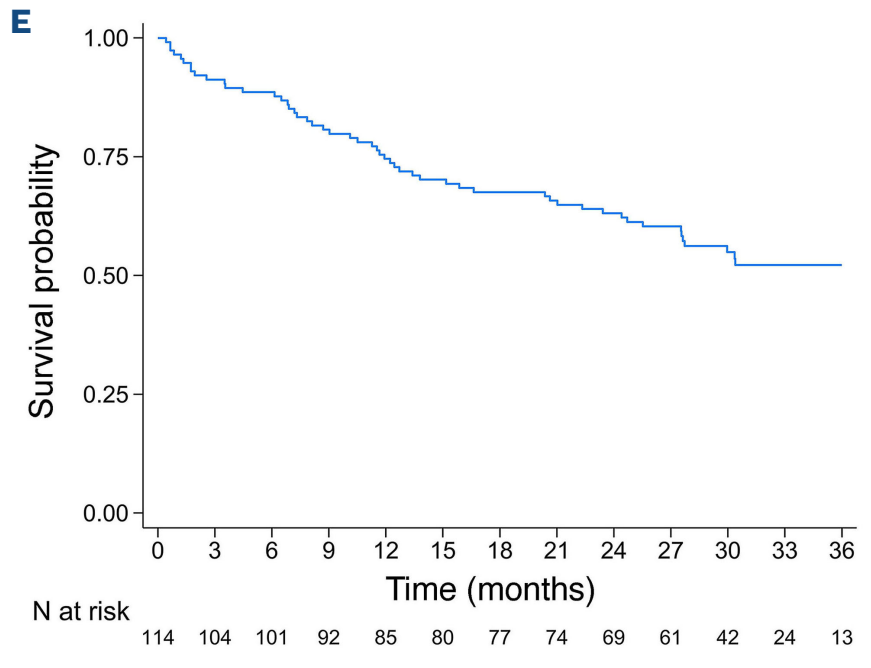
CI: Confidence Interval; CR: complete remission. CRi: complete remission with incomplete hematologic recovery; ELN: European LeukemiaNet; IQR: interquartile range; N: number; NR: not reached.











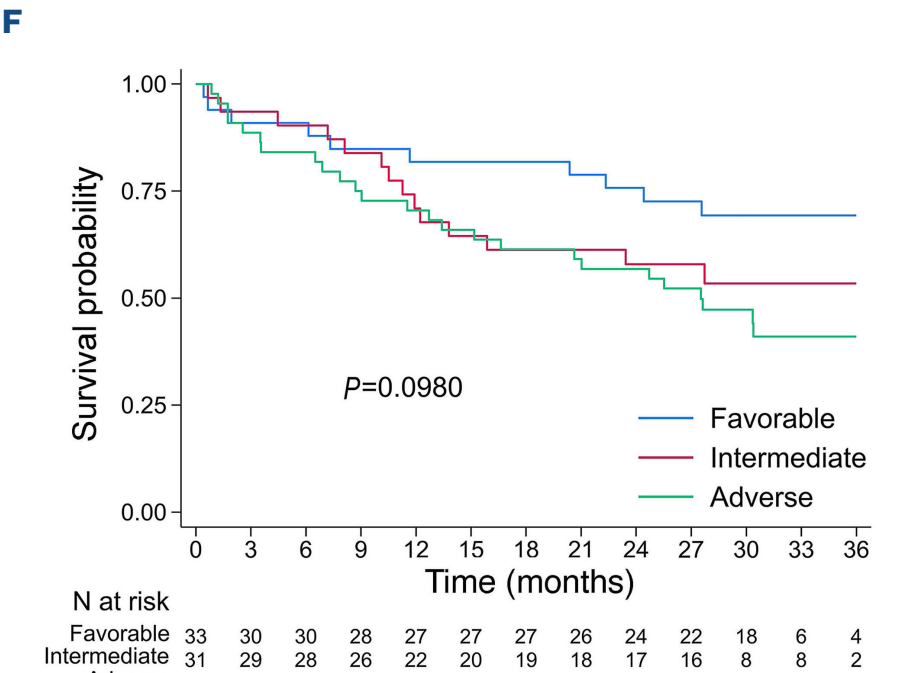


Figure 1. Event-free survival, relapse-free survival and overall survival. (A) Event-free survival in the whole population. (B) Event-free survival according to the 2022 European LeukemiaNet (ELN) classification. (C) Relapse-free survival in the whole population. (D) Relapse-free survival according to the 2022 ELN classification. (E) Overall survival in the whole population. (F) Overall survival according to the 2022 ELN classification. N: number.

matched-unrelated in 12 patients, and haplo-identical in 7 patients. Other CR/CRi patients who were not transplanted in first CR/CRi received a median number of 4 consolidation cycles (IQR: 0-6).

After a median follow-up of 32 months (IQR: 28-35), EFS at two years was 46% (95% CI: 36-54). Median EFS was 19.7 months (IQR: 6-not reached) in the whole population, not reached (IQR: 8.6-not reached) in the 2022 ELN favorable-risk group, 20.4 months (IQR: 6.6-not reached) in the intermediate group, and 12.4 months (IQR: 1.8-not reached) in the adverse group (Figure 1).

In patients who experienced CR/CRi, relapse-free survival (RFS) at two years was 52% (95% CI: 42-62). Median RFS was 26.7 months (IQR: 9-not reached) in the whole population, not reached (IQR: 7-not reached) in the 2022 ELN favorable-risk group, 20.1 months (IQR: 7-not reached) in the intermediate group, and 22.3 months (IQR: 9-not reached) in the adverse group. Forty-eight patients (42%) received a second-line therapy with intensive chemotherapy in 13 patients, hypomethylating agents in 23 patients or small molecule inhibitors including *FLT3* inhibitors in 7 patients or IDH inhibitors in 10 patients.

Overall survival (OS) at two years was 63% (95% CI: 54-71). Median OS was neither reached (IQR: 12-not reached) in the whole population nor in the 2022 ELN favorable (IQR: 24-not reached) or intermediate (IQR: 11-not reached) risk groups, and 27.5 months (IQR: 9-not reached) in the adverse group.

Since dexamethasone displayed anti-leukemic activity in samples with *NPM1* mutations,[5] we performed sensitivity analyses in the 43 *NPM1*-mutated patients. Forty-one patients (95.3%) achieved CR or CRi by the end of induction chemotherapy and one patient died at d30. Of the 30 CR or CRi patients who were evaluated locally using qPCR for measurable residual disease (MRD) monitoring after induction chemotherapy, 9 had negative MRD, and 14 had low level (<2%) MRD. Median EFS, RFS and OS were not reached. EFS at two years was 56% (95% CI: 40-69). In CR/CRi patients, RFS at two years was 56% (95% CI: 39-69). OS at two years was 74% (95% CI: 59-85) (*Online Supplementary Figure S2*).

The DEXAML-02 trial is one of the first studies to evaluate the role of an anti-inflammatory approach combined with intensive chemotherapy in older fit patients with AML.[8] Results showed that this regimen is safe and associated with promising anti-leukemic activity.

The risk of severe sepsis and invasive fungal infections is of concern when using glucocorticoids in patients with neutropenia.[9] However, the safety profile of the 3-day course of dexamethasone at the beginning of induction chemotherapy was acceptable, especially regarding the risk of infection.

With 2-year EFS and OS at 46% and 63%, respectively, the outcome of patients included in the DEXAML-02 study compares favorably with other studies. In the HOVON-SAKK trial evaluating high-dose daunorubicin, 2-year EFS and OS rates in patients with intermediate cytogenetic risk were 21% and 34%, respectively.[10] The ALFA-0701 trial evaluating GO in 50-70 year old patients (median age 62 years) demonstrated 2-year EFS and OS rates of 47% and 65% in the GO arm in patients with favorable or intermediate cytogenetic risk.[2] In the German inter group trial comparing different chemotherapy strategies *versus* a common standard arm in patients aged over 60 (78% favorable or intermediate cytogenetic risk), 2-year EFS and OS stood at 20% and 30%.[11]

Patients with NPM1 mutations may benefit from the addition of dexamethasone (95% CR/CRi and 74% 2-year OS). Overexpression of inflammatory gene signatures in patients with *NPM1* mutation has been revealed by transcriptomic analyses.[5,12]

Integration of myelodysplasia-related gene mutations into the new 2022 ELN risk classification has meant that a significant proportion of patients with intermediate cytogenetic risk have switched to the adverse group.[1] Our results showed that the 2022 ELN classification poorly discriminated intermediate and adverse risk groups in patients selected on the basis of cytogenetics only.[13]

The DEXAML-02 trial had some limitations such as the limited number of participants and the single arm trial design. We also acknowledge that lomustine in the induction chemotherapy backbone is not widely used. A randomized trial is required to confirm whether dexamethasone may improve outcome in this patient population. Nevertheless, this study updates the results of intensive chemotherapy in older patients with a high CR rate, an early death rate <5%, and a median survival not reached.

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SB declares a consulting or advisory role with Abbvie, Astellas, BMS-Celgene, Jazz Pharmaceuticals as well as Servier, and received travel grants from Abbvie and Pfizer. CR declares a consulting or advisory role with Abbvie, Amgen, Astellas, BMS, Boehringer, Jazz Pharmaceuticals, J&J as well as Servier, received research funding from Abbvie, Amgen, Astellas, BMS, Iqvia and Jazz Pharmaceuticals, and support for attending meetings and/or travel from Abbvie, Novartis and Servier. PP declares a consulting or advisory role with Abbvie, BMS as well as Servier, and received research funding from Astellas and Jazz Pharmaceuticals. NV declares a consulting or advisory role with Abbvie, Amgen, BMS, Boehringer, Janssen, Jazz Pharmaceuticals, Novartis as well as Servier, and received research funding from Novartis and Jazz Pharmaceuticals. AP declares a consulting or advisory role with Astellas, BMS, Servier, Abbvie, Gilead, Jazz Pharmaceuticals, Novartis, Pfizer, received research funding from Astellas, BMS, Roche, Servier, and support for attending meetings and/or travel from Servier and Abbvie. All other authors have no conflicts of interest to disclose.

Contributions

CR, SB and EB contributed to the study conception and design. SB, PP, RG, YD, YH, OB, MC, MH, AB, MB, EG, AS, SC, GRG, VD, LS, MPGH, CE, LV, CH, CS NV, AP and CR treated patients and participated in clinical data collection and assembly. CR, SB, FV, IL, LL, ED and EB analyzed the data. IL reviewed all cytogenetic results. LL and ED performed next-generation sequencing. FV carried out flow cytometry analyses. EB conducted statistical analyses. CR wrote the first draft of the manuscript. CR and EB wrote the manuscript. All authors had full access to all the data in the study, contributed to writing the manuscript, and provided final approval of the submitted version.

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Data-sharing statement

Requests for sharing deidentified data should be directed to the corresponding author.

References

1. 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.
2. Castaigne S, Pautas C, Terré C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet. 2012;379(9825):1508-1516.
3. Lancet JE, Uy GL, Newell LF, 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(7):e481-e491.
4. Pigneux A, Béné MC, Salmi LR, et al. Improved survival by adding lomustine to conventional chemotherapy for elderly patients with AML without unfavorable cytogenetics: results of the LAM-SA 2007 FILO trial. J Clin Oncol. 2018;36(32):3203-3210.

5. Bertoli S, Picard M, Bérard E, et al. Dexamethasone in hyperleukocytic acute myeloid leukemia. Haematologica. 2018;103(6):988-998.
6. Cerrano M, Chevret S, Raffoux E, et al. Benefits of dexamethasone on early outcomes in patients with acute myeloid leukemia with hyperleukocytosis: a propensity score matched analysis. Ann Hematol. 2023;102(4):761-768.
7. Récher C. Clinical implications of inflammation in acute myeloid leukemia. Front Oncol. 2021;11:623952.
8. Peterlin P, Garnier A, Le Bourgeois A, et al. Tocilizumab in combination with a standard induction chemotherapy in acute myeloid leukaemia patients (TOCILAM study): a single-centre, single-arm, phase 1 trial. EClinicalMedicine. 2023;64:102254.
9. Inaba H, Pui CH. Glucocorticoid use in acute lymphoblastic leukaemia. Lancet Oncol. 2010;11(11):1096-1106.
10. Löwenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med. 2009;361(13):1235-1248.
11. Niederwieser D, Lang T, Krahl R, et al. Different treatment strategies versus a common standard arm (CSA) in patients with newly diagnosed AML over the age of 60 years: a randomized German inter-group study. Ann Hematol. 2023;102(3):547-561.
12. Corrigan DJ, Luchsinger LL, Justino de Almeida M, Williams LJ, Strikoudis A, Snoeck HW. PRDM16 isoforms differentially regulate normal and leukemic hematopoiesis and inflammatory gene signature. J Clin Invest. 2018;128(8):3250-3264.
13. Rausch C, Rothenberg-Thurley M, Dufour A, et al. Validation and refinement of the 2022 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. Leukemia. 2023;37(6):1234-1244.