Intensifying Induction Therapy in Acute Myeloid Leukemia: Has a New Standard of Care Emerged?

By Jacob M. Rowe and Martin S. Tallman

Induction therapy for acute myeloid leukemia (AML) has been fairly standardized over the past two decades, with major controversies addressing the optimal postremission therapy. Nevertheless, whereas the most common induction therapy for AML consists of 3 days of an anthracycline, usually daunorubicin, and 7 days of cytarabine (3 + 7), many trials have been conducted in an attempt to improve this standard by introducing a more intensive combination with potential to improve the complete remission rate, remission duration, or the number of patients cured.

Modern therapy with AML begun some 30 years ago with the introduction of cytosine arabinoside and daunorubicin. With either of these single agents, 30% to 40% of adults attained a complete response and a small proportion of these patients were long-term survivors. Significant further improvement occurred with the introduction of combination chemotherapy for AML induction. For much of the past two decades, induction therapy has consisted of daunorubicin, cytarabine, and 6-thioguanine (DAT). Most investigators now have eliminated 6-thioguanine from the standard induction regimen because its inclusion was not shown to improve overall results. Although there is no single established induction regimen, the most widely used combination for treatment of newly diagnosed AML has been daunorubicin (the first available anthracycline) at a dose of 45 mg/m² intravenously for 3 days and cytarabine at a dose of 100 mg/m² intravenously by continuous infusion for 7 days. This is the standard against which most new regimens are tested. With this regimen, between 50% and 75% of adult patients with AML achieve complete remission, but 25% to 40% of patients require more than one course of induction to achieve complete remission. A randomized study by the Cancer and Leukemia Group B (CALGB) established that reducing the dose of daunorubicin to 30 mg/m² resulted in a lower response rate, particularly in adults less than 60 years of age.

Increasing the intensity of induction has generated considerable recent interest and such a strategy may be effective in at least two ways. First, because achieving complete remission is considered a sine qua non for prolonged disease-free survival, it is likely that any combination that alters the complete remission rate will affect the long-term outcome. Second, intensified induction therapy may affect the long-term survival without an apparent effect on the initial response rate. However, reports of improved disease-free survival attributable to intensified induction therapy need to be cautiously interpreted. Such benefit may be impossible to determine without regard to the choice of postremission therapy, much like the difficulty in evaluating the results of consolidation therapy without considering the type of induction. Finally, any strategy to intensify induction may lead to more profound myelosuppression and the potential for toxicity needs to be carefully considered. Such an approach may be associated with more severe treatment-related morbidity and mortality or, alternatively, toxicity may be less if fewer patients require more than one course of induction therapy.

Several studies have explored the benefits of amsacrine, aclarubicin, mitoxantrone, and idarubicin. Several well-conducted randomized trials showed that idarubicin, aclarubicin, and amsacrine may be superior to daunorubicin in younger adults. Furthermore, a randomized study suggested that mitoxantrone is at least as effective as daunorubicin. However, these agents have been compared with daunorubicin at a dose of 45 mg/m². Notwithstanding theoretical advantages to the use of idarubicin, it is not clear that any observed improvement represents an inherent biologic advantage of a particular drug rather than biologic dose equivalence. There are no data to suggest that a higher dose of daunorubicin is more effective, because a prospective comparison of daunorubicin 45 mg/m² versus 60 mg/m² or higher has not been conducted. However, studies by the Southwest Oncology Group (SWOG) have reported a substantially better complete response rate with daunorubicin at a dose of 70 mg/m² compared with 45 mg/m². Although this was not a randomized comparison, these were sequential studies by the same cooperative group in which only the dose of daunorubicin varied. Randomized data comparing...
idarubicin with daunorubicin may illustrate this point. Whereas three randomized studies demonstrated an unequivocal or a trend towards improved results for idarubicin when compared with daunorubicin at 45 mg/m², sequential studies by the Eastern Cooperative Oncology Group (ECOG) have shown that the complete response rate, achieved in more than 800 patients, with idarubicin at a dose of 12 mg/m² was identical to the historical control in a similar number of patients that used 60 mg/m² of daunorubicin.34,35

Comparisons of dose intensity in AML are complicated by many factors such as patient age, antecedent myelodysplasia, supportive care, and patient selection. For example, a complete response rate of 81% achieved with 90 mg/m² of daunorubicin has been reported.36 However, this study is not easily compared with other studies of AML in adults because the median age was only 31 years. Similarly, it is difficult to interpret the pilot study in which a higher dose of mitoxantrone (80 mg/m² as a single bolus infusion) was shown to be more effective than by continuous infusion was shown to be more effective than bolus injection.11 Several prospective studies have compared induction regimens that modify both the dose of anthracycline and cytarabine.46,47 Therefore, meaningful interpretation is difficult. A regimen frequently used in Europe, consisting of mitoxantrone, etoposide, and cytarabine,48 has not been shown to be superior to standard induction therapy.

Cytarabine has also been used in induction in high doses (HDAC) since the initial report of its utility in refractory AML.39 Response rates as high as 90% have been reported with HDAC at doses of 1.5 to 3.0 g/m² every 12 hours for 3 to 6 days.30-33 Most of these studies used HDAC either as a single agent42 or as a combination with either daunorubicin,33 amsacrine,51 or asparaginase.30 Toxicity was considerable; relatively small cohorts of patients were treated and the response rates were compared with historical controls. Only two randomized studies have directly compared HDAC with standard induction therapy while using the same postremission therapy in both arms.33,52 In contrast to earlier uncontrolled trials, these two studies reported that the complete response rate was not higher with HDAC than with standard induction therapy and was associated with increased toxicity. However, both studies noted a significantly longer disease-free survival for those patients receiving HDAC in induction.

The concept that intensifying induction therapy may not improve the initial response rate but may affect the long-term outcome has also been shown in a prospective randomized study when etoposide was added to standard induction therapy.55,56 Although showing that dose intensity of induction therapy may affect the duration of remission in AML, it is not clear that the increased toxicity through more profound myelosuppression is advantageous given the possibility that a similar intensification might be safely added during postremission therapy.

An alternative approach, namely adding HDAC directly after the standard 3 + 7 induction, ie, on days 8 through 10, was recently reported.57 The principle supporting this strategy involves both an intensification of current existing regimen as well as the potential benefit of timed sequential chemotherapy.58-62 Although a high response rate was reported (89%), this result was compared with historical controls. Furthermore, this was a limited-institution study and the literature describing AML therapy is replete with very high response rates initially reported from such limited studies, which could not be reproduced in large cooperative group trials. For example, the initial superior response to cytarabine and amsacrine reported in induction61 or consolidation62 was not confirmed in large cooperative group settings.34,63 Nevertheless, this approach is intriguing and two cooperative groups are currently conducting phase II studies investigating this strategy.

Administering intensive chemotherapy immediately after initial induction may lead to an improved long-term outcome. There are data that suggest that, after initial intensive induction therapy, residual leukemic cells may be recruited into the cell cycle, making them more susceptible to cell cycle-specific agents such as cytarabine.60,61,65,66 Several phase II studies have suggested that a number of patients who receive one or two courses of chemotherapy at time of maximal recruitment (6 to 10 days after initial therapy) could have a prolonged disease-free survival without further therapy.60,65,67 Whether these results are due to the biologic recruitment of cell cycle-specific agents or whether this represents the most effective consolidation at the optimal period of minimal residual disease is unknown. However, administering a repeat course of induction shortly after completion of the first course has been tested and its toxicity is known, because approximately 25% to 40% of adult patients with AML require a second course of induction at day 11 through 14 after the start of induction chemotherapy.14,17 Therefore, an alternative method of intensification may be to administer a second course of induction therapy on days 10 through 14 to all patients, including those who achieve marrow hypoplasia. Such a concept appears effective in children,68 but has never been tested in adults, although several attempts at administering a repeat or second induction at intervals of 21 days have been successfully reported.69

Hematopoietic growth factors have been shown to shorten the period of neutropenia after induction therapy for AML.70,71 and several studies have reported reduced morbidity.17,72,74 There are also promising preclinical data exploring the use of thrombopoietin to shorten the period of thrombo-
Table 1. Potential Methods for Intensifying Induction Therapy for AML

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Comments</th>
<th>Potential Studies</th>
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<tbody>
<tr>
<td><strong>I. Modulation of anthracycline</strong></td>
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<tr>
<td>Substitution for daunorubicin (DNR)</td>
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<tr>
<td>1. Idarubicin (IDA)</td>
<td>More effective (cf DNR 45 mg/m²)²⁴,²⁶</td>
<td>Phase III studies of DNR v IDA v MITO in progress</td>
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<td>2. Amsacrine</td>
<td>Probably more effective (cf DNR 50 mg/m²)²⁹</td>
<td></td>
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<tr>
<td>3. Aclarubicin</td>
<td>Possibly more effective (cf DNR 45 mg/m²)²⁹</td>
<td></td>
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<tr>
<td>4. Mitoxantrone (MITO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Increasing dose of anthracycline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Daunorubicin</td>
<td>Not yet studied in a prospective comparison.</td>
<td>45 mg/m² - 60-90 mg/m²</td>
</tr>
<tr>
<td>2. Idarubicin</td>
<td>Not yet studied in a prospective comparison.</td>
<td>12 mg/m² - 15-20 mg/m²</td>
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<td><strong>II. Modulation of cytosine arabinoside</strong></td>
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<tr>
<td>Increasing standard dose (100 – 200 – 500 mg/m²)</td>
<td>No improvement²⁷,³¹,³²</td>
<td>Phase III studies (cf standard 3 + 7) encouraged.</td>
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<tr>
<td>Increasing standard duration (7 – 10 days)</td>
<td>Modest gains at best²⁷,³¹,³²</td>
<td></td>
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<tr>
<td>High dose (HDAC) (1.5-3.0 g/m² × 6-12 doses)</td>
<td>No effect on CR. Prolongs DFS.²⁷,³¹,³²</td>
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<tr>
<td><strong>III. Addition of etoposide</strong></td>
<td></td>
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<td><strong>IV. Addition of HDAC after standard 3 + 7</strong></td>
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<tr>
<td><strong>V. Timed sequential therapy (day 6-10)</strong></td>
<td>No effect on CR. Prolongs DFS.²⁷,³¹,³²</td>
<td>Repeat standard induction (eg, 3 + 7) at day 10-14, in adults, not yet studied</td>
</tr>
<tr>
<td><strong>VI. Very early intensification (day 10-21) with repeat induction or similar</strong></td>
<td>No effect on CR. Prolongs DFS.²⁷,³¹,³²</td>
<td>Repeat standard induction (eg, 3 + 7) at day 10-14, in adults, not yet studied</td>
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cytopenia.⁷⁵ The best clinical use of these cytokines has not yet been described. Despite the potential for reducing morbidity by myelosuppressive therapy, there are no data that more intensive therapy can be safely delivered with cytokine support.

The current standard for inducing complete remission in previously untreated adults with de novo AML remains an anthracycline and cytarabine. Although there are promising areas for clinical investigation, at the present time a new standard of care for induction therapy has not yet emerged. Although there appear to be better agents than 45 mg/m² of daunorubicin, the optimal anthracycline and dose has yet to be described. Prospective studies should determine whether escalating the doses of anthracyclines will yield improved response rates. Similarly, the addition of intensive therapy to the current standard regimen, such as high-dose cytarabine or etoposide, although clearly affecting the long-term remission duration, has not been shown to significantly affect the long-term outcome by comparison with known published postremission therapies.¹⁴,¹⁶ Some of the potential future strategies are summarized in Table 1. With the current high response to induction therapy it is crucial to have prospective randomized studies to determine whether any of these maneuvers are significantly better than standard induction therapy followed by optimal postremission therapy. Single-arm phase II trials should be limited to carefully designed studies describing efficacy and toxicity in regimens involving usually not more than a single change from standard therapy. Cooperative groups have a major role in this regard and should help to define any modifications to current therapy. Unfortunately, at present, only a minority of adults with AML enter cooperative group trials.⁷⁶ Improved accrual must be encouraged, allowing for more rapid generation of data. It is also important to design studies that can be completed within a reasonable time frame, thus stimulating patient and physician interest and leading to further accrual. With these efforts it is hoped that the next decade may clearly identify a better strategy for induction therapy in AML.

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