ORIGINAL ARTICLE

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

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The Swedish population-based acute myeloid leukemia registry contains data from 3251 patients (excluding acute promyelocytic leukemia) diagnosed between 1997 and 2006. Informatice 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/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 recommendations4,5 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 2008,6 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 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...
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anthraclycines, 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)/q21;q26/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)p13;q22/t(16;11)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.XY,inv(3)/q21;q26, −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 regression 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 ECOG/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 karyotype 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.
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 69 years and the median survival was 298 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)(p36q21) (n = 3), t(3;5)(q21;q31) (n = 2), t(3;12)(q26p13) (n = 2) and t(3;21)(q26q22) (n = 3). The median age of these patients was 49 years, and the median survival was 252 days; four of them had alloSCT.

The median age of these patients was 49 years, and the median survival was 252 days; four of them had alloSCT.

The median age of these patients was 70 years, and the median survival was 121 days.

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/del(7q) (P = 0.048). If age and PS were excluded in the analysis, −7/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/del(7q)
In contrast, the present study is based on the Swedish national population-based AML registry\(^\text{17–18}\) 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 kayotypes were available not only from most of the older patients who received intensive treatment but also from from 476 patients who had palliation only (Table 1). For incidence of genetic abnormalities, our report emerges from the largest population-based study\(^\text{23–28}\) and for clinical impact again the largest population-based study, 27,28, and for clinical impact again the largest population-based study,\(^\text{23–28}\) and the study with the largest number of cytogenetically characterized and intensively treated AML patients over 60 years.\(^\text{29–32}\)

### 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.\(^\text{20}\) In contrast, the present study is based on the Swedish national population-based AML registry\(^\text{17–18}\) with karyotypic data retrieved from cytogenetic analyses performed as part of the present study. As such, the study group are still selected owing to the fact that chromosome

### Table 2. Early death and complete remission rates after intensive treatment in relation to age, performance status and cytogenetic subgroup\(^\text{a}\)

|                  | 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               |
|                  |              |                          | 60–79 years               |
| Early death rate\(^\text{b}\) | 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\(^\text{a}\) (%) | 2/49 (4.1) | 2/18 (11) | 1/46 (2.2) | 1/14 (7.1) | 1/3 (33) | 1/4 (25) |
|                  | – 5(del5q) (%) | 4/50 (8.0) | 11/94 (12) | 4/41 (9.8) | 8/79 (10) | 0/7 | 3/12 (25) |
|                  | – 7(del7q) (%) | 7/68 (10)\(^\text{d}\) | 11/99 (11) | 6/58 (10) | 7/83 (8.4) | 1/9 (11) | 4/14 (29) |
|                  | – 17(del17p) (%) | 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) | 11/119 (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\(^\text{a}\) (%) | 4/50 (92) | 15/83 (83) | 43/46 (94) | 12/14 (86) | 3/3 (7) | 3/4 (75) |
|                  | – 5(del5q) (%) | 26/50 (52) | 36/94 (38) | 23/41 (65) | 33/79 (42) | 2/7 (29) | 2/12 (17) |
|                  | – 7(del7q) (%) | 38/68 (56)\(^\text{a}\) | 37/99 (37)\(^\text{a}\) | 35/58 (60) | 35/83 (42) | 3/9 (33) | 2/14 (14) |
|                  | – 17(del17p) (%) | 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)\(^\text{a}\) | 69/159 (43)\(^\text{a}\) | 54/92 (59) | 63/135 (47) | 4/12 (33) | 4/19 (21) |
|                  | ≥ 5 Abnormalities (%) | 37/67 (55)\(^\text{a}\) | 46/115 (40)\(^\text{a}\) | 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. \(^\text{a}\)Early death defined as death within 30 days from diagnosis. Performance status was according to ECOG\(^\text{22/WHO.}\(^\text{4}\)Number of patients with early death/total number of patients (percentage). Performance status was missing in a few patients. \(^\text{b}\)CBF leukemia comprises AML with t(8;21), inv(16) or t(16;16). \(^\text{c}\)CBF leukemia c (%) 45/49 (92) 15/18 (83) 43/46 (92) 12/14 (86) 3/3 (7) 3/4 (75) \(^\text{d}\)5q, 7q and/or 17p loss (%) 59/106 (56) \(^\text{e}\)69/159 (43) \(^\text{f}\)5q, 7q and/or 17p loss in patients 60–79 years: 5q, 7q and/or 17p loss (%) 37/67 (55) \(^\text{f}\)46/115 (40) \(^\text{f}\)35/59 (59) \(^\text{f}\)41/93 (44) \(^\text{f}\)2/7 (29) \(^\text{f}\)3/17 (18) \(^\text{f}\)4/9 (44) \(^\text{f}\)3/20 (15) \(^\text{f}\)

\[X^2 = 38.8, P < 0.0001; \text{and in patients 60–79 years: } X^2 = 40.2, P < 0.0001. \text{CBF or normal karyotype vs 5q, 7q and/or 17p loss in patients < 60 years: } X^2 = 37.8, P < 0.0001; \text{in patients 60–79 years: } X^2 = 49.3, P < 0.0001; \text{in patients 60–79 years: } X^2 = 38.4, P < 0.0001\]

\[(P = 0.033), \text{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.
In the 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. As a comparison, 62% of Swedish patients of this age received intensive treatment with the aim to induce CR.1
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/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 population-based study, a similar impact on outcome of risk-prognostic impact from cytogenetic data.27,29–32 In the present clinical trials, mainly between 60 and 69 years, that demonstrate several reports from selected patients who are included into patients older than 60 years has been unclear, although there are subgroups 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

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

| Factor                              | Including age and PS (n = 498) | Excluding age and PS (n = 509) |
|-------------------------------------|--------------------------------|--------------------------------|
| Category                            | HR    | CI (95%) | P-value | HR    | CI (95%) | P-value |
| Age (years)                         |       |          |         |       |          |         |
<40                                  | 1     |          |         | 1     |          | 1       |
40–49                                | 0.96  | 0.60–1.53|         | 0.68  | 0.37–1.33|         |
50–59                                | 1.34  | 0.89–1.99|         | 1.20  | 0.82–1.71|         |
60–69                                | 1.73  | 1.18–2.53|         | 1.37  | 1.01–1.88|         |
70–79                                | 2.74  | 1.86–4.05| <0.001  | 1.94  | 1.26–2.98| 0.001   |
| PS                                  |       |          |         |       |          |         |
0–II                                 | 1     |          |         | 1     |          | 1       |
III–IV                               | 2.10  | 1.54–2.86| <0.001  | —     | —        | —       |
| Gender                              |       |          |         |       |          |         |
Male                                 | 0.78  | 0.64–0.95| 0.014   | 0.82  | 0.67–0.99| 0.035   |
Female                               | 1     |          |         | 1     |          | 1       |
| Monosomal karyotype                 |       |          |         |       |          |         |
No                                   | 1     |          |         | 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     |          | 1       |
Yes                                  | 1.23  | 0.88–1.71| 0.240   | 1.23  | 0.89–1.70| 0.210   |
− 7/del(7q)                          |       |          |         |       |          |         |
No                                   | 1     |          |         | 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     |          | 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     |          | 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.

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

1 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.

2 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.

3 Koreth J, Schlenk R, Kopecky KJ, Honda S, Sierra J, Dijkhuizen 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.

4 Löwenberg B. Sense and nonsense of high-dose cytarabine for acute myeloid leukemia. Blood 2013; 121: 26–28.

5 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: 1233–1248.

6 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/clinicalguidelines/online/2013/boletines/N51/Section12-NCCN-Acute_Myeloid_Leukemia.pdf

7 Cornelissen JJ, Gratwohl A, Schlenk RF, Sierra J, Bornhäuser M, Juliusson G et al. The European LeukaemiaNet 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.

8 Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri S, Stein H et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th edn. IARC Press: Lyon, France, 2008.

9 Grossmann V, Schnittger S, Kohlmann A, Eder C, Roller A, Dicker F et al. Prognostic performance of chromosomal and molecular abnormalities in acute myeloid leukemia. Blood 2012; 120: 2963–2972.

10 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.

11 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 LeukaemiaNet. Blood 2010; 115: 453–474.

12 Patel JP, Güen M, Figueiredo 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.

13 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.

14 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.

15 Breem DA, van Putten WL, van der Geef GE, van Zelderen-Bhola SL, Gerssen-Schoon 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.

16 Sekeres MA. My AML cytogenetics classification scheme is better than yours. Blood: Marrow Transplant 2012; 18: 160–161.

17 Juliusson G, Billstrom R, Gruber A, Hellstrom-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.

18 Juliusson G, Karlsson K, Vlijazeravec, 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.