

ORIGINAL ARTICLE

Hyperdiploid karyotypes in acute myeloid leukemia define a novel entity: a study of 38 patients from the Groupe Francophone de Cytogenétique Hematologique (GFCH)

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A series of 38 patients with acute myeloblastic leukemia (AML) with 49 or more chromosomes and without structural abnormalities was selected within the Groupe Francophone de Cytogénétique Hématologique (GFCH) to better define their characteristics. The median age of the patients was 65 years, and all FAB subtypes were represented. Although all chromosomes were gained, some seems to prevail: chromosome 8 (68%), 21 (47%), 19 (37%), and 13 and 14 (34% each). Since MLL rearrangement leads patients in a group with an unfavorable prognosis, search for cryptic rearrangements of MLL was performed in 34 patients and showed abnormalities in 5 (15%). When we applied the most frequent definition of complex karyotypes (three or more abnormalities), all patients with high hyperdiploid AML fall in the unfavorable category. Among the 18 patients without MLL rearrangement receiving an induction therapy, 16 (89%) reached CR and 6 (33%) were still alive after a 31-month median follow-up (14–61 months). Although this study was retrospective, these results suggest that high hyperdiploid AML without chromosome rearrangement seems to be a subgroup of uncommon AML (less than 1%), and may be better classified in the intermediate prognostic group.

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Introduction

The classification of acute myeloid leukemia (AML) is based on cytomorphology, immunophenotyping and genetics.¹ Cytogenetics is the most important prognostic factor in AML.^{2–4} Patients are classified into the following three risk categories: favorable, intermediate and unfavorable. AML with

t(15;17), t(8;21) and inv(16) are assigned to the favorable group. The prognosis of some AML associated with 11q23/MLL or trisomy 8 remains controversial, and these cases are classified as intermediate or unfavorable according to study groups. On the other hand, it is usually considered that the complex karyotypes have the worst prognosis. The group of AML with complex karyotypes is heterogeneous. For some investigators, three or more cytogenetic abnormalities^{3–5} are required, whereas for others, five or more are mandatory.² Schoch *et al.* have analyzed 125 cases of complex karyotype with the definition of three or more abnormalities and in 94% of these cases, five or more abnormalities were present. Moreover, the number of chromosomal abnormalities (three vs five or more) had no impact on outcome.⁶ Schoch *et al.* have classified the group of complex karyotypes with typical form depending on the presence of all the following criteria: (1) absence of any of the known recurring balanced abnormality leading to fusion genes, (2) number of karyotype abnormalities ≥ 3 , (3) loss of at least one of the chromosomal regions 5q, 7q or 17p and (4) loss of at least one additional area of regions 18q21q22, 12p13 or 16q22q24 or gain of 11q23q25, 1p33p36, 8q22q24 or 21q11q22. High hyperdiploidy (≥ 49 chromosomes) without structural abnormality is a rare abnormality in AML, and the features of such populations of patients are not well characterized in the literature. According to the definition of Schoch *et al.*, all patients with high hyperdiploid AML without structural abnormality are classified as atypical complex aberrant karyotype, which is less frequent as compared to the typical one (25 vs 177) and have a slightly better prognosis. We report here a largest cohort of 38 patients with high hyperdiploid AML without structural abnormality at the conventional karyotype level, to our knowledge. We analyze the clinical features and the prognosis of this group of patients, and demonstrate that hyperdiploid AML represents a novel entity among the patients with complex karyotype without chromosomal structural abnormality using conventional banding technique.

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Patients and methods

Patients

In all, 4884 cytogenetic studies of patients with AML performed in the laboratories members of the GFCH were screened. This corresponds to AML patients (adults and children) diagnosed in 19 French and Belgium institutions during a retrospective (from 2000 to 2004) and 1-year prospective survey (February 2005–February 2006). We were able to select 38 AML patients with high hyperdiploid karyotype without structural abnormality using conventional cytogenetic.

Conventional cytogenetics

Conventional cytogenetic was performed after 24–48 h of unstimulated culture of bone marrow blasts prior treatment initiation. Metaphases were treated for RHG or GTG banding. Chromosome abnormalities were described according to the International System for Human Cytogenetic Nomenclature (ISCN, 2005).⁷ Karyotypes were centrally reviewed by at least five cytogeneticists of the GFCH. Only high hyperdiploidy, with 49 or more chromosomes without structural abnormality were included in the study.

Fluorescent *in situ* hybridization

Dual color probes for detection of MLL rearrangement were performed in 34 patients (Q-Biogen, Illkirch, France; and Vysis, Downers Grove, IL, USA). Hybridization was performed as recommended by manufacturer's protocols. Slides were mounted and counterstained with antifade 4,6-diamidino-2-phenylindole, visualized using a fluorescent microscope and analyzed with a fluorescent *in situ* hybridization (FISH) analysis software. A total of 100–200 interphase nuclei were scored, and metaphases were studied to identify the partner chromosome when the MLL signals were split.

Cytologic studies

The diagnosis of AML was reviewed in 35 cases by four independent cytologists using telehematology via the internet.⁸

Treatment and criteria for responses

Among the 38 patients with hyperdiploid karyotype, 21 received conventional chemotherapy including 19 patients from French collaborative studies: GOELAMS LAM2001 ($n=7$), ALFA 9801 ($n=7$), EORTC ($n=2$), BGMT ($n=1$), ELAM02 ($n=1$) and SA 2002 ($n=1$). Eleven patients were classified unfit for chemotherapy and received supportive care or low-dose chemotherapy. Five patients died before initiation of therapy. Complete remission (CR) was defined by platelets and neutrophils recovery with a normocellular bone marrow showing normal maturation and containing less than 5% blasts.

Statistical analysis

Contingency tables were analyzed with Fisher's exact test to evaluate the association of chromosomal gains and FAB WHO subtypes and features associated with hyperdiploidy with 49–52 chromosomes and with hyperdiploidy with >52 chromosomes. Kaplan-Meier survival analysis was performed to estimate relapse-free survival (RFS) and overall survival. Statview 5.0 (SAS Institute, Cary, NC, USA) was used for all statistical analysis.

Results

Population study

Thirty-eight patients (12 men and 26 women) with high hyperdiploidy were selected. There were 2 children (1 and 2 years) and 36 adults. Their median age was 65 years (ranging from 16 to 91 years). The median age of the 21 patients treated by chemotherapy was significantly lower compared to the median age of the 11 patients who received supportive care (57 vs 74 years, $P=0.0037$). Eight patients (21%) presented with secondary AML (post-chemo- or radiotherapy in three cases and secondary to myelodysplastic syndrome in five cases). Twenty-one patients (55%) presented cytological signs of myelodysplasia at diagnosis. Patient's characteristics are shown in Table 1.

Cytogenetic analysis

We identified 38 patients out of 4884 (0.78%) with ≥ 49 chromosomes without cytogenetically structural rearrangement. Thirty patients (79%) had a modal number from 49 to 52 chromosomes, 6 had 53–54 chromosomes (16%) and 2 (5%) had 56–59 chromosomes. The distribution of the number of chromosome is represented in Figure 1. Some chromosomes were more frequently gained: chromosome 8 (68%) (19 trisomies and 7 tetrasomies), chromosome 21 (47%) (14 trisomies and 4 tetrasomies), chromosome 19 (37%) (13 trisomies and 1 tetrasomy), chromosomes 13 and 14 (34% each), chromosome 10 (29%) and chromosomes 4 and 11 (26% each). Chromosomes 1 and 17 were gained only in one patient (2.6% each) and chromosomes 2, 3, 5 and 16 in two patients (5.2% each). Eleven patients (7 women and 4 men) (29%) showed gain of sex chromosomes. In men, the sex chromosome gained was always chromosome Y. Autosomal monosomies were not observed. Only two patients (5%), two women (6 and 9), showed loss of one X chromosome only in the leukemic clone. The distribution of chromosomal gains is represented in Figure 2.

FISH analysis

In 34 patients, FISH was performed with MLL dual color probes. Cryptic MLL rearrangement was detected in five patients (14.7%) (1, 9, 16, 25 and 27). Chromosome partners were identified in the following two cases: chromosome 10p12 as a cryptic ins(10;11) expressing the AML-AF10 transcript and 19p13.3. Results of karyotype and FISH analysis are shown in Table 1.

Cytological examination

The morphology of bone marrow specimens from 35 patients with clonal abnormalities was reviewed. The AML subtypes were as follows: AML0 ($n=2$); AML1 ($n=5$); AML2 ($n=13$) among them one secondary AML and three AML with multilineage dysplasia; AML4 ($n=4$) of which two AML with multilineage dysplasia; AML5 ($n=8$), four AML5a and four AML5b; AML7 ($n=2$, the two children) and AML unclassified ($n=4$).

Response to therapy and follow-up

Among the 18 patients treated without MLL rearrangement, 16 achieved CR (89% CR). Among them 10 died, 8 after relapse and 6 were still alive (33%) with a median follow-up of 31 months (range: 14–60 months). The median time to relapse was

Table 1 Patient's characteristics, karyotypes and FISH

Patient	Sex/age (years)	AML subtype	Treatment	CR	Alive/survey	Karyotype	FISH MLL (partner chromosome)
1	F/48	AML5b	Curative	Yes	Yes/10 months	47,XX,+21[2]/49,idem,+15,+19[17]/46,XX[3]	Rearranged
2	F/74	AML unclassified	Unfit	No	No/24 months	47,XX,+8[1]/49,idem,+6,+14[2]/46,XX[4]	—
3	F/56	AML2	Curative	Yes	No/10 months	49,XX,+8,+8,+14[4]/46,XX[18]	—
4	F/88	AML2	Palliative	No	No/1 month	49,XX,+4,+8,+13[6]/49,XX[19]	—
5	F/91	AML1 ^a	Palliative	No	No/13 months	49,XX,+9,+13,+13[7]/46,XX[13]	—
6	F/1	AML7	Curative	Yes	Yes/25 months	49,XX,+8,+21,+21[17]/46,XX[6]	—
7	F/60	AML1	Curative	Yes	Yes/56 months	49,XX,+X,+8,+21[21]/46,XX[4]	No material
8	M/83	AML4 with MD	NA	NA	NA	49,XY,+4,+18,+20[8]/46,XY[17]	—
9	F/60	AML5b	None	No	No/1 day	49,XX,+5,+8,+13[10]/46,XX[3]	Rearranged
10	F/82	AML4	None	No	No/4 days	49,XX,+4,+4,+8[5]/50,idem,+18[4]/46,XX[10]	—
11	M/84	AML1	None	No	No/2 days	48,XY,+13,+21[17]/49,sl,+13[2]/50,sdl1,+21[3]/46,XY[4]	—
12	F/60	AML5b	Curative	Yes	Yes/35 months	48,XX,+4,+10[16]/50,idem,+4,+8[2]/46,XX[1]	—
13	F/43	AML2	Curative	Yes	No/9 months	50,X,-X,+11,+11,+13,+17,+22,[22]	—
14	F/71	AML2 ^a	Palliative	No	No/8 months	50,XX,+X,+14,+19,+21[12]/46,XX[2]	No material
15	F/52	AML5a	None	No	No/3 weeks	50,XX,+X,+8,+10,+15[12]/46,XX[9]	—
16	F/47	AML5a	Curative	No	No/17 days	50,XX,+8,+8,+14,+19[20]	Rearranged (10p12)
17	M/72	AML unclassified	Curative	Yes	No/22 months	50,XY,+3,+13,+19,+21[16]/46,XY[7]	—
18	M/57	AML0	Curative	Yes	No/11 months	50,XY,+5,+10,+14,+21[25]	—
19	M/68	AML2	Curative	Yes	No/18 months	51,XY,+8,+11,+14,+19,+21[30]	—
20	F/79	AML2	Palliative	No	No/1 month	51,X,-X,+4,+10,+13,+14,+16,+20[11]/46,XX[9]	—
21	F/65	AML2 ^a	Curative	Yes	No/?	51,XX,+X,+8,+10,+13,+15[3]/46,XX[27]	—
22	F/67	AML2	Curative	No	No/26 months	51,XX,+11,+12,+13,+14,+22[11]/46,XX[10]	—
23	F/73	AML2 with MD	Curative	Yes	No/23 months	51,XX,+8,+11,+12,+21,+21[3]/46,XX[16]	—
24	M/80	AML4	Palliative	No	No/8 months	51,XY,+Y,+8,+9,+10,+11[16]/46,XY[6]	—
25	M/54	AML2 with MD	Curative	Yes	No/30 months	51,XY,+8,+8,+9,+12,+21[2]/46,XY[18]	Rearranged (19p13.3)
26	F/72	AML0	Palliative	No	No/10 months	51,XX,+2,+8,+13,+19,+21[24]/46,XX[2]	—
27	M/66	AML5a	Palliative	No	No/4 months	52,XY,+4,+8,+8,+11,+19,+22[30]	Rearranged
28	M/70	AML5b	Palliative	No	No/2 months	52,XY,+2,+4,+6,+7,+13,+15[12]/46,XY[3]	—
29	F/51	AML1	Curative	Yes	No/10 months	52,XX,+4,+6,+8,+9,+10,+10[16]/46,XX[11]	—
30	M/65	AML5a	None	No	No/6 days	49,XY,+Y,+8,+18[7]/53,idem,+4,+12,+18,+19[2]/46,XY[7]	No material
31	M/57	AML unclassified	Curative	Yes	No/62 months	53,XY,+Y,+6,+9,+12,+13,+21,+22[2]/46,XY[4]	—
32	F/73	AML2 with MD	Curative	Yes	No/31 months	53,XX,+8,+8,+9,+11,+14,+19,+21[3]/46,XX[15]	—
33	F/50	AML4 with MD	Curative	Yes	Yes/27 months	47,XX,+8[1]/54,idem,+X,+3,+8,+10,+12,+16,+19[21]/46,XX[3]	—
34	F/16	AML1	Curative	Yes	Yes/12 months	54,XX,+4,+6,+7,+8,+14,+20,+21,+22[12]/46,XX[3]	—
35	M/79	AML unclassified	Palliative	No	No/3 months	54,XY,+Y,+6,+8,+10,+11,+14,+19,+21[3]/46,XY[19]	—
36	F/2	AML7	Palliative	No	No/5 months	54,XX,+X,+8,+14,+18,+19,+21c,+21,+22[3]/47,XX,+21c[23]	—
37	F/36	AML2 2ndary	Curative	Yes	Yes/10 months	56,XX,+X,+1,+6,+8,+8,+10,+11,+19,+21,+22[14]	—
38	F/62	AML2	Curative	Yes	No/10 months	59,XX,+X,+6,+7,+8,+9,+10,+11,+13,+14,+19,+19,+21,+21[6]/46,XX[19]	No material

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; F, female; FISH, Fluorescent *in situ* hybridization; M, male; MD, multilineage dysplasia; NA, not available.^aNot reviewed.

658 days (allografted patients censored) and median survival was 565 days.

Discussion

To our knowledge, this is the first report of a large cohort of high hyperdiploid AML (≥ 49 chromosomes) without structural abnormalities. The incidence of the hyperdiploidy AMLs is not precisely known. Among 4884 patients with AML from 19 French or Belgium institutions, members of the GFCH, 38 patients (0.78%) with hyperdiploidy and without karyotypic structural abnormality were selected. Median age of the cohort was comparable to the median age of AML patients. However, 14 patients (37%) are ≤ 60 years, which is unusual for the majority of patients with complex karyotype usually >60 years.⁶ Although all chromosomes may be involved, extra copies of chromosomes 8 (68%), 21 (47%), 19 (37%), 13 and 14 (34% each), 10 (29%), and 4 and 11 (26% each) were the most

common. Trisomy 8 was the most frequent trisomy in *de novo* AML series (9%) followed by trisomy 21 (3%), whereas the other trisomies were less frequent (all together 9%).² Schoch *et al.* showed an incidence of whole chromosomal gains slightly different in 125 cases of AML with complex karyotypes, including numerical and structural abnormalities: chromosomes 8 (24%), 10 (9%) and 22 (8%) then 21 (7%), 1, 9 and 13 (6%), 20 and 11 (4%). Chromosomes 14 and 19 were less frequently gained, around 3 and 2%, respectively (Table 2).⁹

Five patients (13%) showed clonal evolution, suggesting that trisomies were progressively acquired. This hypothesis is in line

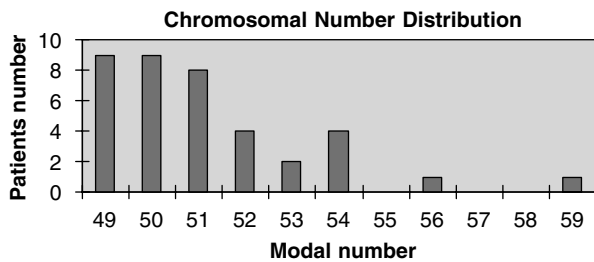


Figure 1 Chromosomal number distribution.

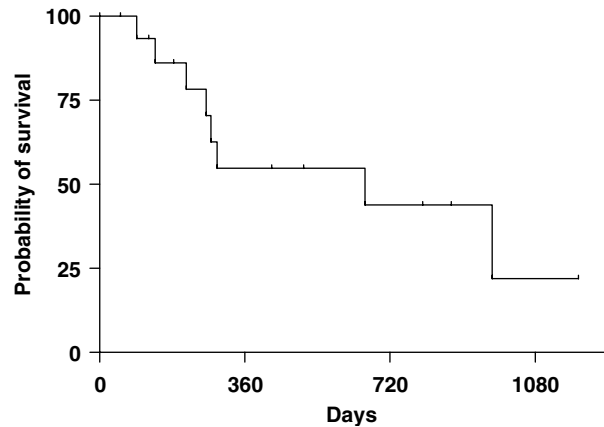


Figure 3 Kaplan-Meier plot of duration of complete remission (CR) in 16 patients in CR after induction therapy. Allografted patients ($n = 3$) were censored at the time of transplantation.

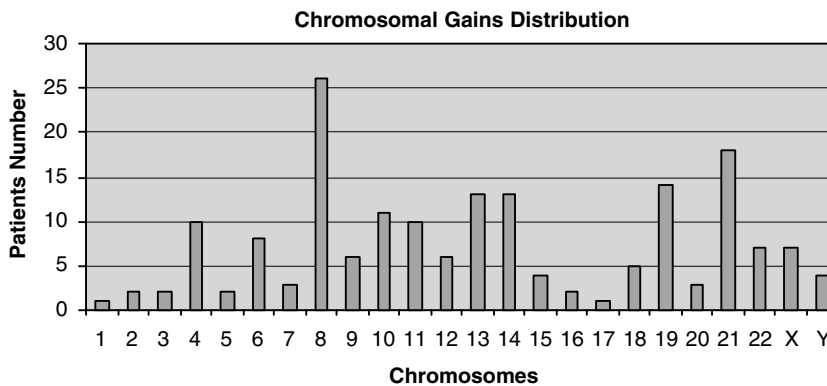


Figure 2 Chromosomal gains distribution.

Table 2 Most common extracopy chromosomes in hyperdiploid AML

Extracopy chromosome	Present series, $n = 38$ (%)	49–52 hyperdiploid group, $n = 29$ (%)	≥ 53 hyperdiploid group, $n = 9$ (%)	Complex karyotype, $n = 125$, Schoch <i>et al.</i> ⁹ (%)
8	68	62 (tetrasomy = 14)	89 (tetrasomy = 33)	24
21	47	38 (tetrasomy = 10)	78 (tetrasomy = 11)	7
19	37	24	78	2
13	34	38	22	3
14	34	28	56	6
10	29	24	44	9
11	26	21	44	4
4	26	28	22	NA

Abbreviations: AML, acute myeloid leukemia; NA, not available.

with the recent published data suggesting that trisomy 8 may be a secondary event in addition to other genetic changes in AML.^{10,11} However, if the acquisition of extra chromosomes in AML occurred step by step, this mechanism should be different from that shown in acute lymphoblastic leukemia (ALL) with hyperdiploidy in which the acquisition of extra chromosome set occurs as only one event.¹² Some chromosomes involved in hyperdiploid ALL (21, 6, 18, X 14, 10 and 4) are also gained in hyperdiploid AML patients, but the incidence of extra chromosome of each chromosome pair is different in the two types of acute leukemias. The distribution of the modal number is different in ALL, with the following three distinct groups: 47–50, around 55 and >60 chromosomes. Trisomy 21 is constant in the common hyperdiploid ALL around 55 chromosomes and the gain of X chromosome is very frequent, whereas gain of chromosome Y is unusual. One cannot thus confuse a profile of hyperdiploid ALL with that of hyperdiploid AML. On a more fundamental point of view, the consequences of gene dosage effects remain to be analyzed as it has been done for some trisomies in AML and in other diseases.^{13,14}

We did not find any association between a particular AML FAB subtype and hyperdiploid AML. Trisomies 9, 11, 14 and 21 were more often associated with AML-M1 and -M2 ($P=0.04$ for trisomy 11), whereas gains of chromosomes 4, 15 and 19 were more often observed in AML-M4 and -M5 ($P=0.04$ for chromosome 4).

Submicroscopic alterations of genetic material are detectable only by molecular genetic techniques.^{15,16} In AML, approximately 5–10% of adult patients with normal karyotype display cryptic rearrangement of the *MLL* gene.^{17,18} Consequently, FISH studies were performed to detect possible rearrangement of the *MLL* gene using a specific dual color probe in 34 patients (89%). Five (15%) exhibited a cryptic *MLL* rearrangement: four patients with AML-M5 (two AML5b and two AML5a) and one with AML-M2 with multilineage dysplasia. This is in agreement with previous studies showing an association between monocytic differentiation and *MLL* rearrangement.^{19,20} Since *MLL* rearrangements define a subcategory in the WHO classification of AML¹ with usually unfavorable prognosis,^{20,21} search of *MLL* rearrangement should be systematically performed in hyperdiploid AML. Array-based comparative genomic hybridization (Array-CGH) studies are needed to know if cryptic aberrations are present in these high hyperdiploid AML, which has been previously demonstrated in high hyperdiploid childhood ALL.²² The search of mutations frequently described in AML, such as FLT3 or NPM1, was not performed in this retrospective study. In the same way, the p53 inactivation reported by Schoch *et al.*⁹ among patients with complex karyotypes was not tested. The AML patients with hyperdiploidy ≥ 49 chromosomes are classified as the poor prognostic group, because they fall in the complex karyotype group according to all classifications, except the MRC one in which at least five abnormalities are required to classify AML in the complex karyotype group. This implicates that all patients with more than 50 chromosomes belong to the complex karyotype subgroup, which represents half of the patients of the present series. Twenty-one patients (55%) received an induction therapy (18 patients without structural abnormality and 3 with a cryptic *MLL* rearrangement). Among the 18 patients without structural rearrangement, CR was achieved in 16 patients (89%). The median time to relapse is 658 days for the 16 patients in CR (including 3 patients censored at the time of bone marrow transplantation) (Figure 3) that is far longer than published duration of CR for patients with complex karyotypes (2, 6 and 21). Although this study was retrospective, these results suggest that patients with hyperdi-

ploid AML without structural rearrangement may not have the same unfavorable prognostic than patients with typical complex karyotype AML.

We suggest that hyperdiploid AML may be classified better in the intermediate prognostic group when hyperdiploidy is the only cytogenetic abnormality. We thus conclude that prospective and larger studies are needed to confirm these preliminary results.

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