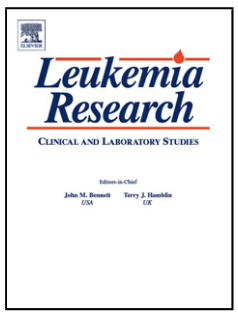

Title: Consolidation with autologous stem cell transplantation in first remission is safe and effective in AML patients above 65 years

Author: Alexander D. Heini Martin D. Berger Katja Seipel Behrouz Mansouri Taleghani Gabriela M. Baerlocher Kurt Leibundgut Yara Banz Urban Novak Thomas Pabst

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Consolidation with autologous stem cell transplantation in first remission is safe and effective in AML patients above 65 years.

Running title: Autologous transplant in elderly leukemia.

Authors: [1]Alexander D. Heini, [1]Martin D. Berger, [2]Katja Seipel, [3]Behrouz Mansouri Taleghani, [3]Gabriela M. Baerlocher, [4]Kurt Leibundgut, [5]Yara Banz, [1]Urban Novak, [1]Thomas Pabst.

Author affiliations: [1]Department of Medical Oncology, [2]Department of Clinical Research, [3]Department of Hematology, [4]Department of Pediatric Hemato-Oncology, and [5]Institute of Pathology; Inselspital, University Hospital Bern, University of Bern Switzerland.

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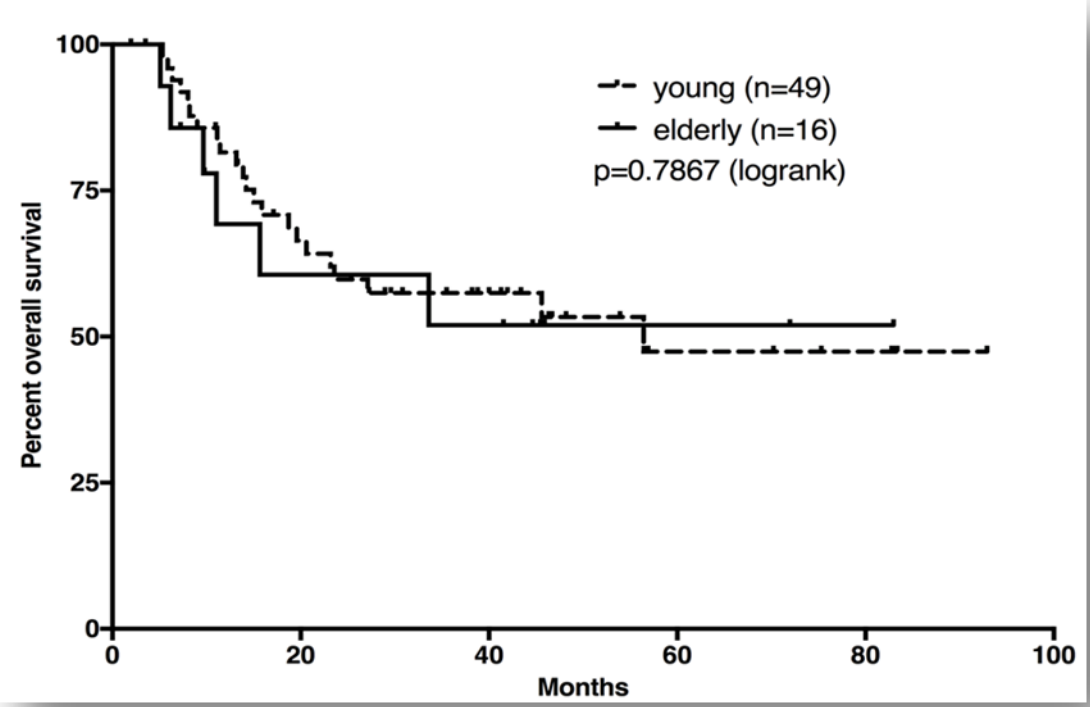
Corresponding author: Thomas Pabst, MD; Associate Professor; Department of Medical Oncology; University Hospital; 3010 Berne; Switzerland.

Tel.: +41 31 632 8430; fax: +41 31 632 3410

E-mail: thomas.pabst@insel.ch

Graphical abstract

Elderly AML patients above 65 years derive similar benefits in overall survival from ASCT consolidation in CR1 as AML patients below 65 years.



Highlights

- The outcome of AML patients ≥65 years remains disappointing.
- Consolidation with autologous transplantation is feasible in elderly AML patients.
- ASCT consolidation in first remission provides longer PFS and OS in elderly AML.
- ASCT provides similar survival benefits in young and elderly AML patients.

Abstract

The outcome of AML patients ≥65 years remains disappointing. Current post-induction strategies for elderly AML patients fit for intensive treatment involve additional cycles of chemotherapy or allogeneic transplantation. Consolidation with autologous transplantation (ASCT) is poorly studied in these patients. In this single-center retrospective analysis, we determined survival rates of AML patients ≥65 years undergoing busulfan/cyclophosphamide conditioning before ASCT in first remission between 2007 and 2015. We found elderly AML patients with ASCT to have longer progression-free survival (PFS; 16.3 vs. 5.1 months, *P*=0.0166) and overall survival (OS; n.r. vs. 8.2 months; *P*=0.0255) than elderly AML patients without ASCT consolidation. In addition, elderly AML patients undergoing ASCT had comparable PFS (*P*=0.9462) and OS (*P*=0.7867) as AML patients below 65 years receiving ASCT consolidation in CR1. Our data suggest that ASCT is an option in elderly fit AML patients who appear to benefit from autologous consolidation similarly to younger AML patients.

Keywords: autologous; transplant; elderly; AML; survival.

1. Introduction

Acute myeloid leukemia (AML) is predominantly diagnosed in elderly people with a median age at diagnosis of 67 years [14]. The outcome of elderly AML patients remains disappointing due to the overrepresentation of adverse prognostic factors [13]. Even if complete remission rates are achieved in up to 60% after standard intensive induction treatment in elderly AML patients, relapses are common leading to 2-year survival rates of only 10-20% [11]. Since relapses emerge from residual leukemic cells escaping chemotherapy, intensification of AML treatment appears as a rational strategy. Accepted modalities to prevent relapse in first complete remission in younger AML patients comprise further conventional chemotherapy, allogeneic or autologous stem cell transplantation, whereas in elderly AML patients chemotherapy consolidation and (less commonly) allogeneic transplantation are applied [13].

Autologous stem cell transplantation (ASCT) has become a therapeutic option for first-line consolidation in younger adults with AML with good and intermediate risk features [15]. In such patients, it offers distinct anti-leukemic effectiveness and prolongs survival similar to allogeneic transplantation while avoiding morbidity and mortality of graft versus host disease associated with allogeneic transplantation [2,17]. However, prospective studies in elderly AML patients comparing chemotherapy consolidation with autologous stem cell transplantation (ASCT) or allogeneic transplantation are lacking.

Various retrospective reports have investigated the use of ASCT in elderly AML patients with promising results, albeit mostly in highly selected patients [1,5,7,12]. Acceptable toxicity and a low rate of transplant-related mortality were reported without compromising the rate of relapse, which, irrespective of age, still remains the

major cause of treatment failure after ASCT in AML. However, the definition of an elderly AML patient has widely varied among the available studies. Whereas earlier reports separated such patients as being older than 50 years [1], more recent studies defined such patients as older than 60 years [12]. However, an analysis investigating the benefit and tolerance of ASCT consolidation specifically in AML patients ≥65 years in first remission is currently missing.

2. Patients and methods

2.1 Pretreatment assessments

In this single-center, retrospective analysis, we investigated busulfan/ cyclophosphamide conditioning before ASCT in AML patients ≥65 years in first remission treated at the University Hospital Bern, Switzerland between 2007 and 2015. We compared this cohort to two control groups: (I) AML patients ≥65 years in first CR (CR1) after one or two induction cycles without subsequent consolidation treatment, and (II) AML patients <65 years undergoing ASCT in CR1 after two cycles of induction treatment in the same study period. Patients with acute promyelocytic leukemia (APL) were excluded.

2.2 Definitions

Patients were considered in CR1 if they had a bone marrow blast count of <5% and had completed hematologic recovery with platelets above 100 G/L and neutrophils above 1.0 G/L. Overall survival was calculated from the date of achieved CR1 to death or date of last follow-up. Patients still alive or lost to follow-up were censored at the last date when they were known to be alive. Progression-free survival was

calculated from date of achieved CR1 to disease progression or relapse, death or last follow-up whatever occurred first.

2.3 Statistical analysis

All reported p-values were from two-tailed Fisher's or unpaired t tests, and a value of $P<0.05$ was considered as statistically significant. Survival analysis was performed using the log-rank method, and analyses were performed using GraphPad Prism® Version 7 (GraphPad Software, Inc., La Jolla, CA).

3. Results

3.1. Treatment

40 AML patients ≥65 years in CR1 after one or two cycles of intensive induction chemotherapy were identified. Patients in this period were treated in subsequent HOVON/SAKK protocols (HOVON-81, -93, and -103), and 24 of these patients received no consolidation treatment as per protocol. 16 Patients ≥65 years diagnosed with AML in interval periods without an active protocol and considered to be fit for consolidation treatment underwent ASCT for consolidation of first remission. Induction consisted in two cycles of chemotherapy in all patients, with cytarabine and daunorubicin in cycle 1, and six days of 1000mg/m2 of cytarabine every 12 hours in cycle 2, respectively. Conditioning treatment before ASCT consisted of busulfan 4mg/kg/day p.o. for four days and cyclophosphamide 60mg/kg/day i.v. for two days.

3.2 Patient characteristics

Baseline characteristics including cytogenetic and molecular risk groups at diagnosis of AML patients ≥65 years with and without ASCT are summarized in Table I. In elderly AML patients with ASCT, we observed more favorable risk patients (31.3% vs. 16.7%) and less adverse risk patients (12.5% vs. 37.5%) than in elderly patients without ASCT; however, these differences were not significant (*P*=0.4414 and *P*=0.1478).

3.3 Survival and efficacy

Elderly AML patients with ASCT consolidation achieved longer progression-free survival (PFS; 16.3 vs. 5.1 months; *P*=0.0166) and overall survival (OS; n.r. vs. 8.2 months; *P*=0.0255) than elderly patients without ASCT consolidation (Figure 1). At 24 months after achievement of CR1, PFS rates were 48.2% in the ASCT cohort and 15.6% in the non-ASCT group. OS rates were 60.6% in the ASCT cohort compared to 29.8% in patients without ASCT. Early mortality in the first 100 days after achievement of CR1 was lower in the ASCT group (6% vs. 20.8%); however, this difference was not significant (*P*=0.3752), nor was the difference in the rates of relapse (43.8% vs. 66.6%, *P*=0.1991).

In addition, we compared the outcome after ASCT consolidation of AML patients ≥65 years to patients <65 years with ASCT in CR1. (Table I). We identified 49 patients younger than 65 years, who underwent ASCT in this same study period at our institution. Baseline characteristics between these two groups were balanced apart from CEBPA mutations, which were more frequently present in elderly patients (0% vs. 18.8%, *P*=0.0128). We observed no differences in PFS (16.3 vs. 30.8 months,

P=0.9462) and OS (n.r. vs. 56.4 months, *P*=0.7867; Figure 2). At 24 months after ASCT, PFS and OS rates were 48.2% and 60.2% in the elderly, and 59.8% and 50.0% in the younger cohort. We observed no treatment-related deaths in both groups, and all early deaths (6.2% in elderly vs. 0% in younger AML patients, *P*=0.2462) were due to disease progression. The median time from diagnosis to ASCT was similar in younger and elderly patients (105 and 123 days, respectively; *P*=0.9138).

3.4 Subgroup analysis

We further compared survival between different cytogenetic ELN risk groups [11]. Survival of all patients undergoing ASCT stratified according to the four different cytogenetic risk groups are depicted in Figure 3A. We identified no survival differences between the three cohorts favorable, Intermediate-I and adverse groups (*P*=0.1918, *P*=0.6491, and *P*=0.1291, respectively). Noteworthy, the very small group of intermediate-II patients ≥65 years with ASCT (n=4) had better survival rates than elderly patients without ASCT (n=4) and also than younger patients undergoing ASCT (n=9; *P*=0.0214; data not shown). Finally, the various ELN risk groups showed different survival rates (Figure 3B) in younger AML patients undergoing ASCT whereas the subgroups in our cohort of elderly AML patients were too small to allow such conclusions (data not shown).

4. Discussion

Our data suggest that fit AML patients ≥65 years may tolerate ASCT consolidation in CR1 and equally benefit from such treatment as young AML patients in CR1.

Obvious limitations of this study are its retrospective, single center and non-randomized design inevitably leading to a relevant selection bias. Accordingly, physicians may have tended to offer ASCT more likely to patients with favorable risk features, good tolerance of induction treatment, and achievement of early remission (already after one induction cycle). As one of the consequences, our study identified a higher percentage of patients with adverse cytogenetic abnormalities in the subgroup of elderly patients without ASCT consolidation as compared to elderly patients with ASCT consolidation, thereby affecting the comparison between these two groups.

The selection process of patients is considerable, since we have diagnosed a total of 78 patients aged ≥65 years with AML in the study period, and 55 of these patients ultimately underwent intensive chemotherapy induction treatment. We observed that 40 of these 55 patients achieved CR1, and only 16 (29%) of all elderly AML patients were finally treated with ASCT consolidation. Whereas these rates are comparable to previous studies, they illustrate the significant selection bias involved in such retrospective studies [12].

To the best of our knowledge, this is the largest study so far reporting on the use of ASCT after busulfan/ cyclophosphamide conditioning in AML patients ≥65 years and the comparison to the same age cohort of AML patients not receiving ASCT consolidation. Our data support a concept that ASCT is feasible in selected elderly AML patients considered to be fit for intensive treatment. Elderly AML patients receiving ASCT in CR1 appear to benefit from both reduced risk of relapse and longer overall survival, with a remarkable overall survival rate of 60.6% 24 months after achievement of CR1. The rates of overall and progression-free survival were comparable with previous reports [5]. However, our data challenge earlier

observations of longer PFS and OS in patients younger than 50 years compared to those of patients older than 50 years [1]. The assessment of the benefit of ASCT in elderly AML patients for specific cytogenetic risk groups is limited by the small number of patients in these groups in our cohort. However, differing outcome rates in various risk groups were observed in our somewhat larger group of younger patients undergoing ASCT (n=49) suggesting that the benefit of ASCT consolidation is limited to favorable risk groups of AML.

A prerequisite of ASCT is the successful preceding collection of a sufficient number of autologous stem cells obtained usually following hematologic recovery after the second induction cycle and after confirmed achievement of complete remission. Differences in stem cell mobilization and collection success rates between younger and elderly AML patients are rarely reported. In a retrospective analysis including 40 patients, Ferrara et al. demonstrated similar CD34 yield and successful mobilization rates in patients above and below 60 years and concluded that age does not significantly affect mobilization and collection of peripheral stem cells [4]. However, others have reported reduced proliferative potential of stem cells in elderly stem cell donors [10].

Compared to chemotherapy consolidation, ASCT provides timely hematologic recovery, thereby reducing the probability of infectious or hemorrhagic complications [8,9]. Reduced intensity conditioning (RIC) with allogeneic stem cell transplantation has also been investigated as a consolidation strategy in elderly AML patients. In an analysis of RIC and allogeneic stem cell transplantation in patients 60 years and older, similar OS and PFS rates after 24 months were observed as in our cohort; however, extensive chronic GvHD was observed in 62.5% of these patients [6]. Therefore, in elderly patients with appropriate risk profile consolidation with ASCT

seems to have similar efficacy as RIC allogeneic transplantation while avoiding GvHD. Moreover, graft failure in ASCT is a rare event.

Our report suggests that ASCT can be considered an effective and safe consolidation option for AML patients above 65 years. Age emerges as an unreliable parameter for an individual's physical condition, and biological age tends to vary considerably among people of the same age cohort [13]. Although age is (among others) an important adverse prognostic factor in AML, it fails to explain as a single parameter the poor outcome of elderly AML patients [16]. Accordingly, the overrepresentation of adverse cytogenetic abnormalities, poor performance status and comorbidities also contribute to the poor outcome of elderly AML patients. Our data indicate that age *per se* should not prevent physicians to propose ASCT to the steadily increasing proportion of AML patients ≥65 years for consolidation of first complete remission. However, the selection of appropriate patients remains a challenging task, but our data suggest that the benefit of ASCT consolidation in AML patients ≥65 years merits prospective evaluation.

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Author's contributions

A.H. performed research, analyzed data and wrote the paper; M.D.B. and K.S. analyzed data, reviewed the manuscript and were involved in the final writing of the paper; G.M.B., B.M.T., K.L., Y.B., and U.N. contributed relevant data, reviewed the

manuscript and were involved in the final writing of the paper; T.P. designed research, analyzed data and wrote the paper.

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Figure legends

Figure 1:

Kaplan-Meyer survival curves comparing survival of AML patients ≥65 years undergoing ASCT in first CR (solid line) and AML patients ≥65 years without ASCT in first CR (spotted line). A: progression free survival; B: overall survival.

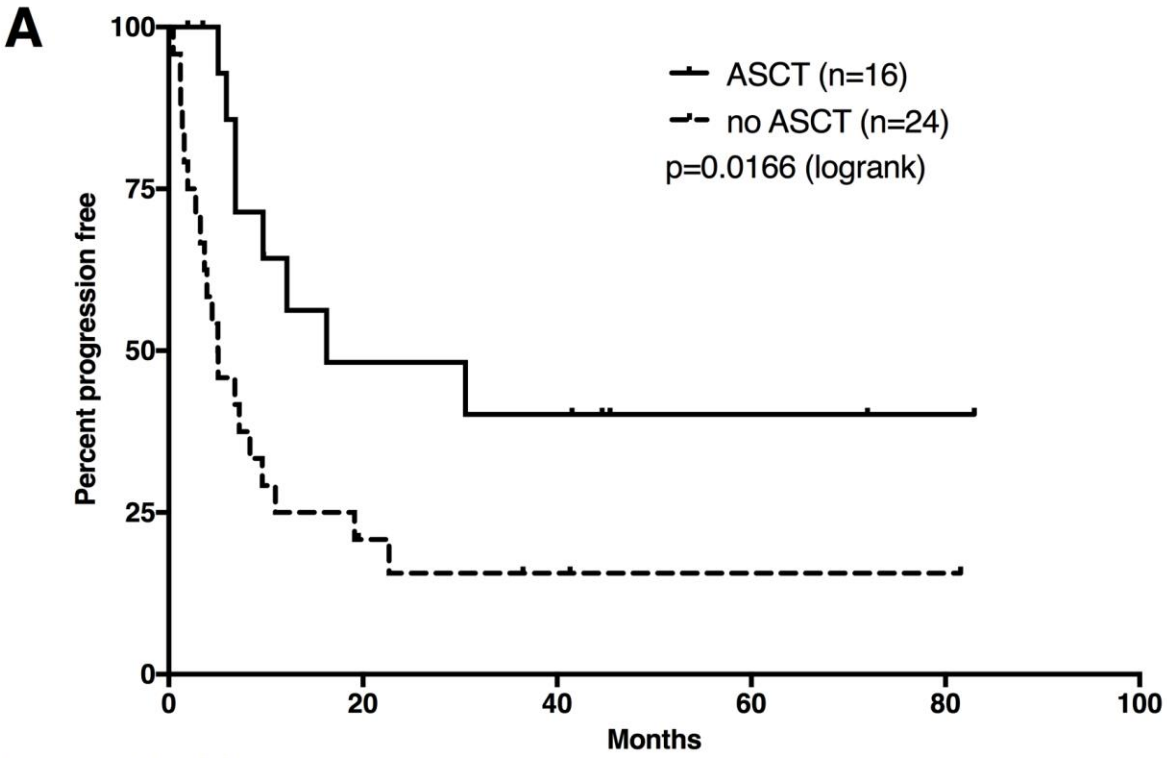
Figure 2:

Kaplan-Meyer survival curves comparing survival of AML patients ≥65 years undergoing ASCT in first CR (solid line) and AML patients <65 years undergoing ASCT consolidation (spotted line). A: progression free survival; B: overall survival.

Figure 3:

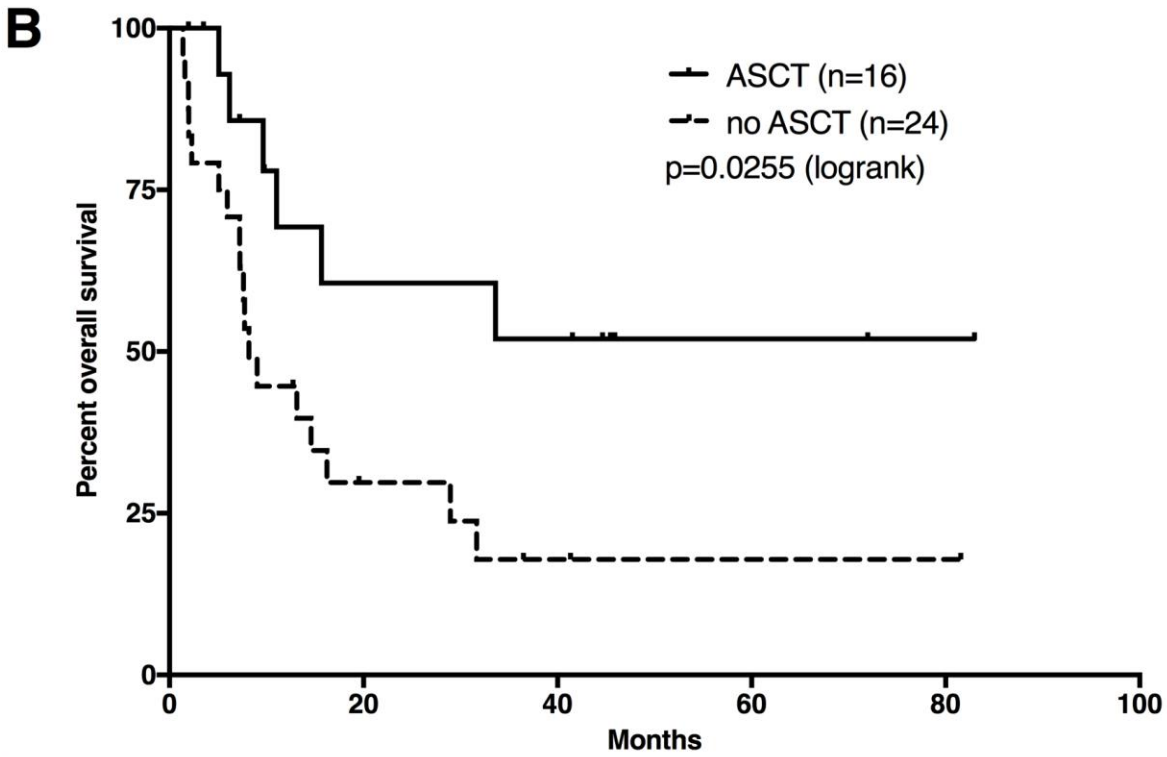
Kaplan-Meyer survival curves comparing survival of AML patients according to cytogenetic risk group. A: all patients; B: patients <65y undergoing ASCT.

Figure 1



Patients at risk (n)

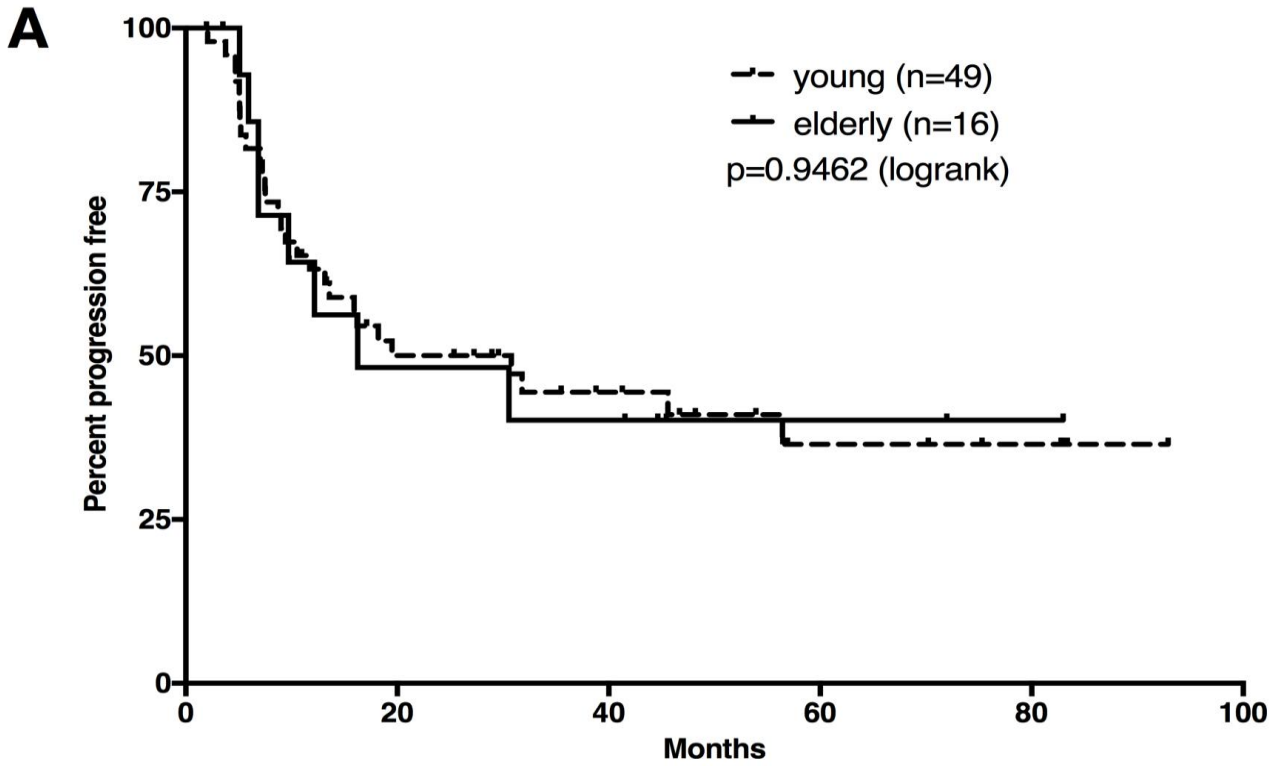
ASCT	16	7	6	3	2	1
no ASCT	24	5	3	2	1	1



Patients at risk (n)

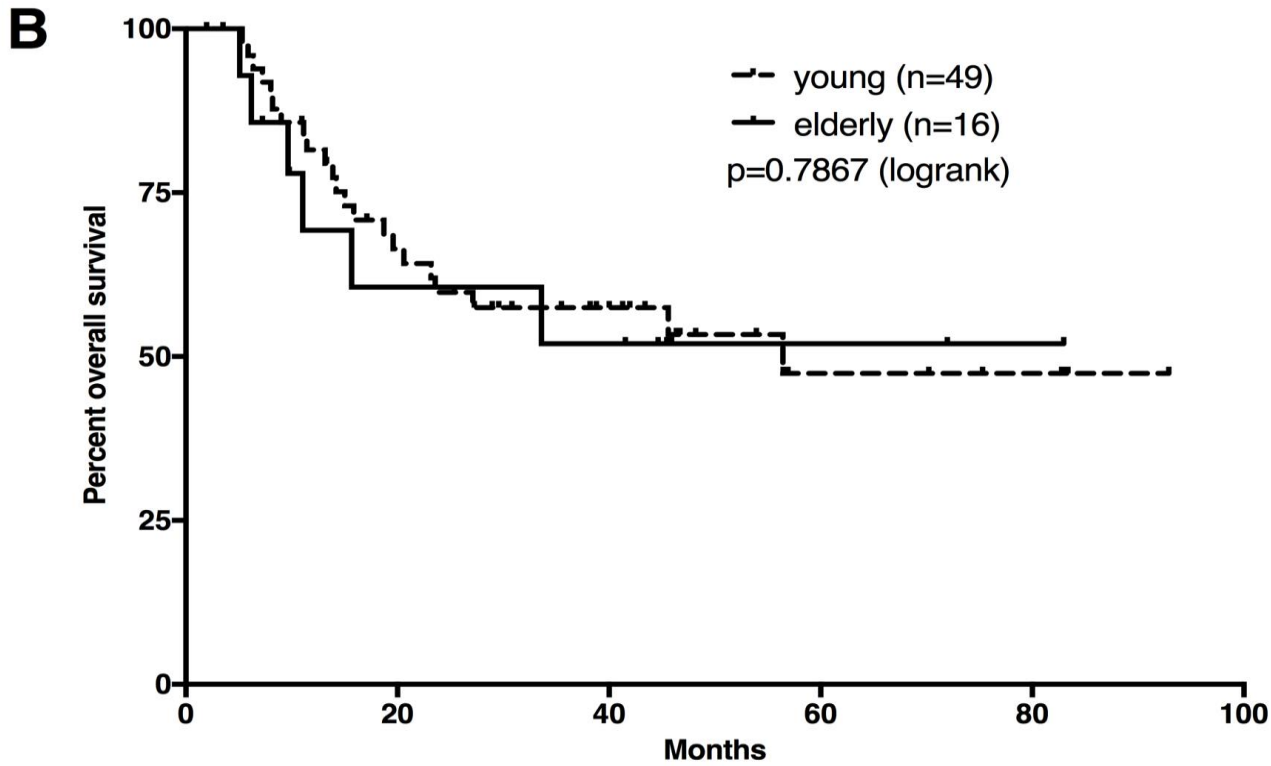
ASCT	16	8	7	3	2	1
no ASCT	24	6	3	2	2	1

Figure 2



Patients at risk (n)

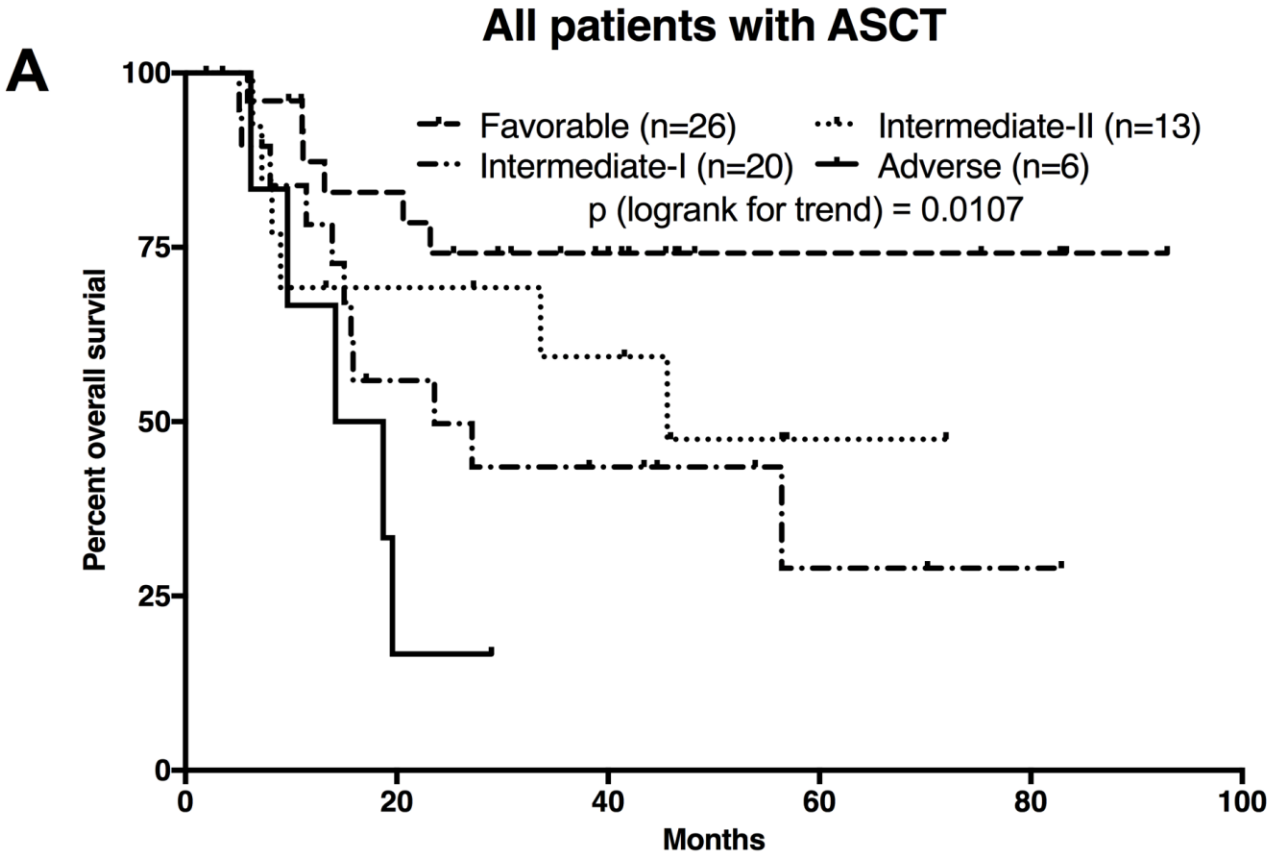
elderly	16	7	6	3	2	1
young	49	23	15	7	5	1



Patients at risk (n)

elderly	16	8	7	3	2	1
young	49	31	18	7	5	1

Figure 3



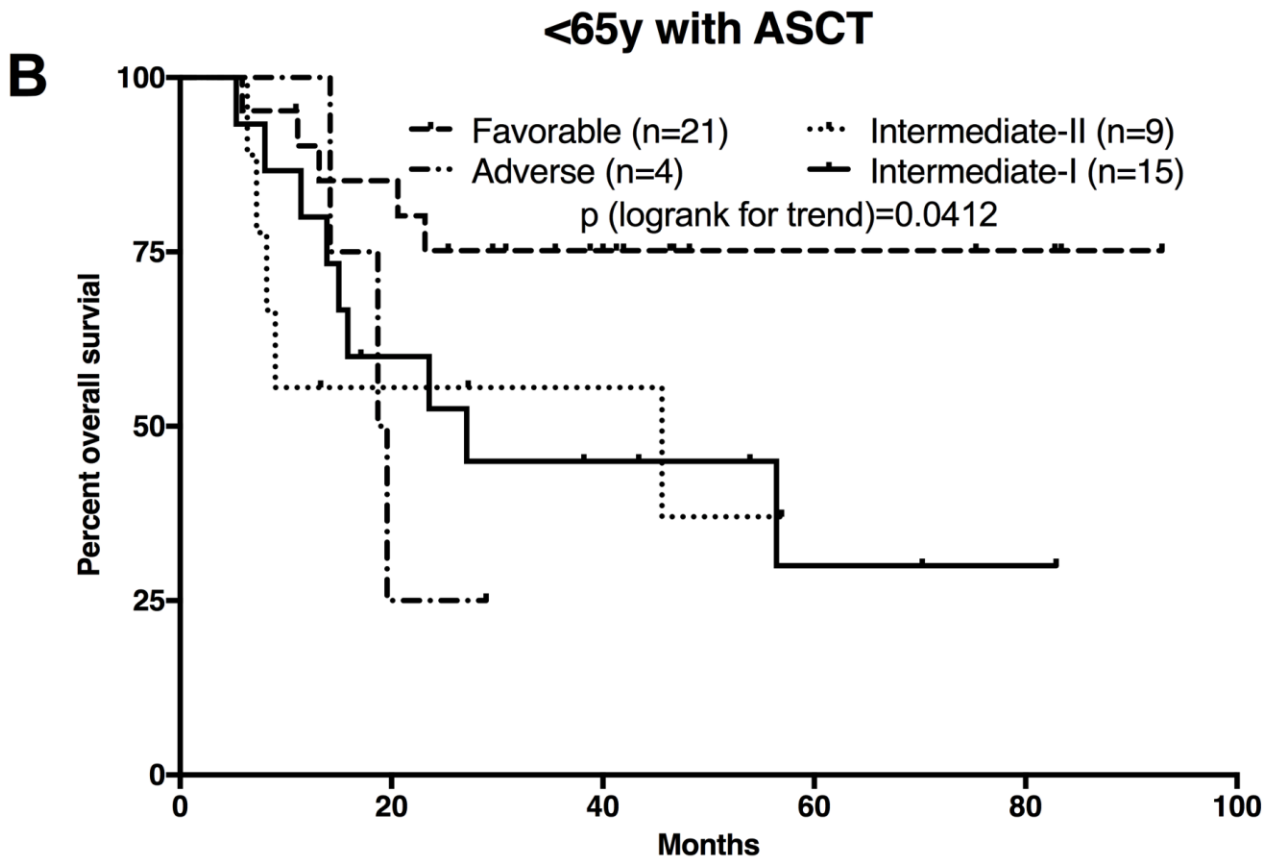


Table legends

Table 1:

Clinical characteristics, outcome and univariate analysis in elderly AML patients with ASCT in CR1 compared to elderly AML patients without ASCT in CR1 and younger patients with ASCT in CR1.

Table I: Clinical characteristics, outcome and univariate analysis in elderly (≥ 65 years) AML patients with ASCT in CR1 compared to elderly AML patients without ASCT in CR1 and to younger (< 65 years) patients with ASCT in CR1.

	elderly pts. with ASCT (n=16)	%	elderly pts. without ASCT (n=24)	%	p	s	young pts. with ASCT (n=49)	%	p	s
Baseline characteristics										
Age, median (range)	66.0 (64.2-72.5)		68.7 (64.1-74.4)		0.1628	ns	51.1 (19.6-63.5)		<0.0001	****
Gender, male	8	50.0	14	58.3	0.7481	ns	27	55.1	0.7782	ns
Hemoglobin (g/L)	96.5 (59.0-133.0)		89.5 (38.0-119.0)		0.1970	ns	88.0 (43.0-151.0)		0.6344	ns
WBC† (G/L)	11.8 (2.4-58.8)		2.8 (0.7-87.1)		0.5440	ns	9.8 (0.9-240.7)		0.2608	ns
ANC‡ (G/L)	1.1 (0.1-10.0)		0.5 (0.1-18.3)		0.8067	ns	1.5 (0.0-50.2)		0.3883	ns
Peripheral blasts (%)	39.5 (1.0-90.0)		6.8 (0-89.0)		0.0199		38.8 (0.0-96.0)		0.8102	ns
Bone marrow blasts (%)	67.8 (20.0-95.0)		37.5 (5.0-90.0)		0.1249	ns	65.0 (0.0-95.0)		0.4986	ns
Platelets (G/L)	62.0 (18-301)		119.5 (13.0-260.0)		0.3598	ns	66.0 (7.0-608.0)		0.7577	ns
LDH (IU/L)	593.5 (288.0-2514.0)		544.5 (198.0-2323.0)		0.2131	ns	755.5 (156.0-8352.0)		0.2877	ns
FAB	16	100	24	100			49	100		
M0	3	18.8	8	33.3	0.4732	ns	5	10.2	0.3952	ns
M1	5	31.3	5	20.8	0.4824	ns	8	16.3	0.2791	ns
M2	3	18.8	4	16.7	1.0000	ns	17	34.7	1.0000	ns
M4	1	6.3	0	0.0	-	-	10	20.4	0.4000	ns
M5	2	12.5	4	16.7	1.0000	ns	6	12.2	1.0000	ns
M6	0	0.0	2	8.3	-	-	1	2.0	-	-
M7	0	0.0	1	4.2	-	-	0	0.0	-	-

sec. from MDS/th-related	1	6.3	0	0.0	-	-	0	0.0	-	-
ND§	1	6.3	0	0.0	-	-	2	4.1	-	-
Adverse risk	**2**	**12.5**	**9**	**37.5**	**0.1478**	**ns**	**4**	**8.2**	**0.6306**	**ns**
-5 or del(5q)	0	0.0	2	8.3	-	-	0	0.0	-	-
t(v;11)(v;q23)	0	0.0	0	0.0	-	-	1	2.1	-	ns
Complex karyotype	2	12.5	7	29.1	0.2717	ns	3	6.1	0.5896	ns
Intermediate-I	**5**	**31.3**	**7**	**29.1**	**1.0000**	**ns**	**15**	**30.6**	**1.0000**	**ns**
NPM1mut+FLT3-ITD	3	18.8	2	8.3	0.3725	ns	5	10.2	0.3952	ns
NPM1wt+FLT3-ITD	0	0.0	1	4.2	-	-	1	2.0	-	-
Normal karyotype	2	12.5	4	16.7	1.0000	ns	9	18.4	0.7178	ns
Intermediate-II	**4**	**25.0**	**4**	**16.7**	**0.6905**	**ns**	**9**	**18.4**	**0.6905**	**ns**
not otherwise classified	4	25.0	4	16.7	0.6905	ns	9	18.4	0.6905	ns
Favorable	**5**	**31.3**	**4**	**16.7**	**0.4414**	**ns**	**21**	**42.9**	**0.5590**	**ns**
t(8;21)	1	6.3	1	4.2	-	-	8	16.3	0.4326	ns
inv(16)	0	0.0	0	0.0	-	-	3	6.1	0.5692	ns
NPM1mut+FLT3wt	1	6.3	0	0.0	-	-	10	20.4	0.2677	ns
CEBPA mut	3	18.8	3	12.5	0.6678	ns	0	0.0	0.0128	*

Outcome										
Progression-free survival										
(months, median)	16.3		5.1		0.0166	*	30.8		0.9462	ns
Overall survival										
(months, median)	not reached yet		8.2		0.0255	*	56.4		0.7867	ns
Early death										
(100 days)	1	6.3	5	20.8	0.3725	ns	0	0.0	0.2462	ns
Follow up										
(months, median)	44.6		36.5		0.9974	ns	43.4		0.3391	ns
Univariate Analysis										
Progression-free survival										
ASCT yes			1.000 (reference)		0.0166	*	1.000 (reference)		0.9462	ns
ASCT no			2.598 (1.238-5.449)				1.027 (0.465-2.274)			
Overall survival										
ASCT yes			1.000 (reference)		0.0255	*	1.000 (reference)		0.7867	ns
ASCT no			2.713 (1.217-6.044)				1.132 (0.444-2.889)			

P: comparison to elderly patients with ASCT; *autologous stem cell transplantation; †white blood cells; ‡absolute neutrophil count; §no data available.