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 re-questioned 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 postremission 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 administers 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>
<thead>
<tr>
<th>Publication</th>
<th>Reference No.</th>
<th>No. of Patients</th>
<th>Age Years</th>
<th>Induction Regimen</th>
<th>% Complete Remissions</th>
<th>Consolidation</th>
<th>Maintenance</th>
<th>% Patients in Remission not included in the longterm results**</th>
<th>% Overall Survival at 4-5 Y</th>
<th>p</th>
<th>% Relapse-free Survival at 4-5 Y</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Büchner et al. 1985</td>
<td>4</td>
<td>334</td>
<td>15-78</td>
<td>Standard dose</td>
<td>61</td>
<td>Standard dose</td>
<td>yes</td>
<td>21</td>
<td>34</td>
<td>.007</td>
<td>21</td>
<td>.001</td>
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<tr>
<td>Preisler et al. 1987</td>
<td>5</td>
<td>668</td>
<td>14-60</td>
<td>Standard dose</td>
<td>56</td>
<td>no</td>
<td>yes</td>
<td>0</td>
<td>35</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bishop et al. 1990</td>
<td>6</td>
<td>264</td>
<td>15-70</td>
<td>Standard dose</td>
<td>58</td>
<td>no</td>
<td>yes</td>
<td>0</td>
<td>19</td>
<td>14</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Dillmann et al. 1991</td>
<td>7</td>
<td>326</td>
<td>16-83</td>
<td>Standard dose</td>
<td>61</td>
<td>no</td>
<td>8 months</td>
<td>0</td>
<td>19</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cassileth et al. 1992</td>
<td>8</td>
<td>449</td>
<td>15-65</td>
<td>Standard dose</td>
<td>68</td>
<td>no</td>
<td>yes</td>
<td>12</td>
<td>22</td>
<td>n.s.</td>
<td>16</td>
<td>0.068</td>
</tr>
<tr>
<td>Ohno et al. 1993</td>
<td>9</td>
<td>252</td>
<td>15-79</td>
<td>Standard dose</td>
<td>78</td>
<td>Standard dose</td>
<td>yes</td>
<td>0</td>
<td>35</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayer et al. 1994</td>
<td>10</td>
<td>1088</td>
<td>16-86</td>
<td>Standard dose</td>
<td>64</td>
<td>yes</td>
<td>yes</td>
<td>0</td>
<td>27</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zittoun et al. 1995</td>
<td>11</td>
<td>941</td>
<td>10-59</td>
<td>Standard dose</td>
<td>66</td>
<td>yes</td>
<td>no</td>
<td>32</td>
<td>30</td>
<td>48</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Rees et al 1996</td>
<td>12</td>
<td>972</td>
<td>1-79</td>
<td>5 days</td>
<td>63</td>
<td>Standard dose</td>
<td>yes/no</td>
<td>0</td>
<td>18</td>
<td>.05</td>
<td>23</td>
<td>0.05</td>
</tr>
<tr>
<td>Kobayashi et al. 1996</td>
<td>13</td>
<td>326</td>
<td>15-82</td>
<td>Standard dose</td>
<td>77</td>
<td>Standard dose</td>
<td>Standard dose x 6</td>
<td>0</td>
<td>38</td>
<td></td>
<td></td>
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</table>
### Table 1: Comparison of Major AML Trials According to Treatment, Outcome, Age Range, and Patient Selection in Remission*

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Age (y)</th>
<th>Treatment</th>
<th>Age Range</th>
<th>Outcome</th>
<th>Std. dose</th>
<th>Std. dose, then</th>
<th>Std. dose, then</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bishop et al. 1996</td>
<td>14</td>
<td>301</td>
<td>Standard dose + high-dose AraC</td>
<td>15-60</td>
<td>yes</td>
<td>73</td>
<td>0</td>
<td>26</td>
<td>.073</td>
</tr>
<tr>
<td>Weick et al., 1996</td>
<td>15</td>
<td>723</td>
<td>Standard dose + standard AraC</td>
<td>15-64</td>
<td>yes</td>
<td>55</td>
<td>0</td>
<td>22 / 11</td>
<td>.049</td>
</tr>
<tr>
<td>Porwit-MacDonald et al. 1996</td>
<td>16</td>
<td>517</td>
<td>Standard dose + high-dose AraC</td>
<td>17-55</td>
<td>yes</td>
<td>31</td>
<td>0</td>
<td>32 / 13</td>
<td>.049</td>
</tr>
<tr>
<td>Hann et al. 1997</td>
<td>17</td>
<td>1857</td>
<td>Standard dose + high-dose AraC</td>
<td>0-55</td>
<td>yes</td>
<td>32</td>
<td>0</td>
<td>33 / 4</td>
<td>.049</td>
</tr>
<tr>
<td>Burnett et al. 1998</td>
<td>18</td>
<td>s. Ref. 17</td>
<td>Standard dose + high-dose AraC then early autol. BMT</td>
<td>0-55</td>
<td>yes</td>
<td>66</td>
<td>0</td>
<td>57</td>
<td>.049</td>
</tr>
<tr>
<td>Löwenberg et al. 1998</td>
<td>19</td>
<td>489</td>
<td>Standard dose + low dose AraC</td>
<td>60-88</td>
<td>yes</td>
<td>42</td>
<td>0</td>
<td>57</td>
<td>.049</td>
</tr>
<tr>
<td>Cassileth et al. 1998</td>
<td>20</td>
<td>740</td>
<td>Standard dose + high-dose AraC</td>
<td>16-55</td>
<td>yes</td>
<td>78</td>
<td>0</td>
<td>33</td>
<td>.049</td>
</tr>
<tr>
<td>Büchner et al. 1999</td>
<td>21</td>
<td>725</td>
<td>Standard dose + high-dose AraC</td>
<td>16-60</td>
<td>yes</td>
<td>65</td>
<td>0</td>
<td>30</td>
<td>.049</td>
</tr>
</tbody>
</table>

* 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
In a study by ECOG, a low dose weekly maintenance found in 5 trials using maintenance and in remission, RFS in the range of 35-42% is only looking at intent-to-treat results including all patients monthly myelosuppressive maintenance, their results were published in the CALGB study. Special studies on maintenance after the CALGB had published their results from monthly myelosuppressive maintenance, 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. An update is seen in figure 1.

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 favor 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 questioned 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 containing two courses of standard dose TAD or TAD followed by high-dose AraC/Mitoxantrone (HAM).

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 in the 1986 study and was randomly compared with one course of sequential HAM (high-dose AraC 1 g/m² in younger and 500 mg/m² in older patients q 12h days 1, 2, 8, 9 and Mitoxantrone 10 mg/m² days 3, 4, 10,11) (S-HAM) instead of maintenance in the 1992 study.

The RFS in patients of all ages (median, 3 years, 5 years) was 16 months, 35%, 28% in the maintenance versus 11 months, 27%, 23% in the S-HAM arm (p=0.040). 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.

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. In a study by ECOG, a low dose weekly maintenance regimen with TG 40 mg/m² q 12h x 4d and AraC 60 mg/m² s.c. on day 5 with no preceding consolidation appeared inferior to one course of consolidation with high-dose AraC 3 g/m² 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.

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 favor of a full dose maintenance following consolidation, give support to a consolidation–maintenance strategy in adults with AML.
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 insufficient 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 studies\(^9,9\). 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\(^5,21,25\) 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\(^27,28\).

**References**

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cytarabine in combination induction and consolidation therapy, and with or without Ubenimex after maintenance/intensification therapy in adult acute myeloid leukemia. JCO 1996;14:204-213.


