Acute Myeloid Leukemia (AML): The Role of Intensive Induction Chemotherapy

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Supported by:
grant no 01ZP8701 of German Federal Minister for Research and Technology and grant no M17/92/Bü1 / 70-2174-Bü3 of Deutsche Krebshilfe

Abstract
Intensive induction therapy-in acute myeloid leukemia (AML), as in some other systemic malignancies- is a strategy fundamentally different from post-remission strategies. Approaches like consolidation treatment, prolonged maintenance, and autologous or allogeneic transplantation in the first remission are directed against minimal residual disease with a malignant cell population having survived the induction treatment. In contrast, induction therapy deals with naive tumor cells possibly different in their sensitivity from their counterparts in remission. Therefore, in AML it has been suggested to introduce intensification strategies into the induction part of treatment as a new step after the preceding intensification steps in the post-remission part. As expected from the dose effects observed in post-remission treatment using more AraC or longer treatment**,** similar dose effects have been found in the induction treatment both by the incorporation of high-dose AraC and by the double induction strategy administered in patients up to 60 years of age. For example, patients with poor risk AML due to an unfavorable karyotype, high LDH in serum, or delayed response, benefited from double induction containing high-dose AraC by a longer survival as compared to that from standard dose AraC. A corresponding dose effect in the induction treatment has been found in patients of 60 years and older receiving daunorubicin 60 vs 30 mg/m^2 as part of the TAD regimen with higher dosage. This treatment significantly increased the response and survival rate in older patients who represented a poor risk group as a whole. Thus, we could demonstrate, both in younger and older patients, that a poor prognosis can be improved by a more intensive induction therapy. High-dose AraC in induction, however, exhibits a cumulative toxicity in that a repetition of courses containing high-dose AraC in the post-remission period is associated with considerable myelotoxicity leading to longlasting aplasias of about 6 weeks. However, after intensive induction treatment, high-dose chemotherapy in remission may become practicable using autologous stem cell rescue and may contribute to a further improvement of the outcome in poor risk as well as average patients with AML. These approaches are currently investigated by the German AMLCG. While there are clear limitations in the intensity of antineoplastic treatment for AML, as for other systemic malignancies, some further intensification may be possible and effective.

Key words: Acute myeloid leukemia, double induction, high-dose AraC, daunorubicin dosage

Introduction: Dose effects in the treatment of AML

In order to define the role of treatment intensity more generally, acute myeloid leukemia (AML) may serve as a useful example for malignant diseases like acute leukemias, advanced Hodgkin and non-Hodgkin-lymphomas and even some disseminated solid tumors. These systemic malignancies have in common 1. The requirement of primary chemotherapy, 2. a chance to respond by a complete remission and 3. a chance to remain permanently disease free. “Is more better?” is a general question applying to all these diseases and equally for both the induction and the postremission treatment. Two major aspects are addressed by this question: 1. whether there are dose response effects that could be used for further improving the results or 2. whether unacceptable toxicity does not allow further intensification.

Actually, the example of AML is clear evidence for dose response effects of chemotherapy. Historically, this was first demonstrated for the induction treatment where the response to seven days of AraC and three days of Daunorubicin was superior to five and two days[(1)]. Then in the post-remission treatment, a prolonged maintenance treatment produced higher cure rates than no maintenance[(2)]. And, finally, in the immediate post-remission treatment with different dosages of AraC, there was a significant dose dependency in the relapse free survival and survival

with the best outcome resulting from the highest dose of 3 g/m^2×6 given in 4 courses[12]. Similarly, as another type of postremission intensification high-dose chemo-/radiotherapy followed by autologous stem cell transplantation, it produced a superior relapse free survival as compared with no further treatment[8].

Dose effects in AML induction treatment

Encouraged by the benefit from high-dose AraC in postremission therapy, similar doses of 3 g/m^2×8[1] or 2 g/m^2×12[5] were combined with Daunorubicin[6, 5] and Etoposide[6] in the remission induction treatment, and compared with standard dose AraC in these combinations. While the remission rates were not improved by the intensified induction with high-dose AraC, this approach had a longterm effect on the relapse-free survival with significantly increased cure rates[5, 6]. As a new way of intensifying the induction treatment, the AMLCG used the new strategy of double induction, where all patients up to 60 years of age receive a second course starting on day 21 of treatment regardless of the response to the first course in the bone marrow. In a historical comparison with conventional induction consisting of mostly one course, double induction increased the relapse-free survival at 5 years by about 10 %[7]. In a randomized trial, we compared double induction by two courses of standard dose TAD (Thioguanine/AraC/Daunorubicin) with double induction containing high-dose AraC (3 g/m^2×6) with Mitoxantrone (HAM) as a second course. The high-dose version resulted in some more remissions (71% vs 65%, p= 0.072, χ^2 test) and no difference in the 5-year relapse-free survival (35% vs 29%, log-rank test). However, in the subgroup of patients with poor prognosis as predicted by an unfavorable karyotype, a high LDH in serum, or a delayed response, there was a significantly higher remission rate (65% vs 49%, p=0.004, χ^2 test) and 5-year overall survival (25% vs 18%, p=0.012, log-rank test) in the high-dose double induction arm as compared to the standard dose arm[8,9]. This result is the first evidence that a poor prognosis can be improved by more intensive chemotherapy. The benefit in response and survival rate was not paid by a higher early and hypoplastic death rate which was 14% in the high-dose double induction arm and 18% in the standard dose arm for all patients treated. The rather favorable therapeutic index of the intensified version of double induction allows us to compare double induction containing one course of high-dose AraC with that containing two courses of high-dose AraC in a current trial.

Figure 1 illustrates the steps of treatment intensification in the trials of the German AML Cooperative Group in patients of up to 60 years of age. The most important effects on the remission duration were produced by the introduction of maintenance therapy and then by the double induction strategy.

Intensification in induction treatment has also been investigated in patients of 60 years and older by the

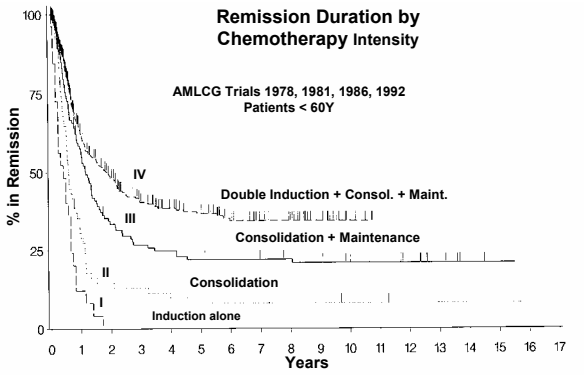

Figure- 1. Steps of intensification of chemotherapy in patients with AML 16-60 years of age in the sequence of trials by the German AML Cooperative Group: 1978 (I), 1981 (II and III), 1986 (IV). Kaplan-Meier plots of remission duration. Important steps were the introduction of any post-remission therapy, at least consolidation, of prolonged maintenance chemotherapy, and of the double induction strategy. Tick marks indicate patients in remission.

AMLCG. These patients received response-adapted 1-2 courses of TAD with standard dose Thioguanine, AraC and Daunorubicin, either in 30 mg/m^2×3 common standard dose, or 60 mg/m^2×3, the highest dosage ever used in a trial on older age AML. In fact, the higher dose produced a higher remission rate (54% vs 43%, p=0.0038, χ^2 test) and a lower early and hypoplastic death rate (17 % vs 27%, p=0.062, χ^2 test). In the more critical subgroup of patients of 65 years and older, the improved response to 60 mg Daunorubicin also occurred with a superior overall survival (p=0.0026)[10] (figure 2).

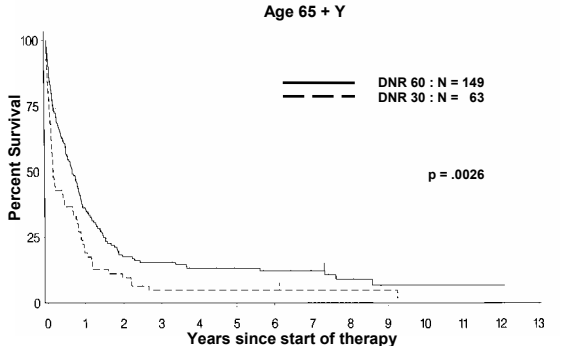

Figure- 2. Overall survival in patients of 65 years and older by the dosage of Daunorubicin (DNR) in induction treatment either 60 or 30 mg/m^2×3. Tick marks indicate patients alive. Solid line, DNR 60 mg/m^2×3 (n=149); broken line, DNR 30 mg/m^2×3 (n=63). *P*=0.0026, log-rank test. The differences in the number of patients between the two arms are explained by closing the 30 mg arm when its inferior response rate becomes obvious. The continuation of the 60 mg arm was necessary in the context of the ongoing trial involving patients at all ages.

It has been shown that AML in older patients is characterized by more unfavorable karyotypes and more frequent expression of the MDR1 gene, functional drug efflux and the CD34$^+$ phenotype[11, 12]. Since by these features older age AML as a whole represents a poor risk disease, the benefits from the higher DNR dose again demonstrate an improvement

of a poor prognosis by a more intensive treatment[9] as already shown (see above) for high-dose AraC in younger patients[8].

Toxicity of intensive induction

The results in the older, as in the younger patients, demonstrate that a more intensive induction treatment dose not necessarily increases the induction lethality and may even reduce it. Concerns about an age-related defective hematopoiesis[13, 14] could not be substantiated since older and younger patients receiving the identical induction treatment by two courses of TAD with Daunorubicin 60 mg/m^2 had the same recovery time for blood neutrophils and platelets[10]. Importantly, however, in the younger patients receiving double induction containing high-dose AraC, while no immediate toxicity was observed**,** there was a late and cumulative myelotoxicity. In a series of patients, who after having received high-dose AraC/Mitoxantrone in the induction treatment received a second similar course in the postremission period, there was a long lasting neutropenia and thrombocytopenia at a median of six weeks duration[15]. Thus, high intensity induction plus similar postremission treatment seems to require autologous stem cell support and may then successfully contribute to the antileukemic armamentarium for AML.

New directions in the intensification of induction treatment

From the data available so far, intensification strategies in induction treatment either by high-dose AraC [6, 5], or double induction with or without high-dose AraC [8] are practicable and effective approaches. It seems that this kind of very early intensification is capable of minimizing the residual disease, thus improving the quality of the complete remission, resulting in an increased definite cure rate. Minimizing the residual disease by intensified induction may also prepare AML patients for a subsequent allogeneic transplantation as a strategy of cellular immunotherapy. The toxicity data from the intensified induction strategies suggest that some further intensification such as double induction by two courses of high-dose AraC/Mitoxantrone may be possible and may further improve the results.

Beyond intensity, higher specificity of treatment may contribute to the improvements. Thus, recent approaches to targeted treatment for AML, use drug resistance modulators[16-19]**,** immune marker directed cytotoxic drugs[20, 21], or tyrosine kinase inhibitors[22]. Therefore, in a study of the Southwest Oncology Group, 226 patients with high-risk AML**,** most of them relapsed, refractory, or RAEB-t**,** were randomized to AraC and Daunorubicin with or without Cyclosporin A. This drug significantly increased the serum concentration of Daunorubicin, reduced resistance, increased RFS and survival[16]. PSC 833, an alternative MDR modulator, showed similar antileukemic effects when combined with Mitoxantrone and Etoposide[17] or with Daunorubicin[18]. The effect was dependent on the inhibition of P glycoprotein by P 833 in vitro[17, 19].

Since the CD33 surface antigen is expressed in about 90 % of AML patients, but not in hematopoietic stem cells, an anti-CD33 antibody was conjugated to the cytotoxic agent Calicheamicin. Given to patients with refractory or relapsed AML, this immunotoxin selectively ablated AML blasts[20] and induced 30 % remission in 142 patients and exhibited a favorable safety profile[21]. Another novel contribution of targeted therapy is first observation of response to specific tyrosine kinase inhibitors in refractory AML[22].

Certainly, an unlimited “more” is not “better”. But a better outcome may result from "some more" in the utilization of dose response effects in AML. Approaches of drug targeting currently under investigation may contribute to these effects. As in other systemic cancers like Hodgkin or non-Hodgkin-lymphoma, multiple myeloma, testicular cancer and sarcomas, systemic antineoplastic treatments are curative approaches and the initial phase of treatment or remission induction may have a particular chance to contribute to the curative strategy.

Intensive chemotherapy and quality of life (QL)

In order to evaluate the effects of double induction, consolidation and maintenance chemotherapy on patients, QL, a longitudinal study was conducted in 101 patients treated according to the AMLCG protocols described above. Using the EORTC QLQ-C30 questionnaire,[23] patients self-assessment of physical and emotional well-being and functional status monitored throughout therapy. At the end of the inpatient treatment, QL was significantly improved when compared to the beginning of therapy and was maintained during the entire further treatment course[24,25]. These observations support the intensive induction strategy for AML.

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