

Impact of treatment delay in acute myeloid leukemia revisited. Juliusson et al.

Supplement Table 1. Clinical characteristics by Time from Diagnosis to Treatment (TDT).

		0-5d N=1587	6-10d N=466	11-15d N=157	>15d N=164	Total: 2374
Sex	Male	848 (54%)	262 (56%)	83 (53%)	96 (59%)	1289 (54%)
	Female	739 (47%)	204 (44%)	74 (47%)	68 (42%)	1085 (46%)
Age (years)	Mean (SD)	59.4 (15)	64.4 (12)	64.9 (12)	63.6 (12)	61.0 (14)
	Median (IQR)	63 (50-71)	66 (60-73)	67 (59-73)	66 (59-71)	64 (53-72)
CR		1270 (80%)	331 (71%)	109 (69%)	113 (69%)	1823 (77%)
AlloSCT	Yes, in CR1	418 (26%)	88 (19%)	32 (20%)	35 (21%)	573 (24%)
	Yes, other	101 (6%)	23 (5%)	8 (5%)	7 (4%)	139 (6%)
	No	1068 (67%)	355 (76%)	117 (75%)	122 (74%)	1662 (70%)
AML type	De novo	1293 (82%)	321 (69%)	104 (66%)	90 (55%)	1808 (76%)
	tAML	86 (5%)	49 (11%)	15 (10%)	33 (20%)	183 (8%)
	Sec AML	208 (13%)	96 (21%)	38 (24%)	41 (25%)	383 (16%)
ECOG Performance Status	0	427 (28%)	159 (35%)	50 (33%)	54 (33%)	690 (30%)
	I	848 (55%)	235 (52%)	79 (52%)	83 (51%)	1245 (54%)
	II	159 (10%)	41 (9%)	19 (12%)	19 (12%)	238 (10%)
	III	66 (4%)	17 (4%)	3 (2%)	5 (3%)	91 (4%)
	IV	35 (2%)	3 (1%)	2 (1%)	1 (1%)	41 (2%)
Bone marrow blast (%)	Mean (SD)	57 (24)	45 (23)	39 (22)	35 (23)	53 (25)
	Median (IQR)	60 (37-80)	40 (25-62)	35 (23-51)	29 (21-47)	50 (30-75)
Hemoglobin g/Liter	Mean (SD)	93 (20)	96 (20)	98 (18)	99 (20)	94 (20)
	Median (IQR)	94 (81-107)	96 (84-108)	96 (87-109)	97 (86-111)	94 (82-107)
Platelet count x10 ⁹ /L	Mean (SD)	86 (90)	106 (102)	116 (97)	114 (125)	94 (96)
	Median (IQR)	60 (32-107)	81 (38-146)	89 (44-157)	74 (40-153)	65 (34-122)
White blood cell count x10 ⁹ /L	Mean (SD)	42.6 (63.7)	17.4 (36.6)	16.0 (31.5)	16.2 (35.6)	34.1 (57.2)
	Median (IQR)	16.1 (3-54)	3.6 (2-13)	3.1 (2-13)	4.5 (2-12)	8.7 (2-40)
WBC groups by cell counts	<5	526 (33%)	267 (57%)	101 (64%)	87 (53.0%)	981 (41%)
	5-10	147 (9%)	50 (11%)	11 (7%)	32 (20%)	240 (10%)
	10-20	182 (12%)	56 (12%)	14 (9%)	18 (11%)	270 (11%)
	20-50	301 (19%)	48 (10%)	15 (10%)	13 (8%)	377 (16%)
	50-100	219 (14%)	26 (6%)	9 (6%)	5 (3%)	259 (11%)
	100-200	153 (10%)	13 (3%)	7 (5%)	8 (5%)	181 (8%)
	>200	55 (4%)	5 (1%)	0 (0%)	1 (1%)	61 (3%)
LDH ukat/L Normal <4.2	Mean (SD)	11.1 (16)	7.9 (12)	8.0 (14)	7.3 (13)	10.0 (15)
	Median (IQR)	6.8 (4-12)	4.5 (4-7)	4.6 (3-7)	4.2 (3-6)	5.9 (4-10)
Heart disease		269 (17%)	109 (23%)	36 (23%)	42 (26%)	456 (19%)
Diabetes		112 (7%)	42 (9%)	19 (12%)	12 (7%)	185 (8%)
FLT3_ITD		303 (28%)	44 (17%)	19 (23%)	9 (13%)	375 (25%)
NPM1-mutation		349 (34%)	64 (26%)	12 (16%)	17 (27%)	442 (32%)
Favorable risk		298 (20%)	57(13.6%)	9(6.7%)	16(11.3%)	380(17.6%)
Intermediate		699 (48%)	203 (48%)	70 (52%)	90 (64%)	1062 (49%)
Adverse		472 (32%)	160 (38%)	55 (41%)	35 (25%)	722 (33%)

Supplement Table 2. Clinical characteristics by TDT, with alternate grouping.

		0-1d N=583	2-3d N=670	4-6d N=469	>6d N=652	Total: 2374
Sex	M	323 (55%)	349 (52%)	254 (54%)	363 (56%)	1289 (54%)
	F	260 (45%)	321 (48%)	215 (46%)	289 (44%)	1085 (46%)
Age (years)	Mean (SD)	57.3 (15)	60.2 (15)	62.1 (14)	64.4 (12)	61.0 (14)
	Median (IQR)	61 (48-69)	64 (52-72)	65 (55-72)	67 (60-73)	64 (53-72)
	Range	17-87	19-84	18-85	18-85	17-87
CR		466 (80%)	541 (81%)	360 (77%)	456 (70 %)	1823(77%)
AlloSCT	Yes, in CR1	167 (29%)	180 (27%)	93 (20%)	133 (20%)	573 (24%)
	Yes, other	38 (7%)	40 (6%)	31 (7%)	30 (5%)	139 (6%)
	No	378 (65%)	450 (67%)	345 (74%)	489 (75%)	1662 (70%)
AML type	de novo	514 (88%)	534 (80%)	334 (71%)	426 (65%)	1808 (76%)
	tAML	23 (4%)	35 (5%)	46 (10%)	79 (12%)	183 (8%)
	Sec AML	46 (8%)	101 (15%)	89 (19%)	147 (23%)	383 (16%)
ECOG Performance status	0	139 (25%)	185 (29%)	151 (33%)	215 (34%)	690 (30%)
	I	297 (53%)	366 (56%)	257 (56%)	325 (51%)	1245 (54%)
	II	68 (12%)	66 (10%)	34 (7%)	70 (11%)	238 (10%)
	III	35 (6%)	23 (4%)	12 (3%)	21 (3%)	91 (4%)
	IV	19 (3%)	9 (1%)	8 (2%)	5 (1%)	41 (2%)
Bone marrow blasts (%)	Mean (SD)	63 (24)	56 (23)	51 (24)	41 (23)	53 (25)
	Median (IQR)	69 (44-85)	56 (35-75)	50 (30-72)	34 (24-55)	50 (30-75)
Hemoglobin, g/L	Mean (SD)	93 (20)	923 (20)	95 (21)	97 (19)	94 (20)
	Median (IQR)	94 (79-107)	93 (80-105)	94 (84-108)	97 (85-109)	94 (82-107)
Platelet count x10 ⁹ /L	Mean (SD)	78 (88)	87 (84)	94 (92)	114 (112)	94 (96)
	Median (IQR)	55 (30-98)	62 (33-114)	70 (33-123)	84 (40-155)	65 (34-122)
White blood cell count x10 ⁹ /L	Mean (SD)	62.6 (77)	35.6 (56)	21.7 (38)	15.9 (34)	34.1 (57)
	Median (IQR)	33 (6-93)	14.5 (2-45)	6.2 (2-24)	3.7 (2-13)	8.7 (2-40)
WBC groups by cell counts	<5	136 (23%)	242 (36%)	223 (48%)	380 (58%)	981 (41%)
	5-10	52 (9%)	54 (8%)	52 (11%)	82 (13%)	240 (10%)
	10-20	57 (10%)	79 (12%)	64 (14%)	70 (11%)	270 (11%)
	20-50	101 (17%)	146 (22%)	69 (15%)	61 (9%)	377 (16%)
	50-100	102 (18%)	84 (13%)	40 (9%)	33 (5%)	259 (11%)
	100-200	94 (16%)	50 (8%)	16 (3%)	21 (3%)	181 (8%)
	>200	39 (7%)	13 (2%)	4 (1%)	5 (1%)	61 (3%)
LDH ukat/L Normal <4.2	Mean (SD)	13.8 (19)	10.1 (13)	8.3 (15)	7.8 (13)	10.0 (15)
	Median (IQR)	8.8 (5-16)	6.5 (4-11)	5.4 (4-8)	4.5 (3-7)	5.9 (4-10)
Heart disease		69 (12%)	133 (20%)	98 (21%)	156 (24%)	456 (19%)
Diabetes		30 (5%)	51 (8%)	42 (9%)	62 (10%)	185 (8%)
<i>FLT3_ITD</i>		150 (35%)	105 (24%)	62 (23%)	58 (18%)	375 (25%)
<i>NPM1</i>		143 (34%)	141 (34%)	83 (32%)	75 (24%)	442 (32%)
Genetic Risk	Favorable	108 (20%)	134 (21%)	70 (17%)	68 (12%)	380 (18%)
	Intermediate	268 (49%)	284 (45%)	212 (51%)	298 (52%)	1062 (49%)
	Adverse	174 (32%)	207 (33%)	132 (32%)	209 (36%)	722 (33%)

Supplement Table 3. Survival analysis by Cox regression.

		N	Univariate			Multivariate		
			HR	CI 95%	P-value	HR	CI 95%	P-value
Time from Diagnosis to Treatment	0-5d	1587	1	-	-	1	-	-
	6-10d	466	1.36	1.20-1.53	<0.001	1.15	1.00-1.33	0.054
	11-15d	157	1.28	1.06-1.55	0.012	1.06	0.85-1.33	0.599
	>15d	164	1.34	1.11-1.62	0.002	1.12	0.89-1.41	0.316
			P(overall): <0.001			P(overall): 0.267		
Sex	Male	1289	1	-	-	1	-	-
	Female	1085	0.97	0.88-1.08	0.609	1.06	0.94-1.18	0.340
Age (years)	(continuous)	2374	1.04	1.03-1.04	<0.001	1.04	1.03-1.04	<0.001
CR	Yes	1823	1	-	-			
	No	546	9.67	8.58-10.90	<0.001			
	Missing	5						
AlloSCT	Yes, in CR1	573	1	-	-			
	Yes, other	139	1.42	1.10-1.85	0.008			
	No	1662	3.58	3.10-4.13	<0.001			
			P(overall): <0.001					
AML type	De novo	1808	1	-	-	1	-	-
	tAML	183	2.00	1.69-2.37	<0.001	1.68	1.38-2.05	<0.001
	Sec AML	383	2.04	1.80-2.31	<0.001	1.66	1.43-1.92	<0.001
			P(overall): <0.001			P(overall): <0.001		
ECOG performance status	0	690	1	-	-	1	-	-
	I	1245	1.29	1.15-1.45	<0.001	1.14	0.99-1.30	0.066
	II	238	1.85	1.55-2.21	<0.001	1.39	1.14-1.71	0.002
	III	91	2.84	2.23-3.63	<0.001	2.62	1.98-3.48	<0.001
	IV	41	3.70	2.62-5.23	<0.001	3.92	2.44-6.28	<0.001
	Missing	69	P(overall): <0.001			P(overall): <0.001		
BM blast %	(continuous)	2297	1.00	1.00-1.00	0.135	1.00	1.00-1.00	0.641
	Missing	77						
Hemoglobin	(continuous)	2368	1.00	0.99-1.00	0.010	1.00	0.99-1.00	0.103
	Missing	6						
Platelet count	(continuous)	2364	1.00	1.00-1.00	0.047	1.00	1.00-1.00	0.306
	Missing	10						
WBC group	<5	981	1	-	-	1	-	-
	5-10	240	1.06	0.89-1.25	0.534	1.44	1.18-1.75	<0.001
	10-20	270	0.91	0.77-1.08	0.290	1.15	0.94-1.39	0.167
	20-50	377	1.06	0.91-1.22	0.468	1.38	1.16-1.64	<0.001
	50-100	259	1.08	0.91-1.27	0.392	1.33	1.08-1.64	0.007
	100-200	181	1.40	1.16-1.68	<0.001	1.87	1.50-2.33	<0.001
	>200	61	1.44	1.06-1.96	0.018	1.56	1.05-2.31	0.027
	Missing	5	P(overall): 0.003			P(overall): <0.001		
Heart disease	No	1918	1	-	-	1	-	-
	Yes	456	1.46	1.30-1.65	<0.001	1.11	0.96-1.28	0.150

			Univariate			Multivariate		
		N	HR	CI 95%	P-value	HR	CI 95%	P-value
Diabetes	No	2189	1	-	-	1	-	-
	Yes	185	1.42	1.19-1.68	<0.001	1.20	0.97-1.48	0.090
Number of cytogenetic abnormalities	No	943	1	-	-	1	-	-
	1	552	1.09	0.95-1.25	0.213	1.13	0.97-1.31	0.115
	2	210	1.29	1.07-1.55	0.007	1.37	1.12-1.68	0.003
	3	88	1.44	1.12-1.87	0.005	1.55	1.16-2.06	0.003
	4	33	1.76	1.16-2.67	0.008	1.67	1.03-2.70	0.037
	≥5	260	2.53	2.16-2.96	<0.001	1.76	1.42-2.18	<0.001
	Missing	288	P(overall): <0.001			P(overall): <0.001		
Genetic Risk	Favorable	380	1	-	-	1	-	-
	Intermediate	1062	1.86	1.57-2.21	<0.001	1.85	1.53-2.22	<0.001
	Adverse	722	3.02	2.54-3.60	<0.001	2.40	1.95-2.95	<0.001
	Missing	210	P(overall): <0.001			P(overall): <0.001		

Supplement Table 4. Survival analysis by Cox regression, with alternate TDT grouping.

		N	Univariate			Multivariate		
			HR	CI95%	P-value	HR	CI95%	P-value
Time from Diagnosis to Treatment	0-1d	583	1	-	-	1	-	-
	2-3d	670	1.08	0.94-1.24	0.290	1.25	1.06-1.47	0.007
	4-6d	469	1.29	1.11-1.50	0.001	1.10	0.92-1.32	0.296
	>6d	652	1.41	1.23-1.62	<0.001	1.15	0.96-1.36	0.121
				P(overall): <0.001			P(overall): 0.058	
Sex	Male	1289	1	-	-	1	-	-
	Female	1085	0.98	0.88-1.08	0.617	1.06	0.94-1.18	0.336
Age (years)	(continuous)	2374	1.04	1.03-1.04	<0.001	1.02	1.01-1.02	<0.001
CR	Yes	1823	1	-	-	1	-	-
	No	546	9.67	8.58-10.90	<0.001	5.20	4.47-6.05	<0.001
	Missing	5						
AlloSCT	Yes, in CR1	573	1	-	-	1	-	-
	Yes, other	139	1.42	1.10-1.85	0.008	1.94	1.46-2.58	<0.001
	No	1662	3.58	3.10-4.13	<0.001	2.53	2.11-3.03	<0.001
				P(overall): <0.001			P(overall): <0.001	
AML type	De novo	1808	1	-	-	1	-	-
	tAML	183	1.99	1.68-2.36	<0.001	1.31	1.06-1.61	0.012
	Sec AML	383	2.03	1.79-2.30	<0.001	1.49	1.29-1.73	<0.001
				P(overall): <0.001			P(overall): <0.001	
ECOG performance status	0	690	1	-	-	1	-	-
	I	1245	1.29	1.15-1.45	<0.001	1.07	0.93-1.23	0.322
	II	238	1.85	1.55-2.21	<0.001	1.02	0.82-1.26	0.875
	III	91	2.85	2.23-3.64	<0.001	2.14	1.61-2.84	<0.001
	IV	41	3.73	2.64-5.27	<0.001	3.78	2.37-6.02	<0.001
	Missing	69		P(overall): <0.001			P(overall): <0.001	
BM blast %	(continuous)	2297	1.00	1.00-1.00	0.161	1.00	1.00-1.00	0.064
	Missing	77						
Hemoglobin	(continuous)	2368	1.00	0.99-1.00	0.009	1.00	1.00-1.00	0.460
	Missing	6						
Platelet count	(continuous)	2364	1.00	1.00-1.00	0.044	1.00	1.00-1.00	0.060
	Missing	10						
WBC group	<5	981	1	-	-	1	-	-
	5-10	240	1.06	0.89-1.25	0.536	1.34	1.10-1.63	0.003
	10-20	270	0.91	0.77-1.08	0.301	1.08	0.89-1.30	0.460
	20-50	377	1.06	0.92-1.22	0.443	1.18	0.99-1.40	0.061
	50-100	259	1.08	0.91-1.28	0.363	1.32	1.08-1.63	0.008
	100-200	181	1.41	1.17-1.69	<0.001	1.56	1.25-1.94	<0.001
	>200	61	1.45	1.07-1.97	0.016	1.61	1.09-2.39	0.016
	Missing	5		P(overall): 0.003			P(overall): <0.001	
Heart disease	No	1918	1	-	-	1	-	-
	Yes	456	1.46	1.30-1.65	<0.001	1.05	0.91-1.22	0.468

		N	Univariate			Multivariate		
			HR	CI95%	P-value	HR	CI95%	P-value
Diabetes	No	2189	1	-	-	1	-	-
	Yes	185	1.42	1.19-1.68	<0.001	1.29	1.05-1.60	0.017
Number of cytogenetic abnormalities	No	943	1	-	-	1	-	-
	1	552	1.09	0.95-1.25	0.213	1.07	0.92-1.24	0.370
	2	210	1.29	1.07-1.55	0.007	1.19	0.97-1.47	0.097
	3	88	1.45	1.12-1.87	0.005	1.48	1.11-1.97	0.008
	4	33	1.76	1.16-2.66	0.008	1.35	0.83-2.19	0.227
	≥5	260	2.54	2.17-2.97	<0.001	1.48	1.19-1.84	<0.001
	Missing	288	P(overall): <0.001			P(overall): 0.008		
Genetic Risk	Favorable	380	1	-	-	1	-	-
	Intermediate	1062	1.86	1.57-2.21	<0.001	2.02	1.67-2.45	<0.001
	Adverse	722	3.02	2.54-3.60	<0.001	2.56	2.05-3.19	<0.001
	Missing	210	P(overall): <0.001			P(overall): <0.001		

Supplement Table 5. Treatment outcomes by Days from Diagnosis to Treatment, with alternate grouping.

		P	Total	0-1d	2-3d	4-6d	>6d
All age classes	CR/CRi (%) [CI]	<0.001	1823/2369 (77.0) [75.2-78.6]	466/582 (80.1) [76.6-83.2]	541/669 (80.9) [77.7-83.8]	360/467 (77.1) [73.0-80.8]	456/651 (70.0) [66.4-73.5]
	Death within 30 days (%) [CI]	0.099	170/2374 (7.2) [6.2-8.3]	50/583 (8.6) [6.4-11.2]	40/670 (6.0) [4.3-8.0]	26/469 (5.5) [3.7-8.0]	54/652 (8.3) [6.3-10.7]
	Death within 60 days (%) [CI]	0.848	275/2374 (11.6) [10.3-12.9]	70/583 (12.0) [9.5-14.9]	74/670 (11.0) [8.8-13.7]	51/469 (10.9) [8.2-14.0]	80/652 (12.3) [9.9-15.0]
	Two-year survival, % [CI]	<0.001	43.9 [41.9-45.9]	49.0 [45.0-53.3]	48.3 [44.6-52.3]	40.9 [36.6-45.6]	36.9 [33.3-40.8]
<=60 years	CR/CRi (%) [CI]	0.169	804/908 (88.5) [86.3-90.5]	260/289 (90.0) [85.9-93.2]	240/266 (90.2) [86.0-93.5]	154/174 (88.5) [82.8-92.8]	150/179 (83.8) [77.6-88.9]
	Death within 30 days (%) [CI]	0.599	30/908 (3.3) [2.2-4.7]	12/289 (4.2) [2.2-8.4]	6/266 (2.3) [0.8-4.8]	5/174 (2.9) [0.9-6.6]	7/179 (3.9) [1.6-7.9]
	Death within 60 days (%) [CI]	0.979	51/908 (5.6) [4.2-7.3]	15/289 (5.2) [2.9-7.1]	16/266 (6.0) [3.5-9.6]	10/174 (5.7) [2.8-10.3]	10/179 (5.6) [2.7-10.0]
	Two-year survival, % [CI]	0.159	60.7 [57.6-64.0]	61.3 [55.9-67.3]	65.7 [60.1-71.7]	57.6 [50.7-65.5]	55.7 [48.8-63.5]
>60 years	CR/CRi (%) [CI]	0.017	1019/1461 (69.7) [67.3-72.1]	206/293 (70.3) [64.7-75.5]	301/403 (74.7) [70.1-78.9]	206/293 (70.3) [64.7-75.5]	306/472 (64.8) [60.3-69.1]
	Death within 30 days (%) [CI]	0.094	118/1466 (8.0) [6.7-9.6]	38/294 (12.9) [9.3-17.3]	34/404 (8.4) [5.9-11.6]	21/295 (7.1) [4.5-10.7]	47/473 (9.9) [7.4-13.0]
	Death within 60 days (%) [CI]	0.342	224/1466 (15.3) [13.5-17.2]	55/294 (18.7) [14.4-23.6]	58/404 (14.4) [11.1-18.2]	41/295 (13.9) [10.2-18.4]	70/473 (14.8) [11.7-18.3]
	Two-year survival, % [CI]	0.088	33.4 [31.0-35.9]	36.8 [31.7-42.9]	37.0 [32.5-42.1]	30.9 [26.0-36.8]	29.7 [25.8-34.2]