# Acute myeloid leukemia treatment in patients over 60 years of age. Comparison of symptomatic, palliative, and aggressive therapy

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State-of-art of aggressive treatment of acute myeloid leukemia (AML) in patients older than 60 years is one of the least satisfactory topics of present-day hematology.

This fact led us to ask the following questions: Does it make sense to administer aggressive treatment to older patients with AML? Could it be that we only complicate the rest of the life of these older patients with AML, by using aggresive treatment? Would they not benefit more from palliative or symptomatic therapy? What is the quality of life of older patients with AML like? Therefore, to try to answer these questions, we performed the next analysis.

A retrospective analysis was performed including (without any selection) all consecutive patients over 60 years of age who were treated with AML in our centre from 1998 till 2003.

We have analyzed data from 137 elderly patients who were diagnosed with AML (excluding acute promyelocytic leukemia). Median survival from diagnosis in the aggressive (curative) therapy group was 4 months, in palliative therapy group 2 months and in symptomatic therapy group 0.8 months. Patients receiving curative therapy spent in a hospital (in-patient stay) 70% (median) of their life after diagnosis of AML, patients receiving palliative treatment 64% (median) of their life after diagnosis, and patients receiving symptomatic treatment 100% (median), respectively.

Only marginal advantage in the median overall survival is observed in the group of aggressively treated patients.

*Key words: acute myeloid leukemia, elderly, survival, treatment*

Acute myeloid leukemia (AML) in particular is a disease of elderly people. More than three-quarters of patients with AML are older than 60 years [2, 11, 19]. While results of treatment of AML have improved steadily in younger adults over the past 20 years, treatment of AML in patients older than 60 years is one of the least satisfactory topics of present-day hematology. Therapeutic results of AML in older patients are regretful indeed. Long-term survival of older patients with AML is only 4–10% among those who attend the care of haematology clinics [7, 13, 15, 17]. Several approaches have been attempted to improve these results, but none of them has led to a significant improvement in overall survival [5, 9, 14]. PULSONI et al have not even proved statistically significant difference in survival of patients who have undergone aggressive and non-aggressive treatment [17].

These facts led us to ask the following questions: Does it make sense to administer state-of-art aggressive treatment to older patients with AML? Could it be that we only complicate the rest of the life of our older patients with AML, when we intend to treat them aggressively? Would they not benefit more from palliative or symptomatic therapy? What is the quality of life of older patients with AML like? If we have to treat aggressively, who should it be then?

Therefore, to try to answer these questions, we performed the next analysis.

## Patients and methods

We have performed a retrospective analysis including (without any selection) all consecutive patients over 60 years of age who were treated with AML (excluding acute promyelocytic leukemia (APL) because of excellent prognosis and different treatment as compared with others AMLs) in our centre from 1998 till 2003. All our patients with AML were from a region of about 2,500,000 inhabitants. The goal of this analysis was to compare not only survival period in patients undergoing aggressive (curative), palliative, and symptomatic treatment, but we have also attempted to com-

pare their quality of life (measured by the total time they spent in hospital [in-patient stay] after their diagnosis was determined). We have also determined the results of treatment in relation to cytogenetic prognostic groups of AML [6].

*Statistical analysis*. Student's t-test, paired or unpaired as indicated, was used for calculation of the statistical significance of differences in survival of patients in three treatment groups. When the distribution of values was not normal, Wilcoxon tests, paired and unpaired (Mann-Whitney), were used. Results of Student's t-test were verified using non-parametric Wilcoxon tests. Probability values of less than 0.05 were considered as significant. The overall survival of patients was calculated from the day of diagnosis.

## Results

We have analyzed data from 137 elderly patients (67 males and 70 females) who were diagnosed with AML (excluding APL). The patients were with *de novo* AML as well as with secondary AML. Aggressive induction therapy was administered to 50 patients (median age 65 years; 60–74), palliative therapy was administered to 52 patients (median age 71 years; 60–82), and symptomatic treatment (erythrocytes transfusions, blood platelet transfusions, analgesics, etc.) was administered to 35 patients (median age 74 years; 60–87). Aggressively treated patients received one or two cycles of induction therapy and two or three cycles of consolidation therapy. Supportive therapy was not selected. The choice of the therapeutic modality for individual patients was led not only by their age and their co-morbidity (greater in patients treated palliatively or symptomatically), but sometimes also by the patients preference, after they have been informed about the prognosis of their disease. There were no patients with favorable cytogenetics in palliative and symptomatic treatment arm.

Aggressive induction therapy was administered in classic chemotherapeutic regimen "3+7" including cytarabine (Ara-C) (in a dose of 100 mg/m$^2$/day for 7 days) with daunorubicin (30–45 mg/m$^2$/day for 3 days) or with mitoxantrone (10–12 mg/m$^2$ for 3 days). Palliative therapy was administered as a low-dose Ara-C (in doses up to 100 mg daily for 5–7 days) or using hydroxyurea (HU; administered daily in doses adjusted according to the blood count parameters). Ara-C was administered to 19 patients; HU was administered to 33 patients.

Median survival from diagnosis in the aggressive therapy group was 4 months (mean 8.0; 0.03–50). First induction therapy reached complete remission (CR) of AML in 19 (38%) of aggressive treated patients. There are still five living patients in CR. Only three patients from our group underwent allogeneic transplant. No patient underwent autologous transplant. All transplanted patients are alive disease free.

Among all patients in only 3 (2%) there were prognostically favorable cytogenetic and molecular-genetic findings (in 2 cases AML1-ETO translocation and in 1 case CBFβ-MYH11 translocation). All these patients were treated aggressively and are alive, without being transplanted. One of them live even in complete molecular remission.

Total survival period in patients who received palliative therapy was 2 months (mean 2.6; 0.06–9.2) and in patients who received symptomatic therapy it was 0.8 months (mean 1.5; 0–6). A comparison of the palliative therapy with HU to the palliative therapy with low-dose Ara-C did not prove any difference neither in survival period of patients nor in the in-patient stays duration after the eliciting of diagnosis.

The evaluation was made by 30th November 2004.

Patients receiving curative therapy spent in a hospital (in-patient stay) 70% (median; 11–100%) of their life after diagnosis of AML, patients receiving palliative treatment 64% (median; 16–100%) of their life after diagnosis, and patients receiving symptomatic treatment 100% (median; 4–100%). The differences in in-patient stay duration are not statistically significant.

In the long-term horizon only 5 patients (4%) among all 137 patients survived without signs of the disease. All these surviving patients were treated by aggressive induction therapy, three of them underwent the allogeneic transplantation.

Main results of our analysis are summed in the Table 1 and in Figures 1–3.

## Discussion

Our analysis showed very poor results of therapy of AML in patients above 60 years of age. Total surviving without signs of the disease of only 4% of patients in agreement with some formerly published data [13, 17]. Total surviving of el-

**Table 1. Overall survival, performance status, and time spent in hospital from the diagnosis of acute myeloid leukemia (AML) until death or day of analysis in patients treated symptomatically, palliatively or aggressively**

| | Overall survival; months (median; min; max) | Performance status 2 – 4; % of patients | Time spent in hospital (in-patient stay) from the diagnosis of AML until death or day of analysis; % of days (median; min; max) | Statistical significance of differences in overall survival |
|---|---|---|---|---|
| Symptomatic therapy | 0.8; 0; 6.0 | 71% | 100%; 4%; 100% | Symptomatic versus palliative $p = 0.02$ |
| Palliative therapy | 2.0; 0.06; 9.2 | 61% | 64%; 16%; 100% | Symptomatic versus aggressive $p < 0.001$ |
| Aggressive therapy | 4.0; 0.03; 50.0 | 30% (no patient with performance status 4) | 70%; 7%; 100% | Aggressive versus palliative $p < 0.001$ |

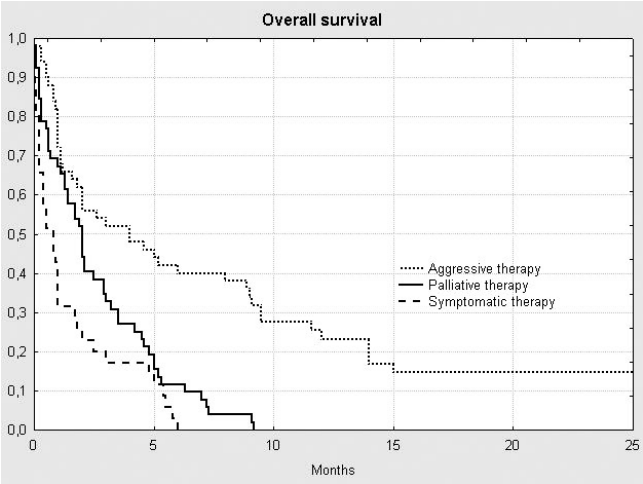


**Figure 1. Overall survival of the patients treated symptomatically, palliatively or aggressively.**

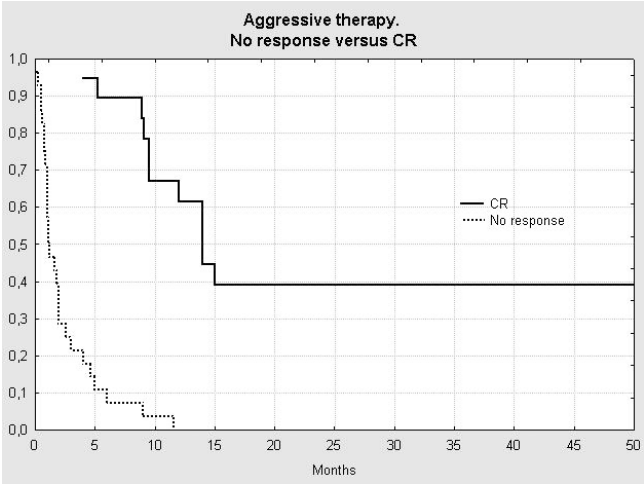


**Figure 2. A comparison of the overall survival of patients who achieved the complete remission (CR) after the aggressive induction therapy to those who did not achieve the CR (p<0.001).**

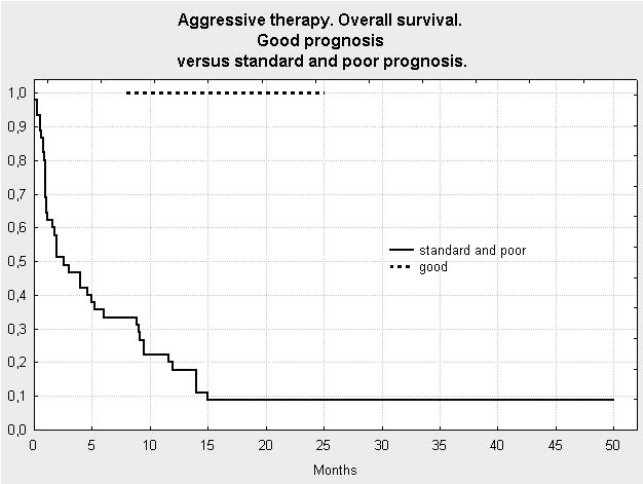


**Figure 3. A comparison of the overall survival of patients with good prognosis leukemia to the patients with standard or poor prognosis leukemia (p<0.001). The prognosis of the disease was estimated on the basis of cytogenetic and molecular genetic features.**

derly patients with AML is probably even worse, as it can be assumed that some patients die before the AML was diagnosed.

Several factors are to be taken in consideration in explaining the poor outcome of elderly patients with AML: the inability of many of these patients to withstand the rigors of aggressive chemotherapy and its expected complications due to an impaired regenerative capacity of bone marrow [11], the occurrence of age-related cardiac, pulmonary, or renal disorders that lead to a greater incidence of acute toxicity from chemotherapy [18, 20], and some well-known, unfavorable prognostic factors that are more common in elderly patients [11, 20]. These factors include genetic mutations, cytogenetic abnormalities, a higher expression of P-glycoprotein [10, 17], unfavorable performance status [17], or a previous history of myelodysplastic syndrome [11, 17]. We found only 2% of prognostically favorable AML in our study group; that corresponds with the published data [20]. The number of CR after the first cycle of aggressive induction therapy also corresponds with the published data [3, 10–12, 16, 21].

Contrary to PULSONI et al [17] we proved statistically significant difference in the survival of patients treated aggressively, palliatively or symptomatically. We must however ask, to what extent is the statistically significant difference in total survival significant clinically. There may be different opinions concerning this question, because the difference in median of the total survival of patients treated palliatively or aggressively is only 2 months. Observed differences in the total survival can additionally be influenced by the fact that our analysis, like the other similar analyses [1, 11, 17] was not randomised. The patients treated palliatively and symptomatically have worse performance status results and higher age; they can also have more advanced disease or less favorable types of AML. In our opinion, it is not possible to perform randomised study that could clearly evaluate the benefit of aggressive and palliative therapy in patients with AML, because of ethical issues. However, aggressive therapy gives patients a chance of complete cure.

The fate of patients in our study group treated palliatively is worse than the fate of patients treated aggressively. Even the relative duration of in-patient stay after the eliciting of the diagnosis in the palliatively treated patients is comparable to the duration of in-patient stay of aggressively treated patients. This is a difference to the formerly cited work of PULSONI et al [17]. We acknowledge that differences in the duration of in-patient stay can be influenced possibly by lack of an efficient home-assistance service in our country and an excellent availability of hospital admission in the Czech Republic. In our practice, there was no difference in the reason

for hospitalisation in each of the groups. We did not find any difference between palliative administration of Ara-C and palliative HU. None of our patients with the low-dose Ara-C showed complete remission, even though such cases were published [4]. It is necessary to continue searching for new possibilities of palliative therapy. Some hope may arise, for example, from orally administered chemotherapeutics other than HU [8].

According to our study patients with favorable cytogenetic characteristics of their disease show a benefit from the aggressive treatment.

## Conclusion

A marginal advantage in the median overall survival is observed in the group of aggressively treated patients, which includes patients with younger age, reduced co-morbidity and, in general, lower risk factors with respect to the groups of patients treated with palliative and symptomatic treatment. The survival advantage observed could be related to a better prognostic combination rather than to the different treatment strategy.

However, we also conclude that, if it only would be possible, elderly patients with AML should be offered the aggressive therapy of their disease; not only the patients with favorable prognostic factors. Only the aggressive treatment gives them hope to be cured.

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