

Allogeneic stem cell transplantation can improve outcome of AML patients without complete cytogenetic response after induction and consolidation treatment

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Our retrospective analysis was performed on 376 consecutive patients diagnosed with AML. A total of 256 (68%) were treated with standard “7+3” induction and high-dose cytarabine and mitoxantrone containing “4+3” consolidation/intensification regimens. Our study focused on patients with presumably very poor prognosis – patients, who did not achieve complete cytogenetic remission (CRc). Twenty-five AML patients without CRc were further analysed for clinical and laboratory parameters. Firstly, the subgroups with or without morphologic CR were compared. Similar cytogenetic abnormalities were observed in both with myelodysplasia related changes being the most common. Complex karyotype with deletion of 5q constituted approximately a third of all karyotypes in both subgroups. There were 1 patient with intermediate risk cytogenetics in the subgroup without morphologic CR and 5 patients in the subgroup with morphologic CR. Interestingly, in 4/25 patients subclones were diminished by the chemotherapy treatment, however cytogenetically less advanced clones proliferated. Secondly, transplanted or nontransplanted patients were analysed. Allogeneic stem cell transplantation (allo-SCT) was found to be the only curative treatment for patients without CRc after 7+3 and 4+3 regimens. In our cohort, 40% of the patients, who underwent allo-SCT, are alive. Importantly, 67% of the patients, who died after allo-SCT, died of causes unrelated to progression of AML. Nonrelapse mortality is therefore one of the fields where survival could be further improved.

Key words: acute myeloid leukaemia, complete cytogenetic remission, cytogenetic abnormalities, stem cell transplantation, nonrelapse mortality

The prognostic importance of some cytogenetic abnormalities identified at diagnosis of acute myeloid leukaemia (AML) has been proved in many extensive studies. Cytogenetic abnormalities were also largely reflected in the latest WHO classification of tumours of haematopoietic and lymphoid tissues [1]. Furthermore, the international working group led by Cheson recommended to use the achievement of complete cytogenetic remission (CRc) after chemotherapy as one of the most important criteria for assessment of treatment outcomes already in 2003 [2]. However, only a few studies focusing on this topic have been published. In fact, a detailed analysis of clinical data together with cytogenetic characteristic of AML patients, who failed to achieve CRc after induction and consolidation/intensification chemotherapy, has not been published

so far. This study adds to the limited amount of research in this important field.

Materials and methods

Our retrospective analysis was performed on a cohort of 376 consecutive patients, who were diagnosed with AML at University Hospital Pilsen between January 2000 and December 2012. A total of 256 (68%) of these patients were treated with the “7+3” induction and high-dose cytarabine and mitoxantrone containing “4+3” consolidation/intensification regimens (both regimens are described below), 71 (19%) were maintained with a different type of chemotherapy or got only 7+3 regimen and 49 (13%) were given

symptomatic therapy. Clinical and laboratory data from 256 patients treated with both regimens were further analysed. The study was approved by the Ethics Committee at our institution and conducted in accordance with the Declaration of Helsinki.

Chromosome G-banding analysis in combination with FISH analysis was performed in unstimulated 24-h cultures of bone marrow samples according to standard procedures. At least 20 metaphase cells were fully analysed to exclude any clonal abnormalities in accordance with ACC (Association of Clinical Cytogeneticists) and UK NEQAS (National External Quality Assessment Schemes) guidelines for clinical cytogenetics. The clonal abnormalities were described according to ISCN 2013 guidelines [3]. Complex karyotype (CK) was defined, in agreement with the WHO 2008 classification [1], as karyotype with 3 or more unrelated abnormalities. Molecular genetic techniques were performed according to standard protocols. The presence of these molecular genetic abnormalities was detected: MLL-PTD, FLT3-ITD, FLT3 Asp835, GSTM1 and GSTT1 polymorphisms, Cyclin D1 and BAALC overexpression, and NPM1 mutations.

Overall survival (OS) was measured from the date of initial treatment until the date of death and censored on the date of the last follow-up if alive. Progression free survival (PFS) was measured from the date of remission until the date of relapse or death and censored on the date of last follow-up if alive. Descriptive statistics were calculated. Kaplan-Meier curves were used to estimate unadjusted OS and PFS. Log-rank tests were used to compare each time-to-event variable between groups. The Cox proportional hazards regression model was used to evaluate the ability of the relevant variables to predict either OS or PFS. SAS 9.3 software (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

Two chemotherapeutic attempts to achieve complete remission (CR) of AML (in line with Cheson et al. [3]) meant application of induction chemotherapy according to 7+3 regimen followed by consolidation/intensification chemotherapy according to 4+3 regimen (HiDAC +Mx). The 7+3 regimen consisted of: cytarabine 200mg/day i.v. continuously for 7 days, idarubicin 12mg/m²/day i.v. for 3 days. The 4+3 regimen consisted of: cytarabine 1500-3000 mg/m² (reduced doses for elderly patients) twice daily i.v. for 4 days, mitoxantrone 10-12mg/m²/day i.v. for 3 days.

In patients in complete or partial remission after the two chemotherapeutic attempts, the allogeneic stem cells transplantation (allo-SCT) was performed within the period of 2-8 weeks after the last chemotherapy regimen. Allo-SCT with reduced intensity conditioning regimen FLU/MEL was administered in elderly patients (the age 50-years and more) and consisted of fludarabine 30 mg/m² i.v. once daily for 4 days (total dose 120 mg/m²) and melphalan 140 mg/m² i.v. once daily one day prior to transplantation. In young patients, the conventional Bu/CY2 conditioning regimen was administered and consisted of busulphan 4 mg/kg p.o. or 3,2 mg/kg i.v. in divided doses for 4 days (total dose 16 mg/kg) and

cyclophosphamide 60 mg/kg once daily i.v. for 2 days (total dose 120 mg/kg).

Results

Normal karyotype at diagnosis was detected in 120 (47%) out of 256 AML patients treated with 7+3 and 4+3 regimens. Abnormal karyotype was found in remaining 136 (53%) patients. CRc was not achieved in 25 (18%) patients following two cycles of chemotherapy. Morphologic CR was not reached in 9 of these 25 patients (no CR/ no CRc; group A). The rest of these patients without CRc (16 patients) achieved morphologic CR (CR/ no CRc; group B).

A total of 9 patients (4 males and 5 females) were included in the group A. 6 patients were diagnosed with "AML with myelodysplasia related changes" (AML-MRC), 2 patients with "AML with inv(3)(q21q26)/t(3;3)(q21;q26)" and 1 patient with "treatment related AML" (t-AML). Clinical data of group A patients are summarized together with group B patients in the Table 1. Only 2 group A patients were found to be suitable for allo-SCT, the rest had disease resistant to all administered chemotherapy and sustained on symptomatic therapy. One of these 2 patients undergoing allo-SCT is alive 6 months after the diagnosis and the other died of pneumonia after 6 months. All of the 7 nontransplanted patients died due to the disease progression.

In the group A, 7 out of 9 patients (78%) had a complex karyotype. The assumed primary cytogenetic changes in CK were: abnormality of 5q in 3 patients, abnormality of 3q in 2 patients, abnormality 1p or 9q in 1 patient and abnormality of 11q in 1 patient (Table 2). Abnormalities of 7q were present in 4 patients and abnormality of 17p in 2 patients, presumably as secondary changes. Noncomplex karyotypes were present in 2 patients: 46,XY,inv(3)(q21q26)[6]/45,idem,-7[19] and 47,XY,+8[3]/46,XY[16] respectively. Interestingly, in 1 patient (patient No. 4) the karyotype 45,XX,der(1)t(1;6)(p33;?),der(6)t(1;6)(p33;q23)t(6;9)(p11;p13),-9[3]/46,idem,+10[16] was revealed at diagnosis, however the subclone with trisomy 10 (secondary change in this case) was diminished by the chemotherapy treatment and the main clone with no recurrent primary change expanded. Complete karyotypes including FISH results of the group A patients are shown in the Table S1 in the Supplemented Materials. The patient with trisomy 8 as a sole abnormality was positive for NPM1 mutation and overexpression of BAALC in molecular genetic analysis (Table 3).

Sixteen patients (8 males and 8 females) were included in the group B. Eleven patients were diagnosed with "AML with myelodysplasia related changes" (AML-MRC), 1 patient with "AML with inv(3)(q21q26)/t(3;3)(q21;q26)" and 4 patients with "AML not otherwise specified" (AML-NOS) (Table 1). Allo-SCT was performed in 13 patients. Five of these 13 patients are alive (6, 8, 64, 66 and 79 months from diagnosis) and 8 patients died. Only 3 of these 8 patients died on disease progression and conversely 5 patients died on reasons not di-

Table 1. Clinical data of 25 patients without CRc after 7+3 and 4+3 regimens

P. No.	Sex	Age	Previous Chemo-therapy	Previous Actino-therapy	Dg. (WHO 2008)	Disease Status after 7+3	CR after 7+3 and 4+3	Allo-SCT	Donor	GVHD	PFS (months)	Alive	OS (months)	Cause of death
1	F	61	No	No	AML-MRC	resistant	No	No	No	No	2.3	No	9.2	resistant disease
2	M	50	No	No	AML-MRC	PR	No	No	No	No	2.6	No	3.0	progresion
3	F	44	No	No	AML-MRC	resistant	No	No	No	No	1.4	No	4.3	progresion
4	F	63	No	No	AML-MRC	resistant	No	No	No	No	2.0	No	5.5	progresion
5	F	60	No	No	AML-MRC	resistant	No	No	No	No	1.9	No	3.2	progresion
6	M	25	No	No	AML with inv(3)	resistant	No	Yes	R	Yes	6.7	Yes	6.7	
7	M	62	No	No	AML with inv(3)	resistant	No	No	No	No	2.0	No	2.3	resistant disease
8	M	61	No	No	AML-MRC	resistant	No	No	No	No	2.0	No	2.0	pneumonia
9	F	62	Yes	Yes	t-AML	resistant	No	Yes	R	No	4.8	No	6.6	pneumonia
10	M	44	No	No	AML-MRC	resistant	Yes	Yes	R	No	2.9	No	13.9	progresion
11	F	52	No	No	AML-MRC	PR	Yes	Yes	U	Yes	23.2	No	24.4	pneumonia
12	M	62	No	No	AML-MRC	PR	Yes	No	No	No	2.8	No	3.5	progresion
13	M	56	No	No	AML-MRC	PR	Yes	No	No	No	5.7	No	8.8	progresion
14	F	63	No	No	AML-NOS	CR	Yes	Yes	U	Yes	5.4	No	5.4	GVHD
15	M	57	No	No	AML-MRC	PR	Yes	Yes	U	Yes	24.4	No	24.4	lung failure
16	F	50	No	No	AML-MRC	PR	Yes	Yes	R	No	79.3	Yes	79.3	
17	M	53	No	No	AML-MRC	CR	Yes	Yes	U	Yes	13.9	No	15.3	CNS infection
18	F	47	No	No	AML-MRC	PR	Yes	Yes	U	Yes	36.4	No	57.6	progresion
19	F	48	No	No	AML-MRC	PR	Yes	Yes	U	Yes	6.5	No	7.4	suicide
20	M	63	No	No	AML-MRC	CR	Yes	Yes	U	Yes	5.9	Yes	6.7	
21	F	56	No	No	AML-MRC	PR	Yes	Yes	U	Yes	8.3	Yes	8.3	
22	F	63	No	No	AML with t(3;3)	resistant	Yes	No	No	No	3.9	No	4.0	progresion
23	F	52	No	No	AML-NOS	PR	Yes	Yes	U	Yes	64.0	Yes	64.0	
24	F	54	No	No	AML-NOS	resistant	Yes	Yes	R	Yes	66.8	Yes	66.8	
25	M	66	No	No	AML-NOS	CR	Yes	Yes	U	Yes	32.4	No	38.9	progresion

Dg.=diagnosis; CR=complete remission; Allo-SCT=allogeneic stem cell transplantation; R=related; U=unrelated; GVHD=graft versus host disease; PFS=progression free survival; OS=overall survival;

rectly related to disease progression (pneumonia, graft versus host disease, lung failure, CNS infection, and suicide).

In the group B, CK was found in 7 patients (44%) and 9 patients had noncomplex karyotypes. The assumed primary

Table 2. Primary cytogenetic changes of 9 patients without hematological remission after 7+3 and 4+3 regimens

Abn.\P.No.	1	2	9	3	6	7	5	4	8
Complex karyotype	X	X	X	X		X		X	X
Abn. 5q/-5	X	X	X						
Abn. 3q				X	X	X			
Trisomy 8							X		
Abn. 1p								X	
Abn. 9q/-9								X	
Abn. 11q									X

Abn.=abnormality;

cytogenetic changes in CK were: abnormality of 5q in 6 patients and abnormality of 12p in 1 patient (Table 4). Abnormality of 7q was present in 3 patients and abnormality of 17p in 2 patients, presumably as secondary changes. Primary cytogenetic changes observed in the noncomplex karyotypes were: der(7)del(7)(p12)del(7)(q11.2); +8 (3 patients); t(2;3)(p13;q26); del(7)(q22q36); t(3;3)(q21;q26); t(9;11)(p22;p15); del(20)(q11.2). In 3 patients subclones were reduced by the chemotherapy treatment, however main clones or other subclones proliferated. After the chemotherapy, subclone with monosomy 7 was diminished in the patient No. 11, subclones unseen at the diagnosis were detected in the No. 17 and on the other hand main clone with the sole abnormality – deletion of 5q – unseen at diagnosis was present in the No. 21. Complete karyotypes including FISH results of the group B patients are shown in the Table S2 in the Supplemented Materials. One of the 5 patients with intermediate risk cytogenetics was positive for NPM1 mutation

and overexpression of BAALC and 2 patients were positive for overexpression of BAALC in molecular genetic analysis (Table 3).

All of the patients from the groups A and B were included in the statistical analysis. Median follow-up for the whole group (25 patients) was 7.4 months, median PFS was 0.5 years and median OS was 0.8 years. Statistically significant differences in survival parameters were found between two groups – transplanted and nontransplanted patients. PFS and OS were significantly higher than patients who underwent allo-SCT in comparison to nontransplanted group. PFS and OS in transplanted patients were 2.7 and 2 years, in nontransplanted patients 0.2 and 0.3 years respectively (Log-Rank test, $P=0.0001$, Figure 1 and Figure 2). Patients without transplantation had 22.8 times higher risk of disease progression and 12.5 times higher risk of death (Cox Regression Hazard Model).

Discussion

In 1997, Grimwade et al. [4] published the results of the 10th UK MRC AML trial. One of the trial's objectives was to determine the role of autologous bone marrow transplantation in AML patients lacking an HLA-matched sibling. Among 101 of 190 patients with AML characterised by abnormal karyotype at diagnosis, persistence of the disease-related clone in eight patients (8%), revealed by conventional cytogenetic assessment at bone marrow harvest whilst in morphologic CR, was found to predict a poor prognosis [4].

Fung et al. [5] reviewed the records of 68 patients who consecutively underwent transplantation at the City of Hope Cancer Center with allogeneic SCT for primary refractory AML between July 1978 and August 2000. Allogeneic SCT can cure approximately one third of patients with primary refractory AML. Cytogenetic characteristics before SCT correlate with transplantation outcome and posttransplantation relapse [5].

AML patients treated on Cancer and Leukemia Group B front-line studies were included in the work of Marcucci et

Table 3. Molecular genetic results of 25 patients without CRc after 7+3 and 4+3 regimens

P.No.	Positive molecular genetic results
1	NPM1
2	neg.
3	unk.
4	FLT3/ITD, BAALC
5	BAALC
6	BAALC
7	neg.
8	NPM1, BAALC
9	BAALC
10	unk.
11	neg.
12	neg.
13	neg.
14	FLT3/ITD, BAALC
15	BAALC
16	neg.
17	BAALC
18	unk.
19	FLT3/ITD, BAALC
20	neg.
21	BAALC
22	neg.
23	NPM1, BAALC
24	neg.
25	BAALC

neg.=negative;unk.=unknown;

al. [6] published in 2004. Cytogenetic samples were obtained at diagnosis and on the first day of documented morphologic CR following induction chemotherapy. Patients with abnormal cytogenetics at diagnosis, and normal cytogenetics at morphologic CR (NCR; $n=103$) were compared with those with abnormal cytogenetics both at diagnosis and at morphologic CR (ACR; $n=15$) for overall survival (OS), disease-free sur-

Table 4. Primary cytogenetic changes of 17 patients with hematologic but without cytogenetic complete remission

Abn.\P.No.	12	13	17	20	21	14	15	16	23	18	22	10	19	11	24	25
Complex karyotype	X	X	X	X	X	X										X
Abn. 5q/-5	X	X	X	X	X	X										
Trisomy 8							X	X	X							
Abn. 3q										X	X					
Abn. 7q/-7												X	X			
Abn. 12p																X
t(9;11)(p22;p15)																X
Abn. 20q																X

Abn.=abnormality;

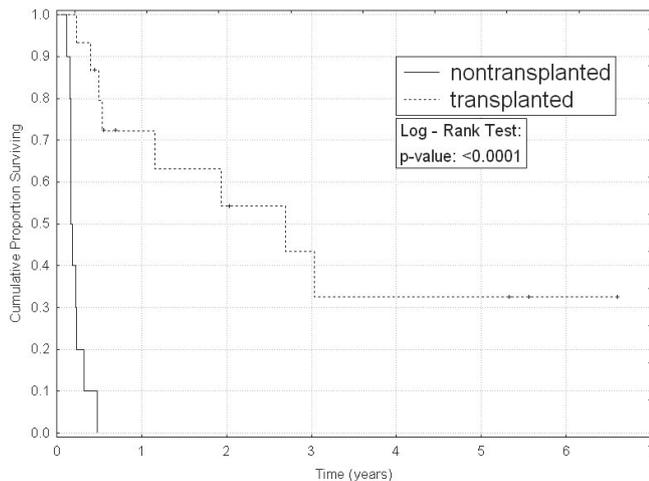


Figure 1. Comparison of progression free survival (Kaplan-Meier survival curves) between transplanted (n=15) and nontransplanted (n=10) patients from our cohort of 25 patients without CRc after 7+3 and 4+3 regimens (Log-Rank test, $P<0.0001$), median progression free survival was 2.7 and 0.2 years respectively.

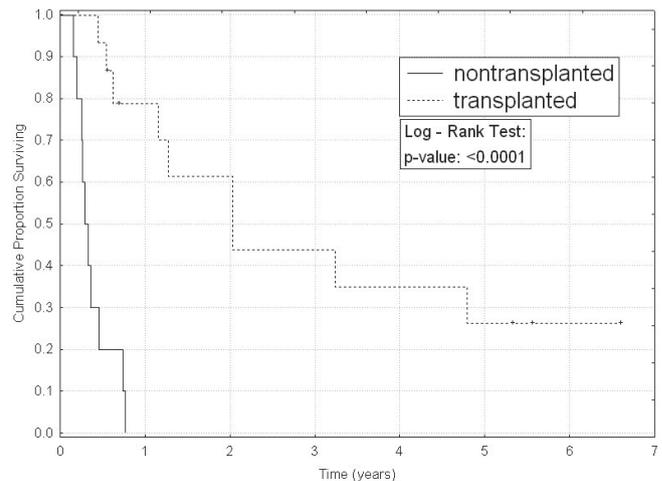


Figure 2. Comparison of overall survival (Kaplan-Meier survival curves) between transplanted (n=15) and nontransplanted (n=10) patients from our cohort of 25 patients without CRc after 7+3 and 4+3 regimens (Log-Rank test, $P<0.0001$), median overall survival was 2.0 and 0.3 years respectively.

vival (DFS), and cumulative incidence of relapse (CIR). ACR patients had significantly shorter OS, DFS and higher CIR. The relative risk of relapse or death was 2.1 times higher for ACR patients than for NCR patients [6].

118 high-risk MDS or AML patients with an abnormal karyotype at diagnosis and a second cytogenetic analysis performed after induction chemotherapy were included in the retrospective study of German researchers in 2009 [7]. The authors confirmed that the persistence of minimal disease on a cytogenetic level in patients with de novo or secondary AML as well as high-risk MDS who achieved morphologic CR following conventional induction therapy was an independent prognostic parameter for the probability of shorter OS [7].

Data from 254 adult patients with AML (excluding acute promyelocytic leukaemia) who achieved CR after induction chemotherapy on various first-line protocols were examined by Chen et al. [8] in 2011. Persistent cytogenetically abnormal cells at CR predict a significantly shorter relapse-free survival and OS. SCT in CR1 may improve the clinical outcome of patients lacking cytogenetic remission after induction although this depends on patient selection [8].

Our study focused on AML patients with presumably very poor prognosis – patients, who did not achieve CRc after two chemotherapeutic attempts (7+3 and 4+3 regimens). The frequency of patients with this condition can be estimated to be as high as 18% between consecutive AML patients. Some of these patients have normal karyotype and CRc cannot be evaluated. In our study, 25 AML patients without CRc, who had an abnormal karyotype at diagnosis, were analysed for clinical and laboratory parameters. Approximately a third of these patients did not achieve even morphologic CR.

Firstly, we compared two subgroups – with or without morphologic CR. Similar cytogenetic abnormalities were observed in both subgroups with myelodysplasia related changes being the most common. CK with deletion of 5q, as suspected primary cytogenetic change, constituted approximately a third of all karyotypes in both subgroups. There were only two noncomplex karyotypes in the subgroup without morphologic CR. Interestingly, one of them had trisomy 8 as a sole abnormality. Molecular genetic analysis revealed NPM1 mutation and overexpression of BAALC in this patient. There were 5 patients with intermediate cytogenetics risk in the subgroup with morphologic CR. Three of them were positive for some of the negative prognostic markers tested in molecular genetic analyses. From cytogenetic point of view it is interesting that in 4/25 patients subclones were diminished by the chemotherapy treatment, however cytogenetically less advanced clones proliferated.

Secondly, we made statistical analyses on other two subgroups – transplanted or nontransplanted patients. Allogeneic stem cell transplantation was found to be the only curative treatment for patients without CRc after 7+3 and 4+3 regimens. In our cohort, 40% of the patients, who underwent allo-SCT, are alive. Importantly, 67% of the patients, who died after allo-SCT, died of causes unrelated to progression of AML. Nonrelapse mortality is therefore one of the fields where survival of patients without CRc could be further improved. However, there is still a lack of knowledge and further studies are needed to explore this very important topic.

Supplementary information is available in the online version of the paper.

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Supplementary Information

Allogeneic stem cell transplantation can improve outcome of AML patients without complete cytogenetic response after induction and consolidation treatment

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Supplementary Table

Table S1. G-banding and FISH results of 9 patients without hematologic complete remission

P. No.	At AML diagnosis	After 7+3 and 4+3 (HiDAC+Mx)
1	44,XX,del(4)(q27?),-5,der(5)t(4;5)(?q27;q21),der(7)t(5;7)(q13;q22),?der(8),der(9)t(5;9)(p13;q21),der(12)del(12)(p11)del(12)(q21),-16[12]/46,XX[6], FISH: 85% deletion EGR1(5q31),80% deletion D7S486(7q31),75% deletion CBFβ(16q22)	44,XX,del(4)(q27?),-5,der(5)t(4;5)(?q27;q21),der(7)t(5;7)(q13;q22),der(9)t(5;9)(p13;q21),der(12)del(12)(p11)del(12)(q21),-16[8] FISH: 90% deletion EGR1, 90% deletion D7S486
2	68-71<3n>,XXY,+Y,del(5)(?q12q35),+del(5)(?q12q35),+6,del(7)(q22q36),der(7)t(7;17)(p14;p12)x2,+del(7)(q22q36),+8,-9,-10,-11,-13,+14,-16,-17,-18,+19,+20,+der(?)t(17;?)?q;?,+1-3mar[cp20] FISH: 6% deletion EGR1(5q31),92% deletion EGR1x2,10% deletion D7S486(7q31),87% deletion D7S486x2,95% tetrasomy 8	67-71<3n>,XXY,+Y,del(5)(?q12q35),+del(5)(?q12q35),+6,del(7)(q22q36),der(7)t(7;17)(p14;p12)x2,+del(7)(q22q36),+8,-9,-10,-11,-13,+14,-16,-17,-18,+19,+20,+der(?)t(17;?)?q;?,+1-5mar[cp15] FISH: 90% deletion EGR1x2,80% trisomy 12 and disomy 13
3	45-46,X,der(X)t(X;?)?,der(3)del(3)(?q)t(3;?6)(?q;q24),der(6)t(3;6)(?q;q23),der(7)del(7)(p12)del(7)(q21),-14,-15,+der(?)t(X;?)?,+der(?)t(3;?)?[cp20]	Persistent massive infiltration by blasts of AML in bone marrow and peripheral blood by cytology, cytogenetic analysis not performed
4	45,XX,der(1)t(1;6)(p33;?),der(6)t(1;6)(p33;q23)t(6;9)(p11;p13),-9[3]/46,idem,+10[16], FISH: 90% deletion 9q21, 50% trisomy 10	45,XX,der(1)t(1;6)(p33;?),der(6)t(1;6)(p33;q23)t(6;9)(p11;p13),-9[13]/46,XX[1] FISH: 80% deletion 9q21, <1% trisomy 10
5	46,XX,+1,der(5)del(5)(q22q31)ins(5)(q31p15p1?1),i(8)(q10),-17,der(18)t(17;18)(q11.1;p11.1)[4]/47,sl,+i(8)(q10)[10]/48,sdl1,+i(8)(q10)[3]/48,sdl1,+mar1[1]/49,sdl1,+mar1,+mar2[1] FISH: 99% deletion EGR1(5q31),22% trisomy ETO(8q22),52% pentasomy ETO,12% septasomy ETO	46,XX,+1,der(5)del(5)(q22q31)ins(5)(q31p15p1?1),i(8)(q10),-17,der(18)t(17;18)(q11.1;p11.1)[2]/47,sl,+i(8)(q10)[9]/48,sdl1,+i(8)(q10)[3] FISH: 90% deletion EGR1,8% trisomy ETO,45% pentasomy ETO,25% septasomy ETO
6	46,XY,inv(3)(q21q26)[6]/45,idem,-7[19] FISH: 90% traslocation EVI1 (3q26), 90% monosomy 7	46,XY,inv(3)(q21q26)[4]/45,idem,-7[13]/46,XY[3] FISH: 77% traslocation EVI1, 84% monosomy 7
7	46,XY,inv(3)(q21q26),t(4;12)(q2?5;p13),der(11)del(11)(p11)del(11)(q13),der(13)t(11;13)(p11;p11)[4]/46,XY[1], FISH: 74% deletion MLL(11q23), 80% deletion TEL(ETV6,12p13), 70% translocation EVI1(3q26)	46,XY,inv(3)(q21q26),t(4;12)(q2?5;p13),der(11)del(11)(p11)del(11)(q13),der(13)t(11;13)(p11;p11)[5]/46,XY[1] FISH: 74% deletion MLL(11q23)
8	47,XY,+8[3]/46,XY[16], FISH: 45% trisomy 8	47,XY,+8[1]/46,XY[14], FISH: 3% trisomy 8
9	46,XX,del(5)(q12q33)[2]/45,idem,der(7)(17?pter-17?p13-7?q11.2::17?q21-17?q25::20q11.2-20qter),-17,der(20)(20pter-20q11.2::17q-?17qter)[17] FISH: 85% deletion EGR1 (5q31), 85% deletion D7S486 (7q31)	G-banding unsuccessful FISH: 66% deletion EGR1

Table S2. G-banding and FISH results of 17 patients with hematologic but without cytogenetic complete remission

P. No.	At AML diagnosis	After 7+3 and 4+3 (HiDAC+Mx)
10	46,XY,der(7)del(7)(p12)del(7)(q11.2)[1]/46,XY[1], FISH: 75% deletion D7S486(7q31), 14% monosomy 7	G-banding unsuccessful FISH: 9% deletion D7S486, 4% monosomy 7
11	46,XX,der(2)ins(2;16)(q31;q22q?)t(2;12)(q33;q21-23),del(7)(p11), der(12)del(12)(p12)t(?;12)(q33;q21-23),del(16)(q11)[3]/45,idem,-del(7) (p11)[11]/ 46,XX[1], FISH: 93% deletion TEL(ETV6), 80% monosomy 7	46,XX,der(2)ins(2;16)(q31;q22q?)t(2;12)(q33;q21-23),del(7)(p11),der(12) del(12)(12)t(?;12)(q33;q21-23),del(16)(q11)[4]/46,XX[11], FISH: 20% deletion TEL(ETV6), <1% monosomy 7
12	42-45,XY,der(1)t(1;?)p13;?),?i(1)(q10),-4,der(5)t(5;?)q14-21;?),del(7) (p11),-10,der(11)(?),-12,?der(12)(?),der(15)t(15;?)p11;?,-16,+der(18;21) (q10;q10),-19,+1-4mar[cp22] FISH: 78% deletion EGR1(5q31), 82% deletion TP53(17p13)	44,XY,del(1)(p13),-4,der(5)t(1;5)(p13;q13),del(7)(p10),-10,-11,-12,-15,- 16,-19,+5mar[1]/43,idem,-18[1]/46,XY[23] FISH: 12% deletion EGR1(5q31)
13	44-49,XY,-4,add(5)(q13),del(7)(q11.2),der(11)(q?),der(?14;15)(q10;q10),- 15,0-5mar[cp4]/43-49,idem,der(12)add(12)(p1?)del(12)(q?),+der(?) t(12;?)(q?;?)cp13]/46,XY[2] FISH: 91% deletion EGR1(5q31),92% deletion 7q31(D7S486),96% am- plification MLL(11q23),70% deletion TEL(ETV6, 12p13)	46,XY[15] FISH: 8% amplification MLL,7% deletion TEL
14	46,XX,der(5)t(5;11)(q32-34;q14-22),del(11)(q13),der(12)ins(12;11) (q24;q13q14-22)[2]/48,idem,+8,+13[13] FISH: 57% trisomy 8; deletion EGR1 (5q31) and MLL negative	48,XX,der(5)t(5;11)(q32-34;q14-22),+8,del(11)(q13),der(12)ins(12;11) (q24;q13q14-22),+13[7]/46,XX[8] FISH: 80% trisomy 8
15	47,XY,+8[8]/48,XY,+8,+21[12], FISH: 50% trisomy ETO(8q22)+trisomy AML1(21q22), 40% trisomy ETO(8q22)	47,XY,+8[9]/48,XY,+8,+21[6], FISH: 50% trisomy ETO(8q22)+trisomy AML1(21q22), 40% trisomy ETO(8q22)
16	47,XX,+8[13]/46,XX[3], FISH: 56% trisomy 8	46,XX[15], FISH: 10% trisomy 8
17	47,X,der(Y)t(Y;13)(p11.3;q22),-3,der(5)ins(5;3)(p1?4;?)del(5)(q12), +der(5)ins(5;3)(p1?4;?)del(5)(q12),+8,del(13)(q13),del(20)(q11.1) [19]/46,XY[1] FISH: 86% deletion EGR1(5q31), 87% trisomy 8, 88% deletion D20S108(20q12)	46,XY,der(3)t(3;5)(p21;p1?4),-5,+8[2]/48,XY,-3,der(5)ins(5;3)(p1?4;?) del(5)(q12), +der(5)ins(5;3)(p1?4;?)del(5)(q12),+8,+?del(20)(q11.1) [5]/46,XY[11] FISH: 63% deletion EGR1(5q31), 54% trisomy 8
18	46,XX,t(2;3)(p13;q26)[15], FISH: 95% translocation EVI1	46,XX,t(2;3)(p13;q26)[14]/46,XX[1], FISH: 90% translocation EVI1
19	46,XX,del(7)(q22q36)[4]/46,XX[16] FISH: 31% deletion D7S486 (7q31), 18% deletion 9q21	46,XX[20] FISH: 2% deletion D7S486
20	49-61,XY,+X,+1,+1,+3,+4,+5,del(5)(?q15q33),+6,+7,+7,del(7) (?q22q36),+8,+9,+11,der(11)del(11)(p11.2)del(11)(q12),der(11)t(11;?) (q21;?),+12,del(13)(?q12q14),+del(13)(?q12q14),der(13)t(13;?)(?;?),+15,+ 17,+18,+19,+20,+der(?t(11;?)(q21;?),+der(?t(13;?)(?;?),+1-2mar[cp20] FISH: 80% deletion EGR1(5q31), 79% deletion D7S486(7q31), 62% trisomy 17	51-56,XY,+5,del(5)(?q15q33) or t(5;?)(?;?),+6,+7,del(7) (?q22q36),+11,der(11)del(11)(p11.2)del(11)(q12),der(11)t(11;?) (q21;?),del(13)(?q12q14),+del(13)(?q12q14),der(13)t(13;?) (?;?),+15,der(17)t(17;?)(q?25;?),+der(17)t(17;?)(q?25;?),+19,+20,+1- 5mar[cp9]/46,XY[6] FISH: 18% deletion EGR1(5q31), 20% trisomy 17
21	41,XX,del(5)(q14-21q32-34),der(11)t(11;12)(p15;q13),-12,der(13;22) (q10;q10),der(14;15)(q10;q10),-17,der(?21)(21qter→21q21::22q11.2→22 q12::21p11.2→21q21::21q11.2→21qter),-22[11]/46,XX[9] FISH: 56% deletion EGR1(5q31), 61% monosomy 17	46,XX,del(5)(q14-21q32-34)[2]/46,XX[13] FISH: 6% deletion EGR1; monosomy 17 negative
22	45,XX,t(3;3)(q21;q26),-7[14]/46,XX[1], FISH: 91% monosomy 7	45,XX,t(3;3)(q21;q26),-7[1]/46,XX[9], FISH: 1,5% monosomy 7
23	47,XX,+8[9]/46,XX[8], FISH: 73% trisomy 8	46,XX[15], FISH: 1,5% trisomy 8
24	46,XX,t(9;11)(p22;p15)[20]	46,XX,t(9;11)(p22;p15)[1]/46,XX[19]
25	46,XY,del(20)(q11.2)[20], FISH: 97% deletion D20S108(20q12)	46,XY,del(20)(q11.2)[11]/46,XY[3], FISH: 80% deletion D20S108