



LUND UNIVERSITY

Incidence and prognostic significance of karyotypic subgroups in older patients with acute myeloid leukemia: the Swedish population-based experience.

Lazarevic, Vladimir; Hörstedt, Ann-sofi; Johansson, Bertil; Antunovic, P; Billström, R; Derolf, A; Hulegårdh, E; Lehmann, S; Möllgård, L; Nilsson, C; Peterson, Stefan; Stockelberg, D; Uggla, B; Wennström, L; Wahlin, A; Höglund, M; Juliusson, Gunnar

Published in:
Blood Cancer Journal

DOI:
[10.1038/bcj.2014.10](https://doi.org/10.1038/bcj.2014.10)

2014

[Link to publication](#)

Citation for published version (APA):

Lazarevic, V., Hörstedt, A., Johansson, B., Antunovic, P., Billström, R., Derolf, A., Hulegårdh, E., Lehmann, S., Möllgård, L., Nilsson, C., Peterson, S., Stockelberg, D., Uggla, B., Wennström, L., Wahlin, A., Höglund, M., & Juliusson, G. (2014). Incidence and prognostic significance of karyotypic subgroups in older patients with acute myeloid leukemia: the Swedish population-based experience. *Blood Cancer Journal*, 4(Feb 28), Article e188. <https://doi.org/10.1038/bcj.2014.10>

Total number of authors:
17

General rights

Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

ORIGINAL ARTICLE

Incidence and prognostic significance of karyotypic subgroups in older patients with acute myeloid leukemia: the Swedish population-based experience

V Lazarevic^{1,2}, A-S Hörstedt³, B Johansson^{4,5}, P Antunovic⁶, R Billström⁷, Å Derolf⁸, E Hulegårdh⁹, S Lehmann⁸, L Möllgård⁹, C Nilsson⁸, S Peterson³, D Stockelberg⁹, B Uggla¹⁰, L Wennström⁹, A Wahlin¹¹, M Höglund¹² and G Juliusson^{1,2}

The Swedish population-based acute myeloid leukemia registry contains data from 3251 patients (excluding acute promyelocytic leukemia) diagnosed between 1997 and 2006. Informative cytogenetic data from 1893 patients were retrospectively added, including 1054 patients aged between 60 and 79 years. Clonal abnormalities were found in 57% of the informative karyotypes. Karyotypic patterns differed by age: t(8;21), inv(16) and t(11q23) were more common in younger patients, whereas loss of 5q, 7q and 17p, monosomal karyotype (MK) and complex karyotypes were more common in older patients. Loss of 5q, 7q and 17p often occurred together within MK. Patients with ≥ 5 chromosome abnormalities had worse overall survival than those with fewer abnormalities or normal karyotype in all age groups. Loss of 5q, 7q and/or 17p had, in contrast to MK, a further negative impact on survival. Multivariable Cox regression analyses on risk factors in patients < 80 years with cytogenetic abnormalities and intensive treatment revealed that age and performance status had the most significant impact on survival (both $P < 0.001$), followed by sex ($P = 0.0135$) and a karyotype including $-7/\text{del}(7q)$ ($P = 0.048$).

Blood Cancer Journal (2014) 4, e188; doi:10.1038/bcj.2014.10; published online 28 February 2014

INTRODUCTION

Acute myeloid leukemia (AML) is a disease of all ages, but the incidence increases with age, resulting in a median of 71 years in Sweden.¹ However, most clinical and biological data are based on younger patient cohorts, mostly from clinical studies including highly selected patients.^{2,3} The backbone of therapy has not changed for many years, comprising a combination of an anthracycline and cytosine arabinoside, with dose recommendations^{4,5} that may depend upon patient age.^{5,6} After consolidation, allogeneic stem cell transplantation (alloSCT) is an option for selected patients.^{3,7}

Cytogenetic characterization is essential for proper subclassification according to WHO 2008,⁸ identifying, for example, entities with specific treatment requirements, such as acute promyelocytic leukemia, core binding factor (CBF) leukemias and tyrosine kinase-activated AML. In fact, establishment of driver mutations is the basis for the development of new targeted therapies.^{9,10} At present, cytogenetic risk stratification is routinely used for choice of therapy and for selecting patients for alloSCT.⁷ There is an abundance of algorithms in use for classifying various cytogenetic abnormalities and karyotypic patterns, such as complexity and monosomal karyotype (MK), into different risk groups.^{11–16}

The Swedish Acute Leukemia Registry is population-based with almost full coverage of Swedish adult patients with a diagnosis of AML since 1997, with continuous clinical follow-up.^{1,17–19} In the present study, all available karyotypic strings were retrospectively

ascertained and reviewed, enabling cytogenetic subclassification and clinicogenetic analyses of a large, well-defined, representative and thus predominantly old AML population, and used to assess the impact on outcome of cytogenetic risk classification systems in this patient cohort.

PATIENTS AND METHODS

The Swedish Adult Acute Leukemia Registry was founded in 1997 by the Swedish Society of Hematology, in collaboration with the Regional Tumor Registries, subsequently the Regional Cancer Centers, covering the entire Swedish population of about 9 million. The Swedish Association of Local Authorities and Regions (SKL) support the registry, and ethics review boards have approved data registration and analysis. Reporting of data on all newly diagnosed adult patients with acute leukemia, *de novo* or secondary (excluding blastic phase of chronic myeloid leukemia), is compulsory, with three separate registrations (pathology, clinical report to national cancer registry and report to leukemia registry). Pediatric patients (< 18 years) are reported to the Nordic Society of Pediatric Hematology and Oncology database, and are not included here. The AML registry contains 98% of all adult patients diagnosed from 1997 to 2006 and reported to the Swedish national cancer registry, irrespective of management, and includes basic parameters such as performance status (PS) and intention-to-treat (intensive vs no or palliative therapy), response to induction therapy and complete survival follow-up. Analysis by *de novo* versus secondary AML will be reported separately. Most of the patients, and the logistics to collect the data, have been reported.^{1,17–19} Standard intensive induction therapy was based on cytosine arabinoside and

¹Department of Hematology and Coagulation, Skåne University Hospital, Lund, Sweden; ²Department of Hematology/Transplantation, Stem Cell Center, Lund University, Lund, Sweden; ³Regional Cancer Center in South Sweden, Skåne University Hospital, Lund, Sweden; ⁴Department of Clinical Genetics, University and Regional Laboratories Region Skåne, Lund, Sweden; ⁵Division of Clinical Genetics, Department of Laboratory Medicine, Lund University, Lund, Sweden; ⁶Department of Hematology, Linköping University Hospital, Linköping, Sweden; ⁷Department of Medicine, Central Hospital Skövde, Skövde, Sweden; ⁸Hematology Center, Karolinska University Hospital, Huddinge and Stockholm, Sweden; ⁹Department of Medicine, Sahlgrenska University Hospital, Göteborg, Sweden; ¹⁰Department of Medicine, Örebro University Hospital, Örebro, Sweden; ¹¹Department of Radiation Sciences, Umeå University, Umeå, Sweden and ¹²Department of Hematology, Academic Hospital, Uppsala, Sweden. Correspondence: Professor G Juliusson, Department of Hematology/Transplantation, Stem Cell Center, Lund University, BMC B10, Lund SE-22185, Sweden.

E-mail: gunnar.juliusson@med.lu.se

Received 7 January 2014; revised 24 January 2014; accepted 29 January 2014

anthracyclines, followed by repeated intensive consolidation, as previously reported,^{1,17–20} and about one-third of all patients up to the age of 55 years underwent alloSCT.¹⁸

From the start of the registry and up to 2007, registered cytogenetic data were restricted to whether chromosome banding analysis had been performed or not. To perform the clinicogenetic association studies reported herein, we retrospectively collected and reviewed all karyotypic strings in all patients diagnosed with AML during 1997–2006. In this report, we have excluded acute promyelocytic leukemia. Mutation analyses of AML-associated genes, such as *CEBPA*, *FLT3* and *NPM1*, were not routinely performed during the study period, and such data are hence not included.

To obtain cytogenetic data, lists of AML patients were created by the Regional Tumor Registries and sent to regional hematologists who, after contact with one of the six departments in Sweden performing cytogenetic analysis, retrieved karyotypic strings from their respective databases. The cytogenetic information was subsequently transferred to the Regional Tumor Registry in Lund. Three of the authors (VL, GJ and BJ) independently checked that the karyotypic strings were written in accordance with the ISCN²¹ and then classified them into 10 different, non-hierarchical abnormality/karyotypic pattern subgroups:

(1) inv(3)(q21q26)/t(3;3)(q21;q26), (2) –5/del(5q), (3) –7/del(7q), (4) t(6;9)(p22;q34), (5) t(8;21)(q22;q22), (6) t(9;11)(p21;q23), (7) other 11q23/*MLL* rearrangements, (8) inv(16)(p13q22)/t(16;16)(p13;q22), (9) –17/del(17p) and (10) MK, defined as two or more autosomal monosomies or a single autosomal monosomy in the presence of structural abnormalities (excluding markers and ring chromosomes).¹⁵ In addition, the number of clonal chromosome changes (1, 2, 3, 4 and 5 or more) per case was registered. As the grouping was non-hierarchical, a case could be included in more than one subgroup; for example, a case with the karyotype 45,X,Y,inv(3)(q21q26), –7 would be classified both as 'inv(3)/t(3;3)' and as '–7/del(7q)'. The patients were subsequently assigned into risk categories using established¹³ criteria.

We also looked further into aberrations in frequently involved chromosomes, and rare but recurrent structural abnormalities.

Clinical data were collected and updated as previously described, and survival was updated through the Swedish Population Registry in May 2012. The median follow-up of surviving patients is 9.6 years, with a minimum of more than 5 years. Analyses on complete remission (CR) rate, early death (ED) rate and overall survival (OS) from date of diagnosis were performed only on patients below the age of 80 years who received intensive treatment.

The incidence by age for AML cases with genetic abnormalities listed above was calculated using the Swedish population in 2001 from Statistics Sweden (www.scb.se). When calculating abnormality-specific incidences, AML patients with uninformative karyotypes, that is, not performed or karyotypic failures, were also included with the assumption that the karyotypic patterns of these cases would be similar to those that were cytogenetically informative in the same age group. Kaplan–Meier estimates were used for survival curves, and *P*-values were computed from a Cox proportional hazards model. To accommodate for the impact of age on survival, age was used as a continuous covariate in the model unless otherwise stated. The presented age cohorts were chosen according to the number of observations to facilitate notions of similarities and differences. Data were analyzed by the R-program software (<http://www.r-project.org>). The Cox proportional hazards regression was used to investigate risk factors for mortality following diagnosis. Multivariable analyses thus included factors for age, sex, PS according to ECOG²²/WHO and genetic risk groups.

The survival curves presented graphically are based on OS, which, because of the poor survival of older AML patients, is very similar to relative survival, that is, OS in relation to an age- and sex-matched population without AML. However, relative survival was also evaluated in the regression models.

RESULTS

Basic karyotypic features

A total of 3251 patients diagnosed with AML (excluding acute promyelocytic leukemia) were analyzed. Of these, informative karyotypes, that is, normal or abnormal, were available in 1893 (58%), mostly from patients eligible for intensive treatment (Table 1). Karyotypes could be uninformative owing to insufficient sampling, no metaphases, technical failure, missing report and no attempt for analysis. An informative karyotype was found in 80%

of patients <60 years, 72% in those between 60 and 69 years, 58% in patients between 70 and 79 years and in 25% of patients who were 80 years or older.

As expected, patients with informative karyotypes and with intensive treatment were younger than those with uninformative karyotypes and palliative treatment (Table 1). The proportions of karyotypic subgroups differed by age for most subgroups. CBF leukemias (t(8;21) or inv(16)/t(16;16)), 11q23/*MLL* rearrangements, inv(3)/t(3;3) and t(6;9) were more common in younger patients, whereas the proportions of –5/del(5q), –7/del(7q), –17/del(17p), complex karyotypes and MK generally increased by age, albeit with somewhat different patterns. In contrast, a normal karyotype was found in 43% of the patients with informative karyotypes, with no clear-cut age difference.

Most karyotypes with abnormalities resulting in the loss of 5q, 7q or 17p were also complex (≥ 3 or ≥ 5 abnormalities) and MK. Among intensively treated AML patients below the age of 80 years with 5q loss, 90% had ≥ 3 abnormalities, 77% had ≥ 5 abnormalities and 81% were MK. The corresponding frequencies in cases with 7q and 17p losses were 67%, 51% and 62%, and 95%, 85% and 91%, respectively. Similarly, among these 219 cases with MK, 171 (78%) also displayed loss of 5q, 7q and/or 17p.

ED rates

ED was defined as death within 30 days from diagnosis. The ED rates in older patients were strongly impacted by PS.¹ Patients aged 60–79 years with good PS (that is, ECOG/WHO 0–II) had ED rates between 5 and 13%, depending on karyotypic subgroup, whereas those with PS III/IV had ED rates of approximately 25% irrespective of karyotype (Table 2).

CR rates

For patients below the age of 60 years, the CR rates differed depending on the karyotypic subgroup, being approximately 90% in CBF leukemias and in cases with a normal karyotype but close to 50% in those with high-risk karyotypes (Table 2). The CR rates in older patients with a normal karyotype decreased from 77% in those aged 60–69 years to 62% in those aged 70–79 years. The corresponding CR rates for cases with high-risk cytogenetics by age were 50% and 25%, respectively.

OS

Risk classification according to MRC criteria¹³ clearly separated short-term and long-term survival in both younger and older patients (Figure 1a–b). One-third, that is, five of the older patients with low-risk karyotypes, had a long-term survival plateau, whereas the long-term survival was approximately 10% in those with intermediate-risk karyotypes.

The number of clonal abnormalities separated survival curves in all age groups (Figures 2a–c). The greatest difference was observed between those with 3–4 and ≥ 5 or more abnormalities. Including data on MK did not add to the separation of high and very high-risk cytogenetics in any of the age groups (Figure 3a–c). However, abnormalities resulting in the loss of 5q, 7q and/or 17p had strong prognostic impact. If only one of these losses was found, the outcome was better than that for AML cases with two or all three losses (Figure 4a). In patients with abnormal karyotype, excluding CBF leukemias, those with MK including 5q, 7q and/or 17p losses had the worst outcome, whereas MK without 5q, 7q or 17p loss had the same impact as non-MK (Figure 4b). Similarly, patients with high-risk cytogenetics without 5q, 7q and/or 17p loss had the same survival as intermediate-risk patients (data not shown).

Other abnormalities

Trisomy 8 was found in 81 patients, mostly as a single abnormality (*n* = 60), and in only 10 patients as part of complex karyotypes.

Table 1. The AML patient cohort in relation to age, karyotypic features, therapy and incidence

Characteristics	Age (years)					Total	Median Age (years)
	18–39	40–59	60–69	70–79	≥80		
No. of patients	193	612	650	1007	789	3251	71
No. of informative ^a , karyotypes (%) ^b	154 (80)	486 (79)	466 (72)	588 (58)	199 (25)	1893 (58)	66
Intensively treated patients (%)	148 (96)	449 (92)	393 (84)	364 (62)	63 (32)	1417 (75)	62
Not intensively treated patients (%)	6 (4)	37 (8)	73 (16)	224 (38)	136 (68)	476 (25)	76
No. of uninformative ^c karyotypes (%)	39 (20)	126 (21)	184 (28)	419 (42)	590 (75)	1358 (42)	
Intensively treated patients	36	101	122	158	38	455	67
Not intensively treated patients	3	25	62	261	552	903	81
No. with a normal karyotype (%)	57 (37)	212 (44)	211 (45)	240 (41)	90 (45)	810 (43)	66
No. with an abnormal karyotype	97	274	255	348	109	1083	
<i>Specific karyotypic subgroups^d</i>							
inv(3)(q21;q26)/t(3;3)(q21;q26) (%)	2 (1.3)	10 (2.1)	2 (0.4)	4 (0.7)	1 (0.5)	19 (1.0)	58
– 5/del(5q) (%)	7 (4.5)	54 (11)	56 (12)	91 (16)	30 (15)	238 (13)	70
t(6;9)(p22;q34) (%)	3 (1.9)	0	0	0	0	3 (0.2)	36
– 7/del(7q) (%)	11 (7.1)	66 (14)	62 (13)	86 (15)	24 (12)	249 (13)	67
t(8;21)(q22;q22) (%)	11 (7.1)	13 (2.7)	6 (1.3)	4 (0.7)	2 (1.0)	36 (1.9)	55
t(9;11)(p21;q23) (%)	3 (1.9)	5 (1.0)	3 (0.6)	1 (0.2)	1 (0.5)	13 (0.7)	58
11q23 rearrangements; not t(9;11) (%)	3 (1.9)	12 (2.5)	0	6 (1.0)	0	21 (1.1)	54
inv(16)(p13;q22)/t(16;16)(p13;q22) (%)	16 (10)	13 (2.7)	8 (1.7)	5 (0.9)	0	42 (2.2)	47
– 17/del(17p) (%)	2 (1.3)	36 (7.4)	42 (9.0)	67 (11)	19 (10)	166 (8.8)	71
Loss of 5q, 7q and/or 17p (%)	19 (12)	104 (21)	106 (23)	152 (26)	50 (25)	431 (23)	68
Monosomal karyotype (%)	15 (9.6)	77 (16)	79 (17)	128 (22)	41 (21)	340 (18)	69
≥3 Abnormalities (%)	29 (19)	106 (22)	103 (22)	166 (28)	51 (26)	455 (24)	69
≥5 Abnormalities (%)	10 (6.5)	67 (14)	62 (13)	106 (18)	31 (16)	276 (15)	69
<i>Swedish population, millions^e</i>							
Incidence per million and year ^f	2.57	2.42	0.84	0.69	0.46	6.97	—
CBF leukemia ^g	1.3	1.4	2.4	2.2	1.7	1.9	—
Loss of 5q, 7q and/or 17p ^h	0.9	5.4	18	38	43	11	—
Monosomal karyotype	0.7	4.1	13	32	35	8.4	—
≥3 Abnormalities	1.4	5.6	17	41	44	11	—
≥5 Abnormalities	0.5	3.5	10	26	27	6.8	—
Normal karyotype	2.9	11	36	60	77	20	—

Abbreviations: AML, acute myeloid leukemia; CBF, core binding factor. ^aEither abnormal or normal karyotypes. ^bPercentage of the total number of informative and non-informative karyotypes, and percentage of informative karyotypes for other subgroups. ^cNot performed or karyotypic failures. ^dAs the grouping was non-hierarchical, a case may be included in more than one cytogenetic subgroup. ^eData on the Swedish population aged 18 years or more in 2001 according to Statistics Sweden (www.scb.se). ^fIncidence calculated using the assumption that the karyotypic patterns are similar in cytogenetically informative and uninformative cases. ^gCBF leukemia comprises AML with t(8;21), inv(16) or t(16;16). χ^2 -analysis comparing the number of CBF patients/million/year in ages <60 years vs 60–79 years: $\chi^2 = 1.95$, $P = 0.16$. ^h χ^2 -analysis comparing the number of patients with 5q, 7q and/or 17p loss/million/year in ages <60 years vs 60–79 years: $\chi^2 = 415.3$, $P < 0.0001$. χ^2 -analysis comparing number of patients with 5q loss/million/year in ages <60 years vs 60–79 years: $\chi^2 = 258.1$, $P < 0.0001$.

The median age of those patients was 68 years, and the median survival was 298 days.

del(13q)/monosomy 13 was found in 71 patients, in all but four as part of complex abnormalities and MK. The median age was 69 years and the median survival was 98 days.

del(3p)/monosomy 3 was found in 62 patients, in all but four as part of complex abnormalities and MK. The median age was 67 years and the median survival was 121 days.

12p abnormalities were found in 48 patients, mostly within complex (n = 38) and MKs. Non-complex 12p aberrations always involved 12p12 or p13, in two of them with concurrent del(5q). The median age was 60 years, and the median survival was 150 days.

Translocations involving either 3q21 or 3q26 were found in 10 patients, in all but one within non-complex abnormalities. These were t(1;3)(p36;q21) (n = 3), t(3;5)(q21;q31) (n = 2), t(3;12)(q26;p13) (n = 2) and t(3;21)(q26;q22) (n = 3). The median age of these patients was 49 years, and the median survival was 252 days; four of them had alloSCT.

der(1;7)(q10;p10) was found in three patients, in two of them as a single abnormality. Their ages ranged between 24 and 76 years. One of them survived following alloSCT.

Multivariable analysis

Multiple Cox regression analyses of predictive factors for survival in patients below the age of 80 years with clonal abnormalities and eligible for intensive treatment revealed that age and PS had the most significant impact (both $P < 0.001$) (Table 3). The close correlation between older age and other negative risk factors, such as the number of clonal changes and high-risk abnormalities, should be considered. There was an additional impact of sex ($P = 0.0135$) and karyotype including $-7/\text{del}(7q)$ ($P = 0.048$). If age and PS were excluded in the analysis, $-7/\text{del}(7q)$ had the strongest impact on OS ($P = 0.014$), followed by sex ($P = 0.035$) and number of abnormalities ($P = 0.054$) (Table 3). In a further analysis evaluating risk factors (excluding PS) for relative survival, age retained its significance ($P < 0.001$), as did $-7/\text{del}(7q)$

Table 2. Early death and complete remission rates after intensive treatment in relation to age, performance status and cytogenetic subgroup^a

	All patients		Performance status 0–II		Performance status III–IV	
	<60 years	60–79 years	<60 years	60–79 years	<60 years	60–79 years
Early death rate^b						
Normal karyotype (%)	11/258 (4.3)	24/347 (6.9)	10/242 (4.1)	15/305 (4.9)	1/13 (7.7)	9/38 (24)
CBF leukemia ^c (%)	2/49 (4.1)	2/18 (11)	1/46 (2.2)	1/14 (7.1)	1/3 (33)	1/4 (25)
– 5/del(5q) (%)	4/50 (8.0)	11/94 (12)	4/41 (9.8)	8/79 (10)	0/7	3/12 (25)
– 7/del(7q) (%)	7/68 (10) ^d	11/99 (11)	6/58 (10)	7/83 (8.4)	1/9 (11)	4/14 (29)
– 17/del(17p) (%)	3/36 (8.3)	9/71 (13)	3/30 (10)	6/55 (11)	0/5	3/12 (25)
5q, 7q and/or 17p loss (%)	7/106 (6.6)	13/159 (8.2)	6/92 (6.5)	9/135 (6.7)	1/12 (8.3)	4/19 (21)
≥ 5 Abnormalities (%)	4/67 (6.0)	17/115 (15)	4/59 (6.8)	12/93 (13)	0/7	5/17 (29)
Monosomal karyotype (%)	5/82 (6.1)	16/137 (12)	5/72 (6.9)	11/111 (9.9)	0/9	5/20 (25)
Complete remission rate						
Normal karyotype (%)	224/258 (87)	247/347 (71)	209/242 (86)	224/305 (73)	12/13 (92)	20/38 (53)
CBF leukemia ^c (%)	45/49 (92)	15/18 (83)	43/46 (94)	12/14 (86)	2/3 (67)	3/4 (75)
– 5/del(5q) (%)	26/50 (52)	36/94 (38)	23/41 (65)	33/79 (42)	2/7 (29)	2/12 (17)
– 7/del(7q) (%)	38/68 (56) ^e	37/99 (37) ^e	35/58 (60)	35/83 (42)	3/9 (33)	2/14 (14)
– 17/del(17p) (%)	17/36 (47)	22/71 (31)	15/30 (50)	19/55 (35)	2/5 (40)	1/12 (8.3)
5q, 7q and/or 17p loss (%)	59/106 (56) ^e	69/159 (43) ^e	54/92 (59)	63/135 (47)	4/12 (33)	4/19 (21)
≥ 5 Abnormalities (%)	37/67 (55) ^e	46/115 (40) ^e	35/59 (59)	41/93 (44)	2/7 (29)	3/17 (18)
Monosomal karyotype (%)	48/82 (59)	56/137 (41)	44/72 (61)	51/111 (46)	4/9 (44)	3/20 (15)

Abbreviations: AML, acute myeloid leukemia; CBF, core binding factor; CR, complete remission; ED, early death. ^aEarly death defined as death within 30 days from diagnosis. Performance status was according to ECOG²²/WHO. ^bNumber of patients with early death/total number of patients (percentage). Performance status was missing in a few patients. ^cCBF leukemia comprises AML with t(8;21), inv(16) or t(16;16). ^d χ^2 -analysis comparing ED rate with CBF or normal karyotype vs 7q loss in patients <60 years: $X^2 = 4.05$, $P = 0.044$. ^e χ^2 -analysis comparing CR rate with CBF or normal karyotype vs 7q loss in patients <60 years: $X^2 = 37.8$, $P < 0.0001$; and in patients 60–79 years: $X^2 = 40.2$, $P < 0.0001$. CBF or normal karyotype vs 5q, 7q and/or 17p loss in patients <60 years: $X^2 = 49.3$, $P < 0.0001$; in patients 60–79 years: $X^2 = 38.4$, $P < 0.0001$. CBF or normal karyotype vs ≥ 5 abnormalities in patients <60 years: $X^2 = 38.8$, $P < 0.0001$; and in patients 60–79 years: $X^2 = 38.4$, $P < 0.0001$.

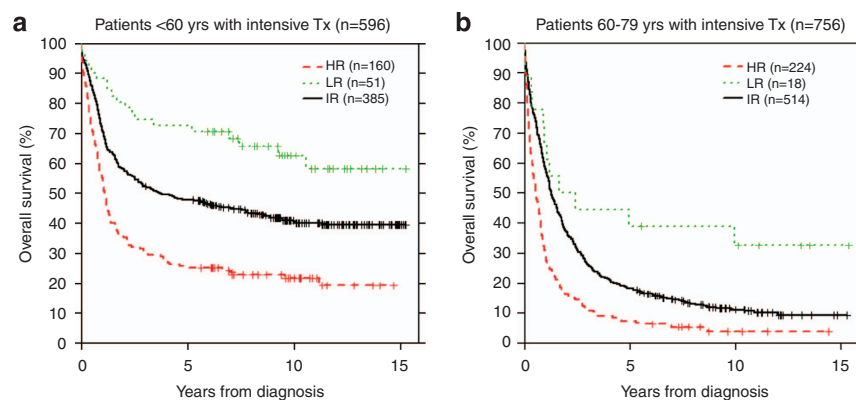


Figure 1. Overall survival for intensively treated patients according to age and cytogenetic-risk group. HR, high risk; LR, low risk (that is, core binding factor leukemia); IR, intermediate risk. (a) Patients below 60 years of age. HR vs IR ($P < 0.001$) and LR vs IR ($P = 0.05$). (b) Patients between 60 and 79 years of age. HR vs IR ($P < 0.001$) and LR vs IR ($P = 0.1$).

($P = 0.033$), and the hazard ratio for female sex was 0.83 ($P = 0.076$). In none of the multivariable analyses did MK impact significantly on survival.

DISCUSSION

Age and karyotype are among the most powerful prognostic factors in AML, and they guide treatment strategy. This notwithstanding, most cytogenetic data on AML have been obtained from studies of young patients. Furthermore, cytogenetic results from older patients have mostly been compiled from clinical studies that recruit highly selected patients.²⁰ In contrast, the present study is based on the Swedish national population-based AML registry^{1,17–18} with karyotypic data retrieved from cytogenetic analyses performed as part of

clinical routine. We were able to collect almost 1900 informative karyotype reports, comprising more than two-thirds of all individual patients aged 60–69 years and more than half of all patients in the age group of 70–79 years. In the end, informative karyotypes were available not only from most of the older patients who received intensive treatment but also from 476 patients who had palliation only (Table 1). For incidence of genetic abnormalities, our report emerges from the largest population-based study,^{23–28} and for clinical impact again the largest population-based study,^{27,28} and the study with the largest number of cytogenetically characterized and intensively treated AML patients over 70 years.^{29–32}

It should, however, be emphasized that genetic data from our study group are still selected owing to the fact that chromosome

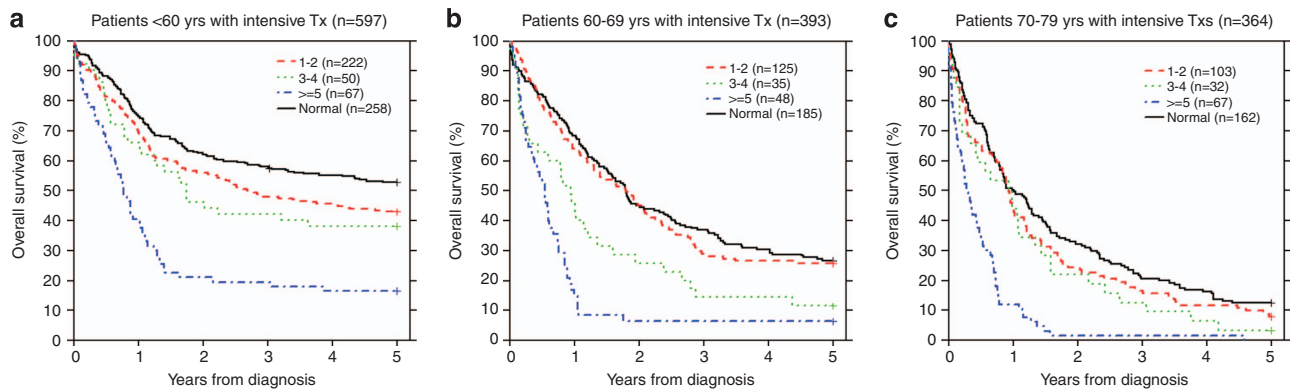


Figure 2. Overall survival for intensively treated patients according to the number of chromosomal abnormalities (CBF leukemias included). Normal karyotype, 1–2 abnormalities, 3–4 abnormalities and ≥ 5 abnormalities. (a) Patients below 60 years of age. Normal vs 1–2 ($P=0.009$), normal vs 3–4 ($P=0.01$) and normal vs ≥ 5 ($P<0.001$). (b) Patients between 60 and 69 years of age. Normal vs 1–2 ($P=0.8$), normal vs 3–4 ($P=0.02$) and normal vs ≥ 5 ($P<0.001$). (c) Patients between 70 and 79 years of age. Normal vs 1–2 ($P=0.2$), normal vs 3–4 ($P=0.09$) and normal vs ≥ 5 ($P<0.001$).

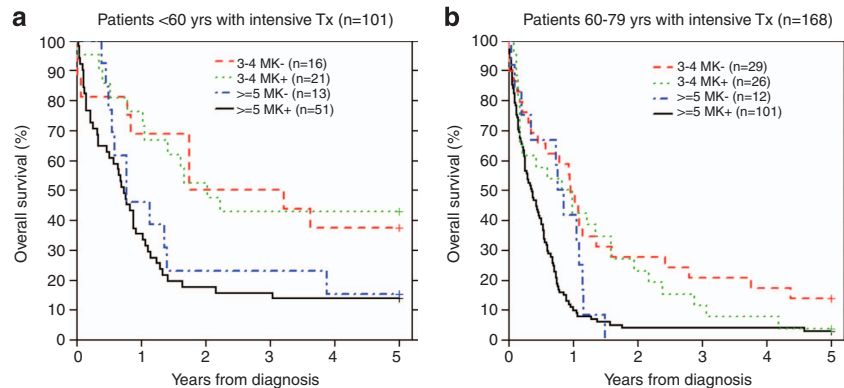


Figure 3. Overall survival for intensively treated patients according to the number of chromosomal abnormalities and monosomal karyotype (CBF leukemias excluded). MK+, monosomal karyotype; MK-, not monosomal karyotype; 3–4 abnormalities and ≥ 5 abnormalities. (a) Patients below 60 years of age. 3–4 and MK+ vs ≥ 5 and MK+ ($P=0.01$), ≥ 5 and MK+ vs ≥ 5 and MK- ($P=0.3$), and 3–4 and MK+ vs 3–4 and MK- ($P=0.9$). (b) Patients between 60 and 79 years of age. 3–4 and MK- vs ≥ 5 and MK+ ($P<0.001$), 3–4 and MK- vs ≥ 5 and MK- ($P=0.3$), ≥ 5 and MK+ vs ≥ 5 and MK- ($P=0.1$), and 3–4 and MK+ vs 3–4 MK- ($P=0.5$).

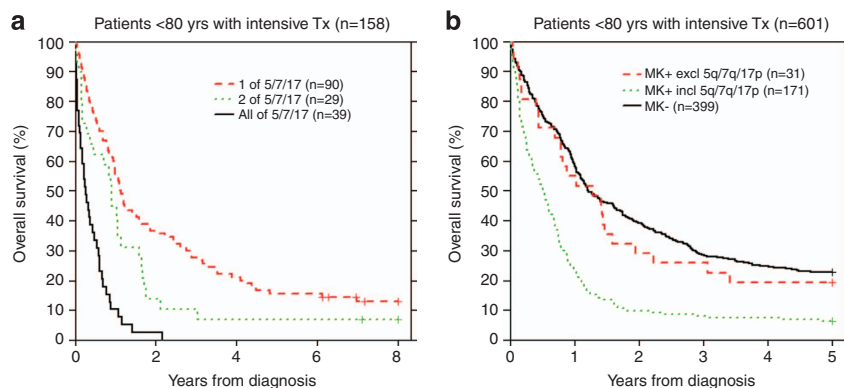


Figure 4. Overall survival for intensively treated patients below the age of 80 years according to loss of 5q, 7q or 17p and monosomal karyotype (CBF leukemias excluded). (a) One, two or three of 5q, 7q and 17p abnormalities. One vs two ($P=0.02$), one vs three ($P<0.001$) and two vs three ($P<0.001$). (b) MK-, cytogenetically abnormal but not monosomal karyotype; MK+ incl 5q/7q/17p, monosomal karyotype with one or more abnormalities resulting in loss of 5q, 7q and/or 17p; and MK+ excl 5q/7q/17p, monosomal karyotype but no losses of 5q, 7q or 17p. MK- vs MK+ excl 5q/7q/17p ($P=0.9$), MK- vs MK+ incl 5q/7q/17p ($P<0.001$) and MK+ incl vs MK+ excl 5q/7q/17p ($P<0.001$).

analysis in Sweden, like elsewhere, is primarily recommended for patients who might become eligible for intensive therapy. In the United States, 52% of *de novo* AML patients in ages 65–79 years received 'infused chemotherapy including hypomethylating

agents' during the period 2000–2007, according to a compilation of SEER and Medicare data.³³ As a comparison, 62% of Swedish patients of this age received intensive treatment with the aim to induce CR.¹

Table 3. Multivariable Cox regression analyses of risk factors for overall survival

Factor	Category	Including age and PS (n = 498)			Excluding age and PS (n = 509)		
		HR	CI (95%)	P-value	HR	CI (95%)	P-value
Age (years)	<40	1					
	40–49	0.96	0.60–1.53	—	—	—	—
	50–59	1.34	0.89–1.99	—	—	—	—
	60–69	1.73	1.18–2.55	—	—	—	—
	70–79	2.74	1.86–4.05	<0.001	—	—	—
PS	0–II	1		—	—	—	—
	III–IV	2.10	1.54–2.86	<0.001	—	—	—
Gender	Male	1	—	—	1	—	—
	Female	0.78	0.64–0.95	0.014	0.82	0.67–0.99	0.035
Monosomal karyotype	No	1	—	—	1	—	—
	Yes	1.16	0.83–1.63	0.387	1.14	0.83–1.57	0.418
– 5/del(5q)	No	1	—	—	1	—	—
	Yes	1.23	0.88–1.71	0.240	1.23	0.89–1.70	0.210
– 7/del(7q)	No	1	—	—	1	—	—
	Yes	1.28	1.00–1.64	0.048	1.35	1.06–1.73	0.014
– 17/del(17p)	No	1	—	—	1	—	—
	Yes	1.24	0.82–1.88	0.317	1.19	0.80–1.79	0.391
No. of abnormalities	1–2	1	—	—	1	—	—
	3–4	1.15	0.83–1.59	—	1.23	0.90–1.68	—
	≥5	1.65	1.06–2.58	0.098	1.68	1.11–2.55	0.054

Abbreviations: CI, confidence interval; HR, hazard ratio (reference expressed as 1); PS, performance status according to ECOG/WHO. Data from patients <80 years with clonal genetic abnormalities and eligible for intensive treatment.

Comparing the frequencies of specific chromosome abnormalities revealed that younger AML patients were more likely to harbor the favorable abnormalities t(8;21) and inv(16), and also some intermediate and poor-risk markers, such as 11q23 rearrangements and inv(3). It is, in this context, noteworthy that the incidence of CBF leukemia, 1.9 per million inhabitants per year, only showed a minor, nonsignificant increase by age ($P=0.16$). In contrast, the incidence of AML with $-5/\text{del}(5q)$ is 0.3/million/year in the age group <40 years, increasing 60-fold to 18/million/year in the age group >70 years ($P<0.0001$; Table 1). Similar data were achieved from the population-based study from northern UK.²⁵ This most likely illustrates different pathophysiologic mechanisms involved in leukemogenesis in different AML groups.

Cytogenetic risk classifications are often ascertained from pooled data from large randomized studies, and are based on the treatment outcome from patients below the age of 60.^{2,11,13,14,34} Whether these classifications are equally useful in patients older than 60 years has been unclear, although there are several reports from selected patients who are included into clinical trials, mainly between 60 and 69 years, that demonstrate prognostic impact from cytogenetic data.^{27,29–32} In the present population-based study, a similar impact on outcome of risk-stratifying genetic findings in younger and older patients was observed; however, older patients had poorer outcome in all risk groups, and there were very few older patients in the low-risk group, when acute promyelocytic leukemia is excluded.²⁰ High-risk cytogenetics was clearly more common in older patients (Table 1). Established risk classifications define high-risk cytogenetics as, for example, the presence of $-5/\text{del}(5q)$, $-7/\text{del}(7q)$, complex karyotypes with ≥ 3 or ≥ 5 abnormalities and MK. Monosomy 17 or deletion of 17p has also been suggested as a high-risk feature. We found a strong overlap between these abnormalities, especially as regards changes of chromosomes 5, 7 and 17. This not only indicates that they identify the same subgroup of patients characterized by poor prognosis, but also

that they cooperate in the leukemogenic process and/or have similar mechanisms behind their occurrence. Furthermore, the prognostic impact of a complex karyotype or MK was clearly influenced by the presence of 5q, 7q and 17p losses. However, MK did not affect the impact of a complex karyotype. Thus, adding MK into the risk stratification of Swedish AML patients did not improve survival prediction. We hence conclude that the negative impact of MK seems to be mostly carried out by abnormalities of chromosomes 5, 7 and 17. This is in contrast to other studies³⁵ but in line with data from the Spanish and German MDS/AML Registry.^{36–37}

The multivariable analyses identified 7q abnormalities as the most significant of the cytogenetic abnormalities, with impact on survival beyond that of age and PS. Deletion of 7q might display a stronger impact than other genetic markers, as it was slightly more evenly distributed in different age groups than other risk-classifying abnormalities (Table 1).

Although the present study is based on a large, unselected and representative AML cohort, a single study has limited power and cannot define the hierarchy of cytogenetic changes, nor can it define the abnormalities that have the greatest clinical utility. In addition, we cannot, as of yet, provide recommendations on the consequences of various therapies, such as alloSCT, based on these findings.³⁸ Such recommendations have to be evaluated in prospective collaborative studies. However, we believe that our large study on the proportions, incidences and clinical impact of specific AML abnormalities/karyotypic patterns in different age groups, with long-term clinical follow-up and focus on the predominant patient group, provides information useful for further studies aimed to improve outcome for the overall AML population that still continues to have a poor outcome.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The six regional tumor registries are acknowledged for their contribution to update registry data and survival follow-up, and the departments performing cytogenetic analyses to assist in collecting karyotype reports. This work was supported by grants from the Swedish Cancer Society. The data were in part presented at the European Haematology Association annual meeting in Stockholm, June 2013. None of the authors had disclosures pertinent to this study.

REFERENCES

- Juliusson G, Antunovic P, Derolf A, Lehmann S, Möllgård L, Stockelberg D et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood* 2009; **113**: 4179–4187.
- Burnett AK, Russell NH, Hills RK, Hunter AE, Kjeldsen L, Yin J et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the Medical Research Council AML15 trial. *J Clin Oncol* 2013; **31**: 3360–3368.
- Koreth J, Schlenk R, Kopecky KJ, Honda S, Sierra J, Djulbegovic BJ et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. *JAMA* 2009; **301**: 2349–2361.
- Löwenberg B. Sense and nonsense of high-dose cytarabine for acute myeloid leukemia. *Blood* 2013; **121**: 26–28.
- Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A et al. High dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med* 2009; **361**: 1235–1248.
- O'Donnell MR, Abboud CN, Altman JK, Appelbaum FR, Arber DA, Attar E et al. NCCN Practice guidelines for acute myeloid leukemia, version 2.2012. Accessed at www.nccn.org/ve/FTPANM/online/2013/boletines/N51/Seccion13-NCCN-Acute_Myeloid_Leukemia.pdf.
- Cornelissen JJ, Gratwohl A, Schlenk RF, Sierra J, Bornhäuser M, Juliusson G et al. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. *Nat Rev Clin Oncol* 2012; **9**: 579–590.
- Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri PS, Stein H et al. *WHO classification of tumours of haematopoietic and lymphoid tissues*. 4th edn. IARC Press: Lyon, France, 2008.
- Grossmann V, Schnittger S, Kohlmann A, Eder C, Roller A, Dicker F et al. A novel hierarchical prognostic model of AML solely based on molecular mutations. *Blood* 2012; **120**: 2963–2972.
- The Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult *de novo* acute myeloid leukemia. *N Engl J Med* 2013; **368**: 2059–2074.
- Döhner H, Estey E, Amadori S, Appelbaum FR, Büchner T, Burnett AK et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood* 2010; **115**: 453–474.
- Patel JP, Gönen M, Figueroa M, Fernandez H, Sun Z, Racevskis J et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med* 2012; **366**: 1079–1089.
- Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood* 2010; **116**: 354–365.
- Byrd JC, Mrózek K, Dodge RK, Carroll AJ, Edwards CG, Arthur DC et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with *de novo* acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). *Blood* 2002; **100**: 4325–4336.
- Brems DA, van Putten WL, de Greef GE, van Zelderen-Bhola SL, Gerssen-Schoori KB, Mellink CH et al. Monosomal karyotype in acute myeloid leukemia: a better indicator of poor prognosis than a complex karyotype. *J Clin Oncol* 2008; **26**: 4791–4797.
- Sekeres MA. My AML cytogenetics classification scheme is better than yours. *Biol Blood Marrow Transplant* 2012; **18**: 160–161.
- Juliusson G, Billström R, Gruber A, Hellström-Lindberg E, Höglund M, Karlsson K et al. Attitude towards remission induction for elderly patients with acute myeloid leukemia influences survival. *Leukemia* 2006; **20**: 42–47.
- Juliusson G, Karlsson K, Vlj Lazarevic, Wahlin A, Brune M, Antunovic P et al. Hematopoietic stem cell transplantation rates and long term survival in acute myeloid and acute lymphoblastic leukemia: real world population-based data from Swedish Acute Leukemia Registry 1997–2006. *Cancer* 2011; **117**: 4238–4246.
- Juliusson G, Lazarevic V, Hörstedt AS, Hagberg O, Höglund M. Acute myeloid leukemia in the real world: why population-based registries are needed. *Blood* 2012; **119**: 3890–3899.
- Wahlin A, Markevårn B, Golovleva I, Nilsson M. Prognostic significance of risk group stratification in elderly patients with acute myeloid leukemia. *Br J Haematol* 2001; **115**: 25–33.
- Shaffer LG, McGowan-Jordan J, Schmid M. *An International System for Human Cytogenetic Nomenclature* (2013). Karger AG: Basel, 2013.
- Oken M, Creech R, Tormey D, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–655.
- Preiss BS, Kerndrup GB, Schmidt KG, Sörensen AG, Clausen NA, Gadeberg OV et al. Cytogenetic findings in adult *de novo* acute myeloid leukaemia. A population-based study of 303/337 patients. *Br J Haematol* 2003; **123**: 219–234.
- Bacher U, Kern W, Schnittger S, Hiddemann W, Haferlach T, Schoch C. Population-based age-specific incidences of cytogenetic subgroups of acute myeloid leukemia. *Haematologica* 2005; **90**: 1502–1510.
- Sanderson RN, Johnson PRE, Moorman AV, Roman E, Willett E, Taylor PR et al. Population-based demographic study of karyotypes in 1709 patients with adult acute myeloid leukemia. *Leukemia* 2006; **20**: 444–450.
- Cheng Y, Wang Y, Wang H, Chen Z, Lou J, Xu H et al. Cytogenetic profile of *de novo* acute myeloid leukemia: a study based on 1432 patients in a single institution in China. *Leukemia* 2009; **23**: 1801–1806.
- Yanada M, Ohtake S, Miyawaki S, Sakamaki H, Sakura T, Maeda T et al. The demarcation between younger and older acute myeloid leukemia patients. *Cancer* 2013; **119**: 3326–3333.
- Gangatharan SA, Grove CS, P'ng S, O'Reilly J, Joske D, Leahy MF et al. Acute myeloid leukaemia in Western Australia 1991–2005: a retrospective population-based study of 898 patients regarding epidemiology, cytogenetics, treatment and outcome. *Int Medicine* 2013; **43**: 903–911.
- Farag SS, Archer KJ, Mrózek K, Ruppert AS, Carroll AJ, Vardiman JW et al. Pretreatment cytogenetics add to other prognostic factors predicting complete remission and long-term outcome in patients 60 years of age or older with acute myeloid leukemia: results from Cancer and Leukemia Group B 8461. *Blood* 2006; **108**: 63–73.
- Fröhling S, Schlenk RF, Kayser S, Morhardt M, Benner A, Döhner K et al. Cytogenetics and age are major determinants of outcome in intensively treated acute myeloid leukemia patients older than 60 years: results from AMLSG trial AML HD98-B. *Blood* 2006; **108**: 3280–3288.
- Wheatley K, Brookes CL, Howman AJ, Goldstone AH, Milligan DW, Prentice AG et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. *Br J Haematol* 2009; **145**: 598–605.
- Mrózek K, Marcucci G, Nicolet D, Maharry KS, Becker H, Whitman SP et al. Prognostic significance of the European LeukemiaNet standardized system for reporting cytogenetic and molecular alterations in adults with acute myeloid leukemia. *J Clin Oncol* 2012; **30**: 4515–4523.
- Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. *Haematologica* 2012; **97**: 1916–1924.
- Damm F, Heuser M, Morgan M, Wagner K, Görlich K, Grosshennig A et al. Integrative prognostic risk score in acute myeloid leukemia with normal karyotype. *Blood* 2011; **117**: 4561–4568.
- Kayser S, Zucknick M, Döhner K, Krauter J, Köhne CH, Horst HA et al. Monosomal karyotype in adult acute myeloid leukemia: prognostic impact and outcome after different treatment strategies. *Blood* 2012; **119**: 551–558.
- Valcárcel D, Ademà V, Solé F, Ortega M, Nomdedeu B, Sanz G et al. Complex, not monosomal, karyotype is the cytogenetic marker of poorest prognosis in patients with primary myelodysplastic syndrome. *J Clin Oncol* 2013; **31**: 916–922.
- Schanz J, Tüchler H, Solé F, Mallo M, Luno E, Cervera J et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. *J Clin Oncol* 2012; **30**: 820–829.
- Cornelissen JJ, Brems D, van Putten WLJ, Gratwohl AA, Passweg JR, Pabst T et al. Comparative analysis of the value of allogeneic hematopoietic stem-cell transplantation in acute myeloid leukemia with monosomal karyotype versus other cytogenetic risk categories. *J Clin Oncol* 2012; **30**: 2140–2146.



This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-sa/3.0/>