original paper

haematologica 2001; 86:814-820
http://www.haematologica.it/2001_08/0814.htm

Aggressive salvage treatment is not appropriate for the majority of elderly patients with acute myeloid leukemia relapsing after first complete remission

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Background and Objectives. The prognosis of acute myeloid leukemia (AML) in the elderly is still poor because of different reasons, including a high incidence of relapse. The aim of this study was to investigate whether aggressive salvage chemotherapy (CHT) results in an actual survival advantage in elderly patients with relapsed AML, as well as to compare hospitalization and load of supportive treatment between patients receiving aggressive management or only palliation.

Design and Methods. One hundred and fifty consecutive patients with relapsed AML (median age 66 years) were analyzed. At relapse, 99 (66%) were treated with CHT, and 51 had palliative management.

Results. Second complete remission (CR2) was achieved in 36/99 patients (36%) receiving CHT, while no CR was observed in the other group (p<0.001). Induction death rate was 22%, while 41% were resistant to CHT. The median survival from relapse was 4 months for the whole patient population; according to management, it was 5 months and 3 months for CHT and palliation, respectively (p=0.01). As to patients given CHT, a CR1 duration of more than 12 months was the only parameter significantly related to a better clinical outcome (survival from relapse: 8 vs. 4 months, p=0.002; CR2 duration: 11 vs. 5 months, p=0.001, respectively). Finally, patients managed with palliation required less hospitalization and less supportive therapy as compared to the CHT group.

Interpretation and Conclusions. Aggressive chemotherapy results in an actual survival advantage only for a minority of elderly patients with relapsed AML, i.e. those with CR1 lasting for more than 12 months.

Key words: acute myeloid leukemia, relapse, elderly patients.

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Acute myeloid leukemia (AML) is prevalently a disease of the elderly, more than half of the cases being currently diagnosed in patients aged over 60 years old.[1-4] Moreover, in elderly people the frequency of the disease is expected to increase further in the years to come, given the progressive aging of the general population. In contrast to the progress achieved in younger adults, the prognosis of AML arising in aged individuals remains poor and the current therapeutic results are largely unsatisfactory.[5,6] This adverse clinical outcome is mainly due to intrinsic differences in the biology of leukemic cells in these patients as well as, to a certain extent, to host-related factors such as comorbid conditions linked to chronologic age.[7-11] Following the administration of conventional induction chemotherapy, complete remission (CR) rates ranging from 40 to 60% are currently reported in AML of the elderly.[12-15] However, the percentage of long-term survivors does not exceed 10-15% of patients enrolled into clinical trials because of the high incidence of AML relapse.[5-11] Therefore clinicians are daily involved in the management of these patients.[16]

While there is general agreement on the opportuneness of administering aggressive salvage therapy to relapsed young-adult patients with AML, aiming to achieve CR2, little is known about the

potential benefits, if any, derived from aggressive management of relapse of AML in elderly individuals.

In this study we analyzed the clinical and hematologic characteristics of 150 AML patients who had relapsed after first CR, with the purpose of establishing whether the administration of aggressive salvage chemotherapy, aimed at achieving CR2, resulted in an actual survival advantage. In addition, we investigated the toxicity of aggressive management as opposed to a palliative approach in terms of toxic death rate, hospitalization and load of supportive therapy.

Design and Methods

From January 1995 to June 1999, 421 patients with AML aged > 60 years were diagnosed at four different institutions in Italy. Ninety-five of them (22%) were excluded from aggressive chemotherapy early at diagnosis because of poor performance status (PS), severe active infections, extremely advanced age or more than one of these reasons. Among the 326 remaining patients, 179 (55%) achieved CR following aggressive induction therapy; 150 of these patients (84%) relapsed from CR1 and were analyzed in the present study. There were 74 females and 76 males, with a median age of 66 years (range 61-79). The diagnosis had been obtained according to FAB criteria[17] and confirmed by immunophenotyping studies as previously described.[18] Patients with acute promyelocytic leukemia were excluded from analysis. In 21/150 patients (14%) a previously diagnosed myelodysplastic syndrome (MDS) preceded the onset of leukemia. Cytogenetic examination was performed in all cases by banding techniques and data were collected from 101 cases (67%) in which a minimum of 20 fully evaluable metaphases were examined. Given the very low number of patients with t(8:21) and inv(16) in the present series (2 out of 101 or 2%), prognostic evaluation of cytogenetics was carried out by encompassing normal karyotypes, t(8;21) and inv(16) into a unique group defined as favorable, while all other aberrant karyotypes were classified as unfavorable. According to the above criteria, 39 cases (39%) were considered to have a favorable karyotype [1 with t(8;21), 1 with inv(16) and 37 normal], while 62 (61%) had different karyotypic abnormalities classified as unfavorable. Karyotypic analysis was not repeated at relapse. Criteria for CR included a normal peripheral blood count in the absence of blast cells, less than 5% bone marrow blasts and absence of extramedullary leukemia. The main clinical and hematologic characteristics of the patients are summarized in Table 1. At diagnosis, 135 patients (90%) had received a combination of either idarubicin (IDA) or mitoxantrone (MITO) + cytarabine (ARA-C) ± etoposide at conventional doses as induction therapy, while 15 patients (10%) had been given the FLAG combination, that is fludarabine + ARA-C + granulocyte colony-stimulating factor (G-CSF) as previously described.[19] Most patients were consolidated with two cycles of the same regimen adopted as induction. The median duration of CR1 was 11 months, the range from 2 to 73 months. At relapse, 99 patients (66%) were managed with aggressive salvage chemotherapy which consisted of high dose ARA-C in 15 patients, FLAG in 50 and a combination of intermediate dose ARA-C plus IDA or MITO in 34. Fifty-one patients (34%) had either no treatment or hydroxyurea (HU) at a conventional dose in the case of leukocytosis (white blood cell count > 30×10^9/L). Details on treatment at diagnosis are shown in Table 1, while Table 2 summarizes the results of therapy after relapse. Of note, the therapeutic choice was based mainly on clinical assessment including PS, presence of active severe infections, evaluation of non-hematologic toxicity caused by previous chemotherapy and concomitant diseases occurring in the meanwhile; however, in a minority of cases other factors such as patient's and relatives' attitude and, less frequently, distance from the hospital played an additional role. There were no significant differences between the two therapeutic groups as far as concerned WBC count, percentage of bone marrow blasts at relapse, percentage of cases with antecedent MDS and cytogenetic findings. Overall survival (OS), CR duration and survival from relapse

Table 1. Clinical and hematologic characteristics of the 150 elderly patients with relapsed AML.

No.	150
Sex M/F	76/74
Median age, years (range)	66 (61-79)
Cytogenetics at diagnosis*	Normal + favorable: 39 (39%) Unfavorable: 62 (61%)
Induction therapy for CR1	Ida or Mito + Ara-C ± Etoposide: 135 (90%) FLAG: 15 (10%)
Median duration of CR1, months (range)	11 (2-73)
Aggressive salvage CHT	99 (66%)
Palliation and/or HU	51 (34%)

**referred to 101 patients with a minimum of 20 evaluable metaphases.*

Table 2. Aggressive salvage treatment at relapse (total number: 99).

Type of treatment	*Number (%)*	*CR (%)*
HD-Ara-C*	15 (15%)	5 (33%)
ID-Ara-C° + IDA or MITO	34 (34%)	10 (29%)
FLAG	50 (51%)	21 (42%)

**3 g/m² q12h days 1,3,5; °1 g/m²/day day 1→5.*

were calculated according to the Kaplan-Meier method[20] and compared by the log-rank test. The differences between the two therapeutic groups, i.e. aggressive treatment versus palliation, were evaluated by the two-sample Mann-Whitney test for non-matched samples or by the chi-squared test. Multivariate analysis was performed according to a Cox proportional hazard regression model.[21]

Results

Among 99 patients managed with aggressive salvage chemotherapy, CR2 was achieved in 36 cases (36%), while no CR was observed in the other group (0/51, 0%). The statistical difference is highly significant ($p < 0.001$). In the subset of patients who were treated aggressively the induction death rate was 22% (22 out of 99); 19 patients died from infectious complications, 2 from cerebral hemorrhage, and 1 from severe digestive tract hemorrhage. Finally, 41 patients (41%) were resistant to salvage chemotherapy. As indicated in Table 2, there was no difference among the three approaches adopted as salvage therapy, CR2 rate being 33% for HD-ARA-C, 42% for the FLAG regimen and 29% for ID-ARA-C plus IDA or MITO (p= 0.48). The median survival from relapse for the whole patient population was 4 months (Figure 1). According to treatment, it was 5 months for the group which received intensive therapy and 3 months for the palliation and/or HU group (p=0.01), as shown in Figure 2. The median duration of CR2 was 8 months (range 2-46). WBC count at diagnosis or relapse, cytogenetics at diagnosis, diagnosis of previous MDS, serum LDH level and age less or more than 70 years did not significantly influence survival from relapse in either therapeutic group (Table 3). In contrast, for the group of patients who were given aggressive salvage treatment, a CR1 lasting more than 12 months as compared to CR1 < 12 months was significantly related to a better clinical outcome (median survival from relapse being 8 months vs. 4 months, p=0.002), as indicated in Figure 3. In addition, CR2

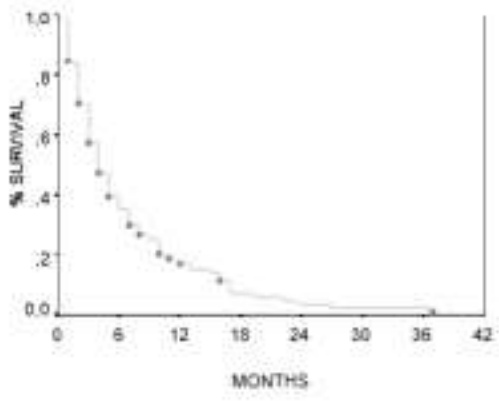

Figure 1. Survival from relapse of the whole patient population (median: 4 months).

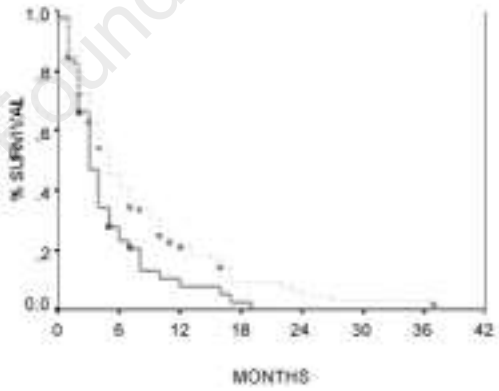

Figure 2. Survival according to treatment (median: 5 months for aggressive salvage chemotherapy vs 3 months for palliation, p = 0.01)

Table 3. Results of multivariate analysis of different prognostic factors on survival from relapse.

Factor	*p value*
WBC count at diagnosis *	0.11
Age more or less than 70 years	0.18
Cytogenetics°	0.09
Serum LDH level§	0.12
Previous MDS diagnosis (yes/no)	0.28
CHT vs. palliation	0.32
CR1 duration (> 12 months vs < 12 months)	0.01

**More or less than 50×10⁹/mL; °favorable vs unfavorable; §normal or abnormal value.*

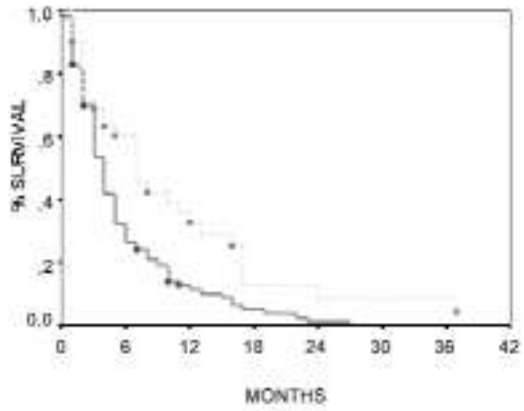

Figure 3. Survival from relapse for patients receiving aggressive treatment according to CR1 duration (median: 8 months for CR1 > 12 months vs 4 months for CR1 < 12 months, *p* = 0.002).

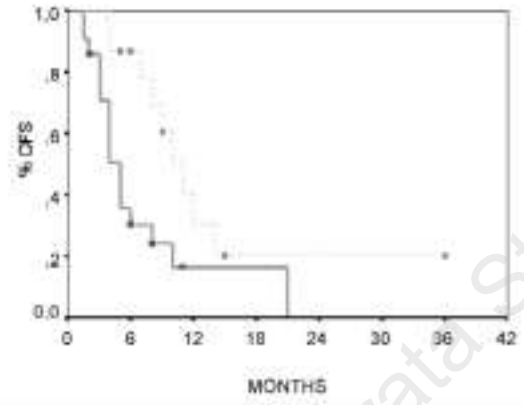

Figure 4. CR2 duration according to CR1 duration (median: 11 months for CR1 > 12 months vs 5 months for CR1 < 12 months, *p* = 0.01).

Table 4. Comparison of toxicity and supportive treatment between patients receiving aggressive salvage therapy and those managed with palliation and/or HU.

	Aggressive CHT	*Palliation and/or HU*	*p value*
Days of hospitalization	32	13	0.001
Blood units	15	9	0.01
Platelet units	10	6	0.02
Days of i.v. antibiotic therapy	18	6	0.009

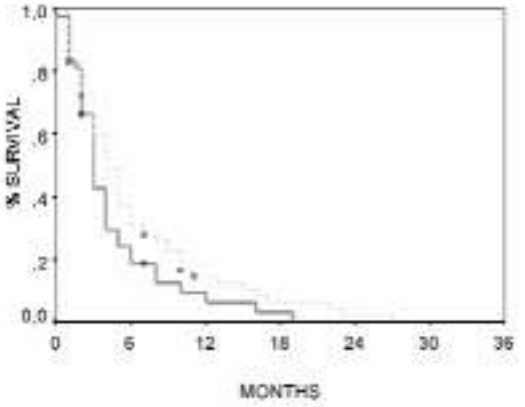

Figure 5. Survival from relapse according to treatment for patients with CR1 < 12 months (median: 4 months for aggressive salvage chemotherapy vs 3 months for palliation, *p* = 0.10).

rate was higher in the group with CR1 > 12 months (16 out of 30, or 53% vs 20 out of 69, or 29%, *p*=0.03). Of note, CR2 duration was also significantly related to the length of CR1 (median CR2 duration 11 months for CR1 > 12 months vs. 5 months for CR1 < 12 months, *p*=0.01), as shown in Figure 4. In contrast, CR1 duration did not significantly affect survival in the group of 51 patients receiving palliative therapy and/or HU (5 months for CR1 > 12 months vs. 3 months for CR1< 12 months, *p*=0.35). Finally, the median survival from relapse was essentially identical (4 months for aggressive treatment vs. 3 months for palliation, *p*=0.10) for the subset of patients with CR1 of less than 12 months, irrespective of the type of treatment (Figure 5). Overall, patients with CR1 > 12 months accounted for 26% of the total group (39 out of 150) and 30 of these 39 (77%) were selected for aggressive therapy as opposed to 69 out of 111 (62%) of those with CR1 < 12 months (*p*=0.11), indicating that the duration of CR1 did not influence the therapeutic choice in this series. As far as concerns CR1 duration analysis, different cut-off points were considered. A cut-off of 12 months resulted as being the most significant value for both CR2 achievement and duration or survival from relapse.

It is worthy of note that the patients managed with aggressive therapy, intended to achieve a CR2, required more days of hospitalization (32 vs. 13, *p*=0.003), more days of intravenous antibiotic therapy (18 vs. 6, *p*=0.009) and more transfusion support (blood units: 18 vs. 10, *p*=0.01; platelet units: 13 vs. 7, *p*=0.01), as detailed in Table 4.

Discussion

In spite of substantial selection operated at diagnosis regarding patients included into clinical trials based on aggressive induction chemotherapy, the prognosis of AML in elderly individuals remains dismal, given the high relapse rate which is still observed in this AML age category.[5-9] The treatment of elderly AML patients with relapsed or refractory disease is, therefore, becoming a daily challenge in hematology units. Surprisingly, in spite of the clinical importance of the problem, little information specifically addressing the management of the elderly patient with AML in relapse has appeared in the literature.

In this study we focused on a series of 150 consecutive elderly patients with AML who relapsed after achieving CR1. The aims were: a) to evaluate the percentage of patients judged as able to receive aggressive salvage therapy; b) to investigate whether intensive treatment at relapse actually resulted in a survival advantage; c) to search for prognostic factors able to predict a more favorable clinical outcome; d) to compare hospitalization and load of supportive treatment between patients aggressively managed and those receiving support and/or hydroxyurea.

Ninety-nine out of 150 patients with relapsed AML (66%) were included into aggressive trials aiming at achieving CR2. As usually happens at diagnosis, an important selection, based mainly on clinical assessment, was operated. Toxicity derived from induction/consolidation chemotherapy was the pivotal reason for the significantly higher exclusion rate at relapse (34%) than at diagnosis (25%). Of interest, factors not strictly related to medical decisions such as patient's and relatives' attitude as well as geographic distance from the hematologic institution played an additional role. Finally, we feel that physicians' attitude also occasionally accounted for the therapeutic choice. Nevertheless, data from our series confirm that a substantial proportion of elderly patients with AML are excluded, either at diagnosis or at relapse, from clinical trials based on aggressive chemotherapy, even though these have been specifically designed for patients with advanced age. Therefore, any overoptimistic conclusion on therapeutic results in AML of the elderly should take into account possible biases in patient selection.

Our study data are based on a retrospective analysis rather than a randomized trial. However, therapeutic selection was based mainly on performance status, aggressive chemotherapy being denied to sicker individuals and this may have accounted for the significant survival advantage for the group of patients receiving aggressive salvage chemotherapy. Notwithstanding, the median survival of these patients was only 5 months, with 64% of them failing to achieve CR2. Induction death rate was 22%, while 42% of patients were refractory to salvage treatment. Unlike in young adults, in whom CR2 rates of 50% or more are commonly observed,[19,22-24] in this series dealing with elderly AML patients a higher percentage of resistant cases was observed, confirming that adverse biological factors significantly account for the poor therapeutic results. On this basis, it appears of utmost importance to try to discriminate which category of patients could get substantial advantage from intensive treatment at relapse. We, therefore, performed a prognostic analysis aimed at identifying parameters predictive of clinical outcome. CR1 duration > 12 months was the only factor significantly related to CR2 achievement and duration as well as to survival from relapse, both in univariate and in multivariate analysis. This finding is in keeping with previous studies, in which the duration of CR1 resulted as being a major prognostic determinant in recurrent AML.[25–28] Other factors recognized as important at diagnosis, such as cytogenetics, serum lactic dehydrogenase level, preceding MDS and WBC count,[29-32] did not influence the therapeutic results. The main adverse relevance of relapse itself could perhaps have softened the prognostic impact of other well-recognized factors. It is worthy of note that as far as the impact on survival from relapse is concerned, all parameters except cytogenetics were evaluated for the statistical analysis both at diagnosis and at the time of relapse (data not shown) and results were essentially identical. As specifically concerns cytogenetics, it should be stressed that most relapses occurred early in the course of the disease, so that considerable changes were unlikely. Of interest, in spite of the previous clinical selection, survival was essentially identical for patients with CR1 <12 months independently of treatment (Figure 5), strongly suggesting that aggressive salvage treatment does not offer these patients any advantage in terms of CR achievement and survival. Furthermore, hospitalization and load of supportive therapy in terms of blood and platelet units needed, as well as of number of days of intravenous antibiotic therapy, were significantly greater for the group of patients receiving aggressive management. In addition, in a significant proportion of them, i.e. those with CR1 < 12 months, accounting for 65% in this series, costs and discomfort deriving from prolonged hospitalization and heavy transfusion support were

not balanced by gain in survival.

In conclusion, our data demonstrate that the majority of elderly patients with relapsed AML do not obtain any benefit from the administration of conventional salvage chemotherapy aimed at achieving CR2. Furthermore, prolonged hospitalization and heavy transfusion requirement are usually needed, and these are not balanced by a real survival advantage. Therefore, a simplistic assessment of performance status and general clinical condition should not be the only basis for a conservative or aggressive therapeutic choice. In our experience, only patients whose CR1 lasted for more than 12 months are good candidates for conventional aggressive management. The remaining patients should be informed about the poor results of conventional chemotherapy and offered an upfront alternative approach, possibly based on drugs with novel mechanisms of action, biological response modifiers, differentiating agents or a combination of these.[33-35] Monoclonal antibodies or other forms of immunotherapy such as interleukin-2 or reduced intensity allotransplants could also be investigated.[36-39] This attempt to tailor treatment could result in an improvement of therapeutic results or, at least, avoid life-threatening toxicity not balanced by an actual benefit in a particularly frail population such as elderly patients with relapsed AML.

Contributions and Acknowledgments

FF, FM and FL conceived the study; FF, FM and BM drafted the paper; RL, MA, EO and EMS collected, analyzed and interpreted the data. FL critically reviewed the paper; FF, FM and FL approved the final version of the manuscript.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Elihu Estey, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Estey and the Editors. Manuscript received May 29, 2001; accepted July 2, 2001.

Potential implications for clinical practice

Elderly patients with early relapse of acute myeloid leukemia do not gain substantial advantage from aggressive salvage chemotherapy and should be offered alternative therapeutic approaches.

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