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Research Article

De Novo Acute Myeloid Leukemia Involving only Granulocyte-Macrophage Line in Octogenarians with Leucocytes over 15 × 10^9/L Exhibit a Favorable Response to Standard-Dose Induction Chemotherapy

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Abstract

Objectives: Octogenarians with Acute Myeloid Leukemia (AML) exhibit poor median survival of 1-3 months after Standard-Dose Induction Chemotherapy (SICT). *De novo* AML without Erythroblastic And/Or Megakaryocytic Dysplasia (EMD) involving only Granulocyte-Macrophage Line (GM-AML) is associated with a 74-86% Complete Remission (CR) rate after SICT and improved survival in adult patients aged below 65 years. Our aim was to study if octogenarians with GM-AML will achieve CR and improved survival after SICT.

Patients and Methods: Consecutive 12 octogenarians with *de novo* non-M3 AML with 48-94% (median 80%) bone marrow blasts, classified as AML FAB types: 2×M2, 7×M4, and 3×M5 were offered 3+7 type of SICT. Criteria for EMD were dyserythropoiesis 30% and/or dysmegakaryopoiesis 50% or higher.

Results: Six cases, all with leucocytes over 15×10^9/L, opted for SICT. Three cases with GM-AML achieved CR and survived 16.5-28 months on maintenance therapy while 3 cases with EMD-AML did not reach CR and had survival 0.4-2.7 months. Genetic findings in GM-AML cases showed 46, XY, del (12) (p13) with deleted *ETV6* gene, 46, XX with *NPM1* mutation and negative for *FLT3*-ITD and in the third case normal karyotype, which was found in two resistant EMD-AML cases. Survival 0.2-4.0 months was observed in the 6 remaining patients (two with GM-AML, 4 with EMD-AML) on palliative or supportive treatment.

Conclusion: Octogenarians with GM-AML even with poor performance status (2×PS 3) may achieve CR and survival benefit after SICT, which is further supported by two other elderly GM-AML cases with over 5 years survival.

Keywords: Acute myeloid leukemia; Octogenarians; Classification; Hematopoietic Myelodysplasia; Molecular genetics; Chemotherapy

Abbreviations

CI: Comorbidity Index; DysE: Erythroblastic Dysplasia; DysG: Granulocytic Dysplasia; DysMg: Megakaryocytic Dysplasia; EMD: Erythroblastic and/or Megakaryocytic Dysplasia; EMD: AML-AML With Erythroblastic and/or Megakaryocytic Dysplasia; GM-AML: AML Involving Only Cells of Granulocytic - Macrophage Line; SICT-Standard-Dose Induction Chemotherapy

Introduction

Survival of octogenarian patients with Acute Myeloid Leukemia (AML) is dismal [1-6]. The first reported retrospective single-institution study on patients with AML aged 80 years and above concluded that currently available chemotherapy is generally not indicated because the treatment, based mostly on high or standard doses of cytarabine (Ara-C) plus 3 doses of anthracyclines, led to median survival of 3-4 weeks in 29 treated patients while 4 untreated patients had median survival 10 weeks [1]. Nine patients (31%) reached Complete Remission (CR) of 3 months median duration and only two survived over one year [1]. In 2006 the same institution reported 82 patients aged 80 years and above treated with similar chemotherapy which induced 37% CR and 54% mortality within 8 weeks and a median survival of 6 weeks [2]. Three studies with highly selected AML octogenarian patients treated with intensive chemotherapy showed 30-37% CR, 33-35% early death rate but significant overall survival benefit in patients who reached CR [3-6]. Various AML guidelines [7-9] did not recommend Standard Dose Induction Chemotherapy (SICT) in patients with AML over 80 years because of high early treatment-related mortality caused partially by more frequent poor Performance Status (PS), significant comorbidities and the well-known therapeutic resistance of AML to SICT in this age group [10-12]. The resistance of these AML to SICT is related to cytogenetics associated with adverse prognosis [2,7-12], the multidrug resistance phenotype [12,7-9], multilineage dysplasia [13-18], and secondary type of AML after previous Myelodysplastic (MDS) or Myeloproliferative (MPS) syndromes, or to previous chemotherapy/radiotherapy-all found with higher frequency with increasing age [2,7,9-12,19-20]. Furthermore, cytogenetic AML

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Table 1: Clinical and laboratory data of 6 patients treated with standard dose induction chemotherapy.

Case	Units	1	2	3	4	5	6
Age/Sex	years/	85/f	80/m	80/f	90/m	83/m	80/f
PS WHO		3	3	1	3	2	3
Charlson CI		1	1	0	3	3	2
HCT CI		1	2	0	3	3	3
Comorbidity		IHD: LVEF 25%	IHD, Bronchiect, ATB	Asthma	IHD, CKD4	IHD, 2xTIA, Dyspnea	CKD4-5, ATB
AML FAB		M4	M4	M4	M4	M5	M2
WBC	10e9/L	33.6	72.3	17.5	97.8	49.7	66.2
Blasts	%	79	80	67	57	65	65
Hb	g/L	74	86	95	74	120	91
Platelets	10e9/L	75	35	148	75	48	27
Bone marrow							
Blasts	%	93	94	91	48	69	68
Erythroblasts	%	3	0.2	2	13.2	4	5.4
DysE	%	19	NE	26	11	14	32
DysMg		1/4	8/20	5/15	13/20	5/10	8/8
DysG	%	8	74	48	86	19	78
Line involved		GM	GM	GM	GM, Mg	GM, Mg	GM, E, Mg
Cell markers							
CD positive		13,14,65,66,68,DR	13,14,33,38	11b,13,14,33,117,DR	ND	5,13,14,33,38	5,13,15,33,34,117,DR,MPO
CD negative		5,7,11b,15,34,56, 3,4,7,8,10,19	5,10,19,34,DR	1,2,10,19,34		1,2,10,19,34,DR	7,11b,14,56, 1,2,3,4,8,10,19,20
Genetics		46,XX[6]	46,XY,del(12)(p13)[12]/46, XY[1] *ETV6* deleted **Neg:** *CEBPA* mutat, *CBFB-MYH11*	46,XX[20] *NPM1* 4bp mutation **Neg:** *FLT3*-ITD, *CBFB-MYH11*, *RUNX1-RUNX1T1*	46,XY[20]	46,XY[20] **Neg:** *CEBPA* mutat, *RUNX1-RUNX1T1, CBFB-MYH11*	44~45,XX,der(1)t(1;3) (q32;?), -3,der(5)t(5;18) (p13;p11), del(5)(q12q33), -7,der(18) t(18;3;1)(p11;?;q32)[cp22]
Therapy		TAD	MA	DA	TAD	MA + DZR	MA
		Maintenance	Maintenance	DA 5+2		Hydroxycarbamide	
CR duration	months	17.3	19.6	10.1	0	0	0
Survival	months	18.6	28	16.5	1	2.7	0.4

CI: Comorbidity Index; HCT CI: Hematopoietic Cell Transplantation CI; Blasts-myeloblasts + promyelocytes + promonocytes; DysE: Dysplastic Erythroblasts; DysMg: number of Dysplastic/total number of examined Megakaryocytes; DysG: Dysplastic Granulocytes; NE: Not Evaluable; ND: Not Done; Neg: Negative

entities associated with favorable prognosis as t(15;17) (q22;q21), t(8;21) (q22;q22), inv(16) (p13.1q22) /t(16;16) (p13.1;q22) are found with very low frequencies in patients over 70 years old [9-12,20]. Therefore one important task in AML octogenarian patients is to identify those who are likely to achieve CR after SICT and benefit from it [2-9].

Our previous study showed that adult patients (18-64 years) with *de novo* non-M3 AML M0-M5 without Erythroblastic And/Or Megakaryocytic Dysplasia (EMD) treated with Standard Dose 3+7 Type of Chemotherapy (SICT) reached CR in 78.6% in comparison to 28.6% CR in cases with AML plus EMD (EMD-AML, AML involving multiple myeloid lines) [17]. The patients without EMD exhibited a significant survival benefit after consolidations with cycles of high-doses of Ara-C and daunorubicin (DNR) [17]. Similar results were found in patients with AML and normal karyotype [21]. Patients with *de novo* AML without EMD exhibited either normal karyotype or karyotypes associated with intermediate prognosis and represented a special biological AML category involving only one (granulocyte-macrophage) myeloid line with favorable prognosis (GM-AML) [17,21]. Our findings of the high CR rate after SICT in patients with *de novo* GM-AML were supported by results of other studies of adult patients under 60/65 years of age with *de novo* AML [13-16] with CR rates 74-86 % or in patients with AML not otherwise specified without myelodysplasia-related changes [22].

The aim of our study was to investigate if octogenarian patients with *de novo* GM-AML may achieve CR and a survival benefit after SICT similar to adults aged less than 65 years. This report describes our experience with 12 consecutive octogenarian patients with *de novo* AML and the observation that all three of them with GM-AML treated with SICT reached CR and had an improved survival in spite of a poor performance status and significant comorbidities. Our two other elderly GM-AML cases and a review of literature support our findings of the good sensitivity of leukemic cells of GM-AML to SICT and its use in octogenarian patients with *de novo* GM-AML.

Patients and Methods

Ethical aspects

Informed consent for clinical and laboratory examinations and the type of therapy chosen by each patient was obtained according to the principles of the Declaration of Helsinki. The study was approved by the Institutional Scientific Review Board of Hospital Jihlava.

Study group

The 12 consecutive Caucasian patients with *de novo* AML aged 80 years and above were diagnosed between October 1992 and March 2011. Patients with secondary AML were not eligible for this study because of the known poor response to SICT.

The French-American-British (FAB) classification [23] with standard cytochemical and immunophenotyping methods was used for establishing the diagnosis of AML [23,17]. Cytogenetic and I-FISH analyses were made from 24-hour unstimulated cultures of patients' bone marrow cells at diagnosis [17,24]. Molecular-genetic analyses were performed on cDNA obtained by reverse transcription of RNA (or for *CEBPA* from genomic DNA by sequencing the multiplied entire coding region of *CEBPA*) from bone marrow mononuclear cells at diagnosis as reported [24]. Morphological dysplastic features of erythroblasts, megakaryocytes, and granulocytes, in diagnostic Bone Marrow (BM) smears from patients were evaluated according to the FAB criteria [25] independently by two experienced hematologists (PL,JG) [17]. EMD was diagnosed when more than 30% of 50-200 evaluable erythroblasts had to show dyserythropoietic features (DysE, (Table 1,2)) and/or when 50% or more of at least 5 megakaryocytes (DysMg) were dysplastic. Dysgranulopoiesis (DysG) was diagnosed when 50% or more of 50-200 neutrophilic segments, stabs, and metamyelocytes were dysplastic. If less than the required number of cells evaluable for dysplasia was found in any line, the dysplasia in the line was not evaluable (NE - (Table 1,2)) [17,21]. Performance status (PS WHO/ECOG), comorbidities (IHD - ischemic heart disease; CKD - chronic kidney disease, etc.), Comorbidity Index (CI) according to Charlson et al. [26] and Hematopoietic Cell Transplantation (HCT) CI [27] were evaluated at diagnosis (Table 1,2).

Induction chemotherapy [17]

a) 3+7: Daunorubicin (DNR) 45 mg/m^2 i.v. or Mitozantrone (MTZ) 10 mg/m^2 i.v. per day on days 1, 3, 5 and Ara-C 100 mg/m^2 per 3-h infusion every 12 h for 7 days (DA or MA cycle),

b) TAD: Ara-C 100 mg/m^2 per 3-h infusion and Thioguanine (TG) 100 mg/m^2 p.o., both every 12 h for 7 days, and DNR 45 mg/m^2 i.v. on days 5, 6, and 7, in cases with IHD.

Maintenance therapy consisted of repeated 4 cycles. The first with DNR 45 mg/m^2 or MTZ 10 mg/m^2 i.v. on day 1 and Ara-C 100 mg/m^2 per 3-h inf. every 12 h for 5 days was given to patients in CR. The 2nd, 3rd, 4th maintenance cycles were identically composed of Ara-C 60 mg/m^2 s.c. and TG 70 mg/m^2 p.o., both every 12 h for 5 days. Maintenance cycles were administered every 4-12 weeks according to the patient's clinical status and tolerance until relapse. Cardioprotective agent dexrazoxane was administered in maintenance cycles in 30 minute infusion of 250 ml Ringer's lactate solution before DNR or MTZ given in 30-minute infusion of 200ml saline. The dose ratio of dexrazoxane to DNR was 10:1 and to MTZ 50:1 [28].

Standard criteria were used to define CR [29]. CR duration was calculated from the date of achieving CR to the date of relapse or death. Overall Survival (OS) was calculated from the date of diagnosis until the date of death.

Results

The 12 consecutive Caucasian patients (5 men, 7 women) diagnosed with *de novo* AML were 80-90 (median 83) years old. Their clinical and laboratory data, type of therapy administered, outcome of patients with CR duration and OS are summarized in (Tables 1,2). All patients had hypercellular BM films with 48-94% (median 80%) leukemic blasts, classified as AML FAB types: 2×M2, 7×M4, and 3×M5. Eleven patients had hypertension well controlled by medication. Further comorbidities are described in individual cases and (Tables 1,2) with usual abbreviations and summarized as Charlson-CI and HCT-CI. Five patients were febrile and on antibiotics at diagnosis (ATB, (Table 1,2)).

Six patients opted for SICT (Table 1), although four had poor performance status PS 3. Four also had significant comorbidities (HCT-CI 2-3). All 6 cases had higher WBC 17.5-97.8 (median 58.0)×109/L. Three patients (80-85 years old), all with GM-AML, reached CR after SICT on day 33-36 from the start of treatment and two continued on maintenance therapy. Case 1 with IHD and Left Ventricular Ejection Fraction (LVEF) 25% at diagnosis developed cardiac arrhythmia and congestive heart failure after 14 cycles of maintenance chemotherapy but refused pacemaker insertion and died in CR of heart failure and bronchopneumonia shortly after. Case 2 relapsed after the 11th cycle of maintenance therapy (CR duration 19.6 months) and was later treated with hydroxycarbamide and died from progression of AML with CNS hemorrhage and infection 28 months after diagnosis. Case 3 experienced severe mycotic bronchopneumonia during induction treatment and thus was treated later with consolidation DA 2+5 only. She was 10.1 months in CR. At relapse she was treated with two cycles of low-dose Ara-C according to her preference and died of progression of AML. Her OS was 16.5 months.

Three patients with EMD-AML (3×DysMg, 1×DysE) did not achieve CR after SICT. Case 4 died from zygomycotic pneumonia after a month in pancytopenia with persisting leukemic BM infiltration. Case 5 with IHD experienced acute myocardial infarction and Geotrichum capitatum fungaemia during pancytopenia, he recovered from these complications with appropriate treatments but leukemia persisted and his OS was 2.7 months. Case 6 was septic with acute renal failure requiring 7 episodes of haemodialysis and died in septic shock from generalized Candida glabrata infection in pancytopenia on day 10 of therapy. Cases 2-5 had severe mycotic generalized infection or pneumonia in spite of itraconazole prophylaxis with 200-400 mg p.o. daily in pancytopenia.

Six patients were not treated with SICT (Table 2) and died of complications of AML progression. Case 7 with GM-AML and PS 1 preferred 6-Mercaptopurine (6-MP) ambulatory treatment and survived 4 months. Case 8 with GM-AML died of sepsis on day 6 after admission. Cases 9-12 with EMD-AML opted for palliative or Best Supportive Care (BSC) and survived 1.0-2.5 months.

Five patients had GM-AML and did not exhibit any karyotype

Table 2: Clinical and laboratory data of 6 patients treated with palliative or best supportive therapy.

Case	Units	7	8	9	10	11	12
Age/Sex	Years/	82/m	82/f	87/f	83/f	89/f	86/m
PS WHO		1	3	3	2	3	3
Charlson CI		2	2	1	0	0	1
HCT CI		2	3	2	0	1	2
Comorbidity		DM, TIA	CKD4, ATB	Pneumonia mycob. fortuit, ATB	Chr. Pancreat.,CKD3	IHD-AF,CKD3	Tb-surgery,ATB
AML FAB		M4	M5	M4	M2	M4	M5
WBC	10e9/L	31.4	51.4	3	19.9	2.4	9.2
Blasts	%	54	84	50	61	26	46
Hb	g/L	109	74	75	69	72	101
Platelets	10e9/L	153	58	166	12	127	77
Bone marr.							
Blasts	%	59	89	80	89	67	76
Erythroblasts	%	7.2	4.6	4	2.6	10	17
DysE	%	15	20	64	34	72	47
DysMg		2/15	3/12	15/21	NE	9/16	10/12
DysG	%	68	NE	94	75	89	74
Line involved		GM	GM	GM, E, Mg	GM, E	GM, E, Mg	GM, E, Mg
Cell markers							c22,c79a
CD positive		ND	7,11b,33,34,117,DR	7,13,33,34,117,DR,MPO	13,33,MPO	13,33,34,117,DR,MPO	13,33,117,MPO
CD negative			1,2,3,10,19,14	c3,c79a; 2,3,4,10,14,15,19	14,15,34,117,DR,TdT, c3,c79a;2,3,4,7,10,19	c3,c79a,2,3,4,10,19,TdT	c3,2,10,19,34, 14,61,TdT
Genetics		ND	46, XX[20], *FLT3*-ITD, **Neg**: *CBFB-MYH11, RUNX1-RUNX1T1, MLL* gene transloc.	43~44, XX, der(1) t(1;?) (p35;?), del(3) (q?21q?25),del(5)(q22q33), +6,-4,-8,der(11)t(11;?)(q23;?), -14,-15,+21[cp20], **Neg:** *DEK-NUP214*, *RUNX1-RUNX1T1, CBFB-MYH11, PML-RARA*	46,XX[8], **Neg:** *PML-RARA*	46,XX,r(7)(?p?q)[14]/46,XX[14]. nucish, (D7S796,D7S658)x2, (D7S2543,D7S486,D7S2886) x1[98/105]	46,XY[20]
Therapy		6-MP	BSC	BSC	BSC	BSC	Hydroxycarb.
Survival	months	4	0.2	1	1.8	2.5	1.3

CI: Comorbidity Index; HCT CI: Hematopoietic Cell Transplantation CI; Blasts-myeloblasts + promyelocytes + promonocytes; DysE: Dysplastic Erythroblasts; DysMg: number of Dysplastic/total number of examined Megakaryocytes; DysG: Dysplastic Granulocytes; NE: Not Evaluable; ND: Not Done; Neg: Negative

associated with adverse prognosis. Case 2 had 46, XY, del(12) (p13) and three cases normal karyotype. Blasts of Case 3 exhibited *NPM1* mutation and *FLT3*-ITD negativity and in Case 8 were *FLT3*-ITD positive. *CEBPA* mutations were not found in two tested cases. Four patients had bone marrow blasts 89-94 % and all had rapidly rising WBC > 15.0×10^9/L.

Seven patients had EMD-AML and four had normal karyotype and three karyotype associated with adverse prognosis including Case 6 treated with SICT. None of the three cases treated with SICT reached CR and their survival was 0.4-2.7 months similar to survival of 1.0-2.5 months in 4 patients with EMD treated with palliative or Best Supportive Care (BSC). Interestingly we found in EMD-AML that leukemic blasts of two tested cases (No. 5 and 6) expressed surface CD5 antigen and blasts of Case 12 expressed cytoplasmic CD22 and CD79a.

Discussion

Our study showed good response to SICT in three octogenarian cases with *de novo* GM-AML with improved survival in spite of poor PS3 and significant comorbidities in two that usually prevent SICT administration. Sensitivity of GM-AML to SICT seems to be the most important factor for reaching CR in AML similar to results found in adult GM-AML cases aged below 60/65 years in previous studies [17,21], including 156 cases without any dysplasia [15] or in cases without Multi-Lineage Dysplasia (MLD), containing mostly GM-AML cases in comparison to usual poor sensitivity to SICT in AML with MLD (EMD-AML) [13-18,22].

Two further cases of patients over 65 years old enlarge our knowledge of a good sensitivity of GM-AML to SICT. A 67-year old man with *de novo* Near-Tetraploid (NT) GM-AML M0 with WBC 52.9×10^9/L reached CR and survived 51 months in CR after three 3+7 cycles [24] while most European cases with *de novo* NT-AML were EMD-AML with 33 % CR rate and maximal survival 31.5 months after SICT [30]. In 2017-8 we treated an 86-year old man diagnosed with GM-AML, normal karyotype with *NPM1* mutation and *FLT3*-ITD, WBC 33.7×10^9/L in 2011, who reached CR after two cycles of

Low-Dose Ara-C 20 mg s.c. twice daily for 10 days (LDAC) in 4 week intervals. His CR has been maintained on repeated LDAC cycles for 6 years [Dignum H, Lemež P, et al., manuscript in preparation].

These two cases of patients over 65 years with GM-AML and all of our 6 octogenarian cases treated with SICT had WBC over 15×10^9/L, the threshold over which treatment with Hypomethylating Agents (HMA) azacytidine or decitabine has not been recommended [31,32]. A median survival of selected AML cases over 65 years old (PS 0-2, WBC < 15×10^9/L, expected survival 12 weeks) treated with HMA varied between 7.7-10.4 months [31,32] but our three GM-AML octogenarian cases with worse PS exhibited much longer survival 16.5-28.0 months after SICT. Treatment with SICT in GM-AML cases represents a patient-oriented AML-biology targeted therapy.

A retrospective subanalysis of 8 large cooperative AML trials dealing with intensive treatment based mostly on standard or high doses of Ara-C with anthracyclines or mitozantrone in 4584 patients aged over 60/65 years recruited 138 (3%, range 0.5-5.0% per study) octogenarian patients with AML between 1984 and 2010 [4]. Only patients deemed fit for chemotherapy and with good LVEF were selected for this study. Swedish AML population based studies showed that octogenarian AML patients constitute 30-40% of patients aged over 60/65 years [5,6] and thus by our estimate only 5-10% of all octogenarian patients with AML were deemed fit for intensive induction chemotherapy by their hematologists in these 8 studies. Forty-eight octogenarians (34.8%) died within 30 days and 41 (29.7%) reached CR and showed improved relapse-free survival 37% (15 patients) at 1 year (by our estimate approx. 0.5-1.0% of all octogenarians diagnosed with AML) [4]. Only 8 octogenarian patients (one case per trial), all with *de novo* AML, survived more than 3 years. Six of them survived 3 years in continuous CR including three patients of nine who were diagnosed with *NPM1* mutation but dysplastic features had not been reported [4]. The authors concluded that intensive induction treatment is effective in selected fit octogenarian AML patients with normal karyotype and *NPM1* mutation [4] which was found in Case 3.

We conclude that leukemic blasts of *de novo* GM-AML in octogenarians may be sensitive to SICT and this therapy may lead to survival benefit. Patients with *de novo* GM-AML may constitute by our estimate about 20% of all AML among octogenarians, because nearly 50% of AML may represent secondary AML and among *de novo* AML patients with EMD-AML seem more frequent than GM-AML patients [19,5-10]. The quantitative evaluation of dysplastic features according to the FAB criteria [25] requires at least two hematologists experienced in BM cell morphology and two or more well prepared BM smears immediately after BM aspiration. The advantage is that GM-AML or EMD-AML categorization results can be usually obtained within 2 hours. Correlations of GM-AML diagnosis with immunophenotype, karyotype, and molecular genetic findings are needed for better characterization of GM-AML subtypes. Further discoveries of novel molecular targeted therapies for patients with AML [9], including octogenarians, may be useful to further improve their survival in the future after this first step of separation GM-AML and EMD-AML biological categories differing in response to SICT.

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PL diagnosed and treated the patients, performed design of the study and wrote the first draft. JG performed morphological evaluation of dysplastic changes and checked FAB diagnosis. KM, OF, ZZ, JB performed cytogenetic and genetic examinations. AM, MČ, JS contributed to diagnosis and treatment of the patients. All authors reviewed, corrected the manuscript and approved the final version.

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Conflict of Interest

The authors declare no potential conflict of interest.

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