Cancer Chemother Pharmacol (2001) 48 (Suppl 1): S41–S44
DOI 10.1007/s002800100305

**Thomas Büchner · Wolfgang Hiddemann
Wolfgang Berdel · Bernhard Wörmann · Helmut Löffler
Claudia Schoch · Torsten Haferlach
Wolf-Dieter Ludwig · Georg Maschmeyer · Peter Staib
Reinhard Andreesen · Leopold Balleisen · Detlef Haase
Hartmut Eimermacher · Carlo Aul · Herbert Rasche
Jens Uhlig · Andreas Grüneisen · Hans Edgar Reis
Joachim Hartlapp · Wolf-Dietrich Hirschmann
Hans-Josef Weh · Hermann-Josef Pielken
Winfried Gassmann · Maria-Cristina Sauerland
Achim Heinecke**

Remission induction therapy: the more intensive the better?

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 such as consolidation treatment, prolonged maintenance, and autologous or allogeneic transplantation in first remission are directed against the minimal residual disease in which a malignant cell population has survived induction treatment and shows resistance due to special genetic or kinetic features. In contrast, induction therapy deals with naive tumor cells possibly different from their counterparts in remission in terms of their kinetic status and sensitivity. Therefore, in AML the introduction of intensification strategies into the induction phase of treatment has been suggested as a new step in addition to intensification in the post-remission phase. As expected from the dose effects observed in post-remission treatment with high-dose cytarabine (AraC) or longer treatment, similar dose effects have been found in induction treatment both from the incorporation of high-dose AraC and from the double-induction strategy used in patients up to 60 years of age. As a particular effect, patients with poor-risk AML according to an unfavorable karyotype, high LDH in serum, or a delayed response show longer survival following double induction containing high-dose AraC as compared to standard-dose AraC. A corresponding dose effect in the induction treatment of patients aged 60 years and older has been found with daunorubicin 60 vs 30 mg/m^2 as part of the thioguanine/AraC/daunorubicin (TAD) regimen with the higher dosage significantly increasing the response rate and survival in these older patients who represent a poor-risk group as a whole. Thus we have been able to 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 cumulative toxicity in that repeated courses containing high-dose AraC in the post-remission period lead to long-lasting aplasias of about 6 weeks. Thus after intensive induction treatment, high-dose chemotherapy in remission may be practicable using stem-cell rescue and may contribute to a further improvement in the outcome in poor-risk as well as average-risk patients with AML. These approaches are currently under investigation by the German AML Cooperative Group (AMLCG). "The more intensive the better" is certainly

Thomas Büchner, Wolfgang Hiddemann, Wolfgang Berdel, Bernhard Wörmann, Helmut Löffler, Claudia Schoch, Torsten Haferlach, Wolf-Dieter Ludwig, Georg Maschmeyer, Peter Staib, Reinhard Andreesen, Leopold Balleisen, Detlef Haase, Hartmut Eimermacher, Carlo Aul, Herbert Rasche, Jens Uhlig, Andreas Grüneisen, Hans Edgar Reis, Joachim Hartlapp, Wolf-Dietrich Hirschmann, Hans-Josef Weh, Hermann-Josef Pielken, Winfried Gassmann, Maria-Cristina Sauerland, Achim Heinecke: for the German AML Cooperative Group.

This work was supported by grant no. 01ZP8701 from the German Federal Ministry for Research and Technology and grant no. M17/92/Bü1/70-2174-Bü3 from the Deutsche Krebshilfe.

This work was presented at the 16th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "Hematologic malignancies: pioneers in cancer therapy across the century from mustard to molecular targets and beyond," 27–28 October 2000, Nagoya, Japan.

T. Büchner (✉) · W. Hiddemann · W. Berdel · B. Wörmann
H. Löffler · C. Schoch · T. Haferlach · W.-D. Ludwig
G. Maschmeyer · P. Staib · R. Andreesen · L. Balleisen
D. Haase · H. Eimermacher · C. Aul · H. Rasche · J. Uhlig
A. Grüneisen · H.E. Reis · J. Hartlapp · W.-D. Hirschmann
H.-J. Weh · H.-J. Pielken · W. Gassmann · M.-C. Sauerland
A. Heinecke
Department of Medicine, Hematology/Oncology,
University of Münster, Germany
E-mail: buechnr@uni-muenster.de
Tel.: +49-251-8347596
Fax: +49-251-8349667

T. Büchner
University Hospital, Department of Internal Medicine,
Albert-Schweitzer-Strasse 33, 48129 Münster, Germany

not the way to go in the management of AML and other systemic malignancies but some increase in intensity may be possible and better.

Keywords Acute myeloid leukemia · Double induction · High-dose AraC

Introduction: dose effects in the treatment of systemic cancer and AML

In order to find a definitive answer to the question in the title, acute myeloid leukemia (AML) may serve as a useful example of malignant diseases such as acute leukemias, progressed Hodgkin's and non-Hodgkin's lymphomas and even some disseminated solid tumors. These systemic malignancies have in common (1) the requirement for primary chemotherapy, (2) the possibility of responding with a complete remission and (3) the possibility of a permanent cure. "Is more better?" is a general question applying to all these diseases and equally to both the induction and the post-remission 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 and (2) whether unacceptable toxicity prevents further intensification.

Actually, the example of AML gives clear evidence for dose response effects of chemotherapy. Historically, this was first demonstrated for the induction treatment where the response to 7 days of cytarabine (AraC) and 3 days of daunorubicin (DNR) was shown to be superior to 5 and 2 days, respectively [13]. In the post-remission phase a prolonged maintenance treatment has been shown to produce higher cure rates than no maintenance [2], and finally, in the immediate post-remission treatment with different dosages of AraC there is a significant dose-dependency in relapse-free survival and survival with the best outcome resulting from the highest dose of 3 g/m^2 ×6 given in four courses [12]. Similarly, as another type of post-remission intensification, high-dose chemo-/radiotherapy followed by autologous transplantation has been shown to produce a superior relapse-free survival as compared with no further treatment [8].

Dose effects in AML induction treatment

Encouraged by the benefit derived from high-dose AraC in post-remission therapy, similar doses of 3 g/m^2 ×8 [1] or 2 g/m^2 ×12 [15] have been combined with DNR [1, 15] and etoposide [1] in 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 long-term effect on relapse-free survival with significantly increased cure rates [1, 15]. As another method of intensifying induction treatment, the German AML Cooperative Group (AMLCG) used the new strategy of double induction in which all patients up to 60 years of age receive a second course starting on day 21 of treatment regardless of the bone marrow response to the first course. In a historical comparison with conventional mostly one-course induction, double induction has been shown to increase the relapse-free survival at 5 years by about 10% [3].

In a randomized trial we compared double induction containing two courses of standard-dose thioguanine/AraC/DNR (TAD) with double induction containing high-dose AraC (3 g/m^2 ×6) and mitoxantrone as the second course. The high-dose version resulted in a higher remission rate (71% vs 65%, $P=0.072$, χ^2 test) and no significant difference in 5-year relapse-free survival (35% vs 29%, log-rank test). However, in the subgroup of patients with a poor prognosis as predicted by an unfavorable karyotype, 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 with the standard-dose arm [4, 6]. This result provided the first evidence that a poor prognosis can be improved by more intensive chemotherapy. The benefit in response and survival was not paid for 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 allowed us next to compare double induction containing one course of high-dose AraC with that containing two high-dose AraC courses. Figure 1 illustrates the steps of treatment intensification in the trials of the AMLCG in patients 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 AMLCG. These patients received response-adapted one or two courses of TAD with standard-dose thioguanine and AraC and DNR either 30 mg/m^2 ×3, the common standard dose, or 60 mg/m^2 ×3, the highest dosage ever used in a trial in older AML patients. 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 65 years and older an improved response to 60 mg DNR was also seen, with a superior overall survival ($P=0.0026$; Fig. 2) [7]. 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 [10, 11]. Since these features in older AML patients represent poor-risk disease as a whole, the benefits from the higher DNR dosage again demonstrate an improvement of a poor prognosis with a

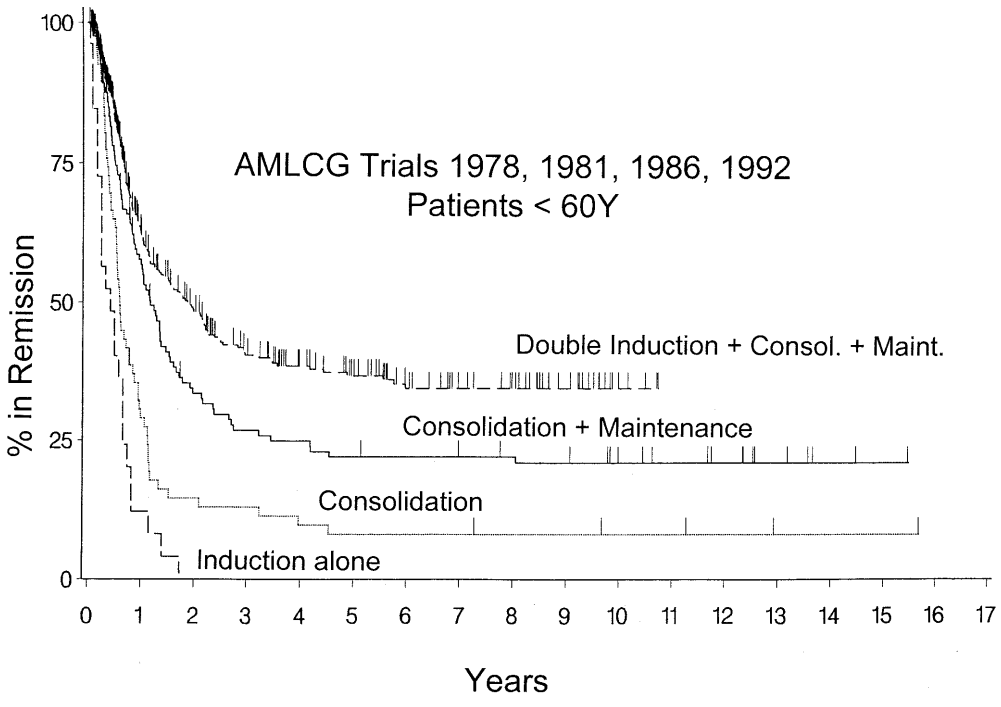

Fig. 1 Steps in intensification of chemotherapy in 16–60-year-old patients with AML in the sequence of trials by the German AML Cooperative Group (1978, 1981, 1986, and 1992). Kaplan-Meier plots of remission duration. Important steps were the introduction of any post-remission therapy including at least consolidation, of prolonged maintenance chemotherapy, and of the double-induction strategy (*ticks* patients in remission)

more intensive treatment [6] as already shown (see above) for high-dose AraC in younger patients [4].

Toxicity of intensive induction

As in younger patients, the results in older patients also demonstrate that a more intensive induction treatment does not necessarily increase the induction mortality and may even reduce it. Concerns about age-related defective hematopoiesis [9, 14] were not substantiated since older and younger patients receiving the identical induction treatment of two courses of TAD with DNR 60 mg/m^2 had the same blood neutrophil and platelet recovery times [7]. 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 induction treatment, received a second similar course in the post-remission period, there was a long-lasting neutropenia and thrombocytopenia with a median of 6 weeks, duration [5]. Thus, high-intensity induction plus similar post-remission treatment seems to

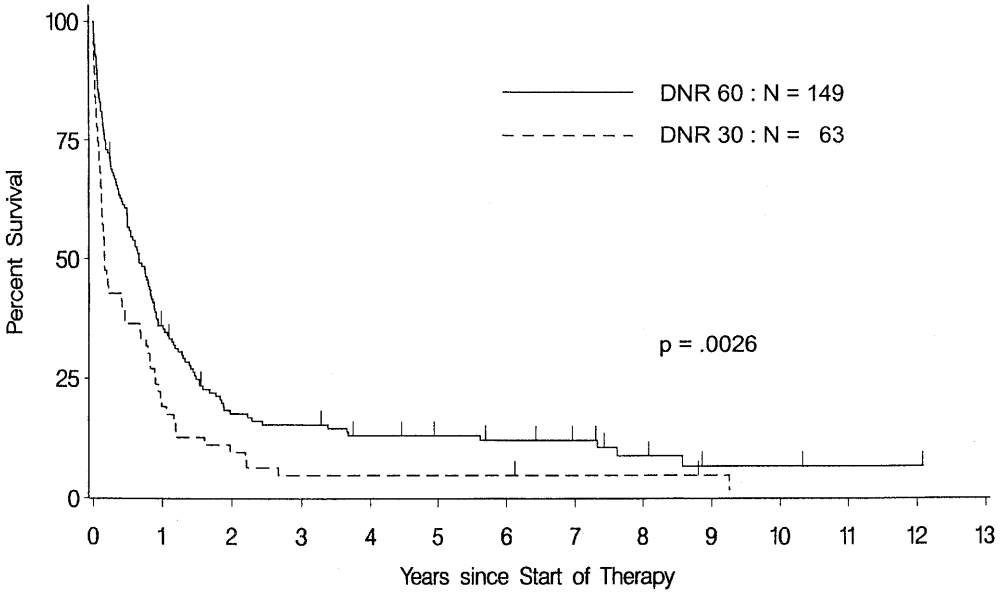

Fig. 2 Overall survival in patients ≥65 years old by DNR dose in induction therapy (*ticks* patients alive; *solid line* DNR 60 mg/m^2 ×3, $n = 149$; *broken line* DNR 30 mg/m^2 ×3, $n = 63$; $P = 0.0026$, log-rank test)

require autologous stem cell support which may enable it to form part of the antileukemic armamentarium in AML.

Directions in the intensification of induction treatment

The data available so far indicate that intensification strategies in induction treatment with either high-dose AraC [1, 15] or double induction with or without high-dose AraC [4] are practicable and effective approaches. It seems that this kind of very early intensification can minimize residual disease, thus improving the quality of the complete remission and resulting in an increased definite cure rate. Minimizing the residual disease by intensified induction may also condition 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 with two courses of high-dose AraC/mitoxantrone may be possible and may further improve the results.

There is clearly a limit to the statement ''the more intensive the better''. However, some improvement in outcome may result from a greater utilization of dose response effects in AML. As in other systemic cancers, such as Hodgkin's or non-Hodgkin's lymphoma, multiple myeloma, testicular cancer and sarcomas, systemic antineoplastic treatments are curative approaches and the initial phase of treatment or remission induction may potentially make a particular contribution to the curative strategy.

References

1. Bishop JF, Matthews JP, Young GA, Szer J, Gillet A, Joshua D, Bradstock K, Enno A, Wolf MM, Fox R, Cobcroft R, Herrmann R, Van Der Weyden M, Lowenthal RM, Page F, Garson OM, Juneja S (1996) A randomized study of high-dose cytarabine induction in acute myeloid leukemia. Blood 87:1710
2. Büchner T, Urbanitz D, Hiddemann W, Ludwig WD, Aul HC, Vaupel HA, Kuse R, Zeile G, Nowrousian MR, König HJ, Walter M, Wendt FC, Sodomann H, Hossfeld DK, von Paleske A, Löffler H, Gassmann W, Hellriegel KP, Fülle HH, Lunscken C, Emmerich B, Pralle H, Pees HW, Pfreundschuh M, Bartels H, Koeppen KM, Schwerdtfeger R, Donhuijsen-Ant R, Mainzer K, Bonfert B, Köppler H, Zurborn KH, Ranft K, Thiel E, Heinecke A (1985) Intensified induction and consolidation with or without maintenance chemotherapy for acute myeloid leukemia (AML): two multicenter studies of the German AML Cooperative Group. J Clin Oncol 3:1583
3. Büchner T, Hiddemann W, Löffler G, Gassmann W, Maschmeier G, Heit W, Hossfeld D, Weh H, Ludwig WD, Thiel E, Nowrousian M, Aul C, Lengfelder E, Lathan B, Mainzer K, Urbanitz D, Emmerich B, Middelhoff G, Donhuijsen-Ant HR, Hellriegel HP, Heinecke A (1991) Improved cure rate by very early intensification combined with prolonged maintenance chemotherapy in patients with acute myeloid leukemia: data from the AML Cooperative Group. Semin Hematol 28 [Suppl 4]:76
4. Büchner T, Hiddemann W, Wörmann B, Löffler H, Gassmann W, Haferlach T, Fonatch C, Haase D, Schoch C, Hossfeld D, Lengfelder E, Aul C, Heyll A, Maschmeyer G, Ludwig WD, Sauerland MC, Heinecke A (1999) Double induction strategy for acute myeloid leukemia: the effect of high-dose cytarabine with mitoxantrone instead of standard-dose cytarabine with daunorubicin and 6-thioguanine. A randomized trial by the German AML Cooperative Group. Blood 93:4116
5. Büchner T, Hiddemann W, Wörmann B, Löffler H, Gassmann W, Haferlach T, Schoch C, Staib P, Lengfelder E, Aul C., Heyll A, Ludwig WD, Maschmeier G, Grüneisen A, Balleisen L, Rasche H, Eimermacher H, Karow J, Eggeling B, Schott G, Reis E, Sauerland MC, Heinecke A (1999) One single course of sequential high-dose AraC/mitoxantrone (S-HAM) has the same long-term effect as three years of maintenance in AML patients after TAD-HAM double induction. Randomized trial by the German AMLCG. Blood 94 [Suppl 1]:383a
6. Büchner T, Hiddemann W, Wörmann B, Löffler H, Haferlach T, Fonatsch C, Haase D, Schoch E, Lengfelder E, Aul E, Heyll A, Maschmeier G, Ludwig WD, Sauerland MC, Heinecke A, for the AMLCG (1999) Improvement of prognosis in poor prognosis AML by intensified induction chemotherapy. Proc Am Soc Clin Oncol 18:6a
7. Büchner T, Hiddemann W, Schoch C, Haferlach T, Sauerland MC, Heinecke A (2000) Acute myeloid leukemia (AML): treatment of the older patient. In: Burnett A (ed) Bailliere's clinical haematology (in press)
8. Burnett AK, Goldstone AH, Stevens R, Hann I, Rees JK, Gray RG, Wheatley K (1998) Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. Lancet 351:700
9. Hamblin TJ (1992) The treatment of acute myeloid leukemia preceded by the myelodysplastic syndrome. Leuk Res 16:4101
10. Leith C, Chen IM, Kopecky KJ, Appelbaum FR, Head DR, Godwin JE, Weick JK, Willmann CL (1995) Correlation of multidrug resistance (MDR1) protein expression with functional dye/drug efflux in acute myeloid leukemia by multiparameter flow cytometry: identification of discordant $MDR^{-}/efflux^{+}$ and $MDR1^{+}/efflux^{-}$ cases. Blood 86:2329
11. Leith CP, Kopecky KJ, Godwin J, McConnel T, Slovak ML, Chen IM, Head DR, Appelbaum FR, Willman CL (1997) Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biological subgroups with remarkably distinct response to standard chemotherapy. A Southwest Oncology Group Study. Blood 89:3323
12. Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, Omura GA, Moore JO, McIntyre OR, Frei E (1994) Intensive post-remission chemotherapy in adults with acute myeloid leukemia. N Engl J Med 331:896
13. Rai KR, Holland JF, Glidewell OJ, Weinberg V, Brunner K, Obrecht JP, Preisler HD, Nawabi IW, Prager D, Carey RW, Cooper MR, Haurani F, Hutchsion JL, Silver RT, Falkson G, Wiernik P, Hoagland HC, Bloodfield CD, James GW, Gottlieb A, Ramanan SV, Blom J, Nissen NI, Bank A, Ellison RR, Kung F, Henry P, McIntyre OR, Kaan SK (1981) Treatment of acute myelocytic leukemia: a study by Cancer and Leukemia Group B. Blood 58:1203
14. Stone RM, Berg TB, George SL, Dodge RK, Paciucci PA, Schulman P, Lee EJ, Moore JO, Powell BL, Schiffer CA, for the Cancer and Leukemia Group B (1995) Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. N Engl J Med 332:1671
15. Weick JK, Kopecky KJ, Appelbaum FR, Head DR, Kingsbury LL, Bacerzak SP, Bickers JN, Hynes HE, Welborn JL, Simon SR, Grever M (1996) A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group Study. Blood 88:2841