Acute Myeloid Leukemia (AML): The Role of Maintenance Chemotherapy

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Abstract
Maintenance treatment for patients with acute myeloid leukemia (AML) in remission has recently been controversially discussed and even abandoned by several groups. An analysis of 16 published multicenter trials, however, revealed the highest probabilities of relapse free survival (RFS) in the range of 35-42 % at 4-5 years only in patients assigned to maintenance treatment when adult age and intent-to-treat conditions were considered. After having demonstrated a superior RFS from 3 year maintenance following standard dose consolidation over that from consolidation alone ($p<0.0001$), the German AMLCG requestioned the effect of maintenance randomly compared with sequential high-dose AraC and Mitoxantrone (S-HAM) in patients having received intensified induction treatment. The RFS shows an advantage for maintenance with 32 % versus 25 % ($p= .021$). We conclude that maintenance treatment continues to substantially contribute to the management of adult patients with AML, even as part of recent strategies using intensified induction treatment, and thus appears necessary in these settings.

Key words: Acute myeloid leukemia, maintenance therapy

Introduction

Even at the onset of the 2000s, acute myeloid leukemia (AML) in adults has remained one of the great challenges. While combined efforts in the field of intensified chemotherapy, allogeneic and autologous transplantation and refined supportive treatment have been producing increasing cure rates, the 50% level has not been reached so far in the overall patients**,** even in those under 60 years of age, when unselected series are considered. As an answer to the frequent questions about the "necessity" of maintenance, this option appears "necessary" if it proves feasible and contributes to the antileukemic potential of treatment. Concerning the question of the effectiveness of post-remission treatment, the present analysis focuses on its chemotherapeutic part, while transplantation strategies are discussed elsewhere[1]. Following a common terminology, postremission chemotherapy can be divided into consolidation and maintenance treatment. While consolidation immediately follows the achievement of complete remission (CR) and represents a repetition or an intensification of the induction regimen, maintenance uses drug combinations reduced in duration and/or dosage as compared to induction treatment and intermittently administerates them over a longer period of time.

Maintenance historically goes back to a study of CALGB where 5 day courses of standard dose AraC were given monthly and were rotatingly combined with a second agent such as Daunorubicin (DNR), 6-Thioguanine (TG), or Cyclophosphamide (CTX)[2]. Maintenance is an approach to progressively eliminate residual leukemic cells when they are spontaneously recruited from a dormant state into proliferation. Other strategies against minimal residual disease are growth factor priming[3] and allogeneic transplantation or cell therapy utilizing the graft-versus-leukemia effect.

Here we analyze the effect of maintenance on the basis of published data from major multicenter trials, and, recent data from two studies of the AMLCG.

Analysis of published data

Table 1 gives a synopsis of trials with their strategies in the induction, consolidation and maintenance of therapy with details on standard dose regimens or the inclusion of high-dose AraC, and randomizations between treatments, drugs, dosages, durations, or numbers of courses.

Of the 16 trials listed, 12 used maintenance regimens[4-10, 12-14, 19, 21], two of them without a preceding consolidation[5, 7] and 10 trials maintenance following consolidation[4, 6, 8-10, 12-14, 19, 21]. As representative endpoints, overall survival (OS) and relapse-free survival (RFS) in 4-5 years, and, the percentage of patients in remission not included in these results are given. The exclusions are due to randomizations in remission after some relapses and deaths and prior

Table 1: Comparison of Major AML Trials According to Treatment, Outcome, Age Range, and Patient Selection in Remission

Publication	Reference No.	No. of Patients	Age Years	Induction Regimen	% Complete Remissions	Consolidation	Maintenance	% Patients in Remission not included in the longterm results**	% Overall Survival at 4-5 Y	p	% Relapse-free Survival at 4-5 Y	p
Büchner et al. 1985 updated	4	334	15-78	Standard dose	61	Standard dose	yes no	21	34 20	.007	21 7	< .0001
Preisler et al. 1987	5	668	14-60	Standard dose	56	no	yes	0	35		18	
Bishop et al. 1990	6	264	15-70	without Etoposide with Etoposide	58	without Etoposide with Etoposide	yes	0	19 19		14 37	0.01
Dillmann et al. 1991	7	326	16-83	Standard dose	61	no	8 months	0	10		10	
Cassileth et al. 1992	8	449	15-65	Standard dose	68	no + high-dose AraC	yes no	12	22 33	n.s.	16 27	0.068
Ohno et al. 1993	9	252	15-79	Standard dose	78	Standard dose	yes	0			35	
							Standard dose x 4	29			34	.066
							Standard dose x 12				48	
Mayer et al. 1994	10	1088	16-86	Standard dose	64	yes	yes	0			27	
						AraC 100 mg/m^2 x 5	4 months	14			21	
						AraC 400 mg/m^2 x 5	4 months				25	.003
						AraC 3 g/m^2 x 6	4 months				39	
Zittoun et al. 1995	11	941	10-59	Standard dose	66	+ high-dose AraC then + high-dose AraC or autol. BMT	no	32			30 48	.05
						or allog. BMT					55	
Rees et al 1996	12	972	1-79	5 days 10 days	63	Standard dose	~~yes/no~~	0	18 23	.05	23 28	.05
Kobayashi et al. 1996	13	326	15-82	Standard dose	77	Standard dose	Standard dose x 6	0			38	

Continued*; Table 1: Comparison of Major AML Trials According to Treatment, Outcome, Age Range, and Patient Selection in Remission

Bishop et al. 1996	14	301	15-60	Standard dose + high-dose AraC	73	Standard dose	yes	0	26 31	.44	23 42	.007
Weick et al., 1996	15	723	15-64	Standard dose + high-dose AraC	55	+ standard or high-dose AraC	no	14	22 / 11 Age </> 50 y 32 / 13		21 / 9 33 / 4	.049
Porwit-MacDonald et al. 1996	16	517	17-55	Standard dose	81	+ high-dose AraC	no		38			
Hann et al. 1997	17	1857	0-55	Standard dose	82	+ high-dose AraC	no	0	40		43	
Burnett et al. 1998	18	s. Ref. 17	0-55	Standard dose	s. Ref. 17	+ high-dose AraC then early autol. BMT or no further treatment	no	66	57 45	.2	54 40	.04
Löwenberg et al. 1998	19	489	60-88	Standard dose	42	Standard dose	yes/no yes low dose AraC no	0 29	8 18 15	.29	8 13 7	.006
Cassileth et al. 1998	20	740	16-55	Standard dose	78	Standard dose, then high-dose AraC or auto. BMT or allo. BMT	no	33			35 35 43	
Büchner et al. 1999	21	725	16-60	without high-dose AraC + high-dose AraC	65 71	Standard dose	yes	0	30 32		29 35	

* AraC: cytosine arabinoside; NS: not significant; autoBMT: autologous bone marrow transplantation; alloBMT: allogeneic bone marrow transplantation

** The exclusions of these patients are at the occasion of randomizations during remission

toxicity or refusal in some patients which prevented a randomization. Randomizations in remission were done in 11 of the trials[4-6, 8-11, 15, 18-20] so that the absolute results of their randomized treatments can not be compared on an intent-to-treat basis. In case overall unselected results were given in the publications, the data has been listed in table 1 in addition to the data from randomizations in the related trials[5, 9, 10, 19].
Looking at intent-to-treat results including all patients in remission, RFS in the range of 35-42 % is only found in 5 trials using maintenance[6, 9, 13, 14, 21] and in one trial without maintenance but with an age range of 0-55 years where 43 % RFS was reported[17].

Special studies on maintenance
After the CALGB had published their results from monthly myelosuppressive maintenance,[2] their regimen was investigated in a randomized study by the AMLCG and resulted in highly superior RFS in the arm with consolidation and maintenance over that with consolidation alone[4, 22]. An update is seen in figure 1.

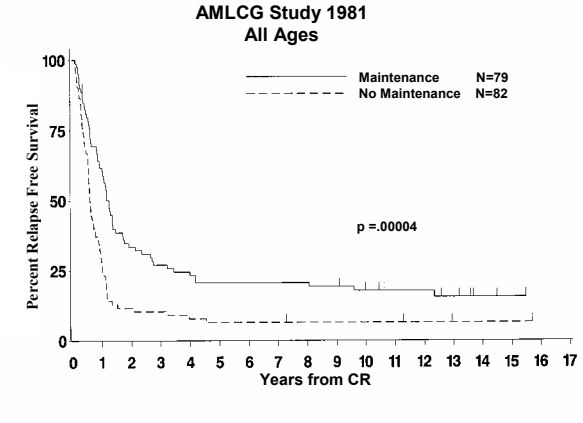

Figure 1: Relapse-free survival in the AMLCG study 1981. Patients 16-78 years of age received 1-2 courses of standard dose TAD for remission induction, and patients entering complete remission were randomized to receive one course of TAD for consolidation and no further treatment or the same consolidation followed by maintenance for three years. Maintenance included monthly courses of 5 days standard dose AraC combined with a second drug which was rotatingly either Daunorubicin or 5-thioguanine or Cyclophosphamide. Tick marks indicate patients alive without relapse at last follow-up.

In contrast, 8 months versus 3 years of maintenance resulted in a similar RFS in a study by the CALGB using a reduced intensity maintenance regimen given only bi-monthly and without preceding consolidation[5]. In a study by ECOG,[8] a low dose weekly maintenance regimen with TG 40 mg/m^2 q 12h x 4d and AraC 60 mg/m^2 s.c. on day 5 with no preceding consolidation appeared inferior to one course of consolidation with high-dose AraC 3 g/m^2 q 12h x 6d (p= 0.068) Following three courses of consolidation, twelve courses of intensive maintenance given every 6 weeks tended to be superior to four courses (p= 0.066) in a study by the Japan Adult Leukemia Group[9].

In summary, the association of the most favorable RFS with the administration of maintenance in unselected adult patients**,** and the results of randomized studies in favour of a full dose maintenance following consolidation**,** give support to a consolidation–maintenance strategy in adults with AML.

Recent data on maintenance from the AMLCG
Since the contribution of maintenance has to be regarded in the context of a complete strategy, including the induction and consolidation treatment, the AMLCG requestioned the role of maintenance in patients receiving highly intensive induction. In our 1986 and 1992 studies, we used the novel strategy of double induction in patients 16-60 years of age[21] containing two courses of standard dose TAD or TAD followed by high-dose AraC/Mitoxantrone (HAM)[23]. Patients of 60 years and over received 1-2 TAD induction courses (1986) or HAM as a second course (1992). All patients in CR received TAD consolidation. Monthly maintenance was as published[4, 8] in the 1986 study and was randomly compared with one course of sequential HAM (high-dose AraC 1 g/m^2 in younger and 500 mg/m^2 in older patients q 12h days 1, 2, 8, 9 and Mitoxantrone 10 mg/m^2 days 3, 4, 10,11) (S-HAM)[24] instead of maintenance in the 1992 study[25]. The RFS in patients of all ages (median, 3 years, 5 years) is 16 months, 35 %, 28 % in the maintenance versus 11 months, 27 %, 23 % in the S-HAM arm (p=0.040)[25]. Figure 2 compares the RFS in the S-HAM arm with that in the combined maintenance groups of the 1986 and 1992 studies in patients of all ages.

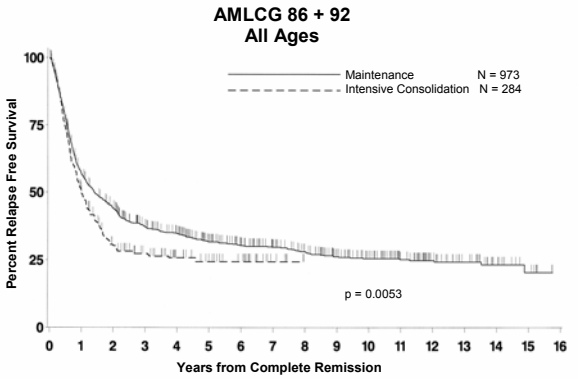

Figure 2: Relapse-free survival in the combined AMLCG studies 1986 and 1992 in patients 16-83 years of age. Induction treatment in patients up to 60 years was double induction by two courses of standard dose TAD or TAD followed by high-dose AraC/Mitoxantrone (HAM), and in patients 60 years of age and older 1-2 courses of standard dose TAD or HAM as a second course. All patients going into complete remission received one course of standard dose TAD for consolidation and randomly either three years of maintenance (see figure 1) or instead of maintenance, one course of sequential high-dose AraC/Mitoxantrone, and no further treatment. Tick marks indicate patients alive without relapse at the last follow-up.

The 5-year RFS is 32 % for maintenance and 25 % for S-HAM (p=0.0053). There is a tendency of survival in

favour of maintenance (p=0.077). In addition, more of the surviving patients in the maintenance group (85 % vs 74%) are still in their first remission.
Thus, one course of sequential high-dose AraC and Mitoxantrone when compared with maintenance on an intent-to-treat basis failed to further improve the survival over that from maintenance treatment. This is not explained by an unsufficient intensity since S-HAM proved highly myelotoxic producing a median recovery time of blood neutrophils and platelets as long as 6 weeks. Maintenance treatment, however, was confirmed to more effectively prolong RFS than S-HAM does.
Since data on survival from maintenance versus no maintenance are scarce with no clear benefit of this strategy, its effect may be underestimated. Among the four studies randomizing for maintenance[4, 9, 19, 25], a significant advantage in survival is only shown in one[4] and no survival data is given in the other study[9]. However, since survival is strongly influenced by second line therapy which is generally not a part of the publications, this data does not allow interpretations of the discrepancies between RFS and survival effects. On the other hand, the superiority in the RFS and the higher proportion of ongoing first remission among the survivors from maintenance versus no maintenance indicates the superiority of maintenance in its curative potential by the first line treatment alone.
The recent study results by the AMLCG[25] strongly suggest the administration of maintenance even in patients having received intensified induction treatment, where maintenance further contributed to the antileukemic effect of this strategy. In their current trial, the AMLCG is investigating maintenance treatment prospectively compared with autologous and allogeneic transplantation, where randomization for the three options is done in every subset of AML such as primary AML, secondary AML, high-risk myelodysplasia, favourable and unfavourable karyotype.

Maintenance therapy, drug delivery and feasibility
The experiences of the AMLCG with the maintenance regimen described above and used in three consecutive trials[4, 21, 25] show that about 80 % of patients receiving TAD consolidation proceed to maintenance. According to the protocol, there is a dose reduction of 50 % for all agents used in maintenance after two courses at 100 % dosage that induced profound neutropenia and thrombocytopenia. Following these guidelines, the majority of patients remain at 50 % dosage and further dose reductions to 25% are only necessary in a minority. In the vast majority of patients achieving a relapse-free survival of at least 3 years, maintenance treatment continues for the complete 3 year duration.

Maintenance therapy and quality of life (QL)
In a longitudinal study with 101 AML patients treated according to the AMLCG protocols described above, QL was evaluated using the EORTC QLQ-C30 questionnaire[26]. There was a significant improvement of QL by self-assessment at the end of the inpatient treatment when compared to the beginning of therapy. During the period of outpatient treatment including maintenance chemotherapy there were no essential further changes in the physical and emotional well-being and QL[27, 28].

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