An antecedent diagnosis of refractory anemia with excess blasts has no prognostic relevance in acute myeloid leukemia of older adult patients

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Background: Conflicting results have been reported about the prognostic relevance of antecedent myelodysplastic syndrome (MDS) in acute myeloid leukemia (AML) of older adults.

Patients and methods: Data from 87 intensively treated AML patients (median age 69 years) were analyzed, with the aim of comparing therapeutic results and toxicity between de novo and AML secondary to a previous MDS (s-AML). Rate of CD34+ cells mobilization and feasibility of autologous stem cell transplantation (ASCT) were also compared.

Results: Complete remission rate, death in induction and primary resistance were not statistically different between the two groups. Median time for neutrophil recovery was similar, while s-AML patients required a longer time for platelet recovery ($P = 0.04$). There was no difference as to eligibility for consolidation as well as for mobilization and feasibility of ASCT. S-AML had negligible impact on overall survival (OS) and disease-free survival (DFS). In the multivariate analysis the only parameter significantly related to either OS or DFS duration was adverse karyotype ($P = 0.02$ and 0.04, respectively).

Conclusions: A diagnosis of s-AML does not represent a clinically relevant prognostic factor in elderly AML patients treated with aggressive therapy. Furthermore, s-AML patients can be mobilized and autografted with comparable results as opposed to de novo cases.

Key words: acute myeloid leukemia, elderly patients, antecedent MDS, prognostic relevance

Introduction

Acute myeloid leukemia (AML) is a malignant stem cell disease affecting predominantly elderly individuals, with a median age at diagnosis over 65 years. Compared with younger adults or children, older AML patients have a poorer prognosis [1–3]. Apart from host related factors, such as presence of concomitant diseases and inferior capacity to withstand the side-effects of chemotherapy, disease related factors including more frequent unfavourable cytogenetics, antecedent hematologic disorder (AHD) and high levels of multidrug resistance protein account for the unsatisfactory outcome of the disease in the elderly [4–6]. However, the results from various clinical trials and single-center studies evaluating the prognostic factors in older patients are conflicting [7–10]. The main reasons of discrepancy rely on either different selection criteria used for enrolment or differences in treatment approaches [11, 12]. In particular, the exclusion in many trials of patients with previously diagnosed myelodysplastic syndrome (MDS) renders uncertain the evaluation of the prognostic relevance of secondary AML (s-AML), defined as AML arising after either a history of chemotherapy or radiotherapy for a previous malignancy, or a preceding history of MDS or other AHD [13–15]. In a previous study on 63 AML patients aged over 60 years, we demonstrated that continuous sequential infusion of fludarabine and cytarabine (CI-FLA) was feasible with a promising complete remission (CR) rate of 67% [16]. Here we report data from a larger series of 87 patients affected by AML with a median age of 69 years, homogeneously treated with CI-FLA as induction/consolidation therapy, with the aim of comparing therapeutic results, toxicity and hematopoietic recovery between de novo and s-AML. In addition, results in terms of CD34 positive (CD34+) cell mobilization and collection, as well as overall feasibility of autologous stem cell transplantation (ASCT), were compared.

Patients and methods

Patients older than 60 years with a morphological diagnosis of AML according to WHO criteria [17], with the exception of acute promyelocytic leukemia, were accrued into the study. In all cases, diagnosis was...
confirmed by immunophenotypic analysis as previously described [18]. Cytogenetic analysis was performed by using the RHG banding on a minimum of 20 fully evaluable metaphases. The prognostic categorization of cytogenetics was defined according to MRC criteria [19]. Patients with AML arising after a previously diagnosed MDS, other AHF (such as myeloproliferative disorders) or with AML secondary to previous chemotherapy or radiotherapy for other malignancies were also included and defined as s-AML, as recently established by WHO criteria [17].

According to WHO criteria [20], patients were required to have a performance status (PS) of 0–3. Criteria for exclusion included severe organ damage not related to AML or left ventricular ejection fraction (LVEF) less than 40% as measured by echocardiography. Written informed consent was achieved in all cases in accordance with local committee criteria. All cases of AML in patients aged over 60 years diagnosed at the two participating institutions during the period of the study were registered in order to assess the ratios between patients observed and patients actually accrued into the trial.

Details of the therapeutic program have been provided elsewhere [16]. Briefly, fludarabine was administered at a loading dose of 10 mg/m² over 15 min at day 1 followed 6.5 h later by continuous infusion (CI) of 20 mg/m²/24 h for 72 h (days 1–3). Cytarabine was given at a loading dose of 390 mg/m² 3.5 h after fludarabine and then as CI over 96 h at 1440 mg/m²/24 h (days 1–4). G-CSF was added at day +15 at a dose of 5 µg/kg. CR was assessed after hematopoietic recovery following induction therapy according to morphologic criteria established by the International Working Group for AML [21]. Patients were required to have less than 5% blasts in the bone marrow, normal blood count and differential and absence of extramedullary leukemia; those with bone marrow blast cells less than 5% and incomplete hematopoietic recovery were defined as CRi. Patients in CR were programmed to receive one additional identical course of CI-FLA as consolidation. However, after the first 20 patients consolidation was shortened by reducing either fludarabine or cytarabine to 2 and 3 days of infusion, respectively, due to excessive toxicity (see Results). Following consolidation, G-CSF at 10 µg/kg was given from day 15 with the aim of shortening neutropenia and mobilizing CD34+ cells. All patients with successful collection of CD34+ cells (≥2 x 10⁶/kg) were programmed to be given ASCT with conditioning regimen consisting of high-dose continuous infusion idarubicin plus busulphan, as previously described [22]. A PS <3, absence of active infection and/or severe organ damage were required to be considered for ASCT. Toxicity was recorded according to WHO criteria [20]. Prophylaxis against infection consisted of oral ciprofloxacin and oral fluconazol, while no antiviral prophylaxis was performed. Indications for antibiotic therapy included fever >38°C with leukocyte count <1 x 10⁹/L, as well as signs or symptoms of infection. Intravenous fluconazole was used for proven candidiasis infection, while amphotericin B was given for aspergillosis or other invasive fungal infections when suspected (fever persisting for more than 7 days while on treatment with broad-spectrum antibiotics) or documented. In all patients red cell concentrates were given to maintain the Hb level >8 g/dl, while platelet concentrates were administered to keep a platelet value >10 x 10⁹/L. All transfused blood products were depleted of leukocytes to minimize the risk of transfusional graft versus host disease.

 Disease-free survival (DFS) was defined as the time from CR achievement to relapse or death from any cause, overall survival (OS) as the time from diagnosis until death from any cause. DFS and OS were calculated by the Kaplan–Meier method [23]. Differences in the distribution of individual parameters among patient subsets were analyzed using the χ² test or the Student’s t-test. All statistical comparisons used two-tailed P value. Multivariate analysis was performed by a Cox proportional hazard regression model. Finally, to calculate the significance of differences between survival curves, the log-rank test was applied. Differences were considered to be significant when the P value was <0.05.

results

patients’ characteristics and accrual

Between December 2001 and August 2005, a total of 166 patients with non-M3 AML older than 60 years were diagnosed at the two institutions involved in the trial. Among these, 91 patients (55%) had de novo AML and 75 (45%) had s-AML. Overall, 79 patients (47.5%), whose median age was 75 years (range 64–88), were considered as ineligible for intensive treatment. Most frequent reasons for exclusion were severe co-morbidities and/or poor PS (90%), which were registered in the vast majority of patients aged 80 years or more. Less frequently (10%), lack of family or social support and refusal accounted for the therapeutic choice. According to age, the rate of inclusion into the trial was 77% and 35% for patients aged 61–70 years and >70 years, respectively (P <0.001). On the contrary, there was no statistically significant difference between de novo and s-AML as to inclusion into CI-FLA program [49 out of 91 (54%) versus 38 out of 75 (51%), respectively; P = 0.80].

Overall, 87 patients (32%) were considered as eligible for the trial and all received the induction therapy. The median age was 69 years (range 61–81). Forty-nine patients (56%) were diagnosed as having de novo AML, while a diagnosis of s-AML was made in 38 cases (44%) and in all cases AML was secondary to refractory anemia with excess blasts (RAEB), defined as bone marrow blasts between 5% and 20% and less than 5% blasts in the peripheral blood [17]. Of note, nine patients with AML secondary to previous RAEB had been treated with chemo/radiotherapy because of previous malignancies (one non-Hodgkin’s lymphoma, two multiple myeloma, six non-hematologic cancer), any treatment being discontinued at least 2 years before the diagnosis of MDS/AML. The median time to transformation from RAEB to AML was 18 months (range 3–35) and no patient had been given any cytotoxic therapy while affected by MDS. Cytogenetic analysis was successful in 76 out of 87 cases (87%). A normal karyotype was found in 45 patients (59%), complex karyotype or other unfavourable chromosomal abnormalities in 31 (41%); no patient had AML with t(8;21) or inv(16). The distribution of adverse karyotype was not different between de novo and s-AML (43% versus 38%, respectively; P = 0.86). In addition, median age, per cent of patients aged over 70 years, distribution according to FAB criteria [24], median white blood cell count (WBC) and median serum LDH at diagnosis were comparable between the two groups, as indicated in Table 1.

TREATMENT RESULTS AND TOXICITY

Therapeutic results are summarized in Table 2. Overall, 56 patients achieved CR (64%), all following one course of CI-FLA. Among these, two were classified as CRi, due to incomplete platelet recovery, not needing platelet transfusion; both patients experienced early relapse at 2 and 6 months from CRi achievement and did not receive further chemotherapy. There were 16 induction deaths (18%), while 15 patients were primary
extrahematologic toxicity occurred during or after induction are summarized in Table 3. Median time from the beginning of chemotherapy to neutrophil recovery to >1.0 \times 10^9/l was similar between the two groups (19 days for de novo AML versus 20 days for s-AML, \( P = 0.04 \)), while patients with s-AML required a longer time for platelet recovery to >20 \times 10^9/l (20 days versus 18 days, \( P = 0.04 \)). No difference was found for transfusion support in terms of either blood or platelet units (\( P = 0.64 \) and 0.18, respectively). Overall, induction deaths were due to infectious episodes occurring during the aplastic phase (\( n = 14 \)) and cerebral hemorrhage (\( n = 2 \)); the incidence of fever of unknown origin as well of documented infection was similar between the two groups, as shown in Table 3. Finally, no difference was recorded as to the occurrence of WHO \( > 2 \) extrahematologic toxicity (12% for de novo as opposed to 13% for s-AML, \( P = 0.86 \)). Median time spent in hospital for induction treatment was 26 days for patients with de novo AML as opposed to 25 for those with s-AML (\( P = 0.21 \)).

Overall, 46 out of 56 (82%) received the programmed mobilization of CD34+ cells, collection being successful in 29/38 (76%). There was no difference between de novo and s-AML patients as far as eligibility for consolidation was concerned (87% versus 77%, \( P = 0.54 \)). Thirty-eight patients were monitored for the mobilization of CD34+ cells, collection being successful in 29/38 (76%).

### Table 2. Therapeutic results

<table>
<thead>
<tr>
<th></th>
<th>de novo AML</th>
<th>s-AML</th>
<th>( P ) value</th>
</tr>
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<tbody>
<tr>
<td>CR</td>
<td>30 (61%)</td>
<td>26 (68%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Induction death</td>
<td>10 (20%)</td>
<td>6 (16%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Refractory</td>
<td>9 (18%)</td>
<td>6 (16%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Consolidation Y/N</td>
<td>26/4 (87%/13%)</td>
<td>20/6 (77%/23%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Mobilization of CD34+ve cells (Y/N)</td>
<td>16/4 (80%/20%)</td>
<td>13/5 (72%/28%)</td>
<td>0.85</td>
</tr>
<tr>
<td>CD34+ cells (x10^9/kg)</td>
<td>6.7 (2.4–60.3)</td>
<td>7 (2.5–39.7)</td>
<td>0.72</td>
</tr>
<tr>
<td>ASCT</td>
<td>14 (47%)</td>
<td>9 (35%)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*Available in 76 patients (87%).

Overall, 23 patients (26% of the total patient population and 41% among remitters) received ASCT. Reasons for not autografting the six mobilizing patients were early relapse (\( n = 2 \)), which occurred in both cases after 2 months from CR achievement, refusal (\( n = 1 \)), infection (\( n = 2 \)) and severe uncontrolled diabetes resulting in ischemic left foot gangrene (\( n = 1 \)). Of note, among remitters the percentage of actually autografted patients did not differ between de novo and s-AML cases [14/30 for de novo AML (47%) versus 9/26 (35%) for s-AML, \( P = 0.52 \)].

At the time of writing 27 patients are alive: 21 are in continuous CR after a median follow-up for surviving patients of 15 months (range 3–47) and six with relapsed disease. Eleven out of 23 patients (48%) relapsed after ASCT. Figure 1 shows the progressive loss of patients from diagnosis to ASCT for de novo AML and s-AML.

Median OS for the whole patient population was 8 months, median DFS was 9 months (Figure 2). OS was significantly better in patients with intermediate karyotype compared with those with unfavourable karyotype, median survival being 10 and 6 months (\( P = 0.02 \)), respectively, as shown in Figure 3. On the contrary, the presence of hemorrhage after CR obtainment (\( n = 1 \)) and extra-hematologic toxicity (\( n = 2 \)). In addition, six patients (three with de novo AML and three with s-AML) died following consolidation, four from infection occurred in the post-therapeutic aplastic phase (two bacterial and two fungal) and two from cardiac infarction apparently unrelated to previous chemotherapy. No infectious or hemorrhagic deaths were observed after reduction of consolidation course from 4 to 3 days of therapy. There was no difference between de novo and s-AML patients as far as eligibility for consolidation was concerned (87% versus 77%, \( P = 0.54 \)). Thirty-eight patients were monitored for the mobilization of CD34+ cells, collection being successful in 29/38 (76%). There was no difference in the successful rate of mobilization between patients with de novo and s-AML (80% versus 72%, respectively, \( P = 0.85 \)). In addition, the median number of stem cells collected was similar in the two groups (6.7 \times 10^9/kg for de novo AML compared with 7 \times 10^9/kg for s-AML, \( P = 0.72 \)).

### Table 3. Toxicity and supportive treatment

<table>
<thead>
<tr>
<th></th>
<th>de novo AML</th>
<th>s-AML</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median days to ANC &gt;1.0 \times 10^9/l</td>
<td>19 (7–34)</td>
<td>20 (11–26)</td>
<td>0.76</td>
</tr>
<tr>
<td>Median days to platelet &gt;20 \times 10^9/l</td>
<td>18 (9–29)</td>
<td>20 (12–38)</td>
<td>0.04</td>
</tr>
<tr>
<td>No. RBC units, median</td>
<td>6 (2–17)</td>
<td>7 (1–38)</td>
<td>0.64</td>
</tr>
<tr>
<td>No. platelet transfusions, median</td>
<td>3 (0–12)</td>
<td>4 (1–19)</td>
<td>0.18</td>
</tr>
<tr>
<td>Documented infections</td>
<td>12 (24%)</td>
<td>9 (24%)</td>
<td>0.86</td>
</tr>
<tr>
<td>FUO</td>
<td>33 (67%)</td>
<td>26 (68%)</td>
<td>0.90</td>
</tr>
<tr>
<td>&gt;2 WHO extrahematological toxicity</td>
<td>6a (12%)</td>
<td>5a (13%)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

*Gastrointestinal: grade 3 diarrhea, seven cases. Hepatic: grade 3 increase of transaminases, three cases. Grade 3 increase of transaminases + grade 4 increase of bilirubin: one case. Cardiac: grade 3 arrhythmia, one case.

Grade 4 infarction, one case. Tumor lysis syndrome, three cases. More than one toxicity was present in five patients.
antecedent MDS had negligible impact on survival (median 8 months for both groups as shown in Figure 4, \(P = 0.53\)) and disease-free survival (median 10 versus 9 months, \(P = 0.41\), as shown in Figure 5). In the multivariate analysis, performed by taking into account age greater or less than 70 years, white blood cell count at presentation (greater or less than \(50 \times 10^9/l\)), previous MDS, median serum LDH at diagnosis and cytogenetic findings, adverse karyotype was the only parameter significantly related to either OS or DFS duration (\(P = 0.02\) and 0.04, respectively). Of note, an antecedent diagnosis of RAEB was not statistically significant in the univariate analysis (\(P = 0.21\)).

discussion

The search for prognostic factors in AML occurring in elderly patients has major clinical relevance in order to select, within a frail population, patients who can take substantial advantage from conventional aggressive chemotherapy either at diagnosis or at relapse [7, 25, 26]. However, while there is a general agreement on the prognostic relevance of karyotype at diagnosis, the situation is less clear as far as the occurrence of AML after a previously diagnosed MDS is concerned. Different reasons can account for the conflicting results reported in the literature. First, it is estimated that no more than 30%–50% of newly diagnosed elderly AML patients enter clinical trials and in some large cooperative studies patients with s-AML are excluded at diagnosis [27]. Secondly, data from many studies refer to the still widely adopted FAB classification, which excludes patients with RAEB in transformation (RAEB-t), considered as AML according to the WHO classification. Finally, main drawbacks from single-center studies are either the small sample size or intrastudy treatment variations.

In this study, we investigated the prognostic impact of a diagnosis of s-AML in a series of 87 homogeneously treated elderly patients with AML. In addition, we evaluated the impact...
patients, in which anthracycline-based chemotherapy was adopted either in induction or consolidation [28]. While concern has been raised regarding the ability to mobilize sufficient PBSCs for autografting after purine analogues in AML [29], after conventional FLAG therapy, we previously reported a 66% mobilization rate in a series of 44 patients with a median age of 61 years affected by de novo AML with trilinear dysplastic abnormalities [30]. It is conceivable that fludarabine given as CI can result in inferior stem cell damage and therefore less impairment of mobilization capacity.

As shown in Figures 4 and 5, differences in median OS and DFS were not significant between de novo and s-AML patients. In addition, in multivariate analysis only cytogenetic at diagnosis retained prognostic relevance, suggesting that a diagnosis of s-AML per se does not represent an adverse factor in AML of the elderly. In this regard some considerations should be made. First, a substantial proportion of apparently de novo patients (accounting for 45% in this series) presented with trilinear dysplastic abnormalities, and therefore we cannot exclude that in some cases a previously undiagnosed MDS may have preceded the onset of leukemia [30]. Secondly, it is conceivable that a stem cell involvement into leukemogenesis can also occur in a proportion of de novo AML cases, namely in the elderly patients, in which some degree of MDS and stem cell dysfunction is probably more frequent than one could hypothesize on the basis of morphologic examination. Finally, the limited number of patients in our series and the relevant selection operated as to inclusion into the aggressive program can account for discordance with data recently reported by Gupta et al. [9]. Nevertheless, a recent survey from a large patient cohort from the GIMEMA group in young adults with AML did fail to show a difference in the outcome between de novo and s-AML [31].

In conclusion, the analysis of our data suggest that antecedent RAEB does not represent a clinically relevant prognostic factor in elderly AML patients treated with aggressive therapy aimed at CR achievement. In addition, we have demonstrated that patients with s-AML can be mobilized and autografted with comparable results as opposed to de novo cases. Accordingly, elderly patients with AML secondary to antecedent MDS should not be excluded from clinical trials based on intensive therapy with curative intent.

references


