ACUTE MYELOID LEUKEMIA

Treatment of AML in biological subgroups

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Risk-adapted therapy summarizes new attempts to further improve the therapeutic outcome in various biologic or prognostic subgroups and thus improve the outcome in AML as a whole. This rises the questions (1) about the present status of therapeutic results in AML overall, (2) data available on therapeutic effects in specific risk groups, (3) present knowledge about risk factors and prognostic groups, (4) an approach to subgroup specific treatment effects, and (5) a more differentiated use of therapeutic options in different risk groups. Since acute promyelocytic leukemia is addressed by an own article in this issue, present report concentrates on the remaining subclasses affecting 80–90% of AML patients.

Present status of therapeutic results

The therapeutic progress in AML is best exemplified by the multicenter randomized trials published since 1981 (overview, 1). Table I shows the cumulative data on complete remissions (CR) and long-term continuous remissions in a total of 16061 patients treated in 28 trials according to two age groups and two time periods of publication. Accepting differences in therapeutic endpoints and patient selection, about 2/3 of patients go into remission and ¼ of them remain relapse-free. Major progress over time is seen in the continuous remission of younger patients while older patients stay far behind this benefit. Thus, overall AML remains a disease mostly responding to chemotherapy by a remission but not continuing relapse-free in more than a minority of patients.

Therapeutic effects in prognostic groups

Improved outcomes by more intensive therapy were first observed in good prognostic groups. Thus, postremission high versus standard dose araC produced longer remissions in CBF AML (t(8;21), inv[16], t(16;16)) and not in other abnormal karyotypes [2]. Autologous stem cell transplantation (SCT) versus chemotherapy alone prolonged the relapse-free survival in the good and not in the poor risk group according to karyotype and early blast clearance from bone marrow [3].

In contrast, the group responding with an improved relapse-free survival to prolonged maintenance treat-
ment versus intensive consolidation were poor risk patients according to unfavorable karyotype or high LDH or high day 16 bone marrow blasts or age ≥60 years, and not the respective good risk patients [4].

Since these trends in trials using different design and risk criteria are contradictory, the role of multiple patient characteristics related to age had to be requestioned [5].

Present knowledge about risk factors and prognostic groups

A new opportunity to analyze the role of multiple risk factors was provided by two consecutive trials of the German AML Cooperative Group (AMLCG) where 1084 patients of <60 years and 750 patients of 60 + years were treated concurrently for de-novo AML. Chemotherapy was TAD–HAM (HAM, high-dose araC/mitox) or HAM–HAM for induction, TAD for consolidation, and reduced TAD for maintenance randomly compared with intensified consolidation [4].

By multivariate analysis and confirming published results we identified cytogenetic groups [6,7], age [4,8], LDH [4,8,9], WBC [10] and day 16 marrow blasts [9,11] as independent prognostic factors, while the treatment modifications did not reach significance.

The only difference between the younger and the older age group was in favorable (14% vs. 7%) and unfavorable (20% vs. 24%) karyotypes. The overall survival at 4 years was 35% in the younger vs. 13% in the older patients. Table II shows the cumulative incidences of ongoing remission in both age groups and in the different prognostic groups [5].

As results of this analysis, age over 60 years as a whole (with the only exception of the 7% favorable karyotype) must be considered poor risk, and there are unknown biological variables such as the age factor essentially determining the outcome of patients beyond the defined risk factors. This awareness gains great importance since 2/3 of patients with AML are 60 years of age or older (Figure 1).

Additional risk factors have been contributed or discussed by others. A history of myelodysplastic syndrome (MDS) or cytotoxic treatment [12,13] is pertinent if these patients are included. Patients at all ages with secondary AML have half the cure rate of those with de-novo AML (AMLCG updates). However, the expression of multidrug resistance has been found to predict for response but not for long-term prognosis [14,15]. AML with morphologic dysplasia was found being related to unfavorable karyotype and not an independent risk factor [8].

Among other abnormalities associated with poor prognosis MLL tandem duplications with 5% [16] and MLL rearrangements by translocation with 2.8% [17] are unfrequent. The recently described unfavorable EVI1 [18] and BAALC expressions [19] require further testing in trials. The frequent Flt3 mutations occurring in 23–32% of AML and predicting poor long-term prognosis [20,21] should become part of the routine risk assessment.

An approach to subgroup-specific effects

In 1999 the German AMLCG started a new trial on major treatment alternatives in de-novo and secondary AML and high-risk MDS, where patients at all ages were up-front randomized to TAD–HAM versus HAM–HAM induction, G-CSF priming versus no G-CSF, and autologous stem cell transplantation (SCT) versus maintenance. Randomizations were balanced against each other and were stratified for age <60 versus 60 + years, cytogenetic groups, LDH ≤700 versus >700U ml⁻¹, and de-novo vs. secondary AML vs. MDS (Figure 2). More than 2000 patients entered the trial so far, and new insights into the relative value of major treatment options in major prognostic subgroups are expected which can contribute to risk-adapted treatment strategies.

Differentiated use of therapeutic options in different risk groups

For the time being and with the limited knowledge about specific treatment effects in prognostic groups the following target groups and their differentiated management may be distinguished.

A. The entire patients 60 years or older (except for the few patients with favorable karyotypes) are considered poor risk. With standard dose induction or intermediate dose araC half of them go

| Table I. Combined data on complete remissions (CR) after induction treatment, and continuous complete remissions (CCR) at 4–5 years in 28 randomized multicenter trials in patients with AML (Overview, 1) |
|---|---|---|---|
| Patients entering | 2686 | 13375 | 16061 |
| Patients entering | CR | CCR | CR | CCR | CR | CCR |
| Age <60 years | 69% | 17% | 72% | 32% | 72% | 30% |
| Age 60 + years | 45% | 11% | 50% | 14% | 50% | 14% |
| All ages | 64% | 15% | 65% | 27% | 64% | 25% |
into remission but their long-term survival and remission with maintenance or repeated consolidations is with 15%. This justifies novel approaches using targeted agents such as tyrosine kinase inhibitors [22], farnesyl transferase inhibitors [23] or immunotoxins [24]. Dependent on their toxicity, these options can be used either alternatively or additionally to the standard chemotherapy (overview, 25). The older patients are also candidates for allogeneic SCT at optimized conditioning including matched unrelated donors [26,27]. Older patients with contraindications against standard chemotherapy may be given a chance by experimental low toxicity agents.

B. Patients under age 60 with unfavorable karyotype: Half of them are brought into remission by standard or double induction, but their long-term survival and ongoing remission is only 10–15%. A high priority allogeneic SCT is indicated in these patients and may be even approached early and without attaining a complete remission.

C. Patients at all ages with favorable karyotypes (CBF leukemias): In the current 1999 trial of the German AMLCG enrolling patients at all ages with de-novo AML, secondary AML, and high-risk MDS, CBF leukemias achieve a CR rate of 71%, an overall survival of 50%, and a long-term remission rate of 68%. A meta-analysis by the German AML Intergroup in 392 patients of 16–60 years with CBF AML the CR rate is 86%, the overall survival is 65% and the relapse-free survival is 60% [28]. The Cancer and Leukemia Group B first demonstrated the advantageous long-term results in CBF leukemias which were found to depend on repetitive cycles of post-remission high-dose araC [2,29,30]. By the German data [28] resulting from different strategies with high-dose araC induction and partly prolonged maintenance the US data seem to be reproduced.

As from the above and other international results (overview, 28) CBF-AML represents a subgroup with an outcome superior to that in other AML patients receiving the same state of the art chemotherapy. Considering the ongoing mortality and morbidity associated with allogeneic SCT

Table II. Probability of ongoing complete remission at 4 years in 2 age groups and multiple prognostic subgroups. Data from German AMLCG enrolling 1834 patients at all ages with de-novo AML concurrently treated and evaluated according to intention-to-treat (Reference 5)

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Figure 1. Age structure of the total population of patients with acute myeloid leukemia according to National Cancer Institute SEER Cancer Statistics Review 1975–2000 (Overview see 1)

Figure 2. Design of the 1999 trial by the German AMLCG as an approach to subgroup-specific treatment effects. All 3 randomizations between TAD-HAM and HAM-HAM induction, G-CSF-priming and no G-CSF and autologous transplantation and maintenance chemotherapy are done in one step up-front and are balanced against each other. In addition, randomizations are stratified for age, LDH, cytogenetics, de-novo or secondary AML or high-risk MDS.
there are good reasons to avoid this procedure in the first-line therapy and postpone it to the event of relapse in this group of patients.

D. Remaining from the categories A–C patients under age 60 with intermediate karyotype represent a large population with average prognosis. Their CR rate is 69%, their 4 years survival is 38% with 44% ongoing remission. This group also includes a part of secondary AML and high-risk MDS achieving 50–60% CR, about 25% survival and 30% ongoing remission (updates AMLCG 1999 trial). Within patients younger than 60 years with intermediate karyotype there is no evidence for a meaningful risk adaption of treatment. The option of allogeneic SCT in first CR mainly with family donors is justified even if investigational.

Conclusions for present and future risk adaption in AML

Based on adequate trial results the group of patients younger than 60 years with intermediate karyotype appears to best representing present therapeutic standard and progress, also including allogeneic SCT in first CR. Even more successful in patients with favorable karyotypes, the state of the art strategy should avoid the risk of allogeneic SCT as first line therapy in this good prognostic group. High priority, early allogeneic including matched unrelated donor SCT gives almost the only chance of cure to younger patients with unfavorable karyotypes. New comparative data suggest patients over age 60 as a largely homogeneous group of poor prognosis. Novel approaches including allogeneic SCT at optimized conditioning are required and justified in this group, actually contributing the majority to the AML population. New target groups for more specific treatment options may result from ongoing prospective and stratified clinical investigation.

References


