Long-term survival can be achieved in a significant fraction of older patients with core-binding factor acute myeloid leukemia treated with intensive chemotherapy

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SUPPLEMENTARY METHODS

Chemotherapy

Induction regimens used for the patients in this study were categorized as follows:

1. **"3+7"** regimens (n= 100 patients), consisting of Daunorubicin 45-60 mg/m^2 days 1-3 + intravenous Cytarabine continuous infusion 100-200 mg/m^2 days 1-7 (i.e. D3A7), or other similar 2-drug regimens consisting of minimal two daily doses of anthracycline (e.g. Idarubicin, 12 mg/m^2 days 1-2 or 1-3, Mitoxantrone, 7-10 mg/m^2 days 1-2 or 1-3) plus 7-days intravenous continuous-infusion 100-200 mg/m^2 Cytarabine; this group was considered together with "lower intensity regimens", based on the same drugs and scheme as "3+7", but administered for shorter periods (eg D1A5, D1A7, D2A5, overall n= 8)

2. **"3+7+ other drugs"** (n= 101 patients), incorporating experimental drugs to the D3A7 skeleton in specific trials (e.g. Midostaurin – 1 patient, G3139 – 9 patients, Bortezomib – 4 patients, Dasatinib 17 patients, Avastine 1 patient, Gemtuzumab Ozogamicin 4 patients and others), considered together with "IDAC/HiDAC-based" 2-drug regimens including intermediate-to-high dose Cytarabine (IDAC: 1-1.5 g/m^2 bid days 1-5, or HiDAC 3 g/m^2 bid days 1-5) plus an anthracycline (e.g., HAM, HiDAC + Idarubicin); Etoposide 50 mg/m^2 days 1-5 or other drugs (e.g. Thioguanine 200 mg/m^2 days 1-5 or 1-7), with the exception of purine nucleoside analogues, to anthracyclines and Cytarabine (eg, ICE, MICE, DAV/IAV/DAE/DCE, MEC, BARTS, ETI, AAT); FLA-Ida regimens and similar (e.g., FLAG-Ida, FLAI5, FLAIRG, FLAN) consisting of Fludarabine 25-30mg/mq days 1-5 together with IDAC/HiDAC and an anthracycline;

3. **"NO anthracycline - based"** regimens (n= 28 patients), consisting of 2-drug Fludarabine/Clofarabine plus Cytarabine regimens, with no anthracycline; or on other low-dose chemotherapy without anthracyclines (AraC/VP16, Clofarabine alone)

Supplementary Table 1. Characteristics of patients consolidated by autologous Hematopoietic Stem Cell Transplantation as part of frontline treatment.

CBF type	Age (yrs)	Time of therapy	Induction therapy	Response	Consolidation therapy	MRD post-consolidation	Reason for auto-HSCT	Status at follow-up
t(8;21)	70.1	2004	FLAN	CR1 (FISH pos)	MTN+AraC + IDAC	pos	MRD pos	Deceased in CR1 (heart failure)
inv(16)	62	2007	D3A7	CR1	Ida+AraC (IC) + IDAC (A8)	pos	MRD pos	Deceased (relapse)
inv(16)	60.7	2004	FLA	CR1	FLA	pos	MRD pos	Alive CR2 (after rescue and allo-HSCT)
inv(16)	67.6	2006	My-AIG	CR1	My-AIG + Ida-HiDAC	pos	MRD pos	Alive CR1
inv(16)	63.3	2009	IAV	CR1	IAV	neg	Clinical decision	Alive CR1
t(8;21)	66	2004	FLAI-5	CR1	HiDAC x 2	ND	Clinical study	Alive CR1
t(8;21)	65.6	2009	D3A7	CR1	HiDAC x 3	Neg	Clinical decision	Alive CR1

CR= complete remission; **ND**= not done; **allo-HSCT**: allogeneic hematopoietic stem cell transplant;

Supplementary Table 2. Characteristics of patients consolidated by allogeneic Hemtopoietic Stem Cell Transplantation as part of frontline treatment.

CBF type	Age (yrs)	Time of therapy	Induction therapy	Response	Consolidation therapy	MRD post-consol.	Reason for allo-HSCT	Status at follow-up
inv(16)	62.7	2017	MICE	CR1 (2 cycles)	MICE	ND	Late CR	Alive CR1
inv(16)	66	2013	I3A7	CR1	Ida+HiDAC + HiDAC	pos	MRD pos	Alive CR1
inv(16)	61.4	2009	I1A7	CR1	I1A7 + HiDAC	pos	MRD pos	Alive CR1
inv(16)	62.6	2009	I3A7	CR1	IC + A8 + A8	pos	MRD pos	Alive CR1
inv(16)	69.5	2016	MICE	CR1	HiDAC x 2	pos	MRD pos	Deceased (CR1)
inv(16), secondary AML	63.6	2016	MICE	CR1	HiDAC x 3	pos	MRD pos + sAML	Alive CR1
t(8;21), therapy-rel. AML	63.9	2011	D3A7 + Dasatinib	CR1	HiDAC	ND	tAML	Deceased (CR)
t(8;21)	69	2013	D3A7	CR1	HiDAC	ND	Clinical study	Alive CR1
t(8;21)	60.5	2009	MEC	CR1	HiDAC x 2	ND	Clinical Decision	Deceased (relapse)
t(8;21), secondary AML	61	2006	D3A7	NR	Direct to allo-HSCT	Active disease	NR after induction	Deceased (relapse)
t(8;21)	60	2009	D3A7	CR1	IDAC x 3	ND	Clinical Decision	Deceased (relapse)
t(8;21)	68.7	2014	D3A7	CR1	IDAC	ND	Clinical study	Alive CR1
inv(16)	62.3	2008	D3A7	CR1	HiDAC	ND	Clinical Study	Deceased (CR)
inv(16)	61	2013	D3A7	NR	rescue MEC + HiDAC	ND	NR after induction	Alive CR1
t(8;21), secondary AML	70	2012	Clofarabine - AraC	PD	direct to allo-HSCT (FLAMSA)	Active disease	PD after induction	Deceased (relapse)

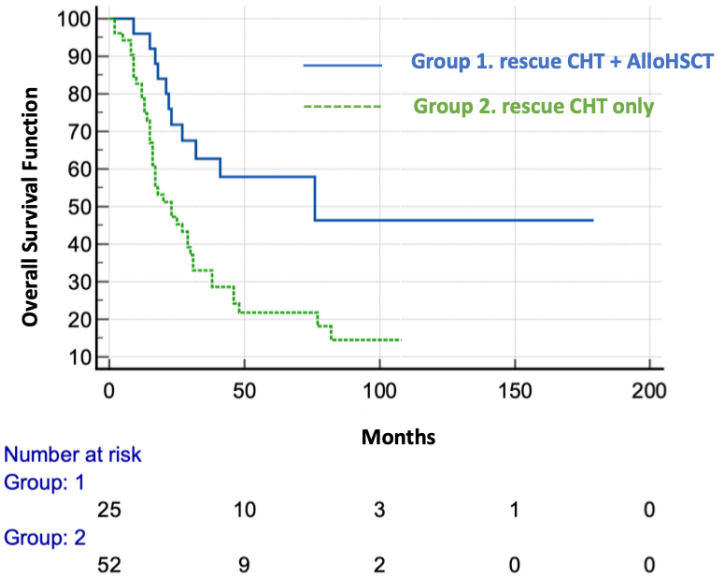
CR= complete remission; **NR**= not response; **ND**= not done; **allo-HSCT**: allogeneic hematopoietic stem cell transplant;

Table 3. Univariate analysis for Event Free Survival – cytogenetic and molecular data*

	HR	C.I. 95%	P
Complex karyotype	1.16	0.47-2.90	.3
Mutated FLT3	0.26	0.03-1.44	.2
Mutated NPM1	0.93	0.23-3.82	.8
Mutated KIT	6.85	3.42-11.71	.04

- ***Only for patients (115) with available data**

Supplementary Figure 1. Overall Survival of relapsing patients according to rescue treatment



CHT= chemotherapy; **alloHSCT**: allogeneic hematopoietic stem cell transplant