Disease course of *FLT3* mutated extramedullary acute myeloid leukemia and efficacy of gilteritinib

Extramedullary involvement by acute myeloid leukemia (AML) refers to the proliferation of neoplastic blasts outside the bone marrow and can occur in any organ or tissue. It can present either concurrently with AML or in an isolated form, which is, however, almost invariably followed by development of disease in the bone marrow. At the time of AML diagnosis, extramedullary AML (eAML) has a reported incidence ranging from 0.2% to 2.8%, which increases up to 25% in cases relapsed after allogeneic hematopoietic stem cell transplantation (allo-HSCT).[1] A higher risk of developing eAML has been reported in association with the expression of specific surface antigens (CD11b and CD56), cytogenetic abnormalities such as t(8;21), inv(16) and trisomy 8, and different mutations (*NPM1, FLT3*-ITD, *PTPTN11*).[1,2] The prognostic impact of eAML remains controversial, and even more limited evidence exists regarding the disease course of eAML in the context of specific mutations.[1] This is particularly relevant for those with targetable mutations such as *FLT3*-internal tandem duplications (ITD)/tyrosine kinase domains (TKD), since clinical trials investigating the *FLT3* inhibitor gilteritinib did not report the outcomes of patients with eAML and excluded those with central nervous system (CNS) disease.[3,4] While evidence regarding the activity of targeted agents in eAML is starting to appear, most previous studies were conducted before the emergence of these therapies.[1,5] In this study, we set out to investigate the disease course and treatment patterns of patients with eAML and *FLT3* mutations, with a particular focus on outcomes after treatment with gilteritinib.

We conducted a multicenter, retrospective study across ten referral hematology centers in Italy. Institutions were chosen based on their willingness to participate and availability of data. Each institutional record was screened by the local investigators for patients with eAML diagnosed from January 2010 until May 2024 and cross-referenced with mutational data. Eligible patients had a diagnosis of AML with *FLT3* mutations detected in bone marrow or peripheral blood and histologically confirmed synchronous eAML presenting either at diagnosis or at disease relapse. In the case of isolated eAML the presence of *FLT3* mutations had to be confirmed on eAML tissue. Response was assessed by positron emission tomography (PET)/computed tomography (CT) or PET/magnetic resonance imaging (MRI) according to each institute's protocol, and by full clinical examination in the case of skin eAML. CNS involvement required the presence of AML blasts in the cerebrospinal fluid by cytological examination or flow-cytometry. CNS sterilization required both flow-cytometry negativity and disappearance of any contrast-enhancing lesions by MRI. Data regarding clinical and biological variables were obtained from each institution after review of the medical records. Overall survival (OS) was calculated from the time of eAML presentation until death or last follow-up date (censored). All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (1430/A3).

Table 1. The clinical and biological characteristics of the whole population at the time of first occurrence of extramedullary acute myeloid leukemia.

Characteristics	Values
Total patients, N (%)	27 (100)
Disease status, N (%) Newly diagnosed Relapsed/refractory	 14 (52) 13 (48)
Sex, N (%) Female Male	 11 (41) 16 (59)
Age, years, median (range)	61 (30-81)
2022 ELN risk category,* N (%) Favorable Intermediate Adverse	 5 (19) 20 (74) 2 (7)
Karyotype, N (%) Normal Complex Other	 20 (74) 2 (7) 5 (19)
FLT3 mutations, N (%) Internal tandem duplication Tyrosine kinase domain	 21 (78) 6 (22)
NPM1 status, N (%) Mutated Wild-type	 19 (70) 8 (30)
IDH status, N (%) *IDH1* *IDH2* Wild-type Not done	 3 (11) 2 (7) 12 (45) 10 (37)
WBC, x10^9/L, median (range)	15.1 (0.8-285)
Neutrophils, x10^9/L, median (range)	5.3 (0.4-48)
Hemoglobin, g/L, median (range)	87 (64-119)
Platelet count, x10^9/L, median (range)	47 (11-196)
Bone marrow blasts, %, median (range)	56.5 (0-93)
Peripheral blood blasts, %, median (range)	30 (0-98)

*As evaluated at the time of the diagnosis of acute myeloid leukemia. ELN: European LeukemiaNet; WBC: white blood cells.

A total of 27 patients were included in the study. The median age was 61 years (range, 30-81 years). Sixteen (59%) patients were female. At diagnosis, five (19%) were classified as favorable-risk, 20 (74%) as intermediate-risk and two (7%) as adverse-risk according to the European LeukemiaNet 2022 risk classification. Fourteen (52%) patients presented with eAML at diagnosis while 13 (48%) at the time of disease relapse. Among the latter, all patients received a single line of therapy before eAML occurrence and only one (8%) had a previous allo-HSCT. Twenty-six patients (96.3%) had synchronous eAML and one (3.7%) had isolated eAML. Cytogenetic and molecular analyses were performed on bone marrow/peripheral blood blasts in all 26 cases with synchronous eAML. *FTL3* testing was performed also on eAML tissue from four patients (3 in blasts from cerebrospinal fluid; 1 skin biopsy) detecting the same mutation identified in the bone marrow, and in the one patient with isolated eAML in the mammary gland. The most common *FLT3* mutation was *FLT3*-ITD (N=21, 78%) *versus* *FLT3*-TKD (N=6, 22%). Nineteen (70%) patients harbored concomitant *NPM1* mutations (Table 1).

Most patients had a single eAML localization (N=23, 89%) while four (11%) had multiple localizations. The most common sites of initial eAML presentation were the skin in 15 (56%) patients and the CNS in eight (30%), followed by soft tissues in three (11%), and the mammary gland, ovary, rectum, stomach, lymph nodes and spleen in one each (4% for each) (Figure 1). Of the four patients with multiple sites affected by eAML, two had disease in the skin and CNS, one in the skin and soft tissues, and another one in skin, lymph nodes and spleen.

eAML at the first occurrence was treated with intensive chemotherapy in 14 (56%) patients of whom five (19%) also received midostaurin, with gilteritinib in ten (37%) patients, and with triple intrathecal therapy alone, upfront allo-HSCT and venetoclax-decitabine each in one (4%) patient. The overall response rate was 81.5%, with 18 (66.7%) complete remissions and four (14.8%) partial responses. Of the five patients not responding to initial treatment, two received no further treatment, two were treated with salvage intensive chemotherapy and one with gilteritinib. Twelve (59%) of the 22 responding patients eventually relapsed, five with disease recurrence only in bone marrow and seven with recurrence in both bone marrow and eAML. Among the latter seven, five (71.4%) relapsed in the same site originally affected by eAML, one relapsed with CNS disease after previous skin eAML, and the last one with previous skin and CNS disease relapsed only with skin eAML. These patients received further therapy with intensive chemotherapy (N=4, 33%), gilteritinib (N=5, 42%) or venetoclax-azacitidine (N=2, 17%), while one (8%) died without receiving further treatment. Upon further relapse or disease refractoriness, two more patients received gilteritinib and one intensive chemotherapy. The overall response rate for the 14 patients receiving salvage therapy was 64.3% (9 complete remissions, 4 stable disease, 1 not evaluable). eAML treatments are summarized in *Online Supplementary Table S1* and treatment trajectories for all patients are represented in Figure 2. At the time of eAML diagnosis 23 of the 27 (85.2%) patients were considered eligible for allo-HSCT, with nine of the 23 (39%) undergoing allo-HSCT.

The median OS was 11.1 months (95% confidence interval [95% CI]: 10.3 – not reached [NR]) in the whole cohort (*Online Supplementary Figure S1*), 11.1 months (95% CI: 10.4 – NR) in patients with the first presentation of eAML at diagnosis and 10.7 months (95% CI: 4.14 - NR) in those with first eAML presentation at relapse. There was no significant difference in survival between newly diagnosed and relapsed or refractory patients (*P*=0.5). Skin localization of eAML was associated with longer OS (hazard ratio [HR]=0.27; 95% CI: 0.08-0.95; *P*=0.03), and the same was true for undergoing allo-HSCT (HR= 0.10; 95% CI: 0.01-0.78; *P*=0.004). CNS

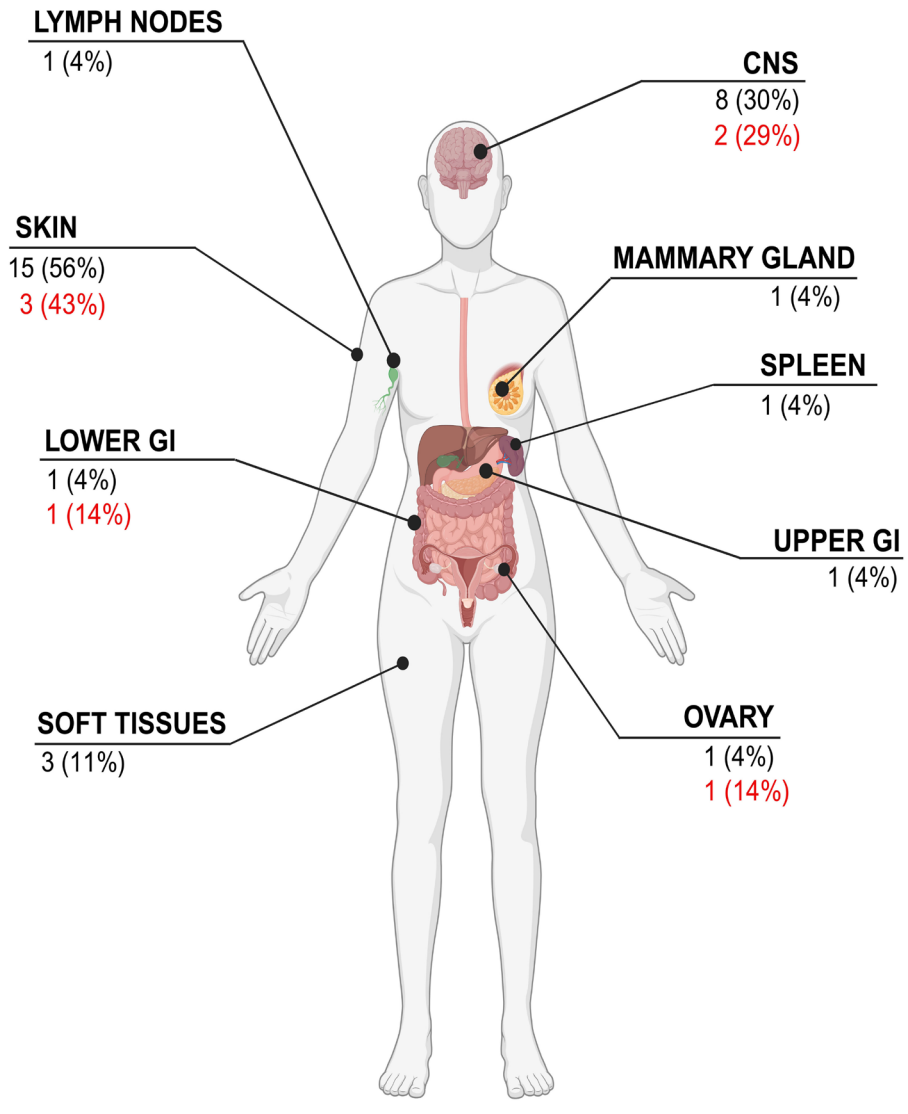


Figure 1. Prevalence of sites affected by extramedullary acute myeloid leukemia at first occurrence and at relapse. The prevalence of sites affected by extramedullary acute myeloid leukemia at first occurrence is represented in black while the prevalence at relapse is shown in red. Percentages are calculated out of the total number of patients at first diagnosis (N=27; including 4 patients with multiple localizations) and at extramedullary relapse (N=7). Created in BioRender. Angotzi, F. (2026) *https://BioRender.com/kmgknbx* CNS: central nervous system; GI: gastrointestinal system.

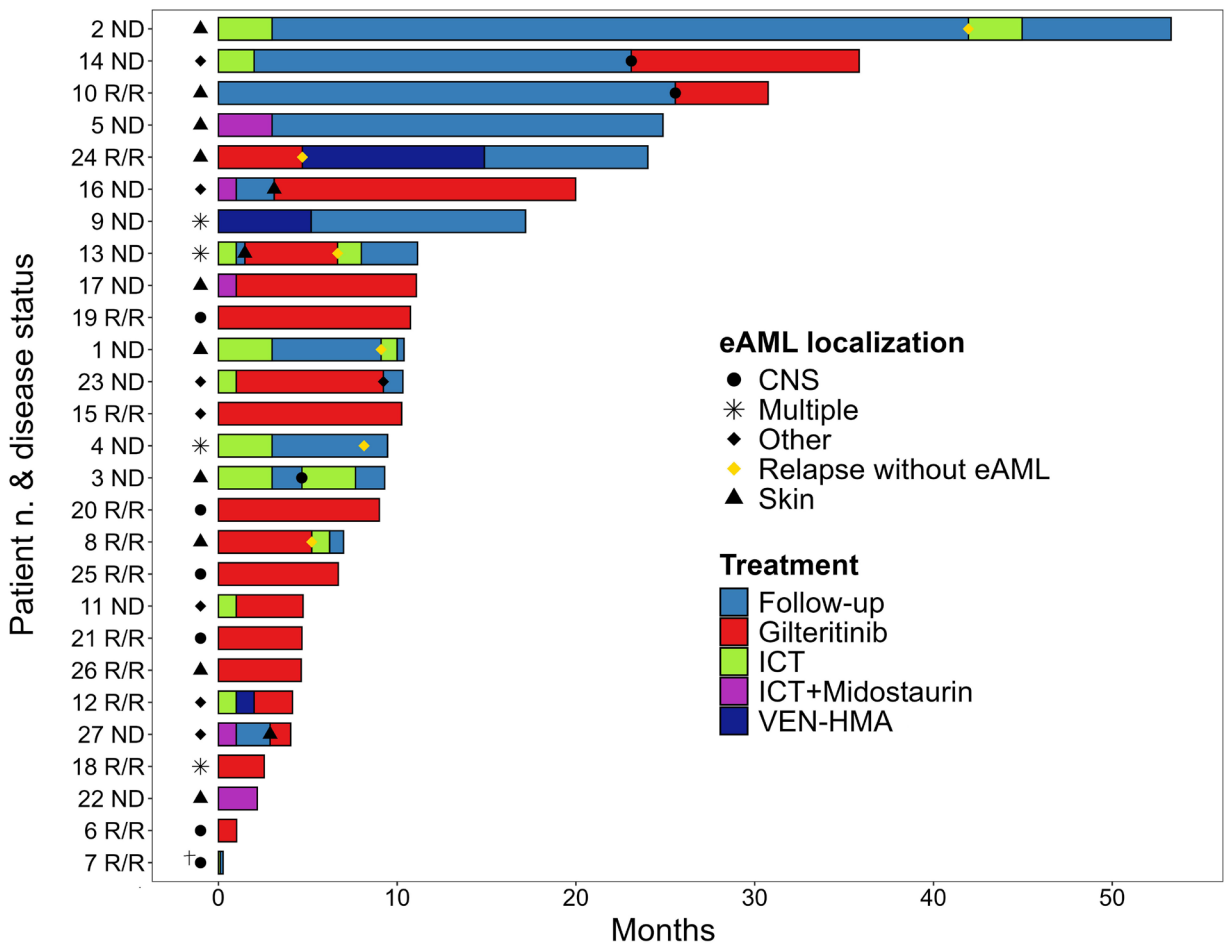


Figure 2. Swimmer plot outlining treatment trajectories and localization of extramedullary acute myeloid leukemia in the enrolled patients. †Received only triple intrathecal therapy as treatment. ND: newly diagnosed acute myeloid leukemia; R/R: relapsed/refractory acute myeloid leukemia; eAML: extramedullary acute myeloid leukemia; CNS: central nervous system; ICT: intensive chemotherapy; VEN-HMA: venetoclax-hypomethylating agents.

involvement at diagnosis was associated with a trend towards shorter OS (HR=3.3; 95% CI: 0.98-10.9; *P*=0.05). The presence of *NPM1* mutations (HR=1.10; *P*=0.9), type of *FLT3* mutations (ITD *vs*. TKD; HR=0.66; *P*=0.5), or age (HR=1.04; *P*=0.1) had no impact on OS.

In total, 19 (70.4%) patients received gilteritinib for the treatment of eAML in the context of relapsed or refractory disease, achieving an overall response rate of 63% (11 complete remissions, 1 partial response and 4 no responses). Moreover, out of 11 patients with CNS involvement, seven (64%) were treated with gilteritinib + triple intrathecal therapy, with six (85.7%). achieving a complete remission. The median OS from the start of therapy with gilteritinib was 9.6 months (95% CI: 9.0 - NR). Before the start of gilteritinib treatment, 12/19 patients (63%) were considered eligible for allo-HSCT, with four of these 12 (33%) being successfully bridged to allo-HSCT and two also receiving post-allo-HSCT maintenance.

Major limitations of this study include the small sample size, retrospective nature, and the heterogeneity of administered treatments. Furthermore, the efficacy of gilteritinib on CNS disease should be interpreted with caution given the inability to separate its effect from triple intrathecal therapy. Given the small cohort, particular caution should also be exercised in interpreting the prevalence of eAML localization in different organs and the better outcomes observed with skin localization.

Despite these limitations, the observed high rate of CNS localization is in keeping with evidence suggesting that AML with *FLT3* mutations has a predisposition for disease dissemination in the CNS, accounting for 29% of AML with CNS involvement.[6] The purported mechanisms driving CNS dissemination by AML are still unknown, but may be related to *FLT3* fostering cell survival and proliferation in both hematopoietic and neural tissues.[6,7] Also, previous case reports demonstrated high gilteritinib penetration in the cerebrospinal fluid, possibly pointing towards a role in eradication of CNS disease.[8-11]

Patients developing eAML at diagnosis in our cohort had a similar OS to those developing eAML at relapse which may indicate reduced survival in the former. However, this finding is likely affected by the small sample size and previous studies have not demonstrated consistent inferior survival in patients with eAML at diagnosis.[12]

Nonetheless, and still considering the aforementioned limitations, a relevant finding of this study is the favorable activity of gilteritinib in *FLT3*-mutated eAML, including in patients with CNS involvement when coupled with triple intrathecal therapy. The response rates and survival outcomes observed in our cohort after treatment with gilteritinib were comparable with those reported from both real-life studies and the prospective trials ADMIRAL and COMMODORE,[3,13] and are in keeping with evidence demonstrating extensive tissue distribution of gilteritinib.[14,15]

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CV has received honoraria from and attended advisory boards for AbbVie Inc, Astellas Pharma, Jazz Pharmaceuticals and BMS. GM has received research funds from AbbVie, Astellas, AstraZeneca, Daiichi Sankyo, Pfizer and Syros and was a consultant or was included in speakers' bureau for AbbVie, Astellas, AstraZeneca, Enable lifescience, FlowView Diagnostics, Immunogen, Janssen, Jazz, Menarini/Stemline, Pfizer, Ryvu, Servier, Syros, Takeda and Uknequas. FA, EB, CS, MBG, ET, MT, FL, EA, VF, FG, AV, FF, CG and FL have no conflicts of interest to disclose related to this study.

Contributions

FA wrote the manuscript, performed statistical analyses, created figures and tables and collected data. EB, CS, MBG, GM, ET, MT, FL, EA, VF, CV and FG collected data, reviewed the manuscript and provided intellectual output. AV, FF, LT and CG revised the manuscript and provided intellectual output. FL conceptualized the study, reviewed the manuscript and provided intellectual output.

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Data-sharing statement

The data generated and presented in this manuscript are available upon reasonable request from the corresponding author.

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