Induction Chemotherapy for Acute Myeloid Leukemia – Experiences from the AML-CG Studies

Jan BRAESS

Department of Internal Medicine III, Laboratory for Leukemia Diagnostics, Klinikum Grosshadern, Ludwig-Maximilians University, Munich, Almanya

Over the last three decades the overall prognosis of patients suffering from AML has steadily improved. Nowadays, complete remissions are achieved in 60 – 70% of all patients with long-term disease free survival and potential cure in 25 – 40% of cases. A more detailed analysis indicates that this progress has mainly been achieved in patients <60 years of age while in older patients little improvements have been obtained [1-5].

When analyzing the approaches that underlie the progress in AML therapy two major developments appear essential: the intensification of therapy and the improvement of supportive care.

In the last few years increasing insights into the biology of AML have been gained. It has become clear that AML is a not a homogeneous disease but rather a group of different subtypes. These subtypes differ not only in their biology but also in their prognosis. Therefore genetic markers have become mandatory to discriminate prognostic subgroups and to adjust treatment according to distinct risk groups [6-12]. However the definition of distinct subgroups of AML is still mainly descriptive and the major challenge for clinicians and translational researchers remains how to treat these different subgroups most effectively and how to improve on their current outcome. Except for acute promyelocytic leukemia the better understanding of AML biology and the development of "targeted" therapies so far has not resulted in significant improvements in overall survival.

The standard induction therapy for AML is still a "3+7" type regimen comprising three days of Daunorubicin and seven days of standard-dose Cytosine Arabinoside (AraC) as continuous infusion [13,14]. Based on cell biologic data, the German AML-CG modified the 3+7 regimen and established the TAD-9 regimen which is the combination of Thioguanine, AraC, and Daunorubicin [15]. The TAD-9 regimen resulted in a high CR rate and has been part of the induction strategies of the German AML-CG since 1979. For the dosing of Daunorubicin in particular an improvement in overall survival was demonstrated for full dosing as compared to reduced dosing in patients older than 60 years [16,17].

In an attempt to improve the long-term prognosis of patients with AML, the AML-CG introduced the concept of "double induction". This strategy is primarily focussed on patients < 60 years of age. It consists of two courses of chemotherapy irrespective of the degree of cytoreduction in the bone marrow after the first course with the second course starting on day 21 unless severe complications prohibit its application.

This strategy resulted in a significantly longer remission duration and overall survival as compared to standard induction [18]. In order to further improve on these results double induction with two courses of TAD 9 was compared to a first course of TAD 9 followed by high dose AraC (HD-AraC) plus Mitoxantrone (HAM) as second course. While no significant differences in outcome were observed for the overall group of patients a favourable effect of HAM was seen in the subgroup of high-risk patients as defined by unfavourable karyotype and/or elevated LDH level and/or residual day 16 bone marrow blasts with an OS at five years of 25% vs. 18% (p = 0.0118)

[19]. The subsequently performed comparison of two courses of HAM (HAM/HAM) versus the TAD-9/HAM sequence, however, showed no significant differences between HAM-HAM and TAD-HAM in terms of CR rate (71% vs. 65%), RFS at five years (35% vs. 29%), and OS at 5 years (32% vs. 30%) [20]. While the escalation of drug doses thus obviously has reached a limit, further intensification of therapy by shortening the time interval between induction cycles appeared as a promising new approach. This strategy was first evaluated in patients with relapsed and refractory AML. Based on prior studies by Burke et al. and Archimbaud et al. [21,22] the HAM regimen was modified into a sequential application of two HAM courses (S-HAM). S-HAM comprises HD-AraC bid on days 1, 2, and Mitoxantrone on days 3, 4; after a rest period of only three days the identical sequence is repeated on days 8 and 9 (HD-AraC) and 10 and 11 (Mitoxantrone), respectively.

The S-HAM protocol was highly effective in patients with advanced disease (primary refractory or relapsed AML) with a CR rate of more than 50% but was complicated by a high early death rate from infections [23], [24,25]. Subsequent supportive therapy with G-CSF, however, reduced the duration of critical neutropenia from 40 to 36 days (p=0.008) and the ED rate from 30% to 21% (not significant) [26]. First results of dose dense therapy in first line therapy of de-novo AML were gained by a prospective randomised comparison of conventional versus dose dense therapy in children with AML. In the COG (Children Oncology Group) study 2891 dose dense therapy comprising Dexamethasone, Cytarabine, Thioguanine, Etoposide and Rubidomycin (DCTER) given on days 0-4 and 10-14 regardless of response was compared to the standard DCTER regimen given on days 0-4 and 14-18 or later, depending on response. Dose dense treatment resulted in a significantly longer disease-free and overall survival after 3 years of 55 % versus 37 % (p=0.0002) (DFS) and 52±6% versus 42±6 % (OS), respectively [27]. In adult patients a French study showed that a similar sequential approach (however not involving high-dose AraC) resulted in a surprisingly low hematological toxicity and a lower cumulative incidence of relapse as compared to conventional induction [28].

These results prompted the AMLCG to assess the efficacy and feasibility of dose-dense therapy with S-HAM in newly diagnosed de novo AML in a phase II study. Supportive therapy with pegfilgrastim was mandatory [29].

Of 172 de-novo AML patients (excluding acute promyelocytic leukemia) 61% reached a complete remission, 22% a complete remission with incomplete peripheral recovery, 7% had persistent leukemia, 10% succumbed to early death - resulting in an overall response rate of 83%. Kaplan Meier estimated survival at 2 years was 75% for the whole group [patients with unfavourable karyotypes 38%; patients with favourable karyotypes 69%; patients with intermediate karyotypes 75%] after S-HAM treatment. Importantly the compression of the two induction cycles into the first 11 - 12 days of treatment was beneficial for normal hematopoesis as demonstrated by a significantly shortened duration of critical neutropenia of 31 days as compared to 46 days after conventionally timed double induction.

In conclusion the dose-dense intensive S-HAM regimen is a highly effective treatment regimen with a response rate of 83% and a low early death rate of 10% in the first 65 days which is most probably due to the short duration of critical neutropenia. In spite of these promising results a prospective randomized comparison of such a dose-reduced but intensely-timed therapy versus conventional double induction is required to prove the potential superiority of the new approach. This trial has been initiated within the next generation of the AML-CG studies (AML-CG 2008).

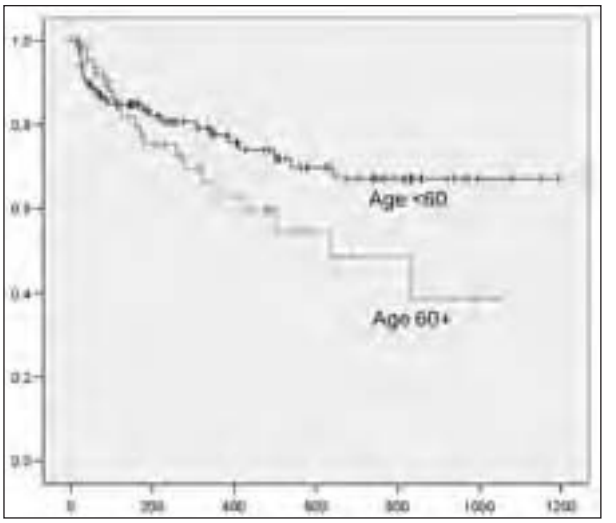

Figure 1. Overall survival according to age (< 60 and 60 + years)

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