Acute myeloid leukemia in very old patients

More than half of all Swedish adult patients with acute myeloid leukemia (AML) are 70 years or older at diagnosis.[1,2] The incidence of AML currently peaks at age 80-84, and declines among even older adults, in accordance with the general cancer incidence by age.[3-5] AML biology according to age has again come into focus due to the concept of age-related clonal hematopoiesis.[6] We have previously shown that most patients up to 80 years tolerate and benefit from intensive chemotherapy,[2] and the outcome has improved over the last twenty years,[7] whereas patients older than 80 have a very poor outcome with no improvement over time. However, now new therapies with much less toxicity are available[8,9] which could potentially be tolerated by the oldest patients, who therefore need to be better characterized.

We previously reported the karyotypic profile in older patients.[10] Herein we report the clinical and diagnostic features according to age with a specific focus on the very old (Table 1) and a comparison to younger patients. Data

Table 1. AML patient characteristics by age (n=7069).

		<70 yrs	70-74 yr	75-79 yr	80-84 yr	85-89 yr	90+ yr	All 70+ yr	All
Males	number	1728	558	574	476	244	72	1924	3652
Females	number	1520	443	526	491	300	137	1897	3417
Age, yrs	mean	54	72	77	82	87	92	79	68
	median	58	72	77	82	86	91	79	71
Hemoglobin, g/L	mean	95	94	94	94	93	91	94	94
	median	95	94	94	94	93	92	94	94
WBC, x10^9/L	mean	33	34	34	33	36	42	35	34
	median	8.5	10	6.8	8.4	6.3	12.8	8.4	8.5
ANC, x10^9/L	mean	3.6	4.9	4.7	4.5	5	4.5	4.7	4.1
	median	0.9	1.3	0.9	1.1	1.2	1	1.1	1
Blast count, x10^9/L	mean	19	18	19	17	21	23	19	18.9
	median	2.1	2	1.1	1.6	1.6	2.5	1.6	1.7
Platelets, x10^9/L	mean	89	97	97	90	82	87	92	91
	median	57	65	62	63	61	69	63	60
BM blasts, %	mean	51	49	48	48	48	49	49	50
	median	50	45	43	43	43	48	48	46
LDH, ukat/L	mean	10.1	10	9.4	10.4	8.3	8.4	9.7	9.9
(normal 1.9-4.2)	median	6	5.8	5.1	5.3	4.7	5.2	5.2	5.6
Genetic data									
Evaluable karyotypes	number	2681	679	610	359	111	16	1775	6211
	% evaluable	83	68	55	37	20	8	46	63
Normal karyotype	% of evaluable	28	33	29	28	26	19	30	29
Complex karyotype	% of evaluable	16	23	26	24	26	50	25	19
Genetic risk	% Favorable	19	10	8	7	8	*	9	15
	% Intermediate	53	57	55	57	50	31	56	54
	% High risk	28	33	37	36	42	56	36	31
Secondary AML	% *de novo*	74	61	63	67	74	80	66	70
	% tAML	10	13	12	9	6	5	10	10
	% AHD AML	16	27	25	25	20	15	24	20
Morphology	% AML NOS	16	22	24	27	34	44	27	22
	% M0-M2	38	33	34	31	28	19	31	37
	% M4-M5	19	17	15	16	12	14	16	17
ECOG	% 0-I	77	62	53	46	39	26	50	63
Obesity	% BMI>25	54	57	51	45	42	31	49	51
Therapy	% intensive	89	68	45	18	5	0	36	60
CR with intensive Tx	% CR	74	57	52	47	38	NA	53	67
Therapy 2012-2016	% hypometh	2	11	18	17	11	**	14	9

*indicates one patient with t(8;21) and one patient with acute promyelocytic leukemia, i.e., 12.5%. NA, not assessed, no patient 90+ years received intensive therapy. **one of 64 patients aged 90+ years received hypomethylating agent. AML: acute myeloid leukemia; ECOG: Eastern Cooperative Oncology Group performance status; WBC: white blood cell count; ANC: absolute neutrophil count; BM: bone marrow; LDH: lactic dehydrogenase; tAML: therapy-related AML; AHD: antecedent hematologic disease; NOS: not otherwise specified; BMI: body mass index; CR: complete remission, may include CR with incomplete recovery from cytopenia.

from patients diagnosed between 1997 and 2016 was extracted in March 2017 from the Swedish AML registry.[1,2] Laboratory data, body mass index (BMI) and information on hypomethylating therapy were available from 2007. Data on geriatric assessment[11] and detailed comorbidity[12] were not available.

There are obvious clinical differences by age. The male to female patient number ratio is lower in older patients, despite the higher male incidence up to age 95 years,[1] due to the corresponding sex ratio in the population. Older patients undergo less diagnostic procedures, such as morphological subclassification and genetic evaluation, due to the lack of impact on clinical management in the past. Nevertheless, AML subclassification according to The French-American-British/The World Health Organization (FAB/WHO) was performed in a higher proportion of Swedish patients over 90 years than in all ages according to The Surveillance, Epidemiology, and End Results (SEER) program.[13] Older patients have poorer Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, and fewer receive intensive therapy, of whom a minority achieve complete remission (CR)[2] (Table 1). Older patients are, according to Swedish guidelines, less likely to receive salvage therapy if they do not respond to the first induction attempt. Thus, survival is increasingly poor with advancing age (Figure 1).

On the other hand, there were no major clinically distinct differences by age in blood counts at presentation. The total white blood cell (WBC) counts and blood absolute blast counts were slightly higher in patients over 85 years (P=0.03 and P=0.0001, respectively), but lactic dehydrogenase (LDH) was less elevated in older subjects (P=0.02 by non-parametric statistics). Obesity is a risk factor for AML,[14] but fewer older patients were obese (BMI>25, P<0.0001). Underweight (BMI<18.5) was present in 2.5% of both patients younger than 70 years and those over 70 years, but possibly somewhat more common in patients of 90 years or over.

The pattern of genetic changes is hard to interpret due to low coverage among the oldest patients. It is likely that adverse findings, such as complex and monosomic karyotypes, deletions of 5q and 7q, and *TP53*-mutations are more common in this group.[10] However, we also found acute promyelocytic leukemia and core-binding factor leukemia with t(8;21) in patients over 90 years. Secondary AML was most common in those aged between 70 and 80,[2,15] and, perhaps surprisingly, less common among the very old (P<0.0001), despite the fact that the age-related incidence of myelodysplastic syndromes (MDS) is more skewed towards the elderly than in AML.

Twenty-six patients aged 85 or over (89 being the oldest) received intensive therapy, and half of them survived for more than six months; the longest survival time was three years. Nineteen 85-year-old or older patients received primary hypomethylating agents, and 11/19 (58%) survived for more than six months (median 205 days), with the longest survival time being 46 months. The oldest recipient of AML-specific treatment was a 91-year-old male with AML M2, performance status 0, bone marrow blasts of 26% and a WBC count of 1.0 x10^9/L who received azacytidine, and survived for 640 days.

Twelve patients of 90 years or older survived for one year or more; eight of them had ECOG performance status 0-I, and their median marrow blast count and WBC count were below average at 26% and 1.7x10^9/L, respectively, but their median hemoglobin and platelet counts and morphologic subtype were similar to that of others [hemoglobin 86 g/L, platelets 45 x10^9/L, M1 (n=1), M2 (n=1), M5 (n=2), AML with multilineage dysplasia (n=2), and without further specification (n=6)]. One patient had a normal karyotype, whereas the others did not have their karyotypes evaluated.

The interpretation of biological differences and similarities between very old and younger patients is hampered by the lack of diagnostic procedures in the very old, and

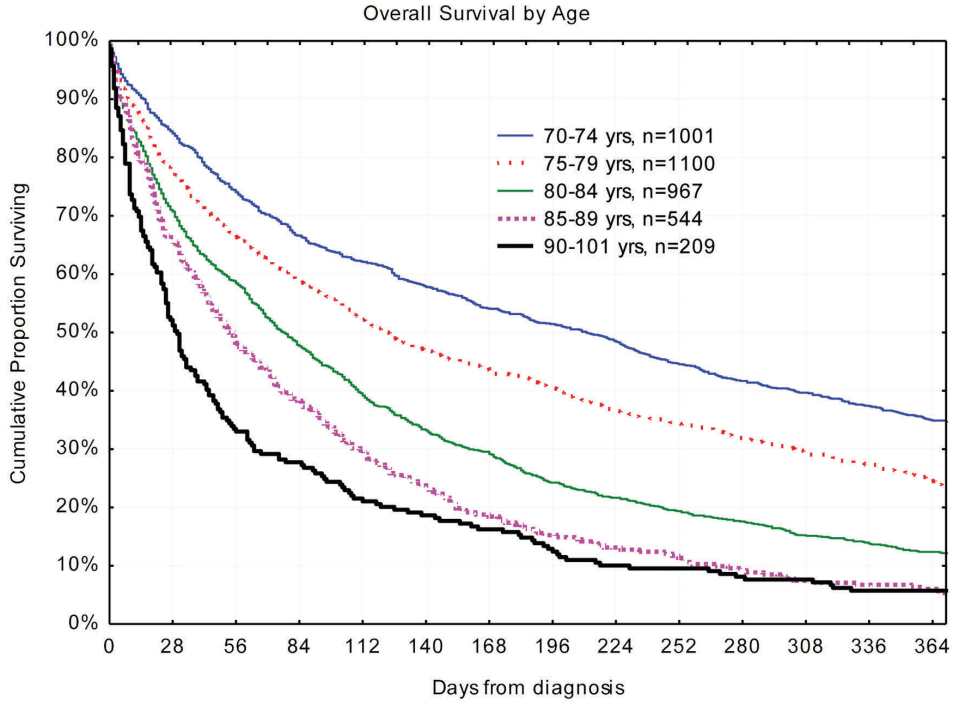

Figure 1. Overall survival in days by age at diagnosis.

even the primary diagnosis may be missing in critically ill older people. Older patients with modest MDS-related cytopenia may go undiagnosed until they develop AML, and older patients with end-stage MDS may not have their AML transformation diagnosed and reported.

In summary, AML is a very heterogeneous disease, but in this unique population-based analysis of very old patients there seems to be only modest differences in the clinical subsets of AML between younger and older patients, with the proviso that molecular data are as yet not available. Thus, therapeutic improvements which are being developed for patients aged from 70 to 80 may also benefit even older patients, which should be studied specifically.

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