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Extramedullary infiltration in pediatric acute myeloid leukemia: Results of the Therapeutically Applicable Research to Generate Effective Treatments dataset

Weiya Li[1], Mingyue Shi[1], Pan Zhou[1], Ying Liu[1], Xiaobo Liu[1], Xingjun Xiao[1], Suqiong Zuo[1], Yanliang Bai[1], and Kai Sun[1]

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April 04, 2024

Abstract

Background: The outcome of extramedullary infiltration (EMI) in pediatric acute myeloid leukemia (AML) is controversial, and little is known about the implications of stem cell transplantation (SCT) and gemtuzumab ozogamicin (GO) treatment on AML patients with EMI. **Methods:** We retrieved the clinical data of 713 pediatric AML patients from the TARGET dataset and analyzed the clinical and prognostic characteristics of patients with EMI at initial diagnosis and relapse. **Results:** A total of 123 patients were identified to have EMI at initial diagnosis and 64 presented with EMI at relapse. We discovered that the presence of EMI was associated with age [?]2 years, M5 morphology, abnormal karyotype, and KMT2A rearrangements. Hyperleukocytosis and complex karyotype were more prevalent in EMI relapse patients. Additionally, patients with EMI at diagnosis showed a reduced incidence of FLT3 ITD-/NPM1+, whereas EMI relapse patients displayed a lower frequency of FLT3 ITD+. Patients with EMI at diagnosis exhibited a lower rate of CR1 and higher incidence of relapse. Importantly, EMI at diagnosis independently predicted both shorter EFS and OS. Regarding relapse patients, the occurrence of EMI at relapse showed no impact on OS. However, relapse patients with myeloid sarcoma exhibited a poorer OS compared to those with exclusive CNS involvement. Furthermore, in reference to patients with EMI at initial diagnosis, SCT failed to improve the survival, whereas GO treatment may potentially enhance OS. **Conclusion:** EMI at initial diagnosis is an independent prognostic risk factor, GO treatment has the potential to improve survival for patients with EMI at diagnosis.

Extramedullary infiltration in pediatric acute myeloid leukemia: Results of the Therapeutically Applicable Research to Generate Effective Treatments dataset

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Text word count: 3173 characters.

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Abstract word count: 250 characters.

The number of tables: 3.

The number of figures: 2.

Brief Running title: EMI in pediatric AML: results of TARGET dataset

Keywords: Pediatric acute myeloid leukemia; Extramedullary infiltration; Initial diagnosis; Relapse; Prognosis; Gemtuzumab ozogamicin

Abbreviations

AML	acute myeloid leukemia
EMI	extramedullary infiltration
EMD	extramedullary disease
TARGET	Therapeutically Applicable Research to Generate Effective Treatments
CNS	central nervous system
MS	myeloid sarcoma
GO	gemtuzumab ozogamicin
IT	intrathecal
WBC	white blood cell
BM	bone marrow
PB	peripheral blood
FAB	French-American-British classification
SCT	stem cell transplantation
CR	complete remission
MRD	minimal residual disease
OS	overall survival
EFS	event-free survival
RFS	relapse-free survival
HR	hazards ratio
CI	confidence interval

Abstract:

Background: The outcome of extramedullary infiltration (EMI) in pediatric acute myeloid leukemia (AML) is controversial, and little is known about the implications of stem cell transplantation (SCT) and gemtuzumab ozogamicin (GO) treatment on AML patients with EMI.

Methods: We retrieved the clinical data of 713 pediatric AML patients from the TARGET dataset and analyzed the clinical and prognostic characteristics of patients with EMI at initial diagnosis and relapse.

Results: A total of 123 patients were identified to have EMI at initial diagnosis and 64 presented with EMI at relapse. We discovered that the presence of EMI was associated with age [?]2 years, M5 morphology, abnormal karyotype, and KMT2A rearrangements. Hyperleukocytosis and complex karyotype were more prevalent in EMI relapse patients. Additionally, patients with EMI at diagnosis showed a reduced incidence of FLT3 ITD-/NPM1+, whereas EMI relapse patients displayed a lower frequency of FLT3 ITD+. Patients with EMI at diagnosis exhibited a lower rate of CR1 and higher incidence of relapse. Importantly, EMI at diagnosis independently predicted both shorter EFS and OS. Regarding relapse patients, the occurrence of EMI at relapse showed no impact on OS. However, relapse patients with myeloid sarcoma exhibited a poorer OS compared to those with exclusive CNS involvement. Furthermore, in reference to patients with EMI at initial diagnosis, SCT failed to improve the survival, whereas GO treatment may potentially enhance OS.

Conclusion: EMI at initial diagnosis is an independent prognostic risk factor, GO treatment has the

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potential to improve survival for patients with EMI at diagnosis.

Introduction

Pediatric acute myeloid leukemia (AML) is a complicated and relatively rare hematological malignancy, constituting 15-20% of the total number pediatric acute leukemia patients. The prognosis of pediatric acute myeloid leukemia has seen notable improvements over the past few decades, with long-term survival rates of up to 70%. However approximately 30% of pediatric AML patients may experience relapse[1]. There are significant disparities in terms of clinical progression, outcomes, and genetic features between pediatric and adult AML patients[1,2].

Extramedullary infiltration (EMI), also known as extramedullary disease (EMD), in AML presents as the infiltration of malignant clonal blasts in diverse anatomical sites apart from the bone marrow. These include other normal hematopoiesis from embryonic development onward (such as spleen, liver, thymus, and lymph nodes), soft tissue, skin, central nervous system (CNS), and other various organs or tissues[3,4]. The occurrence of EMI in pediatric AML patients ranges from 5.7% to 40% (commonly 10-25%)[4], much higher than in adult patients which is around 4.7-14.21%[5,6]. Furthermore, approximately 3.5% of pediatric AML patients post-transplantation experience isolated extramedullary relapse[7].

In pediatric AML patients, the presence of EMI at diagnosis has been reported to be associated with young age, high WBC count, and FAB-M4/M5 subtypes[8-12]. Moreover, chromosomal abnormalities such as 11q23 abnormalities[10-12], and t(8;21)[12,13], have also been described in several studies. The outcome of EMI in pediatric AML patients is still controversial[4]. Some studies indicate that the presence of EMI at diagnosis was associated with a poorer prognosis[11,14,15], while others indicate no significant influence on overall prognosis[9,10]. In certain subgroups, there were even suggestions of a potential association with improved outcomes[12,16]. However, there is a paucity of research on EMI at relapse in pediatric AML patients and little is known about the effect of SCT and GO treatment on the survival of AML patients presented with EMI.

The present study is a retrospective review of pediatric AML patients enrolled in COG trials AAML0531 and AAML03P1 from the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) dataset. We analyzed the clinical and prognostic characteristics of those who were identified with EMI (including myeloid sarcoma and/or CNS involvement in this study) at different time points (initial diagnosis and relapse) to gain a better understanding of this specific AML entity.

Methods

2.1 Patients

Clinical data of pediatric AML patients enrolled in Children's Oncology Group (COG) trials AAML0531 and AAML03P1 were extracted from the TARGET dataset (*https://portal.gdc.cancer.gov*). Cases diagnosed with acute promyelocytic leukemia, significant data missing, and age [?]21 years were excluded. A total of 713 cases were included in the present study after data filtering. The treatment protocols of the three clinical trials have been reported previously[17,18]. AAML0531 and AAML03P1 shared similar conventional chemotherapy dosages and durations. However, in the AAML03P1 trial, patients routinely underwent GO therapy during two cycles of chemotherapy, whereas in the AAML0531 trial, patients were subject to random allocation, determining their eligibility for the GO regimen. Lumbar puncture was carried out as a component of the diagnostic assessment. CNS disease was defined as the presence with any leukemic blasts in cerebrospinal fluid (CSF) without blood contamination, clinical manifestations of CNS leukemia, or radiographic evidence of intradural myeloid sarcoma. Myeloid sarcoma was confirmed by pathology and/or imaging.

In the AAML0531 and AAML03P1 trials, CNS prophylaxis involved administering intrathecal (IT) cytarabine on the first day of induction I/II and intensification I/II or biweekly, with a maximum of six doses. Patients with CNS involvement received IT cytarabine biweekly until the CSF was transparent and two additional IT cytarabine treatments. Patients were excluded from the trials when CNS leukemia still persisted after receiving six doses of IT cytarabine.

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2.2. Statistical analysis

Significance testing for comparisons in categorical variables was performed using the Chi-square test or Chi-square with Yates' correction, while the Mann-Whitney U test was utilized for continuous variables. Multinomial logistic regression was employed to calculate odds ratios of impact factors for the occurrence of EMI at different time points. Event free survival (EFS) and overall survival (OS) were analyzed by Kaplan-Meier method and the comparison of survival distributions was conducted using the log-rank test. Cox-proportional hazard models were employed for multivariate analysis of prognostic markers. Statistical significance was defined as P value less than 0.05.

Results

In this cohort, a total of 713 patients were included, with 628 originating from AAML0531, 85 from AAML03P1. The median follow-up period was 2035 days. Among these patients, 123 (17.3%) were diagnosed with EMI at initial diagnosis. 255 (35.8%) patients experienced relapse, out of which, 64 (25.2%) were present with extramedullary infiltration at relapse.

Clinical characteristics of pediatric AML patients with EMI at initial diagnosis

The clinical characteristics of patients with EMI at initial diagnosis are presented in Table 1. Among the 123 patients who had EMI at the time of initial diagnosis (EMI positive group), 36 exclusively presented with CNS involvement only, 75 were diagnosed with myeloid sarcoma, and 12 displayed concurrent CNS involvement and MS. Out of these patients, 24 (19.5%) exhibited hyperleukocytosis (WBC [?]100×10^9/L), and the median WBC count, BM blast percentage, and PB blast percentage were 27.0×10^9/L, 70.0%, and 41.0%, respectively, which were not significantly different from those without EMI at diagnosis (EMI negative group) (p>0.05). In the EMI positive group, 30.9% (38/123) of patients were [?]2 years old, which was a significantly higher proportion than that in the EMI negative group (30.9% vs. 15.3%, p <0.0001). According to the FAB classification, only 6.5% (8/123) of EMI positive group patients were classified as M1, which was significantly lower than the corresponding percentage in the EMI negative group patients (6.5% vs. 13.9%, p=0.0247). Moreover, the EMI positive group had a higher frequency of M5 morphology (32.5% vs. 19.7%, p=0.0017). In the analysis of molecular genetics, only 1 patient (0.8%) in the EMI positve group had *FLT3 ITD-/NPM1+* , which was significantly lower than that in the EMI negative group (0.8% vs. 5.9%, p=0.0183). There were no significant differences in the occurrence of *CEBPA* , *WT1* and *C-KIT* gene mutations between the two groups (p > 0.05). Additionally, we found that the EMI positive group exhibited higher frequencies of*KMT2A* gene rearrangements than the EMI negative group (27.6% vs. 16.3%, p=0.0030). In cytogenetic analysis, there were no statistically significant differences in the prevalence of complex karyotypes, t(8:21), inv(16), del5q/del7q/-5/-7, trisomy 8/trisomy 21, and minus X/minus Y between the two groups. However, we observed that the proportion of normal karyotype in the EMI positive group was significantly lower than that in the EMI negative group (12.2% vs. 26.6%, p=0.0007).

Table 1. The clinical characteristics of *de novo* pediatric AML patients with and without EMI at initial diagnosis, and relapse patients with and without EMI involvement.

Patient parameters	Total (n=713)	*De novo* AML patients (n=713)	*De novo* AML patients (n=713)	*p* Value	Total (n=255)	Relapse AML patients (n=255)	Relapse AML patients (n=255)	*p* Value
		With EMI at diagnosis (n=123)	Without EMI at diagnosis (n=590)			With EMI at relapse (n= 64)	Without EMI at relapse (n= 191)	
Trials								
AAML0531	628	117	511		220	57	163	

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AAML03P1	85	6	79		35	7	28	
EMI types								
CNS only		36				35		
MS only		75				16		
CNS and MS		12				13		
Gender, male/female	377/336	69/54	308/282	0.4313	137/118	36/28	101/90	0.6398
Age, years, n (%)								
[?] 2	128 (18.0)	38 (30.9)	90 (15.3)	<0.0001	50 (19.6)	23 (35.9)	27 (14.1)	<0.0001
> 2, [?] 14	385 (54.0)	56 (45.5)	329 (55.8)	0.0383	130 (51.0)	27 (42.2)	103 (53.9)	0.1040
>14	200 (28.1)	29 (23.6)	171 (29.0)	0.2248	75 (29.4)	14 (21.9)	61 (31.9)	0.1263
Laboratory tests								
WBC [?]100×10^9/L, n (%)	157 (22.0)	24 (19.5)	133 (22.5)	0.4607	66 (25.9)	23 (35.9)	43 (22.5)	0.0338
Median WBC, ×10^9/L (range)	31.6 (0.2-827.2)	27.0 (1.6-446)	32.6 (0.2-827.2)	0.8580	40.9 (0.2-519)	63.9 (2-519)	32.7 (0.2-402)	0.0715
Median BM blast, % (range)	71.0 (0-100)	70.0 (0-100)	71.0 (6-100)	0.4923	72.0 (0-100)	70.0 (0-96)	74.1 (14-100)	0.1885
Median PB blast, % (range)	45.0 (0-98)	41.0 (0-97)	45.0 (0-98)	0.3533	49.5 (0-98)	57.6 (0-97)	46.5 (0-98)	0.3217
FAB classification, n (%)								
M0	21 (2.9)	2 (1.6)	19 (3.2)	0.5104[a]	12 (4.7)	2 (3.1)	10 (5.2)	0.7271
M1	90 (12.6)	8 (6.5)	82 (13.9)	0.0247	29 (11.4)	3 (4.7)	26 (13.6)	0.0516
M2	175 (24.5)	33 (26.8)	142 (24.1)	0.5174	49 (19.2)	7 (10.9)	42 (22.0)	0.0521
M4	177 (24.8)	31 (25.2)	146 (24.7)	0.9149	69 (27.1)	21 (32.8)	48 (25.1)	0.2312

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Patient parameters	Total (n=713)	*De novo* AML patients (n=713)	*De novo* AML patients (n=713)	*p* Value	Total (n=255)	Relapse AML patients (n=255)	Relapse AML patients (n=255)	*p* Value
M5	156 (21.9)	40 (32.5)	116 (19.7)	0.0017	66 (25.9)	25 (39.1)	41 (21.5)	0.0054
M6	12 (1.7)	1 (0.8)	11 (1.9)	0.6604[a]	6 (2.4)	0 (0.0)	6 (3.1)	0.3378
M7	36 (5.0)	3 (2.4)	33 (5.6)	0.1461	8 (3.1)	2 (3.1)	6 (3.1)	0.9948
NOS	46 (6.5)	5 (4.1)	41 (6.9)	0.2363	16 (6.3)	4 (6.3)	12 (6.3)	0.9925
Gene mutation, n (%)								
CEBPA +	39 (5.5)	3 (2.4)	36 (6.1)	0.1042	8 (3.1)	3 (4.7)	5 (2.6)	0.6834
WT1+	44 (6.2)	5 (4.1)	39 (6.6)	0.2859	20 (7.8)	5 (7.8)	15 (7.9)	0.9916
FLT3_-ITD+	122 (17.1)	18 (14.6)	104 (17.6)	0.4227	47 (18.4)	6 (9.4)	41 (21.5)	0.0308
NPM1+	61 (8.6)	6 (4.9)	55 (9.3)	0.1090	14 (5.5)	3 (4.7)	11 (5.8)	0.9931
FLT3_-ITD/NPM1 status								
FLT3_-ITD+/NPM1+	25 (3.5)	5 (4.1)	20 (3.4)	0.9196[a]	7 (2.7)	1 (1.6)	6 (3.1)	0.8204
FLT3_-ITD+/NPM1-	97 (13.6)	13 (10.6)	84 (14.2)	0.2804	40 (15.7)	5 (7.8)	35 (18.3)	0.0454
FLT3_-ITD-/NPM1+	36 (5.0)	1 (0.8)	35 (5.9)	0.0183	7 (2.7)	2 (3.1)	5 (2.6)	0.8298
FLT3_-ITD-/NPM1-	555 (77.8)	104 (84.6)	451 (76.4)	0.0488	201 (78.8)	56 (87.5)	145 (75.9)	0.0496
KIT+, +/-	47/153	8/31	39/122	0.6239	21/35	5/11	16/24	0.5412
Karyotype, n (%)								
Complex karyotype	122 (17.1)	26 (21.1)	96 (16.3)	0.1923	54 (21.2)	20 (31.3)	34 (17.8)	0.0227
Normal karyotype	172 (24.1)	15 (12.2)	157 (26.6)	0.0007	49 (19.2)	3 (4.7)	46 (24.1)	0.0007
t(8;21)	111 (15.6)	26 (21.1)	85 (14.4)	0.0610	24 (9.4)	4 (6.3)	20 (10.5)	0.3169
inv(16)	96 (13.5)	14 (11.4)	82 (13.9)	0.4571	35 (13.7)	11 (17.2)	24 (12.6)	0.3524
del5q/del7q/-5/-7	39 (5.5)	6 (4.9)	33 (5.6)	0.7510	14 (5.5)	2 (3.1)	12 (6.3)	0.5204
trisomy8/trisomy21	90 (12.6)	18 (14.6)	72 (12.2)	0.4603	33 (12.9)	10 (15.6)	23 (12.0)	0.4598
Minus X/Minus Y	59 (8.3)	12 (9.8)	47 (8.0)	0.5122	14 (5.5)	4 (6.3)	10 (5.2)	0.7578

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Gene fusion, n(%)								
KMT2A rearrangements	130 (18.2)	34 (27.6)	96 (16.3)	0.0030	66 (25.9)	25 (39.1)	41 (21.5)	0.0054
NUP98 fusions	45 (6.3)	6 (4.9)	39 (6.6)	0.4724	15 (5.9)	1 (1.6)	14 (7.3)	0.1645
Others								
EMI at diagnosis					58 (22.7)	24 (37.5)	34 (17.8)	0.0011

WBC, white blood cell; BM, bone marrow; PB, peripheral blood; FAB, French-American-British classification; SCT, stem cell transplantation.

[a] Chi-square with Yates' correction.

Clinical characteristics of pediatric AML patients with EMI at relapse

255 patients experienced relapse in this cohort, out of which, 64 (25.1%) patients were observed to have EMI at relapse. 37.5% (24/64) of patients initially presented with EMI at diagnosis, all of these patients achieved CR after induction therapy, but later experienced bone marrow relapse or progression of extramedullary disease. A total of 35.9% (23/64) of these patients were [?]2 years at the time of initial diagnosis, which was significantly higher than those without EMI at relapse (35.9% vs. 14.1%, p=0.0001). Furthermore, patients developed EMI at relapse had a higher incidence of hyperleukocytosis at initial diagnosis (35.9% vs. 22.5%, p <0.0338). Similarly, the group of patients with EMI at relapse had a higher proportion of M5 cases (39.1% vs. 21.5%, p=0.0054). In molecular genetics and cytogenetic analysis, there were no differences in the occurrence rates of*CEBPA* , *NPM1* , *WT1* , and *C-KIT* gene mutations between the two subgroups. Notably, patients with EMI at relapse had a higher frequency of *KMT2A* gene rearrangements (27.3% vs. 15.0%, p=0.0177) and a lower frequency of a normal karyotype (10.9% vs. 28.0%, p=0.0060). Unexpectedly, it is observed that patients with EMI at relapse presented with a lower frequency of *FLT3-ITD* mutation (9.4% vs. 21.5%, p=0.0308). Other karyotypes and gene rearrangements had similar occurrence rates in both subgroups (p >0.05) (Table 1).

Treatment and clinical outcomes

In the whole cohort, 106 patients (14.9 %) received stem cell transplantation after first complete remission (SCT in first CR), and 392 patients (55.0%) received gemtuzumab ozogamicin (GO) treatment. The proportions of SCT in the first CR and treatment with GO were similar between the group of patients with EMI at initial diagnosis and the group without EMI at initial diagnosis. However, patients with EMI at initial diagnosis had a significantly lower CR1 rate (67.5% vs. 76.8%, p=0.0299) and higher relapse rate (47.2% vs. 33.4%, p=0.0038) compared to patients without EMI at initial diagnosis, while there were no significant differences in CR2 rate and MRD negativity rate between the two groups (Table 2).

According to Kaplan-Meier analysis, the group with EMI at initial diagnosis had shorter event-free survival (EFS) (p=0.0037) and potentially shorter overall survival (OS) (p =0.0791) (Figs. 1A and 1B). However, in analyzing the overall survival among relapse patients, no significant difference (p =0.8686) was observed between those with and without EMI (Fig. 1E). Upon further analysis of patients with various sites of EMI, our finding revealed that individuals with MS (regardless of CNS involvement) demonstrated similar EFS and OS compared to those with CNS-only involvement (p >0.05) (Figs. 1C and 1D). Interestingly, among

patients with EMI at relapse, those with MS exhibited a poorer OS compared to those with exclusive CNS involvement (p=0.0262) (Fig. 1F).

Table 2 . Treatment and therapeutic outcomes in AML patients with and without EMI at diagnosis.

Patient parameters, n (%)	Total (n=713)	*De novo* AML patients	*De novo* AML patients	*p* Value
		With EMI at diagnosis (n=123)	Without EMI at diagnosis (n=590)	
SCT in first CR	106 (14.9)	18 (14.6)	88 (14.9)	0.9365
GO treatment	392 (55.0)	64 (52.0)	328 (55.6)	0.4821
CR status at end of course 1	536 (75.2)	83 (67.5)	453 (76.8)	0.0299
CR status at end of course 2	614 (86.1)	108 (87.8)	506 (85.8)	0.5513
MRD at end of course 1 (+/-)	182/416	24/77	158/339	0.1099
MRD at end of course 2 (+/-)	87/434	12/75	75/359	0.4259
Induction failure	62 (8.7)	12 (9.8)	50 (8.5)	0.6463
Relapse	255 (35.8)	58 (47.2)	197 (33.4)	0.0038

SCT, stem cell transplantation; CR, complete remission; MRD, minimal residual disease.

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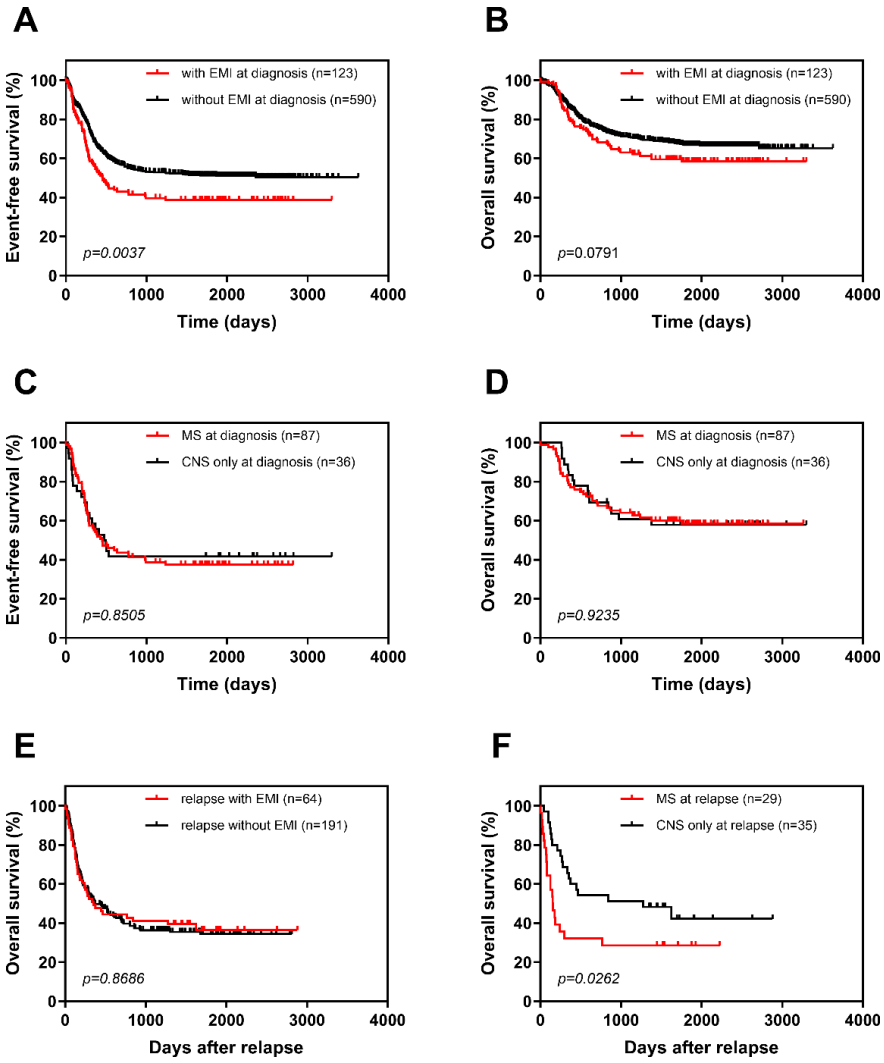

Figure 1. Event free survival (EFS) and overall survival (OS) of pediatric AML patients with and without EMI at initial diagnosis (A, B); Regarding pediatric AML patients with EMI at initial diagnosis, EFS and OS of patients with MS and CNS only (C, D). OS of relapse patients with and without EMI (E); OS of relapse patients with MS and CNS only (F).

The implication of SCT and GO treatment on the prognosis of patients with EMI at initial diagnosis.

Additionally, we evaluated the prognostic significance of SCT in first CR and GO treatment for patients with EMI at initial diagnosis. The data revealed that SCT in the first CR did not significantly affect either EFS or OS in patients with EMI at initial diagnosis ($p > 0.05$) (Figs. 2A and 2B), whereas patients received GO treatment displayed potentially prolonger OS ($p=0.0811$ by log-rank test, and $p=0.0399$ by Wilcoxon test) while maintaining similar EFS ($p=0.1610$) compared to those who did not receive GO treatment (Figs. 2C and 2D).

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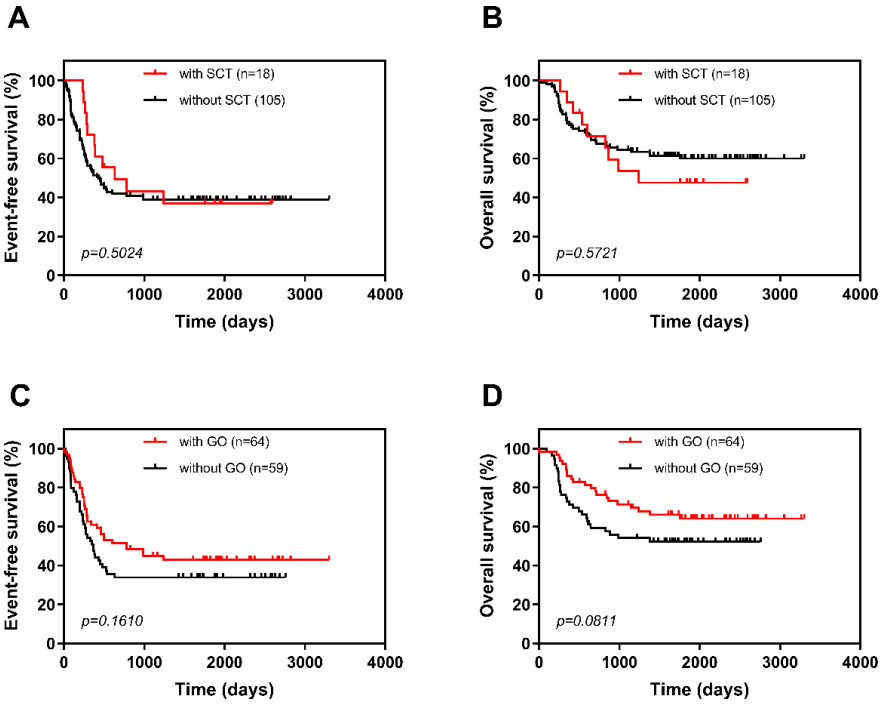

Figure 2. Regarding pediatric AML patients with EMI at initial diagnosis, event free survival (EFS) and overall survival (OS) of patients underwent SCT or not (A, B); EFS and OS of patients underwent GO treatment or not (C, D).

Univariate and multivariate analysis of impact factors for prognosis

In accordance with univariate analysis, apart from the EMI at diagnosis, thirteen factors (Table 3), were considered as covariates in the Cox models due to their potential to impact the prognosis of pediatric AML patients. These factors encompassed age [?]2 years, WBC [?]100×10^9/L, t(8;21), inv(16), del5q/del7q/-5/-7, trisomy 8/trisomy 21, minus X/minus Y, *CEBPA* +, *FLT3 ITD-/NPM1+* , *FLT3 ITD+* , *WT1+* , *KMT2A* rearrangements, NUP98 fusion, SCT and GO treatment. The multivariate analysis demonstrated that EMI at diagnosis emerged as an independent prognostic risk factor for both shorter OS (HR 1.425, 95% CI 1.033-1.964, p=0.0307) and EFS (HR 1.672, 95% CI 1.283-2.179, p=0.0001). Furthermore, WBC [?]100x10^9/L, *WT1+* , and del5q/del7q/-5/-7 were identified as independent predictors of poorer outcomes. Conversely, the remaining five factors, including t(8;21), inv(16), *CEBPA+* , *FLT3 ITD-/NPM1+* , and SCT, were associated with improved survival (Table 3).

Table 3. Univariate and multivariate analysis of OS and EFS in pediatric AML patients.

Variable		Univariate analysis	Univariate analysis	Univariate analysis	Univariate
		EFS	EFS		OS
	HR (95%CI)	HR (95%CI)	*p* Value	*p* Value	HR (95%
Age [?]2 years	1.226 (0.943-1.594)	1.226 (0.943-1.594)	0.1284	0.1284	1.086 (0.7
WBC [?]100´10^9/L	1.501 (1.189-1.895)	1.501 (1.189-1.895)	0.0006	0.0006	1.208 (0.9
Normal karyotype	1.085 (0.853-1.380)	1.085 (0.853-1.380)	0.5050	0.5050	1.082 (0.8
Complex karyotype	1.093 (0.834-1.432)	1.093 (0.834-1.432)	0.5186	0.5186	1.290 (0.9
t(8;21)	0.437 (0.306-0.626)	0.437 (0.306-0.626)	<0.0001	<0.0001	0.415 (0.2
inv(16)	0.646 (0.461-0.904)	0.646 (0.461-0.904)	0.0109	0.0109	0.338 (0.1
del5q/del7q/-5/-7	1.467 (0.984-2.187)	1.467 (0.984-2.187)	0.0599	0.0599	2.367 (1.5

Variable		Univariate analysis	Univariate analysis	Univariate analysis	Univariate
trisomy8/trisomy21	1.081 (0.793-1.473)	1.081 (0.793-1.473)	0.6217	0.6217	1.438 (1.0
Minus X/Minus Y	0.443 (0.272-0.721)	0.443 (0.272-0.721)	0.0010	0.0010	0.522 (0.2
CEBPA+	0.638 (0.374-1.089)	0.638 (0.374-1.089)	0.0998	0.0998	0.481 (0.2
FLT3_ITD-/NPM1+	0.454 (0.242-0.851)	0.454 (0.242-0.851)	0.0138	0.0138	0.370 (0.1
FLT3_ITD+	1.544 (1.200-1.987)	1.544 (1.200-1.987)	0.0007	0.0007	1.485 (1.0
WT1+	2.114 (1.469-3.043)	2.114 (1.469-3.043)	0.0001	0.0001	1.942 (1.2
KMT2A rearrangements	1.457 (1.136-1.868)	1.457 (1.136-1.868)	0.0030	0.0030	1.331 (0.9
NUP98 fusions	1.538 (1.045-2.262)	1.538 (1.045-2.262)	0.0289	0.0289	1.398 (0.8
SCT	0.620 (0.449-0.855)	0.620 (0.449-0.855)	0.0036	0.0036	0.934 (0.6
GO treatment	0.863 (0.701-1.061)	0.863 (0.701-1.061)	0.1618	0.1618	0.895 (0.6
EMI at diagnosis	1.455 (1.128-1.877)	1.455 (1.128-1.877)	0.0039	0.0039	1.321 (0.9

HR, hazards ratio; CI, confidence interval; WBC, white blood cell; SCT, stem cell transplantation; CR, complete remission; GO, gemtuzumab ozogamicin; EMI, extramedullary infiltration; OS, overall survival; EFS, event-free survival.

Discussion

In the current study, we assessed the clinical and prognostic characteristics of pediatric AML patients who exhibited EMI at different time points. Out of the 713 pediatric AML patients, 123 (17.3%) were diagnosed with EMI at initial diagnosis, which is consistent with previous reported[4]. However, certain patients with EMI may remain asymptomatic or lack bone marrow involvement, and the routine use of lumbar puncture, incorporation of flow cytometry as a part of cerebrospinal fluid assessment, and variations in the type and frequency of imaging examinations could impact the detection rate of EMI[12,19-21].

In this cohort, patients with EMI, both at diagnosis and at relapse, were more commonly found to be [?]2 years old and M5 morphology. Conversely, only patients with EMI at relapse exhibited a higher prevalence of WBC count [?]100×10^9/L. These factors have also been demonstrated to be correlated with EMI in previous studies[8-11,22,23]. Donna L. Johnston et al. conducted a study involving 886 pediatric patients and observed that individuals experiencing CNS relapse exhibited a higher prevalence of age <2 years, FAB-M5 subtype, and higher white blood cell (WBC) counts[24]. In the realm of cytogenetics and molecular biology, a comprehensive investigation involving 315 children participating in the NOPHO-AML 2004 trial revealed an association between extramedullary infiltration (EMI) and *11q23/MLL*(*KMT2A*) rearrangements, which corroborated our own findings[11]. Another study, comprising 240 cases registered with the Japanese Childhood AML Cooperative Study Group, identified a higher prevalence of inv16 and 11q23 abnormalities among patients with EMI[10]. Chromosome 11 abnormalities were also found to be related to CNS relapse in pediatric AML patients[24]. In the context of pediatric low-risk AML, Guan-hua Hu et al. observed that abnormalities such as t(8;21), t(1;11), and *c-KIT* mutation were linked to EMI[25]. Our investigation indicated that patients presenting with EMI, both at diagnosis and at relapse, exhibited a higher incidence of *KMT2A*rearrangements and a lower incidence of normal karyotype. *NPM1*and *FLT3-ITD* mutation was found to be associated with EMI in adult AML patients while *CEBPA* mutation decreased the occurrence of EMI[5,14]. In this cohort, the mutation of the*CEBPA* showed unrelated to the presence of EMI. Intriguingly, we observed that patients with EMI at the initial diagnosis presented a lower frequency of *FLT3 ITD-/NPM1+* , whereas EMI relapse patients displayed a lower frequency of *FLT3-ITD* mutation. Further research is needed to explore the cytogenetic and molecular biological characteristics in pediatric AML patients with extramedullary infiltration.

Although EMI is typically considered a presentation of advanced disease, there is still no consensus on the prognosis of EMI in pediatric patients. In the cohort, patients with EMI at initial diagnosis had a low rate of CR1 and a higher rate of relapse. For initially diagnosed patients, EMI appeared to independently predict both shorter OS and EFS. Sorts of researches insisted our results. In the NOPHO-AML 2004 trial, pediatric

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patients with EMI at diagnosis had significantly lower 5-year OS (64% vs. 73%, p=0.04) but not 5-year EFS (54% vs. 45%, p=0.57) and a higher risk of induction death (8% vs. 1%, p=0.002)[11]. Xiaoli Xin et al. also found that EMI at initial diagnosis [HR 3.313, 95% CI 1.748-13.664, p <0.001] was an independent risk factors affecting the prognosis[14]. The appearance of EMI at diagnosis was also proven to be a significant adverse factor in pediatric *RUNX1-RUNX1T1* (+) AML by Jae Wook Lee et al.[15]. Guanhua Hu et al. found myeloid sarcoma instead of CNS leukemia was a predictor of adverse prognosis for RFS and OS in low-risk pediatric AML[25]. However, sorts of clinical trials have described no significant association between extramedullary infiltration and outcome in pediatric AML patients[9,10]. When analyzing the outcomes of different subgroups of EMI, Donna L. Johnston et al. collected data from patients who participated in CCG trials 2861, 2891, 2941 and 2961 and found patients with orbital-MS and CNS-MS experienced better survival compared to patients with other types of EMI, or without EMI[16]. Another study adopted CCG AML trials 213 or 213P, 2861 and 2891 revealed that the non-skin EML group had the best outcome compared to the skin EML group and the no EML group[12]. In the cohort, patients with myeloid sarcoma at diagnosis showed similar EFS and OS compared to those with exclusive CNS involvement at diagnosis. Due to the limitation of available data, we were unable to further explore the impact of myeloid sarcoma at different site on prognosis.

Bone marrow is the most common site for relapse, while extramedullary relapse also accounts for a considerable proportion[26]. Without the limitation of age, the prognosis of extramedullary relapse in AML patients is controversial. Most previous studies have indicated that the survival of patients who developed extramedullary relapse was slightly better than that of patients who developed bone marrow relapse[26-28]. There is a notable lack of studies focusing on pediatric patients. A retrospective study enrolled 1527 acute leukemia patients (983 ALL and 544 AML) by Volkan Hazar et al. and found that post-HSCT patients with isolated extramedullary relapse (without bone marrow involvement) remained poor prognosis but had slightly better survival than those who developed bone marrow relapse[7]. According to our results, patients with EMI at relapse had similar overall survival compared to those without EMI. This result indicated that the presence of EMI may not contribute to a worse prognosis in patients experiencing relapse. However, when further analyzed the prognosis of different types of EMI, we observed that relapse patients with MS showed a significant shorter OS than those with exclusive CNS involvement. Further studies requiring more cases of EMI relapse are essential to validate the findings and investigate whether the difference in prognosis is associated with special clinical characteristics.

HSCT is a pivotal and widely utilized treatment modality in the context of pediatric AML, but it also carries the risk of additional treatment-related mortality due to graft-versus-host disease, infection, and organ toxicity. Identifying the specific patient population that will derive benefits from HSCT is of paramount importance[29,30]. There is limited research exploring the mutual prognostic significance of stem cell transplantation and EMI in AML patients, especially in pediatric patients. A report of 51 patients (both children and adults were adopted) from the SFGM-TC registry showed that allo-HSCT is a potentially efficient therapy for myeloid sarcoma, with a notable proportion of patients achieving long-term remission[31]. On contrast, a retrospective study enrolled multi-center clinical trials showed that allo-HSCT did not improved the survival[5]. A previous study by Lu-Hong Xu et al. also used data from the TAGART dataset and found that stem cell transplantation did not improve either OS or EFS in patients with myeloid sarcoma[32]. Our studies included patients with myeloid sarcoma as well as those with CNS involvement, and we obtained similar results. Given the limitations in the number of EMI-positive patients who had also underwent SCT, further investigation is needed to assess the prognostic association of between EMI and SCT.

Gemtuzumab Ozogamicin is an antibody-drug conjugate (ADC) composed of an anti-CD33 monoclonal antibody and a cytotoxic agent N-acetyl gamma calicheamicin[33]. The incorporation of GO in the induction treatment was proven to improve the RFS and EFS in AML[34]. Taofeek Owonikoko et al. reported a case involving GO therapy for a 19-year-old AML patient with isolated extramedullary relapse after HSCT[35]. This patient experienced extramedullary relapse at multiple sites, and radiation therapy showed no discernible effect. However, extramedullary remission was achieved after GO treatment. Regarding patients with EMI at initial diagnosis, we evaluated the prognosis between those who underwent GO treatment or not and found possibly significant difference in OS. The immunohistochemical stains in myeloid sarcoma reveled a

positivity rate of CD33 ranging from 55% to 94%[36,37]. GO emerges a potential treatment for extramedullary AML, particularly in cases with CD33 positive upon biopsy.

Conclusion

In conclusion, EMI at diagnosis independently predicts a worse prognosis. While for patients experiencing relapse, the presence of EMI does not significantly impact survival. Moreover, SCT does not lead to a prognosis improvement for patients with EMI at initial diagnosis, whereas GO treatment has the potential to prolong overall survival. This study enhances our comprehension of EMI in pediatric AML patients and demonstrates the potential significance of GO treatment for AML with EMI. With the advancement of flow cytometry and imaging techniques, the diagnostic rate of EMI is expected to increase, and further exploration of treatment approaches is needed to improve the survival of EMI patients.

Conflict of interest statement

The authors have no relevant financial or non-financial interests to disclose.

Acknowledgments

We would like to thank the TARGET project for providing their platforms and contributors for uploading their meaningful datasets. This work was supported by the National Natural Science Foundation of China (No. 81971508) and Henan Provincial Science and Technology Research Project (No. 222102310101).

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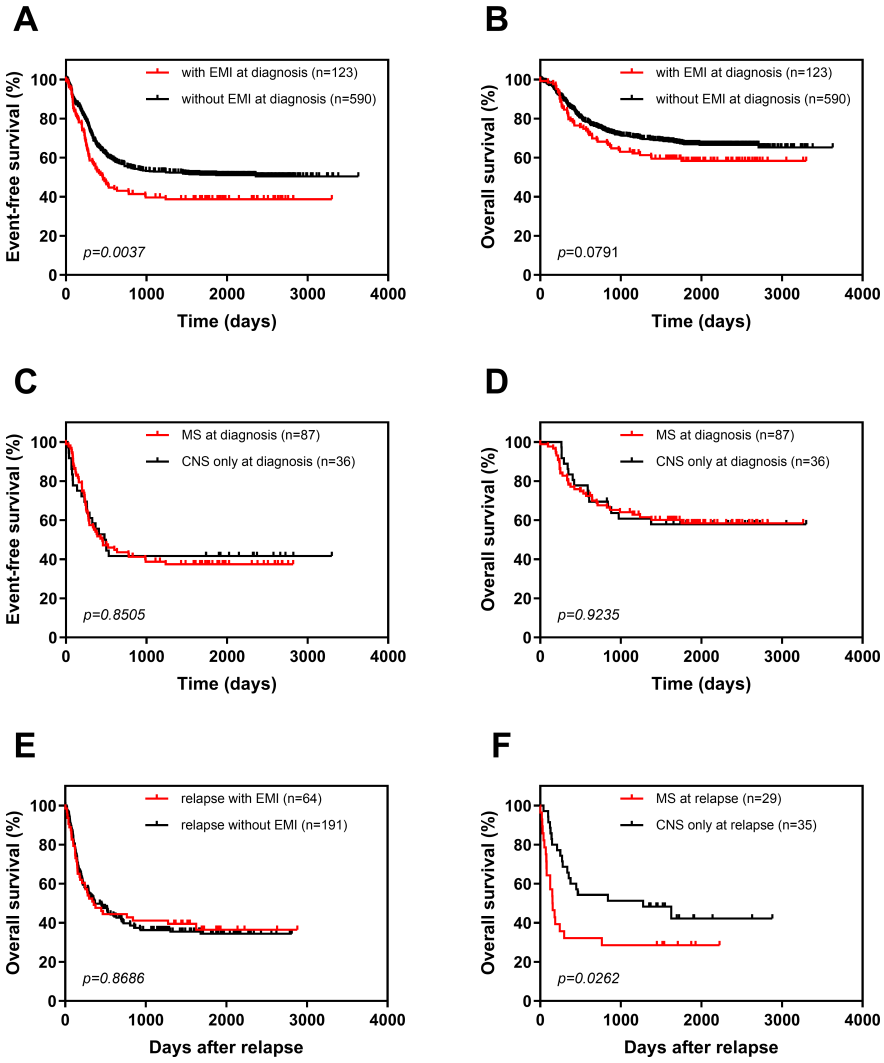

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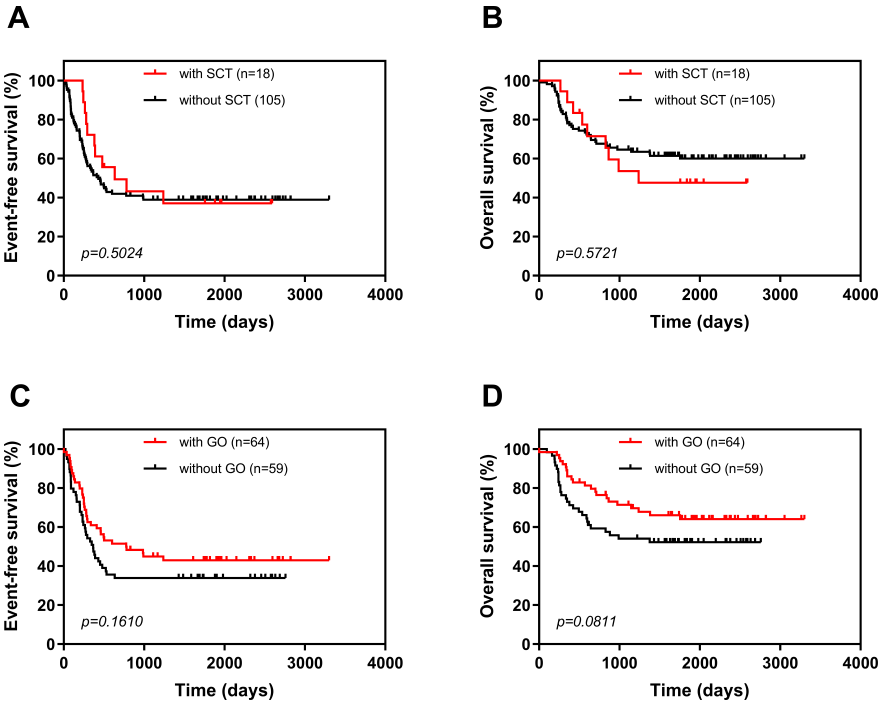

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