Chromosomal Characteristics and Prognostic Analysis of Secondary Acute Myeloid Leukemia

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Abstract

Background

Secondary Acute Myeloid Leukemia (S-AML) patients generally have a poor prognosis, and the chromosomal karyotype of S-AML have been rarely reported in the published literature. We aimed to explore the chromosomal karyotype and its clinical significance in patients with S-AML.

Methods

Clinical characteristics and chromosome karyotypes of 26 patients with S-AML were retrospectively analyzed. The overall survival (OS) was measured from the time of the patients' transition to AML (which means the time of S-AML diagnosis) .

Results

Among the 26 S-AML patients, there were 13 males and 13 females, with a median age of 63 years old (range, 20-77 years old). All of them were secondary to a variety of hematologic malignancies or solid tumors, and most of them were secondary to myelodysplastic syndrome (MDS). About 62% of the S-AML patients showed chromosome abnormalities. The level of serum lactate dehydrogenase (LDH) in S-AML patients with abnormal chromosome karyotype was higher than those with normal chromosome karyotype. Apart from the differences in treatment regimens, S-AML patients with chromosomal karyotype abnormalities had shorter OS ($P<0.05$).

Conclusions

S-AML patients with abnormal chromosomal karyotype have higher LDH and shorter OS than normal chromosomal karyotype, and the OS of hypodiploidy was much shorter than hyperdiploid.

Introduction

Secondary acute myeloid leukemia (S-AML) refers to AML developing either after a prior hematologic disorder, usually myelodysplastic syndrome (MDS), or after exposure to cytotoxic drugs or chemotherapy[1, 2]. Compared with newly diagnosed primary AML (P-AML), S-AML has a poorer prognosis, lower remission rates, and shorter OS[3, 4]. Although the use of intensive chemotherapy regimens, the prognosis of S-AML patients is still poor, especially in elderly patients[1].

Recent advances in genomic analysis have revealed a large number of chromosomal abnormalities associated with AML onset and recurrence[5]. The recognition and understanding of chromosomal abnormalities for the diagnosis and treatment of AML patients is of great significance[6]. Chromosomal abnormalities are likely to be associated with disease progression in S-AML[7].

Some major clinical features, such as WBC and LDH were significant additive features for OS[8]. A high level of LDH is a poor prognostic factor for AML, and LDH was initially identified as an influence factor for OS[9]. We analyzed the clinical characteristics and chromosomal abnormalities of 26 S-AML patients to further explore the possible pathogenesis of S-AML patients.

Patients And Methods

Patients

A total of 26 S-AML patients who were diagnosed or treated in the Second Affiliated Hospital of Anhui Medical University from January 2009 to January 2020 were collected. All the newly diagnosed S-AML patients met the 2008 or 2016 WHO criteria[10,11]. Clinical characteristics of all the patients were obtained from medical records. The study was performed in accordance with the principles expressed in the Declaration of Helsinki. **Chromosome karyotype analysis**

Of the 26 S-AML patients, 25 had a cytogenetic analysis performed at the time of the patients' transition to AML (which means at the time of S-AML diagnosis). All cytogenetic investigations were carried out in a standardized fashion at the Chromosome Laboratory, Department of Hematology. The analysis specimens were prepared by the bone marrow short-term culture method, and the Gimsa banding method was used. Chromosome analysis of 20 metaphase spreads were examined per patient, if available, and the International System for Human Cytogenetic Nomenclature (ISCN) was used to describe karyotypes[12].

Laboratory examination

According to the results of chromosome karyotype in S-AML patients, the patients were divided into normal group (both number and structure are normal) and abnormal group (number or structure abnormalities), and the differences of some laboratory examination between the two groups were compared. Laboratory examination were obtained from medical records, including red blood cell (RBC) counts, white blood cell (WBC) counts, platelet counts (PLT), lymphocyte counts (LYM), mononuclear cell counts (MO), neutrophil counts (NEUT), hemoglobin (Hb), hypersensitive c-reactive protein (Hs-CRP) and lactate dehydrogenase (LDH), using the fully automated hematology analyzer Sysmex XE-2100 (Sysmex Corporation, Japan) and the fully automated biochemical analyzer AU5831 (Beckman Coulter, America).

Follow up

Patients were followed to the earliest of death, loss to follow-up or the end of the follow-up time on July 20, 2020. OS was calculated from the time of S-AML diagnosis to the date of death or last follow-up. Medical record retrieval and telephone follow-up were performed during the study.

Statistical analysis

Student's t-test was used to test the differences between the two groups for quantitative normally distributed variables and the Mann-Whitney U test was used for non-parametric variables. Kaplan-Meier survival curves were used for estimating OS. Statistical analyses were performed with the IBM SPSS 25.0. Results were considered significant at $p < 0.05$.

Results

Patient characteristics

26 S-AML patients were enrolled in the study, and the median age was 63 years (range, 20–77 years). Of these, half of the patients were men. Most of them were secondary to MDS (one of them was secondary to MDS, but coexisted with chronic lymphocytic anemia (CLL)), the rest of the patients were secondary to myelodysplastic-myeloproliferative neoplasms (MDS/MPN), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia

(CMML), primary myelofibrosis (PMF), gastric diffuse large B cell lymphoma and rectal cancer. Other clinical features were also collected, such as treatment, which is an important determinant of OS, as well as factors that are closely related to patient prognosis.

It is of great significance to choose the appropriate chemotherapy regimen for the efficacy of patients with AML. In clinical practice, individualized treatment regimen is often made according to the patient's tolerance and other specific conditions. In our study, many patients were treated with decitabine in combination with other regimens. Decitabine is a demethylation agent that is effective and safe in older patients with AML, and its combination with another regimen (CAG/HAG, retinoic acid) results in a higher OR rate than decitabine alone[13]. However, other optional regimens such as azacytidine, IA/IAG regimen, and intrathecal injection have also been used in the treatment of patients, depending on the patient's condition. The basic characteristics of 26 S-AML patients was shown in Table 1.

Table 1
The basic characteristics of 26 S-AML patients

No	Gender	Age	Original diagnosis	AML	Treatment(after the time of S-AML diagnosis)	Outcome (until July 20, 2020)	OS (Days)
1	Male	72	MDS	M7	Decitabine alone	death	80
2	Female	56	MDS	M2	Decitabine + CAG(Ara-C, Aclarubicin, and G-CSF), HAAG(Homoharringtonine, Ara-C, Aclarubicin, and G-CSF)	death	211
3	Male	76	MDS	M2	Decitabine + CAG(Ara-C, Aclarubicin, and G-CSF) + ATO	death	575
4	Female	65	MDS	M4	No, and we don't know if the patient was treated at any other hospital	survival	600
5	Female	66	MDS	AML(unclassified)	No, and we don't know if the patient was treated at any other hospital	death	485
6	Female	62	MDS	AML(unclassified)	CAG(low dose Cytarabine, Aclarubicin, and G-CSF) + ATO + EPO	death	55
7	Female	65	MDS	M2	IAG(idarubicin + Ara-C + G-CSF), DA(Daunorubicin + Ara-C) Azacitidine + HAG(Homoharringtonine, Ara-C, and G-CSF) intrathecal injection(MTX, DXM, and Ara-C) Decitabine, thalidomide, ubenimex, Lenalidomide, Tretinoin, TPO	death	108
8	Male	61	MDS	AML(unclassified)	Decitabine + CAG(Ara-C, Aclarubicin, and G-CSF)	loss to follow-up	10

No	Gender	Age	Original diagnosis	AML	Treatment(after the time of S-AML diagnosis)	Outcome (until July 20, 2020)	OS (Days)
9	Male	70	MDS	AML(unclassified)	low dose Decitabine + EAG(epirubicin , Ara-C, and G-CSF) Decitabine + MAG(mitoxantrone, Ara-C, and G-CSF) Decitabine + CMG(Ara-C,mitoxantrone and G-CSF) Thalidomide	death	105
10	Male	61	MDS	AML(unclassified)	Decitabine + HAG(homoharringtonine, Ara-C, and G-CSF) ubenimex, Tretinoin, azacitidine	survival	210
11	Female	77	MDS	M2	Tretinoin + ATO + decitabine + HAG(homoharringtonine, Ara-C, and G-CSF) +EAG(epirubicin , Ara-C, and G-CSF)+MAG mitoxantrone, Ara-C, and G-CSF	loss to follow-up	213
12	Female	20	MDS	M2	IA(Idarubicin, Ara-C) Decitabine + CAG(Ara-C, Aclarubicin, and G-CSF) + ATO Decitabine + CHG(Ara-C, Homoharringtonine, and G-CSF) + ATO	loss to follow-up	150
13	Female	66	MDS	AML(unclassified)	No	loss to follow-up	60
14	Male	69	MDS/MPN	M2	Low dose Ara-C, interferon, and dasatinib	loss to follow-up	60
15	Female	64	MDS	M2	CAG(Ara-C, Aclarubicin, and G-CSF) + decitabine	death	226
16	Female	30	gastric diffuse large B cell lymphom	M3	Tretinoin + ATO + intrathecal injection(MTX, DXM, and Ara-C)	survival	1305

No	Gender	Age	Original diagnosis	AML	Treatment(after the time of S-AML diagnosis)	Outcome (until July 20, 2020)	OS (Days)
17	Male	46	CML	AML(unclassified)	DA(Daunorubicin + Ara-C) Idarubicin HAG(Homoharringtonine, Ara-C, and G-CSF) Dasatinib + Imatinib(Oral administration of dasatinib and imatinib was subsequently discontinued because of the T325I mutation, which suggested resistance to all tyrosine kinases), Hydroxycarbamide, etoposide, and ATO.	death	180
18	Male	61	CMML	M2	IA(Idarubicin, Ara-C) Decitabine + CAG(Ara-C, Aclarubicin, and G-CSF) Decitabine + HAG(homoharringtonine, Ara-C, and G-CSF)+Tretinoin + ATO Stanozolol, etoposide, ubenimex, and thalidomide Dorubicin liposomes and hexadecadrol Low dose methotrexate, and azacitidine	death	323
19	Female	55	PMF	M2	Decitabine + IA(Idarubicin, Ara-C) Hematopoietic stem cell microtransplantation DAE (Doxorubicin + Ara-C + Etoposide)	death	143
20	Male	61	MDS(coexist with CLL)	AML(unclassified)	ATO + VP-16 + Ara-C + G-CSF	death	62

No	Gender	Age	Original diagnosis	AML	Treatment(after the time of S-AML diagnosis)	Outcome (until July 20, 2020)	OS (Days)
21	Female	66	CMML	M4	Decitabine + HAG(homoharringtonine, Ara-C, and G-CSF) Low dose Decitabine + ATO + DAG(Daunorubicin + Ara-C + G-CSF) Etoposide, Ara-C, and azacitidine	loss to follow-up	328
22	Male	38	PMF	M5	ME (Mitoxantrone, Etoposide), homoharringtonine, Ara-C, ATO	loss to follow-up	450
23	Male	72	rectal cancer	M2	Decitabine + CAG(Ara-C, Aclarubicin, and G-CSF) CTK cell infusion G- CSF, Ara-C, ATO Decitabine + darubicin or Pirarubicin + Ara-C	survival	2560
24	Female	67	rectal cancer	AML(unclassified)	Decitabine + Ara-C	death	21
25	Male	32	CML	AML(unclassified)	MA(Mitoxantrone, and Ara-C) CAG(Ara-C, Aclarubicin, and G-CSF) Dasatinib, methotrexate intrathecal injection(MTX, DXM, and Ara-C)	death	270
26	Male	44	CML	M2	No	loss to follow-up	5

Chromosome Karyotype Test Results

More than half of the S-AML patients had chromosomal abnormalities (16/26), and the majority of patients (10/16) with abnormal chromosome karyotypes had detected abnormalities on chromosome 5 or 7. Chromosome abnormality showed numerical abnormalities and structural abnormalities which involved in most chromosomes. Hypodiploidy and hyperdiploidy were two more classifications of AML. In our study, hypodiploid karyotype was found in 5 patients and hyperdiploid karyotype in 7 patients. The abnormalities include: addition (add), insertion (ins), deletion (del), marker chromosome (mar), incomplete karyotype (inc), derived chromosome (der), inversion (inv), isochromosome (i), ring chromosome (r), etc. Karyotypes from the 26 patients with clonal aberrations were listed in Table 2.

Table 2
Chromosome karyotypes of the 26 S-AML patients

Karyotypes (N)		Chromosome of S-AML
Normal (10)	Diploid (10)	46,XY
Abnormal (16)	Diploid ** (7)	46,XY,-7,+marker.[10]
		46,XX[3]/46,XX,+der(8)del(q22),del(12)(p11),-2,-5,-7,-11,-17,+22,+marker*3[17]
		46,XY,del(5)q(23),add(17)p(12),-9,12,20,marker×3.[5]
		46,XY,t(9;22)(q34;q11),t(2;12;15),(p13;q13;p11),+8.[20]
		é 46,XY,t(9;22)(q34;q11)[8]/46,XY,t(9;22)(q34;q11),ins(3;3)(q25;q21q25)[5]
	hypodiploid* (5)	45,XY,add(3)(q29),del(5)(q23),add(12)(p15),-7.[20]
		# 43–46,XX,-2,-3,?add(3)(q11),del(5)(q13q31),del(7)(q31),add(11)(p15),-15,-17,add(17)(p13),-18,add(19)(p13),add(22)(q13) + mar,inc[cp20].
		43,X,t(5;19)(q21;q13),7q+,-7,-12,-20,-Y,+marker.[7]/44,XY,5q-,7q+,-12,-18,-20,+marker1,+marker2.[13]
		45,XY,-5,-9,+mar[7]/45,XY,del(5)(q15),-9,add(11)(q25)[4]/44,XY,add(5)(p15),del(5)(q15),del(7)(q11),der(12)del(12)(p12)add(12)(p12),-13,-19,-21,+mar[5]
	hyperdiploid* (7)	* 40–48 XX,add(1)(p36),add(2)(q37),del(5)(q15),add(12)(p13),-8,-9,-11,-22,+marker×3.inc.[cp15]
		47,XX,+8.[20]
		48,XXX,del(20)(q13),+X,+marker.[8]/48,XX,del(20)(q13),+14,+marker.[3]
		48,XY,inv(3)(q21q26),+8,t(9;22)(q34;q11),i(17)(q11),+der(22)t(9;22)(q34;q11)[20]
		48,XY,20q-,+8,+13.[5]
		48,XX,t(1;?)(q21;?),+der(1)t(1;?)(p32;?)-6,-7,+14,+19,+r.[8]/48,XX,t(1;?)(q21;?),+der(1)t(1;?)(p32;?)-6,-7,+14,+19,+marker.[2]
		47,XY,5q-,+8.[15]
éthe chromosome of the patient was collected at primary diagnosis (2 months ago); *the chromosome contains in all the three kinds of abnormal karyotypes of chromosome ; #the chromosome contains in both diploid and hypodiploid of abnormal karyotypes of chromosome.		

Chromosome Karyotypes And Laboratory Examination

The S-AML patients were divided into two groups according to whether the chromosomal karyotype was normal or not, and Mann-Whitney U test was used for comparison between the two groups. The results showed that there was a statistical difference in LDH level between the two groups, and LDH level was higher in S-AML patients with chromosomal abnormalities ($P < 0.05$). The scatter diagram was drawn show the level of LDH between normal and abnormal chromosome karyotypes (Fig. 1). RBC, WBC, PLT and other laboratory examination showed no significant difference between normal and abnormal karyotypes (Table 3).

Table 3
Laboratory examination in normal and abnormal chromosome karyotypes

laboratory examination	Normal chromosome karyotypes (n = 10) median (range)	Abnormal chromosome karyotypes (n = 16) median (range)	<i>P</i>
RBC($\times 10^{12}/L$)	2.16(1.47–3.94)	1.98(1.38–5.49)	0.551
WBC($\times 10^9/L$)	1.96(0.3–11.13)	3.28(0.33–47.17)	0.391
PLT($\times 10^9/L$)	13.5(3–269)	28.5(5–207)	0.262
LYM($\times 10^9/L$)	1.09(0.27–2.82)	0.82(0.14–22.08)	0.816
MO($\times 10^9/L$)	0.14(0–2.09)	0.41(0–15.89)	0.165
NEUT($\times 10^9/L$)	0.34(0–9.35)	1.72(0.02–36.62)	0.182
Hb(g/L)	66.5(44–121)	64(49–152)	0.363
hsCRP(mg/L)	61(0.3–87.2) ^a	39(1.5–193.7)	0.452
LDH(U/L)	163.5(65–220) ^b	274(71–1406) ^c	0.008
^a n = 9; ^b n = 8; ^c n = 15			

Overall Survival (os)

The median OS of normal chromosome karyotypes was 212 days, while that for patients with abnormal chromosome karyotypes was 162 days. The outcome of S-AML patients with normal chromosomal karyotype was: 2 died, 3 survived, and 5 were lost to follow-up. The outcome of S-AML patients with abnormal chromosomal karyotype was: 12 were died, 1 was survived, and 3 were lost to follow-up. What's more, All five patients with hypodiploidy karyotype died, with a median survival of 62 days. Of the 7 patients with hyperdiploid karyotype, 5 were died, 1 was still alive, and 1 was lost to follow-up, with median survival time of 211 days. The results of the Kaplan-Meier survival curve showed that the OS of S-AML patients with abnormal chromosome karyotypes was shorter than that of S-AML patients with normal chromosome karyotypes ($P = 0.038$) (Fig. 2). Kaplan-meier survival curve showed that compared with normal chromosomes, the OS of hyperdiploid was shorter, while the OS of hypodiploidy was much shorter ($P = 0.038$) (Fig. 3).

Discussion

S-AML is a heterogeneous disease that increases in frequency with age, remains a challenge to therapy[14]. Myelodysplastic syndrome (MDS) is characterized by cytopenia, osteomyelodysplasia, hematopoietic dysfunction, and a high risk of transition to AML[15]. More than half of the S-AML patients reported in this study converted from MDS to AML. Compared with primary AML patients, S-AML patients have worse clinical prognosis, including complete remission rate (CR), recurrence free survival rate and OS rate[16]. Our previous study showed that abnormal increase of peripheral blood regular T cells (Treg) cells may cause the imbalance of immune status of S-AML patients, which may be relevant to poor chemotherapy effect and short survival time of S-AML patients[17]. It

has been reported in the literature that there are tumor suppressor genes on chromosome 6q, 7p, 10p, 11q, 14q and 20q, which play an important role in the transformation from MDS to AML[18]. Chromosomes are associated with the progression of S-AML patients, and deserved further study. The purpose of this study was to analyze the chromosome karyotype results of S-AML patients and further explore the factors connected with survival and prognosis of S-AML patients in combination with relevant laboratory examinations.

Our results indicated that most S-AML patients had abnormal chromosome karyotype, including autosomal and sex chromosomal abnormalities. Abnormal changes of autosomal karyotypes were more common in S-AML patients and were closely related to survival prognosis. Studies have shown a more incidence of abnormalities on chromosomes 5 and 7 in patients with S-AML[19, 20]. In our study, 62.5% (10/16) abnormal chromosome karyotypes had abnormalities on chromosomes 5 and 7. Admittedly, our data are limited and we do not have much information based on the results of only 26 S-AML patients. Abnormal changes of sex chromosomes have been rarely reported in myeloid malignancies[21]. We found an extra sex chromosome (X chromosome) in a FAB-M4 patient who was transformed from MDS in an elderly woman, and the abnormal chromosome karyotypes were: 48,XXX,del(20)(q13),+X,+marker.[8]/48,XX,del(20)(q13),+14,+marker.[3]. The patient was still alive. We also detected Y chromosome deletion in an elderly male patient with AML transformed by MDS, and the abnormal karyotype was: 43,X,t(5;19)(q21;q13),7q+,-7,-12,-20,-Y,+marker.[7]/44,XY,5q-,7q+,-12,-18,-20,+marker1,+marker2.[13]. Unfortunately, the patient lost to follow-up, and we couldn't know whether the patient lives or dies. Some studies have suggested that Y chromosome loss is an age-related phenomenon with no prognostic significance[22]. Studies have shown that sex chromosome loss increases with age, and that Y chromosome loss reduces the risk of converting MDS patients to leukemia[23]. Loss of X chromosome may be associated with a better prognosis in female AML patients with t (8;21), and loss of Y chromosome may be associated with a high level of recurrence rate in men AML patients with t (8;21)[24]. The relationship between sex chromosome abnormality and survival in S-AML patients needs to be further explored by expanding the data.

LDH not only plays an important role in the early diagnosis and prognosis of many solid tumors, but also plays an important part in evaluating the severity of leukemia patients[25, 26]. LDH is positively correlated with tumor burden and is an independent prognostic factor for early death in hyperleukocytic AML[27]. Compared with the normal karyotype group, our results showed that LDH levels were significantly increased in the abnormal karyotype group. It suggested that the higher LDH level in S-AML patients, the greater the tumor burden, the greater the possibility of chromosomal karyotype abnormality, and the worse the OS rate. To conclude, abnormalities of LDH and chromosomal karyotypes are closely related to the severity and survival prognosis of S-AML patients, which may be a very valuable indicator for further risk stratification of S-AML in the future.

Most AML patients with chromosome number abnormalities may be manifested by an increase of 1–2 chromosomes (47–48 chromosomes), known as low hyperdiploid, and rare high hyperdiploidy (49–65 chromosomes), both of which are associated with poor outcome in AML[28–30]. It has also been reported that there was no difference in 5-year OS and EFS between AML patients with non-hyperdiploid and hyperdiploid karyotypes (48–65 chromosomes)[31]. Hypodiploidy (< 46 chromosomes) has been reported mostly in acute lymphoblastic leukemia (ALL), but rarely in AML[32–34]. However, there is currently lack of further research on the prognosis of survival in S-AML patients with hyperdiploid or hypodiploid. In addition to other factors affecting OS, such as various treatment regimens, our research found that chromosome karyotype were closely relevant to the survival of S-AML patients, and patients with abnormal chromosomal karyotypes demonstrated inferior OS compared with those normal chromosomal. What's more, S-AML patients with hypodiploid showed worse outcome than those with hyperdiploid.

There are some limitations in our study. Firstly, the abnormality of sex chromosomes may be related to the survival prognosis of S-AML, but no definite conclusion could be drawn because of the small number of sex chromosome abnormalities in our study. Apart from this, the accurate information of all patients could not be obtained through telephone follow-up in this study, which may interfere with the experimental results. Additionally, this study is a single-center retrospective study, and the number of included cases is relatively small, so it needs to further expand the sample size for study. Moreover, with the heterogeneity of the individualized treatment among AML patients, treatment regimens would constitute an important source of limitation, which may have exerted some influence on the results.

In conclusion, our research highlights the contribution of chromosomes, as well as LDH, leading to poor prognosis of S-AML, and the abnormality of sex chromosomes may be associated with the survival prognosis of S-AML patients. Understanding the multifactorial contributions will lead to more precise risk classification and treatment strategies. More factors related to the survival and prognosis of S-AML need to be explored, which may contribute to monitoring the progression of the disease, early diagnosis and treatment.

Declarations

Authors' contributions

Qianling Ye and Zhimin Zhai designed the study. Tun Zhang, Huiping Wang and Hao Xiao collected patients' data. Dongdong Yang was responsible for chromosome analysis. Mingzhu Song prepared the figures and drafted the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflicts of interest The authors declare no potential conflict of interest.

Ethical approval and consent to participate The study was performed in accordance with the principles expressed in the Declaration of Helsinki. Written informed consent was not required due to retrospective fashion of this study.

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Figures

A=Normal chromosome karyotypes(n=8)
B=Abnormal chromosome karyotypes(n=15)

Figure 1

LDH level in normal and abnormal chromosome karyotypes.

Figure 2

OS in normal and abnormal chromosome karyotypes of S-AML patients.

Figure 3

OS in normal, hyperdiploid and hypodiploidy chromosome karyotypes of S-AML patients.