ORIGINAL ARTICLE

Reasons for treating secondary AML as *de novo* AML

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Abstract

In a Danish bi-regional registry-based study, we conducted an analysis of the incidence and clinical importance of secondary acute myeloid leukaemia (AML). In a total of 630 cases of AML, we found 157 (25%) cases of secondary AML. The secondary leukaemia arose from MDS (myelodysplastic syndrome) in 77 cases (49%), CMPD (chronic myeloproliferative disorder) in 43 cases (27%) and was therapy-related AML (t-AML) in 37 cases (24%). Median age at diagnosis of AML was 69 yr in secondary cases when compared to 66 yr in *de novo* cases ($P = 0.006$). In univariate analyses, secondary AML was associated with an inferior complete remission (CR) rate ($P = 0.008$) and poorer overall survival (OS, $P = 0.003$) whereas in complete remitters, disease-free survival (DFS) of secondary cases was equal to that of *de novo* cases. Interestingly, in all further analyses of CR-rates, OS and DFS, when correcting for the influence of age, cytogenetic abnormalities, performance status and leucocyte count (WBC), presence of secondary AML completely lost prognostic significance. We conclude that the presence of secondary AML does not *per se* convey an unfavourable prognosis and that patients with secondary AML should be offered the chance of benefiting from treatment according to current frontline AML protocols.

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While unknown in *de novo* AML, the disease states and events preceding leukaemia in secondary AML are to some extent well characterised. Secondary AML is commonly defined as AML secondary to chemotherapy and/or radiotherapy for either a haematological or a non-haematological cancer or disease state, AML preceded by a myelodysplastic syndrome, AML preceded by a myeloproliferative disorder or AML preceded by aplastic anaemia. It is generally believed that the presence of secondary AML represents an independently adverse prognostic factor. Consequently, enrolment onto a significant number of the current clinical trials is for patients with *de novo* AML only (1–3). The attitude of the clinicians towards treating patients suffering from secondary AML by intensive chemotherapy has in many cases been reluctant and rather nihilistic (4, 5). However, most recently, the general reluctance and hesitation in treating elderly patients and patients with secondary AML with intensive remission induction chemotherapies has been challenged (6–8). With the improvement in treatment results of AML over recent years, revision of this issue is clearly warranted (8–10). Adding to complexity, recent results of the large MRC AML11 and LRF AML14 trials suggest an independent, albeit moderate, prognostic importance of secondary AML in the elderly (11, 12).

To address the question of the incidence and clinical significance of secondary AML, we conducted a retrospective registry-based analysis of all patients aged 15 or more diagnosed with AML (of any type, excluding myeloid blast crisis of CML) during the period 01-Jan-2000 to 31-Dec-2008. The study was bi-regional, covering the Regions of Midtjylland and Nordjylland in Denmark. During the study period, the background population remained stable at a population of 1.8 million. Treatment of AML takes place at three hospitals in the two regions, and services for cytogenetic analysis is carried

out and supervised by an experienced cytogeneticist in one single laboratory for the two regions together.

The primary objective of the study was to describe the incidence, demographic, clinical and cancer biological characteristics of secondary AML cases and compare these to the characteristics of *de novo* AML cases of the same cohort. The secondary objective was to evaluate the clinical and biological differences between these two groups with regard to treatment outcomes and prognosis. In this Danish population we show that the incidence of secondary AML is about 25% of the whole AML population. In curatively treated patients, when correcting for differences in age and chromosomal aberrations, the prognosis of patients suffering from secondary AML is not definitively different from that of *de novo* cases. This ultimately suggests that these critically ill patients should preferably be offered the same intensive chemotherapy-based treatments as patients with *de novo* AML.

Methods

Registry and background population

As of 01-Jan-2000 it became mandatory to report newly diagnosed AML cases to the national Acute Leukaemia Database (ALDB). Detailed information on individual cases are, thus, available. Among other, recorded parameters are basic demographic data, type of leukaemia (*de novo* vs. secondary) and in the case of secondary leukaemia information is included on the preceding state/disease and on previous chemotherapy and or radiotherapy, morphological phenotype, WBC, cytogenetic details and information on treatment schedule/protocol (intensive, palliative, other). Follow-up data are recorded and include information on remissions, transplantations (allo/auto), and relapse, thus, allowing for analysis of disease-free survival (DFS) in complete remitters. Survival status was obtained from the Danish Central Personal Registry (CPR). The estimated population of these two Danish Regions together was 1.803 million (rounded 1.8 million) about midterm of the study period 01-Jul-2004 according to available demographic statistics available at the official websites for the Danish Regions (http://www.regioner.dk and http://www.regionmidtjylland.viborgamt.dk). In Denmark, five Regions are responsible for public health care and are responsible for management and operation of hospitals (university- and regional-). No treatment or care of patients with acute leukaemia is carried out at private hospitals. On 01-Jan-2008, the population of the Regions Midtjylland and Nordjylland was 1 815 880 when compared to the total Danish population of 5 475 791 of the same date. This study, thus, covers 33% of the total Danish population.

Patients and treatments

This study cohort comprises 630 patients with AML diagnosed over a 9-yr period from 01-Jan-2000 to 31-Dec-2008 with an age of 15 or more. In June 2009, a data run was performed identifying patients entered into the registry during this 9-yr period. Surviving patients were followed until 30-Jun-2009 (date of last follow-up). All managements of patient data were performed according to procedures approved by the Ethics Committees in Denmark and by the National Board of Data Management (Datatilsynet).

An evaluation of the completeness of the database was performed by data cross-check on 19-Jun-2009 with the National Danish Cancer Registry (http://www.sst.dk/Cancerregisteret) and the National Danish Patients Registry (http://www.sst.dk/Landspatientregisteret). This data cross-check revealed a total of 53 patients who were not reported from the treating centres to the database over the 9-yr period. This accrual deficit was evenly distributed over the whole 9-yr period. Thus, the overall completeness of the data set presented here is estimated to be 91.6%.

For patients treated with curative intent (364 = 58% of patients), first-line remission induction chemotherapy consisted of cytarabine (Ara-C) in combination with an anthracycline. From 01-Jan-2004 eligible patients treated at the centre in Aarhus were offered enrolment onto the MRC AML 15 protocol which opened for enrolment somewhat later in Aalborg (October 2006). A total of 53 patients were treated according to the MRC AML 15 protocol. Patients, who were ineligible or declined enrolment to the MRC AML 15 protocol, were offered treatment according to a standard 3 + 7 (Idarubicin + Ara-C) schedule utilised at both centres. The 3 + 7 remission induction schedule, thus utilised in 190 patients, has previously been described in detail (13). A total of 121 patients were treated according to similar 3 + 7 regimens or 2 + 5 (if elderly and/or frail). Patients with AML FAB-M3 (promyelocytic leukaemia) were treated with ATRA + anthracycline containing regimens according to the MRC AML 15 protocol (one enrolled patient) as did another 21 FAB-M3 patients who were treated according to local procedure. Treatment results (remission rates, OS, and DFS) according to protocol/regimen were compared. These analyses suggested response and survival advantage of the MRC AML 15 protocol over 3 + 7 and over the other employed regimens. Consequently, regimen was entered as a covariate in analyses of response, OS and DFS.

Among patients treated by chemotherapy with palliative intent (128 cases), low-dose Ara-C (LD-Ara-C, 10 mg/m^2, b.d., s.c., daily during 3 wk, 6-wk cycle) utilised in 50 cases, and oral hydroxyurea, to control

leukocytosis, used in another 63 cases were the most frequently used modalities. Finally, another 138 patients were treated with supportive care, i.e. transfusions, antibiotics, and care only.

Definitions and endpoints

CR was defined as fewer than 5% leukaemic blasts in a regenerating normocellular bone marrow showing evidence of maturation of all three cell lines of the bone marrow with peripheral blood neutrophils $> 1 \times 10^9$/L and peripheral blood thrombocytes $> 100 \times 10^9$/L (11, 14, 15).

Survival time (OS) was defined as the time from the date of diagnosis of AML to the date of death of any cause. DFS was defined as the time from the date of attainment of first CR to the date of death of any cause or to the date of first relapse (which ever occurred first). As haematopoietic stem cell transplantation (HCT) may influence DFS to a larger extent than OS (16), patients who underwent HCT were censored in the analysis of DFS (but not OS) at the day of transplantation. Patients who were lost for follow-up (emigration, one case) were censored in survival analyses at the date at which they were last known to be alive.

Cytogenetic analyses

Cytogenetic analyses were performed on 24-h cell cultures of unstimulated bone marrow aspirated at the time of diagnosis. G-banding was carried out using standard protocols. Chromosome analysis was performed in up to 25 metaphases in each case and reported according to ISCN (17, 18). Cases were classified according to the recommendations by Grimwade (19, 20).

Statistical analyses

Comparisons of mean or median values between groups of patients were made by parametric or non-parametric tests depending on distribution. For statistical analysis of differences in contingency tables, we employed the χ^2 test whenever appropriate. For univariate analyses of differences in survival, estimates (Kaplan–Meier) were tested with log-rank tests (with adjustment for linear trend over strata when relevant). For multivariate analyses, logistic regression analyses and Cox regression analyses were performed. Continuous variables were entered as continuous variables in the Cox regression models. Multivariate analyses were always performed with data sets where no value was missing in any parameter. All statistical computations were performed with either the SPSS®-(Version 15 for Windows®) or the SAS 9.1.3 – software or both. 2-sided *P*-values were used throughout.

Results

In this cohort of 630 patients with AML the male/female ratio was 1.35. Basic data on the secondary as well as the patients with *de novo* AML of this cohort are given in Table 1. Median age at AML presentation was 67 yr (mean 63.8, range 15–97 yr). Median WBC at presentation was 12.2×10^9/L (mean 42.3, range 0.1–661.1×10^9/L). Morphological phenotype (FAB) (21–23) was M0 in 38, M1 in 118, M2 in 197, M3 in 22, M4 in 109, M5 in 49, M6 in 20, M7 in 6, myeloid sarcoma/chloroma in 5 and finally was uncertain in 66 cases. Three hundred and sixty-four patients (58%) were

Table 1 Unselected cohort of acute myeloid leukaemia (AML) patients: clinical and cytogenetic characteristics of 157 secondary and 473 *de novo* AML cases

	Number of patients		
Parameter	Secondary	*De novo*	*P*-value of difference
Gender			0.37
Male	95	267	(χ^2 test)
Female	62	206	
Age[1] (yr)			< 0.0001
15–49	12	111	(χ^2 test)
50–59	20	68	
60-69	49	97	
70+	76	197	
WBC (1×10^9/L)			0.63
0-2.99	43	139	(χ^2 test)
3-29.99	53	166	
30+	61	167	
Unknown/missing	0	1	
Performance status (WHO)			0.03
0	25	108	(Mann–
1	59	193	Whitney
2	40	90	test)
3	23	44	
4	10	37	
5	0	1	
Cytogenetic group			0.004
Favourable	2	26	(χ^2 test)
Intermediate	87	269	
Unfavourable	32	54	
Unknown/not performed	36	124	
FAB subtype			0.001
M0	8	30	(χ^2 test)
M1	27	91	
M2	45	152	
M3	2	20	
M4	29	80	
M5	9	40	
M6	2	18	
M7	2	4	
Myeloid sarcoma	1	4	
Uncertain/missing	32	34	

[1]Median age of secondary and *de novo* cases was 69.0 yr and 66.0 yr, respectively ($P = 0.006$, Mann–Whitney test).

treated with curative intent. Among curatively treated patients there was no difference in OS between the (two) treating centres ($P = 0.88$). Likewise, for palliatively treated patients, no difference between three treating centres with respect to OS was seen ($P = 0.48$). Thus, all data were pooled over treating centres in subsequent analyses. Overall incidence of secondary leukaemia was 25% (157/630). AML was preceded by MDS in 77 (12.2% of all cases), CMPD in 43 (6.8%), developed after chemotherapy and/or radiotherapy for a non-haematological cancer or disease in 18 (2.9%), after therapy/chemotherapy and/or radiotherapy for another haematological state, in 10 (1.6%), and developed from chemotherapy and/or radiotherapy for non-Hodgkin lymphoma in 9 (1.4%) cases. Finally, in our cohort, the frequency of secondary AML was 11% (18 of 164 patients) and 15% (32 of 211 patients) among younger patients less than 56 and 60 yr of age, respectively.

Cytogenetic analysis was successful in 470 (75%) of all cases (Table 1). Among patients treated with curative intent, cytogenetic analysis was successful in 317 (87%) cases. Individual cases were classified according to the recommendations of Grimwade. Among successful analyses, 28 (6.0%) cases were favourable, 356 (75.7%) intermediate and 86 unfavourable (18.3%), Table 1. Among secondary cases, 121 (77%) had a successful cytogenetic analysis. Unfavourable cytogenetics were more prevalent in the secondary cases evolving from MDS (frequency 34%) than in the other secondary cases (from CMPD and therapy-related, frequency 20%), $P = 0.04$, Mann–Whitney test.

In patients younger than 60 yr of age, the prevalence of patients not subjected to curative chemotherapy was not statistically different in secondary AML cases (3 of 32 cases, 9.4%) when compared to *de novo* cases (5 of 179, 2.8%), $P = 0.1$, Fisher's exact test. Among patients 60 yr of age or older, there was, however, a statistically significant difference in the prevalence of patients not subjected to curative chemotherapy (57% among *de novo* cases as opposed to 72% in the secondary cases, $P = 0.004$, χ^2 test).

Among curatively treated patients HCT was carried out in 53 (15%) cases. The distribution of HCT's performed was as follows: Standard conditioning allogeneic 23 in first CR, and 9 in second CR; reduced conditioning allogeneic (RIC) 13 in first CR, 5 in second CR; autologous 1 in first CR, and 1 in second CR; other (tandem conditioning during disease progression) (24), 1 case. The overall frequency of HCT was 9.4% (6 cases) in secondary cases and 15.7% (47 cases) in *de novo* cases, $P = 0.2$, χ^2 test.

For the 364 curatively treated patients, median age and OS were 58 yr and 398 d (95% CI 289–507 d), respectively. For the palliatively treated patients, these figures were 77 yr and 71 d (95% CI 52–89 d), respectively. Univariate analyses of factors of importance to attainment of CR revealed significance of the following: type of leukaemia, age at diagnosis, performance status at presentation, cytogenetic findings, and treatment protocol and protocol/regimen (Table 2). The CR rate was 56.3% in secondary cases as opposed to 73.0% in *de novo* cases ($P = 0.008$, χ^2 test). Among these curatively treated patients, logistic regression analysis revealed that the factors that retained statistical significance to probability of attainment of CR (by order of statistical significance) were age, treatment protocol, and cytogenetic findings (Table 2).

In the 364 curatively treated patients, OS was markedly dependent on presence/absence of secondary leukaemia, age at diagnosis, performance status, cytogenetic findings and treatment protocol in univariate analyses (Figs 1 and 2A, and Table 3). In the univariate analysis,

Table 2 Factors of importance to attainment of CR in 364 curatively treated patients with acute myeloid leukaemia (AML) of whom 255 (70%) attained CR

Parameter	Univariate analysis *P*-value	Multivariate analysis (logistic regression) *P*-value
Type of leukaemia (secondary vs. *de novo*)	0.009 (χ^2 test)	0.40
Gender	0.56 (χ^2 test)	0.51
Age	< 0.0001 (Mann–Whitney test)	< 0.0001
WBC	0.22 (Mann–Whitney test)	0.01
Performance status (WHO)	< 0.0001 (Mann–Whitney test)	0.62
Cytogenetic group	< 0.0001 (χ^2 test)	0.001
Treatment protocol/regimen (MRC AML 15 vs. 3 + 7 vs. other)	< 0.0001 (χ^2 test)	< 0.0001

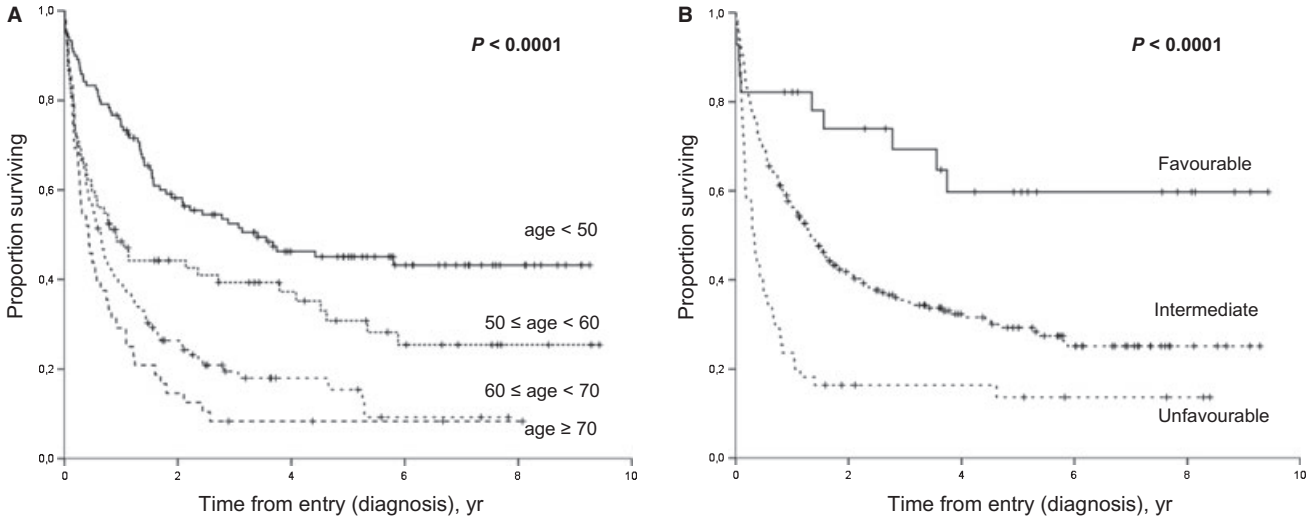

Figure 1 (A) Overall survival of 364 acute myeloid leukaemia (AML) patients treated with curative intent according to age group and (B) according to cytogenetic findings.

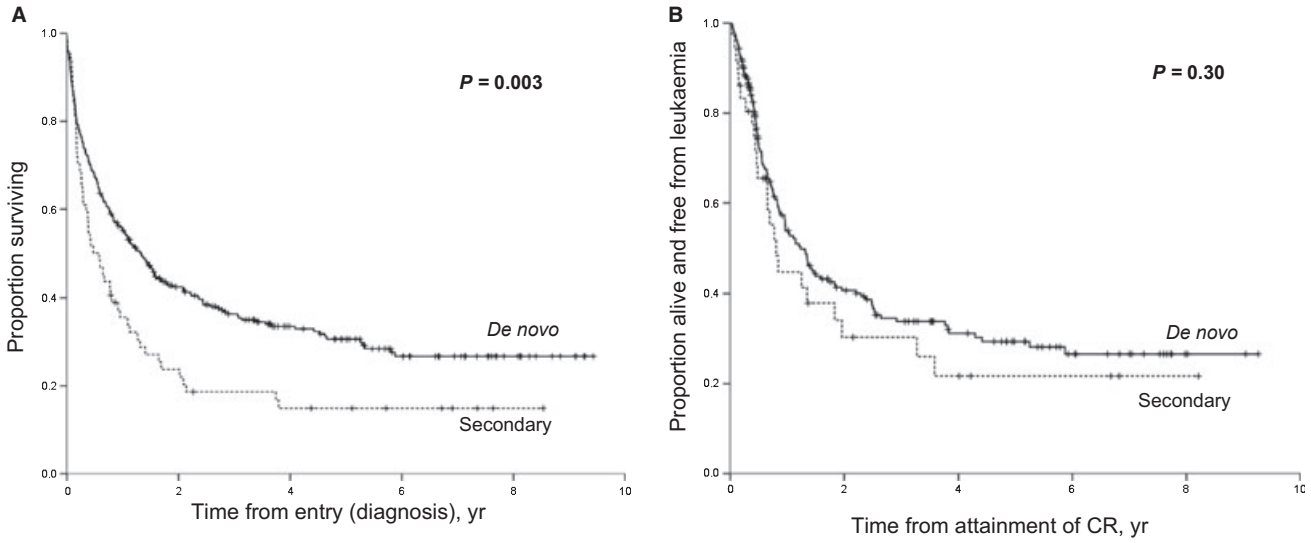

Figure 2 (A) Overall survival of 364 acute myeloid leukaemia (AML) patients treated with curative intent according to type of leukaemia (secondary vs. *de novo*). (B) Disease-free survival of 255 patients with AML in first CR according to type of leukaemia (secondary vs. *de novo*).

median OS was 173 d (95% CI 70–276 d) in secondary cases and 486 d (95% CI 371–507 d) in *de novo cases,* $P = 0.003$, log-rank test. In the subsequent Cox regression analysis, the only factors that retained statistical significance to OS were by order of statistical significance: age, cytogenetic findings, treatment protocol, and performance status (Table 3). In the 255 patients who attained CR, factors of importance to duration of DFS in univariate analyses were cytogenetic findings, age and treatment protocol (Table 3 and Fig. 2B). In the subsequent Cox regression analysis, the only factors that retained statistical significance to DFS were by order of statistical significance: cytogenetic findings and age (Table 3).

A further stratified analysis of the prognostic significance of type of leukaemia was carried out. When stratifying the 364 curatively treated patients according to both type of leukaemia and age group (below or above 60 yr of age), analyses revealed prognostic significance of type of leukaemia to OS only. Thus, the Kaplan–Meier estimates of median OS for the patients were as follows: 990 d (95% CI 471–1509 d, $n = 174$), 293 d (95% CI 0–611 d, $n = 29$), 219 d (95% CI 149–289 d, $n = 126$) and 140 d (95% CI 108–172 d, $n = 35$) for the *de novo* patients with age < 60 yr, the secondary AML patients with age < 60 yr, the *de novo* patients with age equal to or above 60 yr, and the secondary AML patients with age

Table 3 Factors of importance to overall survival (OS) and disease-free survival (DFS) in 364 curatively treated patients with acute myeloid leukaemia (AML)

	OS (n = 364)		DFS (n = 255)	
Factor	Univariate (log-rank test) P-value	Multivariate (Cox regression) P-value	Univariate (log-rank test) P-value	Multivariate (Cox regression) P-value
Type of Leukaemia	0.003	0.59	0.30	0.98
Gender	0.52	0.91	0.67	0.07
Age[1]	< 0.0001	< 0.0001	0.002	0.003
WBC[2]	0.21	0.09	0.83	0.87
Performance status (WHO)	< 0.0001	0.02	0.10	0.06
Cytogenetic group	< 0.0001	< 0.0001	0.001	0.002
Treatment protocol/Regimen[3]	< 0.0001	0.01	0.04	0.20

[1]Age dicotomised for log-rank analyses at age </≥ 60 yr.
[2]WBC tricotomised for log-rank analyses at values < 3×10^9/L; between 3 and < 30×10^9/L; ≥ 30×10^9/L.
[3]MRC AML 15 protocol (n = 53) vs. 3 + 7 (n = 190) vs. other (n = 121).

equal to or above 60 yr, respectively, $P = 0.01$, stratified log-rank test (secondary vs. *de novo,* stratified according to age group), Fig. 3A. Finally, a corresponding stratified analysis of DFS in the 255 complete remitters was carried out. Thus, the Kaplan–Meier estimates of median DFS for the patients were 574 d (95% CI 260–830 d, $n = 144$), 715 d (95% CI 0–1540 d, $n = 21$), 258 d (95% CI 148–368 d, $n = 75$) and 282 d (95% CI 203–361 d, $n = 15$) for the *de novo* patients with age < 60 yr, the secondary AML patients with age < 60 yr, the *de novo* patients with age equal to or above 60 yr and the secondary AML patients with age equal to or above 60 yr, respectively, $P = 0.46$, stratified log-rank test (secondary vs. *de novo,* stratified according to age group), Fig. 3B.

Discussion

Clearly, the most interesting finding of this study is that we, in this consecutive population-based AML cohort, have been unable to confirm an independent adverse prognostic impact of presence of secondary leukaemia to parameters of outcome. By contrast, when, duly adjusting for the influence of other well-established prognostic parameters, our data strongly point at age and cytogenetic findings as being the main carriers of prognostic information.

Using the broad definition of secondary AML, as generally used (6), we in this study have found an incidence rate ratio of 1 : 3 between secondary cases and *de novo*

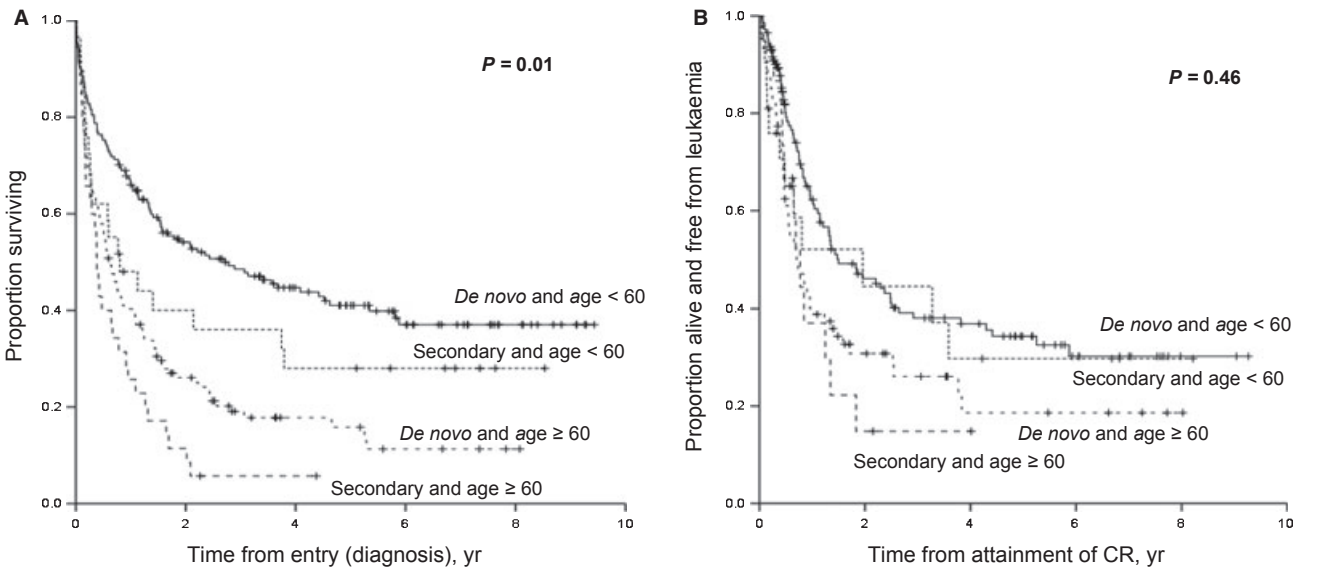

Figure 3 (A) Overall survival of 364 acute myeloid leukaemia (AML) patients treated with curative intent according to type of leukaemia and age group (secondary vs. *de novo and* below or above 60 yr of age, four groups). *P*-value of stratified log-rank test is given. (B) Disease-free survival of 255 patients with AML in first CR according to type of leukaemia and age group (secondary vs. *de novo and* below or above 60 yr of age, four groups). *P*-value of stratified log-rank test is given.

cases. This compares well to a total of 28% in another recent Scandinavian registry-based publication (7). In data of published clinical trials, the incidence of secondary AML has generally been lower with 7% in the MRC AML 10 trial (25), 23% in the MRC AML 11 (20), and 17% in the LRF AML 14 trial (11) being prominent examples. The lower frequency of secondary AML in clinical trials may reflect a significant selection bias against cases of secondary AML in clinical trials. In the data presented herein, we can also demonstrate that selection of secondary AML cases away from intensive treatment modalities clearly takes place. Thus, while comprising 25% of the whole patient cohort, patients with secondary AML only represented 18% (64 of 364) of intensively treated patients. Interestingly, this selection of patients appears to take place on the basis of performance status and not on the basis of age. We, thus, found uneven distributions of age and cytogenetic findings still evident in the 364 intensively treated patients, while the uneven distribution of performance status, that was evident in the total cohort, was absent in intensively treated patients (Tables 1 and 4).

As mentioned above, according to the data presented here, secondary AML is in univariate analysis a relatively strong predictor (with *P*-values of the $< 1\%$ order of magnitude) and adverse factor to attainment of CR and to overall survival. By contrast, neither in univariate, nor in multivariate analysis presence of secondary AML was of significance to DFS. These results are to some extent in line with recent observations by Schoch, Kern *et al.* (26, 27) who in a large cohort of intensively treated AML patients found t-AML to be an independent prognostic factor of significance to OS. In addition, corroborating the findings of our study, they found the presence of t-AML to have a weaker impact on prognosis than karyotypic aberrations. From a therapeutical point of view, it may be argued that prognostic factors of importance to DFS are at least as interesting as factors of importance to OS to a patient in CR. Thus, the therapeutical question at hand with AML at presentation rather is 'to treat or not to treat' whereas later on with the patient in first CR, the question arises whether to opt for transplantation or other types of remission consolidating therapies. Bearing this in mind, we will strongly argue that every effort should be taken to provide each case with the essential information of the karyotype and have a cytogenetic analysis carried out in all cases where a chemotherapeutic treatment of any kind can come into question. As it is not always evident whether a given patient, who may be suffering from severe complications of untreated AML, will at some time be suitable for commencing curative combination chemotherapy, no excuse exists for not carrying out a cytogenetic analysis at disease presentation – excepting obviously hopeless cases.

Interestingly, in no secondary AML case of the present cohort, the disease was secondary to therapy for Hodgkin's lymphoma. We estimate (cancer statistics available at the website of the Danish Cancer Society, http://www.cancer.dk) that 390 patients have been diagnosed and treated for Hodgkin's lymphoma at our centres in the regions during the study period. During earlier periods, treatment for Hodgkin's lymphoma was associated with a very high risk of developing therapy-related myelodysplasia (t-MDS) or t-AML. Thus, this figure was estimated to be 10% or more during the 1970s and 1980s (28).

Very recently, Borthakur *et al.* (29) have published results of a single institution study showing that cases of therapy-related core-binding factor–positive AML have a

Table 4 Relations of type of leukaemia [secondary vs. *de novo* acute myeloid leukaemia (AML)] to age, performance status (WHO), and cytogenetic group in 364 curatively treated patients with AML

Parameter	Secondary AML ($n = 64$)	*de novo* AML ($n = 300$)	*P*-value
Age (yr)	61.5 (Median value) (Mann–Whitney test)	56.5 (Median value)	0.006
Performance status (WHO)			0.30 (Mann–Whitney test)
0	16	93	
1	31	141	
2	13	48	
3	1	11	
4	3	7	
Cytogenetic group			0.05 (χ^2 test)
Favourable	2	26	
Intermediate	41	191	
Unfavourable	16	41	
Unknown/not performed	*5*	*42*	

poorer survival than *de novo* core-binding factor cases. Their material comprised 17 cases of therapy-related core-binding factor–positive AML as opposed to 171 *de novo* cases. In our material we have found a mere 2 cases of therapy-related core-binding factor–positive AML. These are both t(8; 21) positive. Although the data of Bothakur *et al.* are interesting and to some extent contradict the results of our work, we will argue that focussing on a rare subgroup of AML as therapy-related core-binding factor–positive AML and demonstrating inferior survival does not imply much for the larger subgroup of secondary AML as a whole. Interesting as it may be to focus on particular subpopulations of patients with AML, these types of results should also be confirmed in large population-based data sets where adequate adjustments can be performed for influence of other prognostic parameters. To this end, Rizzieri *et al.* (10) very recently published data on 96 intensively treated patients with secondary AML who overall had a favourable (73%) CR rate but short OS (13.6 months). Notably, both CR rate and OS are lower/shorter in our population-based cohort of patients with secondary AML.

Data derived from the consecutive British MRC AML10, MRC AML11, MRC AML12 and LRF AML14 trials data have consistently shown type of leukaemia (secondary vs. *de novo*) to be an independent prognostic parameter in both younger and elderly patients (12, 25, 30). These results have been derived from data of several thousands of patients with AML. Evidently, the data of this study, although being derived from a relatively unselected and representative population-based cohort, cannot match data of the MRC trials by numbers and statistical power. Be that as it may, we welcome the 'global prognostic factor view' that lies behind the development of the prognostic index to be implemented as a tool for decision making between standard and high risk therapy in the current Working Parties on Leukaemia AML 17 trial (see http://aml17.cardiff.ac.uk/files/files.htm). Notably, in the prognostic index employed in the AML 17 trial, type of leukaemia (secondary vs. *de novo*) is entered with the least statistical significance ($P = 0.04$) in the prognostic model. In this prognostic index, the following parameters are found to have greater weight and statistical significance (by order of significance): cytogenetic findings, age, status after first course of chemotherapy, WBC and male sex.

A limitation of the present retrospective analysis is that we are unable to assess the probable influence of differing leukaemia biology of the secondary AML cases evolving from MDS or CMPD. These AML case, some of which were formerly classified according to the FAB classification as RAEB in transformation (31), likely, have a slower leukaemia progression (32). Be that as it may, in spite of accumulating evidence of markedly different leukaemia biologies in AML (33), current curative treatments of AML remain to a large degree uniform and in all cases initially based on intensive combination chemotherapy. Notably, our analyses of treatment outcomes concern the curatively treated patients only.

In conclusion, results of this analyses clearly show that while presence of secondary leukaemia is of importance to probability of attaining CR and to overall survival in univariate analyses, this importance is clearly weakened and neutralised in qualified multivariate analyses (and also stratified analyses) correcting for the influence of age, performance status and cytogenetic findings. We argue that the presence of secondary AML, seen in about 25% of all newly diagnosed AML cases, *per se* neither warrants reluctance to treat older patients intensively, nor does it warrant allocating younger patients to more intensive treatment options, e.g., allogeneic transplantation. If regarded as a prognostic factor at all, secondary AML should be seen as a very weak poor prognostic factor, the significance of which is by far outweighed by other determining parameters such as age and cytogenetic aberrations. For all patients in CR the factors that mainly determine the course of the disease are age and cytogenetic aberrations at diagnosis. Summarising this, our data do not lend support to any nihilistic attitude towards treating patients with secondary AML intensively and, in our opinion, patients with secondary AML should be offered the same chance of benefiting from treatment according to current frontline AML protocols as their *de novo* counterparts.

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Conflicts of interests disclosure

In relation to the present work, the authors have no conflicts of interests to disclose.

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