Outcome of adult acute myeloid leukemia patients with extramedullary disease and treatment with venetoclax/hypomethylating agents

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Abstract

We evaluated response to venetoclax/hypomethylating agents (HMA) in 46 patients with acute myeloid leukemia (AML) characterized by extramedullary disease. The median age of these patients was 65 years (range, 19-81). The patients had a median of two sites of extramedullary disease (range, 1-5) and 35 (76%) had concurrent bone marrow involvement. Twenty (43%) patients had high-risk genetic features according to the European LeukemiaNet 2022 classification. Twenty-nine (63%) had relapsed or were refractory after intensive chemotherapy, including 13 (28%) who had undergone prior allogeneic hematopoietic cell transplantation. Patients received a median of two cycles of venetoclax/HMA (range, 1-31). Twenty (43%) patients achieved complete remission (CR) or CR with incomplete hematologic recovery (CRi) after venetoclax/HMA and five (11%) achieved a partial remission (PR). Six patients were subsequently consolidated with allogeneic hematopoietic cell transplantation (CR/CRi, N=4; PR, N=2). The median follow-up was 49.1 months (95% confidence interval [95% CI]: 26.1 months - not reached) and the median overall survival was 6.4 months (95% CI: 5.1-11 months). One-year and 2-year overall survival rates were 29.3% (95% CI: 18.6-46.2%) and 12.3% (95% CI: 5.5-27.6%), respectively. Age, with a cutoff of 60 years, did not have an impact on overall survival (P=0.90). Relapse occurred in 12 of 20 (60%) patients who achieved CR/CRi after venetoclax/HMA treatment. Of those, all except one succumbed to their disease. Six (30%) patients were in CR/CRi at last follow-up and two (10%) died in CR. In our cohort of patients with AML with extramedullary disease with high-risk features, treatment with venetoclax/HMA resulted in an encouraging overall response rate of 54% with a CR/CRi rate of 43.5%. However, venetoclax/HMA alone may not be effective in maintaining disease control.

Introduction

Extramedullary manifestations of acute myeloid leukemia (AML) are rare, but have a broad clinical spectrum. The overall incidence of extramedullary disease (EMD) has not been clearly established, with reports in the literature ranging from 2.5%[1] to 30%,[2] and varies between different types of AML; patients with monocytic AML[3] and those with t(8;21)(q22;q22)[4,5] or *KMT2* rearrangements[6] have a relatively higher incidence as compared to patients with other subtypes. Furthermore, the prognostic impact of extramedullary manifestations is controversial as they have been associated with worse prognosis in some studies[2,5] but not in others.[7-10] Reports on the prognosis of involvement of specific extramedullary sites, such as the central nervous system (CNS), are also contradictory.[11-13] EMD has traditionally been approached with conventional chemotherapy[14] and/or radiation.[15] Factors influencing the treatment approach when EMD is present include the patient's age, performance status, and comorbidities, disease context (newly diagnosed, or relapsed, including after allogeneic hematopoietic cell transplantation [allo-HCT]) and manifestation (isolated EMD *vs*. synchronous marrow involvement, and size and location of the EMD). However, data supporting various therapeutic strategies are limited because of the rarity of the disease and lack of randomized clinical trials.[15] Recently, venetoclax in combination with hypomethylating agents (HMA) or low-dose cytarabine was approved for the treatment of newly diagnosed AML patients aged ≥75 years old or ineligible for intensive chemotherapy because of comorbidity.[16,17] At present, venetoclax/HMA treatment is the standard of care for older/unfit AML patients.[18] Venetoclax/HMA is also frequently used in patients who have previously received intensive chemotherapy. Currently, there is a paucity of data evaluating the outcome of AML patients with EMD treated with venetoclax/HMA due to the lack of prospective clinical or larger retrospective cohort studies. The current analysis evaluated a series of adult AML patients with EMD. Our objectives were to characterize a series of adult patients with EMD AML and evaluate outcomes after venetoclax/HMA treatment in an international retrospective cohort analysis.

Methods

Patients and treatment

Information on 46 adult AML patients with EMD diagnosed between 2015 and 2022 was collected within a multicenter international cohort, including patients from Denmark, Italy, Germany and the USA. Inclusion criteria were adult AML patients with EMD who were treated with venetoclax/HMA. All patients who fulfilled these criteria were included by clinicians representing the participating groups/institutions. Patients with isolated CNS involvement were excluded since those patients received additional CNS treatment (e.g., high-dose methotrexate, intrathecal cytarabine/methotrexate/dexamethasone and/or radiation). The diagnosis of AML was based on revised International Working Group criteria.[19] Detailed case report forms including information on baseline patient and disease characteristics, prior chemotherapy (if applicable), allo-HCT, venetoclax/HMA treatment and response, and survival were collected from all participating centers. Chromosome banding was performed using standard techniques, and karyotypes were described according to the International System for Human Cytogenetic Nomenclature.[20] A complex karyotype was defined according to the 2017 European LeukemiaNet classification.[21] *FLT3* mutation screening for internal tandem duplications and point mutations within the tyrosine kinase domain was carried out at each institution as previously described.[22,23] Additional mutational testing was performed for *NPM1* (N=45), *TP53* (N=42) as well as spliceosomal mutations (N=40).

Data collection and analysis were approved by the Institutional Review Boards of the participating centers.

Treatment

In total, 17 of the 46 (37%) cases of AML with EMD occurred in newly diagnosed patients with no prior treatment. The other 29 (63%) patients were relapsed or refractory to prior chemotherapy (median number of prior lines, N=1; range, 1-4). Of those, 23 (79%) patients had received prior intensive chemotherapy including allo-HCT in 13 patients. The remaining six patients were treated less intensively: one patient was treated with surgery and low-dose cytarabine for isolated abdominal myeloid sarcoma and achieved complete remission, but relapsed with EMD 1 year later. Five patients received hydroxyurea, of whom two were treated with azacitidine ± an additional agent (APR-246 + azacitidine within a clinical trial, N=1; azacitidine monotherapy, N=1).

Treatment with venetoclax/HMA was given as previously published.[16,17] Extramedullary morphological response assessment was performed by computed tomography scans, magnetic resonance imaging, or positron emission tomography with imaging modality and response adjudicated locally.[24] Bone marrow examination and sampling of the cerebral spinal fluid were performed as clinically indicated based on disease presentation and known sites of AML involvement. Response was assessed according to International Working Group recommendations.[25] Disappearance of EMD lesions is termed a complete response (CR) and regression of at least 50% a partial response (PR). All patients provided written informed consent to participation in one of the treatment trials or to therapy according to local standards.

Statistical analyses

Patients' characteristics were compared with the Kruskal-Wallis rank sum test for continuous variables and the Fisher exact test for categorical variables. The median follow-up time was computed using the reverse Kaplan-Meier estimate.[26] The Kaplan-Meier method was used to estimate the distribution of relapse-free survival and overall survival (OS).[27] OS was

calculated from the start of venetoclax/HMA treatment until death or censored at last follow-up. Relapse-free survival was calculated from achievement of CR after the start of venetoclax/HMA treatment until relapse or death, whatever occurred first, or censored at last follow-up. The confidence interval (CI) estimation for survival curves was based on the cumulative hazard function using the Greenwood formula for variance estimation. Log-rank tests were employed to compare survival curves between groups. The effect of allo-HCT on OS as a time-dependent intervening event was tested by using the Mantel-Byar method for univariable analyses.[28] All statistical analyses were performed with the statistical software environment R, version 4.2.1.[29]

Results

Study cohort

Overall demographic and clinical data were collected at 12 centers from 46 patients diagnosed between 2015 and 2022. Baseline characteristics are summarized in Table 1.

Table 1. Baseline characteristics of the 46 patients with extramedullary manifestations.

Characteristic	Patients N=46
Female, N (%)	16 (35)
Age in years, median (range)	65 (19-81)
ECOG status, N (%)	
0	12 (26)
1	24 (52)
2	10 (22)
Type of AML, N (%)	
De novo	26 (57)
Secondary	19 (41)
Therapy-related	1 (2)
Disease context, N (%)	
Newly diagnosed	17 (37)
Relapsed/refractory	29 (63)
after allo-HCT	13
ELN risk group, N (%)	
Favorable	5 (11)
Intermediate	17 (37)
Adverse	20 (43)
Missing	4 (9)
WBC x10^9/L, median (range)	6.9 (0.6-131.2)
Missing	1
Platelets x10^9/L, median (range)	71 (6-676)
Missing	1
Hemoglobin, g/dL, median (range)	9 (3.6-14.2)
Missing	1
BM blast cells, %, median (range)	40 (0-91)
Missing	5

N: number; ECOG: Eastern Cooperative Oncology Group; AML: acute myeloid leukemia; WBC: white blood cell count; BM: bone marrow.

The median age was 65 years (range, 19-81 years) and all patients had an Eastern Cooperative Oncology Group performance status of ≤2. The patients were more frequently male (N=30, 65%). Overall, patients had a median of two sites of EMD (range, 1-5). Twenty-one (46%) patients had only one extramedullary manifestation while 25 (54%) had more than one involved site. Of those, 18 (9%) had two sites, four patients (9%) had three, two patients (4%) had four and one patient (2%) had five sites involved. The localization of EMD is shown in Figure 1. In addition to EMD, most (N=35, 76%) patients had concurrent bone marrow involvement.

Cytogenetic and molecular analyses

Cytogenetic analyses of bone marrow aspirates or peripheral blood were available for 42 (91%) patients. Of those, 17 (40%) had a complex karyotype, 12 a normal karyotype (28.5%), two (5%) a translocation t(8;21)(q22;q22) and 11 (26%) other abnormalities, most frequently trisomy 8 (N=5). Of the patients with a normal karyotype, only one did not have bone marrow involvement (4% myeloid blasts cells in bone marrow). A total of 45 patients (98%) were tested for *NPM1* and *FLT3* mutations. Of those, eight (18%) and three (7%) harbored *NPM1* and *FLT3*-internal tandem duplica-

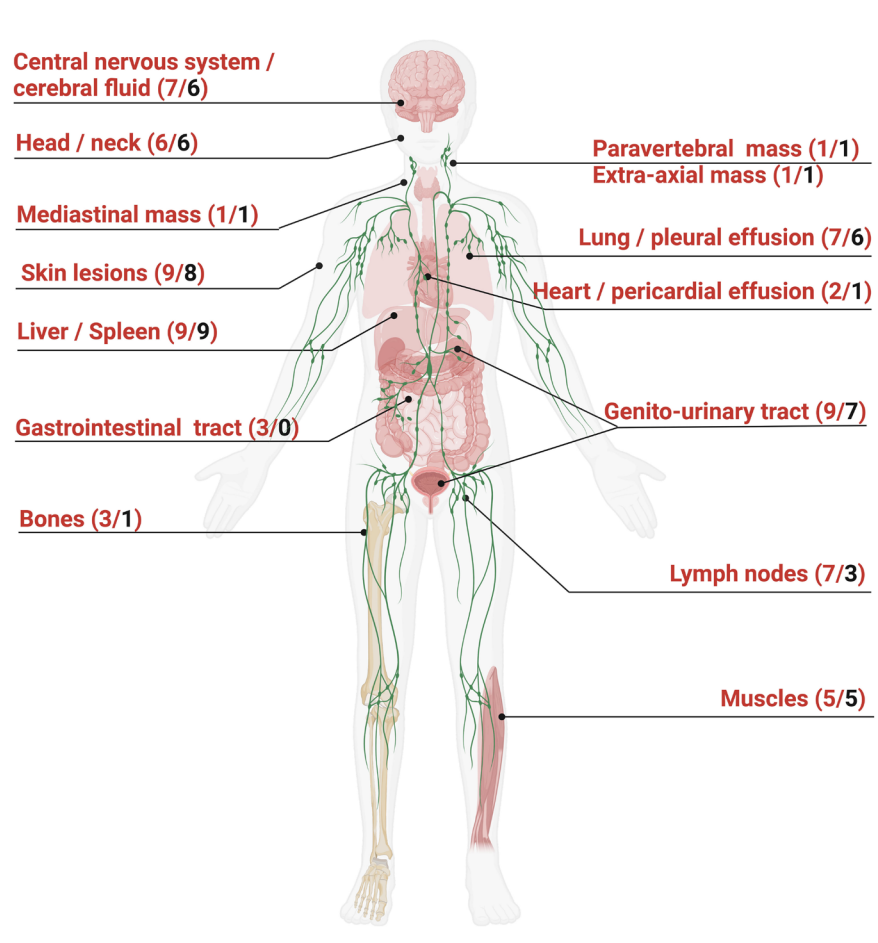

Figure 1. Localization of extramedullary involvement. Numbers are indicated in parentheses (at diagnosis, red; at relapsed/refractory disease, black). Overall, patients had a median of two extramedullary disease manifestations (range, 1-5). Each localization of extramedullary disease was counted separately, so, the total number does not add up to the total number of patients. Figure 1 created with BioRender.com.

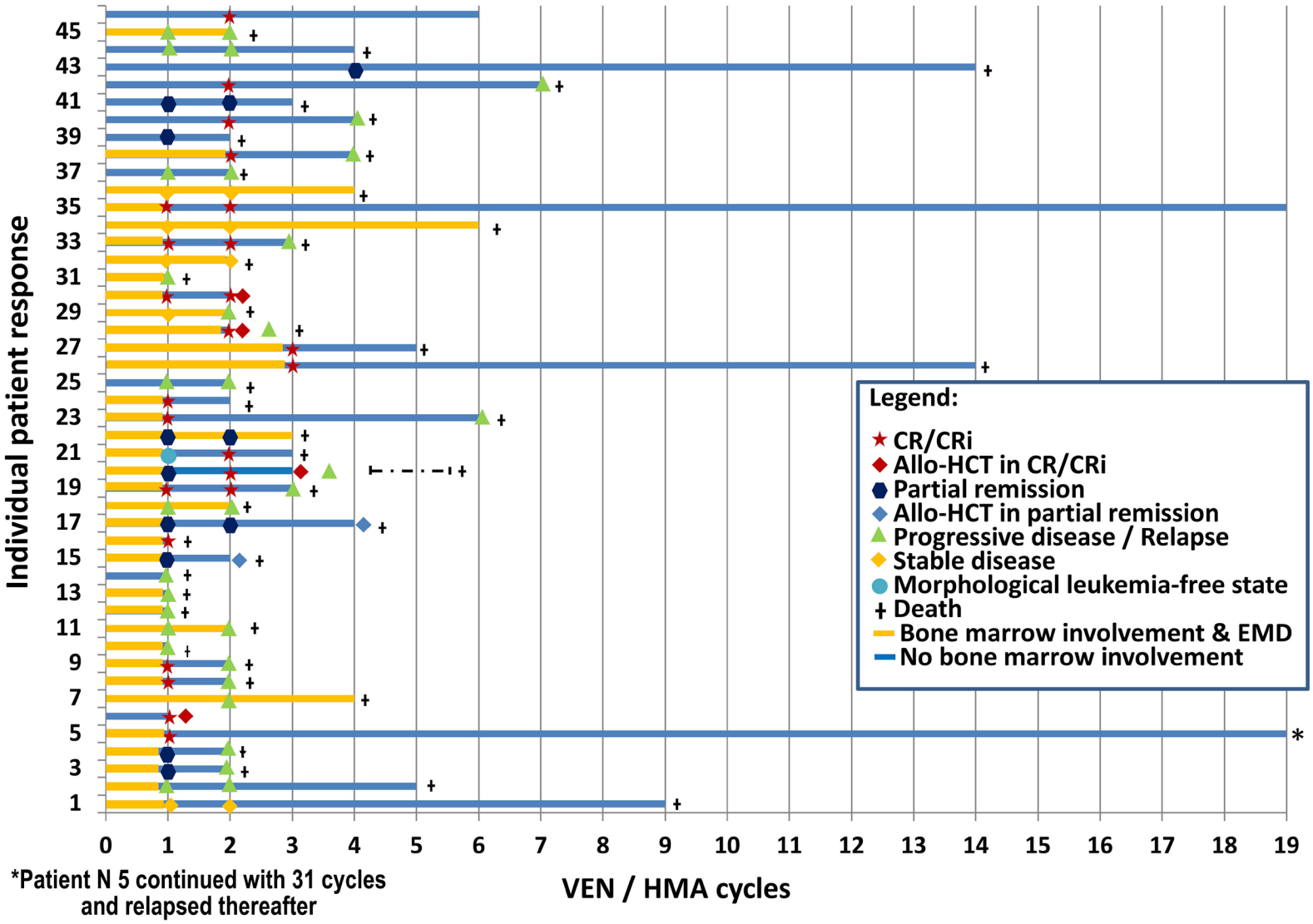

Figure 2. Swimmer plot showing individual patients, treatment duration and response. CR: complete remission; CRi: complete remission with incomplete hematologic recovery; allo-HCT, allogeneic hematopoietic cell transplantation; EMD: extramedullary disease; VEN / HMA: venetoclax/hypomethylating agent.

tion mutations, respectively. One patient (2%) harbored a *FLT3*-tyrosine kinase domain mutation. *TP53* was mutated in 12 (28%) of 43 tested patients. Of those, eight (67%) had a complex karyotype. Spliceosome mutations were present in 13 (32.5%) of 40 tested patients. According to ELN 2022 criteria, 20 patients (43%) had high-risk AML (Table 1).

Response to venetoclax/hypomethylating agents, cumulative incidence of relapse and death

A median of two cycles (range, 1-31) of venetoclax/HMA were administered following published regimens.[16,17] Thirty-nine (85%) patients received venetoclax plus azacitidine and seven (15%) patients venetoclax plus decitabine.

The rate of CR/CR with incomplete hematologic recovery (CRi) was 43.5% (N=20/46), of whom five had been heavily pretreated including allo-HCT. Five (11%) patients achieved a PR, of whom two achieved CR/CRi after allo-HCT (Figure 2). Three patients died in CR/CRi after venetoclax/HMA due to infections (COVID19 infection, septic shock, infection, N=1 each). Of the 20 patients who achieved CR/CRi after venetoclax/HMA, relapse occurred in 13 (65%) after a median time of 2.3 months (range, 0.7 to 44.6 months) on treatment. Of those, all except one succumbed to their disease.

The cumulative incidence of relapse and death for the 20 patients achieving a CR/CRi after 2 years was 56% (95% CI: 33-80%) and 17% (95% CI: ND-36%), respectively. Six patients were bridged to allo-HCT (CR/CRi, N=4; PR, N=2) including one who received a second allo-HCT. Prior to allo-HCT all patients received ≤3 venetoclax/HMA cycles. Conditioning was myeloablative in two and non-myeloablative in four patients.

Survival

The median follow-up was 49.1 months (95% CI: 26.1 months - not reached) and the median OS for all patients was 6.4 months (95% CI: 5.1-11 months) (Figure 3). One-year and 2-year OS rates were 29.3% (95% CI: 18.6-46.2%) and 12.3% (95% CI: 5.5-27.6%), respectively. Age with a cutoff of 60 years had no impact on OS (P=0.90).

There was no difference in OS (P=0.7) according to whether patients had extramedullary manifestations only as compared to EMD and bone marrow involvement. Furthermore, no difference in OS (P=0.3) was observed comparing patients with only one site of EMD *versus* more than one site.

Survival from first treatment with venetoclax/HMA and response to venetoclax/HMA treatment were superior in patients with newly diagnosed AML and EMD (Figure 4A) than in those with relapsed or refractory AML and EMD

(Figure 4B) with a median survival and CR/CRi rate of 8 months (95% CI: 5.1-20.6 months) and 64% compared to 5.8 months (95% CI: 3.3-11 months) and 25%, respectively. Allo-HCT was associated with a trend to better OS as compared to treatment with venetoclax/HMA (median survival, 18.8 months *vs*. 6.4 months; *P*=0.06, Mantel Byar test).

Subgroup analysis according to *TP53* mutational status revealed a shorter OS in *TP53*-mutated patients than in *TP53* wild-type patients (median survival, 4.0 months *vs*. 9.6 months; *P*=0.04). In contrast, *NPM1* mutational status had no impact on OS (*P*=0.4)

Five patients were alive and in CR/CRi at last follow-up, two after allo-HCT and three who did not receive a transplant. All 26 non-responding patients died, most from disease progression (N=22), but some of other causes (infection, N=2; graft-*versus*-host disease, N=1; trauma, N=1).

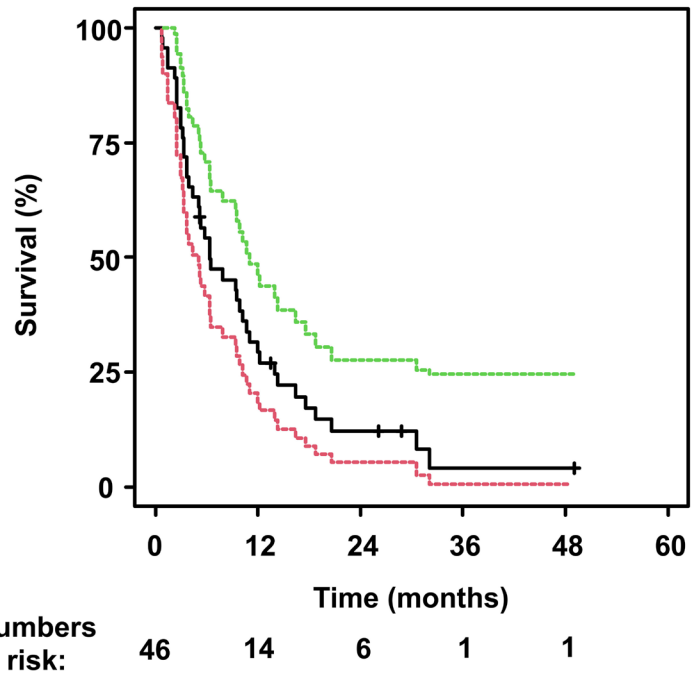

Figure 3. Overall survival of patients with acute myeloid leukemia and extramedullary disease after treatment with venetoclax/hypomethylating agents. Green and red dotted lines indicate upper and lower 95% confidence intervals.

Discussion

EMD has been described with varying incidences, ranging from 2.5%[1] to 30%,[2] and with different incidences in different types of AML.[3] For instance, EMD has been reported to occur more frequently in AML with t(8;21)(q22;q22) abnormalities.[4,5] However, in our cohort, only two patients had AML with t(8;21)(q22;q22) and EMD arguing against a higher incidence in patients with this abnormality. Our data are in line with a recent publication by Ganzel *et al*., who did not find a stronger association of AML with EMD and t(8;21) as compared to other cytogenetic abnormalities.[10] EMD may involve different sites, as observed in our series.[10] Of those, liver/spleen, genito-urinary tract as well as skin lesions were the most common sites reported, with an incidence of 20%, followed by lung/pleural effusions, CNS/cerebral fluid and lymph nodes (15% each). The relatively high incidence of CNS involvement is consistent with a recent report of 103 adult patients with newly diagnosed AML who were submitted to an exploratory lumbar puncture regardless of neurological symptoms.[30] In that study, 32% of the patients had CNS involvement at diagnosis, which is higher than previously reported for newly diagnosed AML patients who underwent a routine lumbar puncture.[31] Thus, the authors concluded that lumbar puncture should be performed routinely.[30] Given the relatively large number of cases with CNS involvement and EMD, we suggest performing lumbar puncture routinely in

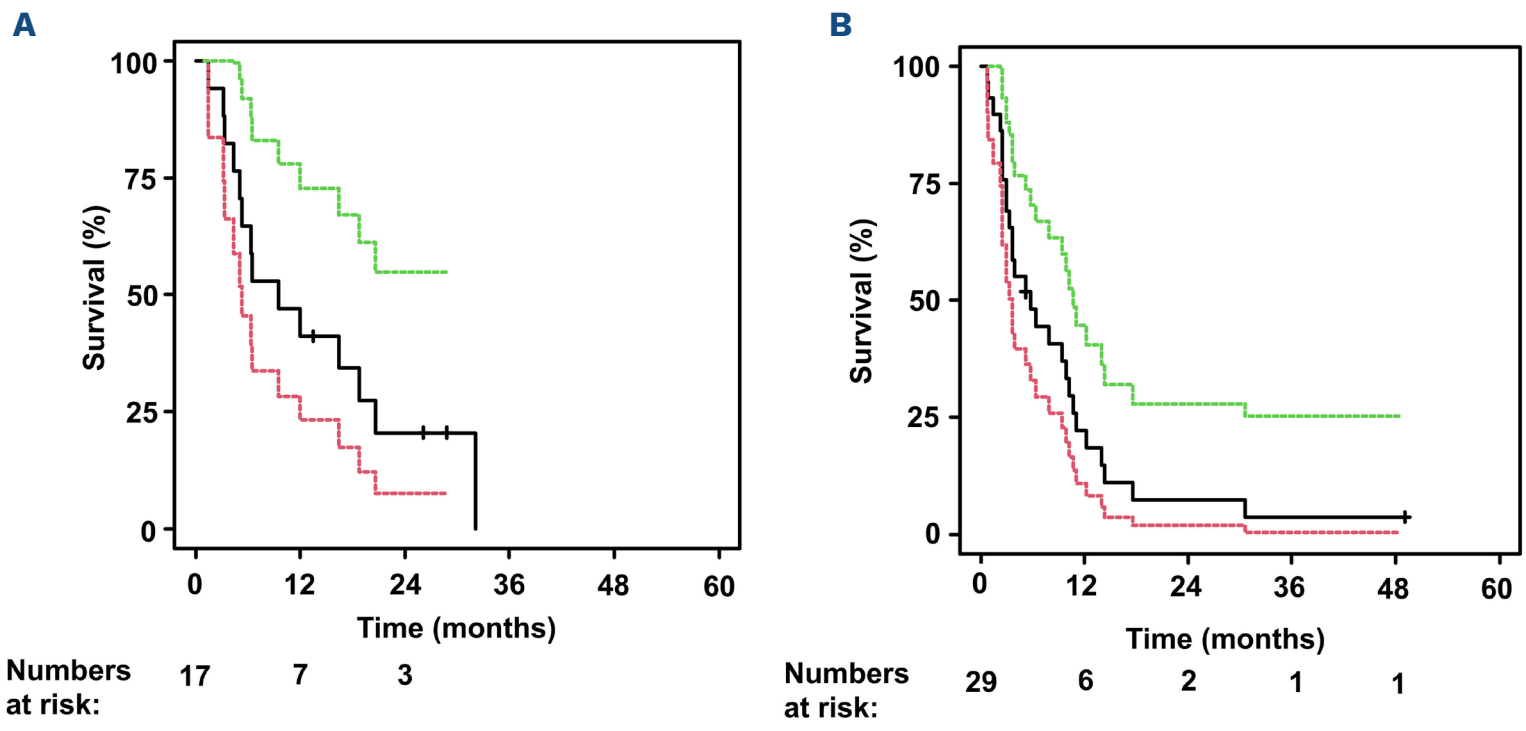

Figure 4. Overall survival of patients with acute myeloid leukemia and extramedullary disease after treatment with venetoclax/hypomethylating agents according to disease status. (A) Newly diagnosed patients. (B) Relapsed or refractory patients. Green and red dotted lines indicate upper and lower 95% confidence intervals.

those patients, particularly since CNS is the only EMD site that mandates a specific therapeutic approach, i.e. intrathecal methotrexate and/or high-dose cytarabine.

In our study, 54% of patients with EMD had more than one involved site; 9% had three sites and some patients even had four or five involved sites. The relatively high rate of multiple-site EMD involvement suggests that the development of EMD is an intrinsic feature of the leukemic cells and depends on factors such as the expression of cell surface adhesion molecules.[2,32] In contrast to published data,[10] no impact on outcome was observed if more than one site was affected. The clinical outcome of patients with EMD in our study compares favorably with recently published data by Bae *et al.*, who reported on 11 patients with relapsed or refractory AML and EMD.[33] In their study the overall response rate was 36.4% (either marrow or extramedullary responses to venetoclax combination therapy) and the median OS was 5.4 months. In our cohort, particularly patients with newly diagnosed AML with EMD had a superior outcome with a CR rate of 64% and a median OS of 8 months after treatment with venetoclax/HMA. Thus, there is a misconception that venetoclax/HMA is less potent than conventional cytotoxic chemotherapy against EMD.

Only a minority of our patients went on to allo-HCT. Nevertheless, 33% were still alive and in an ongoing remission at roughly 61 and 71 months of follow-up. The use of allo-HCT after disease control with venetoclax/HMA needs to be explored.

Our data are comparable to those in other reports on patients with blast phase myeloproliferative disease or myelodysplastic syndrome/AML.[34-37]

In conclusion, venetoclax/HMA resulted in an encouraging CR/CRi rate of 43.5% in a high-risk AML population with EMD. The outcome was particularly good in patients with newly diagnosed AML with EMD, who had a CR rate of 64% and a median OS of 8 months after treatment with venetoclax/HMA. However, responses were not durable. Whether allo-HCT after disease control with venetoclax/HMA is a veritable option needs to be evaluated in the future.

Disclosures

No conflicts of interest to disclose.

Contributions

SK and CP were responsible for the concept of this paper, contributed to the literature search and data collection, contributed patients, analyzed and interpreted data, and critically revised the manuscript. RFS was responsible for the concept of the paper, analyzed and interpreted data, and wrote the manuscript. KS, GM, MRL, AK, MC, DTK, ASR, CS, FG, MR, LR, FS, SG, FL, EB, AEP, MJL, and TJ contributed patients and critically revised the manuscript. All authors reviewed and approved the final manuscript.

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Data-sharing statement

Questions regarding data sharing should be addressed to the corresponding author.

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