Chapter 79

Diagnosis and Management of Acute Myeloid Leukemia

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INTRODUCTION

Acute myeloid leukemia (AML) represents a group of clonal hematopoietic stem cell disorders that is characterized by both failure to differentiate and over proliferation of the stem cell compartment by nonfunctional cells called myeloblasts at the expense of the normal cells that constitute the hematopoietic compartment. AML is a heterogeneous disorder, the current World Health Organization (WHO) classification attempts classify this disorder based on the molecular pathology, where this is known. It is important to recognize at the very onset that the treatment outcome of young adults (< 60 years) has steadily improved over the last three decades (5-year disease-free survival (DFS) from 11% to 37%) while the clinical outcome in the elderly (> 60 years) remains dismal with no significant improvement over the last three decades in spite of these advances (5-year DFS from 6% to 12%).

Accurate diagnosis and optimal use of prognostic markers along with expertise in management of prolonged neutropenia which results from chemotherapy are the key elements for success. A number of these elements are unfortunately available only in tertiary centers and hence it is preferable to refer such cases as soon as possible to such a center. Without adequate infrastructure, it is difficult to diagnose and treat these patients. However, even at a primary physician level it is important to understand and recognize the nature of this condition so that appropriate counseling and decision on referral are made in a timely manner.

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical presentation of acute leukemia is almost always of a very short duration of symptoms and signs related to cytopenia and susceptibility to infections. Bleeding manifestations and a florid disseminated intravascular coagulation are common in acute promyelocytic leukemia (APL). AML subtypes M4 and M5 have a higher incidence of central nervous system (CNS) involvement than other subtypes. Patients can occasionally present with very high white cell counts resulting in features of leukostasis. Diagnosis is usually obvious by the presence of myeloblasts in the peripheral smear though occasionally cases can present with pancytopenia and the diagnosis is only made on evaluation of a bone marrow aspirate. Immaterial of the presence of myeloblasts in the peripheral smear a bone aspirate is mandatory to establish the diagnosis and samples obtained from an aspirate should be sent prior to starting therapy for:

- Aspirate smear for morphology and cytochemistry
- Sample for immunophenotyping (IPT)
- Sample for cytogenetic evaluation
- Sample for molecular markers.

Morphology and Cytochemistry

To make a diagnosis of AML at least 20% blasts must be documented on a bone marrow aspirate smear. Common morphological features of AML include large blasts with abundant basophilic cytoplasm often containing azurophilic granules and perinuclear clearing. Auer rods are frequently found; they appear as long and sharp rods in the cytoplasm and are diagnostic of AML.

Cytochemistry reveals that greater than 3% of the blasts are myeloperoxidase or Sudan black positive; in case of M4 and M5 variants these can be negative but are classically nonspecific esterase positive. Morphological variations such as increase in monocytoid forms, abnormal erythroblasts or abnormal megakaryocytes are seen in different subsets of AML that can be diagnostic or may require additional cytochemistry or immunophenotypic information for accurate subtyping.

Immunophenotyping

Classically myeloblasts are CD13, CD33 positive and myeloperoxidase positive. A significant proportion of blasts are also likely to express immature markers such as CD34 and human leukocyte antigen (HLA)-DR. Lymphoid markers especially CD7 are also frequently detected. IPT is especially important in diagnosis of AML with minimal differentiation (previously AML-M0) that are usually morphologically and cytochemically impossible to differentiate from acute lymphoblastic leukemia with L2 morphology.

Cytogenetics

Cytogenetic evaluation at diagnosis is critical in accurate prognostication and in decision making on optimal consolidation. It continues to remain one of the most robust prognostic markers in the management of AML. Recognition of specific subtypes is important in the current classification of AML as summarized in Table 1. However, in approximately 50–60% of cases the cytogenetic evaluation does not reveal any abnormality.

Molecular Markers

There has been an explosion in the recognition of molecular markers that can convey both good- and poor-risk status. These are specifically relevant to the large proportion of cases that have a normal karyotype (frequently referred to as AML-NK group). The relevance of these markers is evolving though some of them such as nucleophosmin (NPM) and FMS-like tyrosine kinase 3 (FLT3) mutation statuses are well established and are important in risk stratification and deciding on optimal consolidation therapy.
Risk Stratification

The most important prognostic factors still remain the age and cytogenetics at diagnosis. Based on the cytogenetics at diagnosis patients can be divided into three groups: (1) a good-risk group, (2) an intermediate-risk group and (3) a high-risk group (Table 2).

Within the good- and poor-risk group there is significant homogeneity with regards to outcome with currently available treatment options with a few exceptions in the good-risk group.

The intermediate-risk group which accounts for the majority of patients is heterogeneous with regards to response to therapy and newer prognostic markers are being applied in an attempt to rationalize the therapeutic intervention in this group. Table 3 illustrates a recent European Leukemia Net guideline which attempts to combine cytogenetic and molecular markers in a combined strategy for risk stratification.

TREATMENT OF NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

Therapy for newly diagnosed patients can be considered under the following headings and the discussion is limited to patients less than 60 years of age (therapy for older patients should preferably be on clinical trials since the alternative is essentially palliation).

• Induction chemotherapy
• Consolidation: Options include:
  - High-dose chemotherapy (nonmyeloablative chemotherapy)
  - Autologous stem cell transplantation (SCT)
  - Allogeneic SCT.

Induction Chemotherapy

Based on earlier studies the standard induction regimen has consisted of cytosine (Ara-C) administered at 100–200 mg/m² as a continuous infusion for 7 days and daunorubicin (DNR) administered at 45–60 mg/m² for 3 days.

Use of alternative anthracyclines especially idarubicin (IDR) with its potentially superior pharmacokinetic profile has been compared with DNR. In four large trials, there was a significant improvement in complete remission (CR) rates in the group that received IDR; however, in only one of these trials did this translate into an improved DFS. In another large trial conducted by the French Groupe Ouest Est Leucémies Aiguës Myéloblastiques (GOELAM) group, there was no benefit on either remission induction or on long-term survival.

Successful Eastern Cooperative Oncology Group (ECOG) studies have demonstrated that DNR at 60 mg/m² and IDR at 12 mg/m² showed equivalent response rates. More recently data suggests that increasing the DNR dose to 90 mg/m² may be optimal though this is associated with a marginal increase in toxicity. This should be considered with some caution in our setting (developing country) where the major problem following administration of induction therapy is infection (bacterial and fungal) related deaths due to the duration of neutropenia which is likely to further increase with increasing dose of anthracycline (personal opinion).

The role of high-dose cytosine in induction has been considered in a few publications. In the initial Australian Leukemia Study Group (ALSG) study, the treatment-related mortality (TRM) was significantly higher in the high-dose arm (18% vs 11%) compared to the standard induction, though there was a significant improvement in DFS and overall survival (OS). Similar findings were noted in the Southwest Oncology Group (SWOG) trial except that there was no significant difference on the OS. A more recent publication has shown significant advantage of high-dose cytosine in induction and in consolidation with a TRM of 11% comparable to most standard
**Hematology**

Induction regimens. In our setting, the high TRM in induction with these regimens as seen in the earlier trials warrants caution (personal opinion).

Majority of studies have shown a consistent reduction of the duration of neutropenia (3–4 days) when cytokines such as granulocyte colony-stimulating factor (G-CSF) were administered postinduction chemotherapy though this did not translate to either a reduction in morbidity or an improvement in overall/DFS.\(^{13-15}\)

The induction regimen that we follow at our center consists of cytosine administered at 200 mg/m\(^2\) as a continuous infusion for 7 days along with DNR administered at 60 mg/m\(^2\) for the first 3 days and this based on the available data could be considered standard of care.

**Consolidation**

Following achievement of CR after induction chemotherapy (achieved in 75–85%) failure to give consolidation therapy will lead to 100% of the patients relapsing.

Prior to starting induction chemotherapy, it is very important to assess if the patient and family has adequate resources and support to proceed with consolidation therapy. If this is not possible it is better not to proceed with standard induction therapy that is expensive and will only function as a very expensive form of palliation.

For patients who achieve remission (CR1) following induction chemotherapy, the options of consolidation therapy include:

- Intensive nonmyeloablative consolidative chemotherapy
- Autologous SCT
- Allogeneic SCT

Intensive consolidation chemotherapy is associated with the lowest TRM, but it has the highest risk of disease relapse in contrast to an allogeneic SCT, which is associated with the lowest risk of disease recurrence, but it has the highest risk of TRM.\(^5\) An autologous SCT has an intermediate risk of TRM, with most prospective trials demonstrating a reduced relapse risk in comparison with chemotherapy alone (Table 4).

There has also been a steady improvement in the management of patients undergoing SCT; this has resulted in lower TRM and improved OS. This improvement makes it difficult to apply the data from the large prospective clinical trials, most of which were initiated a decade ago, to current algorithms.

The options of consolidation therapy are strongly influenced by the cytogenetic risk group. The good-, intermediate- and unfavorable-risk groups have 25%, 50% and greater than 70% probability of relapse and a 4-year probability of survival of greater than 60%, 40–50% and less than 20%, respectively.\(^{16}\) Additional parameters, such as age, white blood cell count at diagnosis, response to induction chemotherapy, and type of consolidation therapy, influence and potentially alter these predicted outcomes.

In the good-risk group generally an allogeneic SCT is not considered in view of the TRM of 15–30% associated with this procedure when repetitive cycles of high-dose nonmyeloablative consolidation chemotherapy can achieve long-term DFS greater than 60% with a less than 5% TRM. In the unfavorable-risk group, the choice would be to proceed if possible with an allogeneic SCT in CR1, not as much as because of the data supporting this but rather due to the well recognized dismal outcome with chemotherapy or autologous SCT. In the intermediate-risk group, which constitutes close to 40–50% of all patients with AML, the options in CR1 are less clearly defined. This group is heterogeneous in their response to therapy and most of them have a normal karyotype. New markers could help identify subsets at a high-risk of relapse and candidates for an SCT.

**Intensive Nonmyeloablative Consolidation Chemotherapy**

Using repetitive courses of high-dose Ara-C (HiDAC) alone or in combination with other drugs has been found to be effective in the treatment of AML.

Repetitive cycles of HiDAC as a single agent has been found to be effective in the management of good-risk AML.\(^{17,18}\)

A more recent Cancer and Leukemia Group B publication addressed the issue of single agent HiDAC versus combination chemotherapy in patients less than 60 years of age and found no significant difference in the DFS between the two groups.\(^{19}\)

Based on the available data good-risk patients would benefit from repeated courses of HiDAC. The number of courses should be more than one and preferably three to four cycles.\(^{17}\)

Since patients who do relapse are easily salvaged in this subgroup, it would be reasonable to limit this to three cycles. In the intermediate-risk group, the optimal therapy is evolving and the exact role of chemotherapy alone is unclear. There is probably no role for young patients with AML in the high-risk group to receive chemotherapy alone as consolidation therapy. At our center for patients in the good-risk group, we would administer three cycles of HiDAC alone postinduction.

**Autologous Stem Cell Transplantation**

The early phase II trials of autologous bone marrow transplantation in AML in CR1 showed an overall DFS ranging from 40–60%, relapse rates of 30–50% and a TRM of 5–15%. Subsequent phase III trials (Table 4) confirmed a reduced relapse risk compared to intensive chemotherapy. In two of these trials, this reduction translated into an improved DFS; however, there was not a significant difference in OS in any of the patients. A recently published meta-analysis confirms these observations.\(^{20}\) All of these prospective trials had limitations such as variable numbers of patients who actually received the assigned therapy and a high TRM (average of 12%).

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**TABLE 4** | Results from large prospective randomized clinical trials illustrating risk of relapse (%) after different forms of consolidation therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Allogeneic SCT</th>
<th>Autologous SCT</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIMMEMA</td>
<td>24%</td>
<td>40%</td>
<td>57%</td>
</tr>
<tr>
<td>GOELAM</td>
<td>28%</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>MRC</td>
<td>19%</td>
<td>35%</td>
<td>53%</td>
</tr>
<tr>
<td>ECOG/SWOG</td>
<td>29%</td>
<td>48%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Abbreviations: GIMMEMA, Gruppo Italiano Malattie Ematologiche Maligne dell’Adulto; GOELAM, Groupe Ouest Est Leucémiées Aigües Myéloblastiques; MRC, Medical Research Council; ECOG/SWOG, Eastern Cooperative Oncology Group/Southwest Oncology Group
Most of these trials were initiated a decade ago and there has been significant interval improvement in the management of patients undergoing an autologous SCT. Most current large single center data are consistent with our own experience and demonstrate no significant difference in TRM compared to high-dose consolidation chemotherapy. Improvement in TRM could potentially translate into reduced relapse risk and improved DFS and OS after autologous SCT. From the available data, some generalizations can be made; with a few exceptions good-risk group patients would probably not gain additional benefit from an autologous SCT in CR1, in the unfavorable group, there is no data to suggest a benefit of an autologous SCT over chemotherapy. The outcomes after both these options appear dismal. The intermediate-risk group are candidates for an autologous SCT, especially subsets with a high risk of relapse as defined by additional parameters. However, this remains to be validated in large randomized clinical trials. At our center we would offer an autologous SCT for patients in the intermediate-risk group who do not have a HLA-matched donor. We would do this after three cycles of HIDAC-based therapy.

Allogeneic Stem Cell Transplantation

Large prospective trials have consistently shown that an allogeneic SCT with standard myeloablative conditioning regimen is the most potent antileukemia treatment for CR1 AML with a relapse risk of 24–36% compared to 46–61% with autologous SCT or chemotherapy. However, none of these trials showed a benefit with regards to OS. This result is mainly because of the high TRM, which ranges from 10–25%. This therapy is not an option for patients in the good-risk cytogenetic group. In this group of patients even those who relapse after consolidation chemotherapy respond well to an autologous or autologous SCT in second remission (CR2), hence, this should be reserved for patients in CR2. In the intermediate and unfavorable cytogenetic groups, the TRM associated with an allogeneic SCT may be acceptable in an effort to improve the DFS and OS. In the unfavorable group in CR1, an intergroup study showed a 5-year survival rate of 44% versus 15% with chemotherapy or an autologous SCT, whereas a similar but less dramatic difference was noted in the European Organization for Research and Treatment of Cancer (EORTC)/Gruppo Italiano Malattie Ematologiche Maligne dell’Adulto (GIMEMA) AML-10 trial. Two other studies failed to show an advantage of an allogeneic SCT over chemotherapy or an autologous SCT. In all of the studies, the outcome in the unfavorable group with chemotherapy alone or with an autologous SCT was dismal. Based on the available data, if a donor is available, it is reasonable to proceed with an allogeneic-related HLA-identical SCT in CR1 with unfavorable cytogenetics. In the intermediate-risk group, the data from most large prospective clinical trials did not show an improved OS after autologous SCT in CR1; however, in one study, there was a significant improvement in the DFS. The optimal therapeutic strategy in this group of patients in CR1 is still evolving. If a related HLA identical donor is available, other parameters could be used to aid in the decision-making process. Some of the factors that would favor an allogeneic SCT in CR1 include age of patient (< 40 years), high white blood cell count at diagnosis (> 30,000–40,000/ mm³), requirement of more than one cycle of chemotherapy to achieve CR1 and the presence of additional molecular markers that predict a high risk of relapse as discussed earlier. In our setting where finances are a major concern and the option of using an allogeneic SCT as salvage therapy is not an option if the patient’s resources have been exhausted with prior costs of chemotherapy, it would be reasonable to offer an allogeneic SCT in first CR in this group of patients. At our center we would offer an allogeneic SCT for all patients in the intermediate- and high-risk group who have HLA-matched related donor following induction. The exception would be intermediate-risk group patients who are NPMI+ and FLT3– since the outcome in this group with chemotherapy alone is excellent. In the high-risk group, we would also consider a matched-unrelated donor (MUD) transplant if an HLA-matched sibling is not available.

Role of consolidation chemotherapy before an allogeneic stem cell transplantation: Retrospective analysis of the International Bone Marrow Transplant Registry (IBMTR) and European Group for Blood and Marrow Transplantation (EBMT) data suggest that consolidation chemotherapy before an allogeneic SCT does not benefit patients with AML in CR1. Another retrospective analysis from a single center showed similar findings and suggested that multiple chemotherapy courses before an allogeneic SCT had a deleterious effect. Bone marrow versus peripheral blood stem cells (PBSCs): Retrospective analysis of the EBMT and IBMTR database showed a benefit for use of PBSC in patients with advanced AML, but no benefit was shown in patients with AML in CR1, whereas another retrospective study showed a benefit for patients with AML in CR1 who underwent a peripheral blood stem cell transplantation (PBSC). A more recent retrospective analysis of the Acute Leukemia Working Party/EBMT registry suggests that there is improved outcome with the use of bone marrow versus PBSC when the dose of bone marrow CD34+ cells exceeded 2.7 x 10⁶. The only prospective study addressing this issue demonstrated earlier engraftment, reduced TRM and improved DFS with PBSC, but there was no difference in OS.

Based on the available data below is a summary of the strategy that could potentially be considered for newly diagnosed young adults with AML. However, it is important to recognize that there are a number of areas where the available data is not robust enough to make a definitive recommendation and hence some of the approaches taken are center specific and depends on the degree of comfort with doing stem cell transplants on a routine basis.

Based on the above data, the following broad recommendations can be suggested for patients greater than 15 years and less than 60 years in the different cytogenetics risk groups.

CONCLUSION

Significant strides have been made in the management of patients with AML. In addition to the increased understanding of the biology of the disease, ongoing developments in the field of chemotherapy and stem cell transplant continues to contribute to the steady improvement in the outcome of these patients. For the good-risk group, an autologous or allogeneic SCT should be reserved for patients who relapse after consolidation with intensive chemotherapy. In the unfavorable-risk group, it would be reasonable to proceed with an allogeneic SCT in CR1 preferably from an HLA-matched sibling donor. Based on the available data it would be considered reasonable to offer a MUD-SCT to young patients in the unfavorable-risk group with AML in CR1 if they do not have an HLA-matched sibling. The optimal therapy for patients with AML in CR1 in the intermediate-risk group is evolving and several questions remain to be answered. With the available data, some guidelines can be drawn for this group, although no firm conclusions can be made. The use of new markers to identify subgroups at a high risk for relapse would help identify patients who would benefit from a stem cell transplant.
Flow chart 1: Recommendation for different cytogenetic risk groups

**Good-risk group (standard 7/3 induction)**
- Day 14 bone marrow to assess response to therapy
- Day 14 bone marrow shows > 5% blasts with > 20% cellularity
- Consider administering a second induction regimen

**Intermediate-risk group (standard 7/3 induction)**
- Day 14 bone marrow to assess response to therapy
- Day 14 bone marrow shows > 5% blasts with > 20% cellularity
- Consider administering a second induction regimen

**Complete remission (CR) achieved**
- High-dose cytosine × 3 (HIDAC × 3)
- Follow-up

**Not achieved**
- Reinduction
- Allogeneic SCT in donor available
- Autologous SCT if no donor

**CR**
- Donor available
  - Allogeneic SCT
- No donor
  - HiDAC × 3
  - Autologous SCT

**Not in CR**
- Reinduction
- CR*
  - Donor available
  - HiDAC × 3
  - Allogeneic SCT
  - Autologous SCT

**No donor**
- HiDAC × 3
- Allogeneic SCT
- Autologous SCT

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**Section 10**

Contd...

**High-risk group (standard 7/3 induction)**

Day 14 bone marrow to assess response to therapy
Day 14 bone marrow shows > 5% blasts with > 20% cellularity
Consider administering a second induction regimen

**CR**

Donor available

Allogeneic SCT in CR1 (including MUD)

No donor

HiDAC × 3

Autologous SCT

**Not in CR**

Individualize/Clinical trial/Palliation

**CR*** = If fails to achieve CR at this time point to consider palliation/clinical trial

**REFERENCES**

17. Byrd JC, Dodge RK, Carroll A, et al. Patients with t(8;21)(q22;q22) and acute myeloid leukemia have superior failure-free and overall survival when repetitive cycles of high-dose cytarabine are administered. J Clin Oncol. 1999;17(12):3767-75.