How I treat acute myeloid leukemia

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Abstract

Over one quarter of a million adults throughout the world are diagnosed annually with acute myeloid leukemia (AML). Despite considerable progress during the past three decades in the therapy of AML, two thirds of young adults and 90% of older adults still die of their disease. The reported median age has increased over the past few decades, mostly due to a greater willingness of physicians to diagnose and treat older patients, and now is 72 years. The greatest challenge is in this age group. However, much improvement in therapy is needed for all adults with AML. Recent advances in allogeneic transplantation, a better understanding of prognostic factors and development of targeted agents have only modestly improved overall outcome when large populations of patients are considered. While an explosion in knowledge about the molecular pathogenesis of AML has outpaced treatment advances, such insights hold promise for the development of new therapies directed at specific molecular abnormalities which perturb malignant cell survival pathways. The current approach in 2010 to the management of this disease is presented through a discussion of illustrative cases.
INTRODUCTION

Few diseases other than AML engender so much personal and institutional passion regarding treatment strategies. This is attributable to dramatic progress in deciphering the pathogenesis of the disease, the identification of prognostic factors and burgeoning treatment options. However, there is a "great divide" between our understanding of the molecular basis and the development of effective treatment. The median age of AML is 72 years, as reported by the Swedish Acute Leukemia Registry, a model for collection of real world data\textsuperscript{1}. While some improvement during the last 4 decades is apparent among younger patients, still only approximately 35\% of such patients entered on clinical trials are cured of their disease (Figure 1)\textsuperscript{2-5}. Little if any progress among older adults has occurred. In fact, only patients with acute promyelocytic leukemia (APL), a rare subtype, enjoy the excellent outcome and likelihood of cure we all desire. Never-the-less, recent advances in molecular prognostic factors, allogeneic hematopoietic cell transplantation and drug development provide excitement for the future.

To some extent, the management of adults with AML appears to be standardized. However, much of the so-called conventional therapy has been established with a lack of data or without rigorous review of the existing evidence and so, considerable uncertainty remains. Such uncertainty is reflected in the significant diversity in the management of patients with AML, both in induction of older patients and post-remission therapy of all patients. The suggested management described herein reflects an approach for the treatment of AML. The recommendations made here, through clinical vignettes describing patients commonly encountered in daily practice, are not a substitute for enrolling patients on carefully designed prospective clinical studies, which remain vital for improving the current and future management of AML. Rather, they represent how we treat adults with AML bolstered by data where they exist and by a dose of healthy skepticism where conventional wisdom prevails, but without definitive supporting evidence.
Patient 1.

A 43-year-old woman is diagnosed with AML. Her complete blood count (CBC) at presentation reveals a white blood cell count (WBC) of 23,000/μL with 23% blasts; her hemoglobin is 8.7g% and the platelet count is 32,000/μL. Her bone marrow is diffusely infiltrated with myeloblasts that express CD34, CD13 and CD33. The karyotype is normal and evaluation for mutations of the genes encoding for FLT3-ITD, NPM1 and CEBPA are all negative. The patient has an HLA-identical sibling. **What is the optimal induction and post-remission therapy? Is it reasonable to offer standard chemotherapy consolidation and "reserve" an allogeneic transplant to be used if the patient relapses?**

Although in the early 1990s several randomized studies of induction therapy suggested that using idarubicin, mitoxantrone, aclarubicin or amsacrine demonstrated superior results compared with daunorubicin, there is no evidence that these studies reflected a true biologic advantage rather than a lack of dose equivalence. It has now been established that the traditional approved dose of daunorubicin, 45 mg/m² for 3 days, is no longer appropriate as induction therapy for AML. A recent randomized trial for younger patients under age 60 years reported a significantly higher complete remission (CR) rate for patients receiving 90 mg/m² of daunorubicin compared to 45 mg/m². The overall survival was also improved with the higher dose of daunorubicin (Figure 2a and 2b).

Approximately 70% of young adults undergoing induction therapy are expected to achieve a CR. The published data on responses to induction vary considerably between the cooperative trial groups reflecting different criteria for assessment of remission as well as different inclusion criteria for clinical studies. For example, studies in which patients with antecedent hematologic disorders or therapy-related AML are included would have inferior results compared to those that exclude such
patients. A dose of 90 mg/m² of daunorubicin is clearly safe and should become the standard of care, although doses between 60 mg/m² and 90 mg/m² may be as effective.

This patient is in the intermediate risk category given that her karyotype is normal⁷. Advances in the molecular classification of AML, particularly among patients with a normal karyotype, have recently refined this risk group from the traditional 50-70% among AML patients⁷-⁹ to no more than 25-30%.¹⁰ In this patient, the absence of unfavorable mutations, such as FLT3-ITD, or the more favorable mutations, such as NPM1 and CEBPA, suggest that this patient remains best classified in the intermediate risk category¹¹, recognizing that even in this group further discrimination is likely in the coming years with the use of genetic profiling and further molecular characterization.

Allogeneic hematopoietic cell transplantation (allo HCT) provides the most potent anti-leukemic effect of any post-remission strategy in AML, as demonstrated by the lowest rates of relapse in all clinical studies. For patients such as this who have an HLA-identical sibling donor an allo HCT should be offered, preferably if the patient remains negative for minimal residual disease (MRD) prior to transplantation¹². Despite substantial transplant-related mortality of 15-20%, the reduction in the relapse rate significantly outweighs the transplant-associated risk and is considered standard-of-care for such a patient. (Table 1)¹⁰ An exception to this approach may be made for patients whose leukemia cells express more favorable mutations at diagnosis. Several recent reports have indicated a more favorable outcome among patients with a normal karyotype for those who present with mutations of NPM1 or CEBPA. One recent analysis suggested that patients whose cells are NPM1⁺/FLT3-ITD belong more appropriately in the favorable risk group and may not benefit from an allo HCT¹¹. Although fairly widely accepted and having moved into routine practice in many centers¹³, the data supporting such a practice are based on only 38 patients with a donor.¹¹ The CEBPA mutation also confer a more favorable prognosis for patients with a normal karyotype¹¹,¹⁴ and therefore, the same consideration as applicable to NPM1⁺ should be given, although there have
been no specific reports that have demonstrated this. Of note, recent data suggest that the more favorable prognosis in this group is limited to patients with the biallelic CEBP mutations\textsuperscript{15}.

Although there are multiple reports of the use of reduced-intensity conditioning (RIC) regimens in AML, there have been no prospective comparisons with standard regimens, particularly in younger adults. Therefore, at the present time RIC should be reserved for older adults with AML or those with significant co-morbidities which preclude conventional myeloablative conditioning for transplantation. The standard of care for younger adults remains a fully myeloablative conditioning regimen, for which abundant data exist.

Although there are no prospective trials that have addressed the need for any post-remission consolidation chemotherapy prior to an allo HCT, two retrospective analyses from large international registries suggest that there is no benefit to adding any consolidation therapy prior to an allo HCT\textsuperscript{16,17}.

Finally, while the concern for the high transplant-related morbidity and mortality is appropriate, this should not lead to delaying an allo HCT in first complete remission (CR1) and reserving such treatment for patients in the event of a relapse. Reports indicating a successful outcome after relapse with a curative potential of approximately 30%\textsuperscript{18,19} are highly selective and relate only to patients who have survived their relapse and are fit enough to receive a transplant in second remission. The predictive overall survival of relapsed AML patients is exceedingly poor; no more than about 10%.\textsuperscript{20-22} (Figure 3) In our view, delaying transplantation until after relapse is a misleading strategy, although we recognize that no trial has ever randomized patients with donors between immediate and delayed transplant.
This patient should receive induction therapy with daunorubicin 90 mg/m\(^2\) for 3 days together with cytarabine 100 mg/m\(^2\) for 7 days. A dose of daunorubicin between 60 mg/m\(^2\) and 90 mg/m\(^2\) is also reasonable.

As post-remission therapy the patient should be referred for an allogeneic transplant from her HLA-identical sibling and a conventional myeloablative conditioning should be used. "Reserving" an allogeneic transplant for relapse definitely not recommended.

If possible, any consolidation chemotherapy prior to the allogeneic transplant should be avoided.

Patient 2.

A 54-year-old man presents with gingival hypertrophy and bleeding. At presentation his WBC is 39,000/\(\mu\)L with 60% monoblasts; the hemoglobin is 7.9g\% and the platelet count is 6,000/\(\mu\)L. His bone marrow is diffusely infiltrated with monoblasts. Cytogenetic analysis shows a normal karyotype and the leukemic cells express the mutated FLT3-ITD. He does not have any siblings. He received standard induction therapy. His day 14 bone marrow demonstrated some cytoreduction but unequivocal residual leukemia, following which he received a second cycle of identical induction therapy and achieved CR. **Should this patient be referred for an alternative donor transplant?**

**What would be the post-remission strategy in the absence of the mutated FLT3-ITD?**

This patient's course raises several important issues. Firstly, historically, patients with monocytic leukemia were considered to have a poor prognosis and those who did not clear their blasts by day 14 were also considered to be in a poorer risk category, irrespective of subsequent response to therapy. However, while monocytic leukemia presents with unique clinical features, such as extramedullary tissue infiltration and central nervous system involvement, once a CR is achieved,
there is no evidence that with contemporary therapy the ultimate prognosis is determined by this unique morphology alone. Although a day 14 bone marrow generally predicts for a lesser likelihood of achieving a CR with induction, recent data from the Eastern Cooperative Oncology Group (ECOG) suggest that patients who receive a second cycle of induction therapy on day 14, based on the presence of unequivocal residual leukemia, and subsequently achieve a CR, have a prognosis that is similar to those achieving CR with one cycle of induction. Thus, the presence of residual leukemia on day 14 in-of-itself should not alter the post-remission strategy, if the patient responds successfully to the induction therapy. The choice of post-remission therapy should be based solely on the cytogenetic and molecular determinants at diagnosis, and, possibly on minimal residual disease (MRD) after induction therapy, as determined by refined molecular or immunophenotypic analyses. Although the presence of MRD is of concern to any treating physician, at the present time we do not alter the post-remission strategy based on such findings.

The presence of the mutated FLT3-ITD confers a poor prognosis for this patient. The practical issue is whether to offer a transplant from an alternative donor, either a matched unrelated donor (MUD), a genetically haploidentical donor or an umbilical cord donor.

While the indications for an alternative donor transplant have not been properly defined, its performance is nevertheless becoming more widespread as the clinical experience is increasing. The only prospective data demonstrating the beneficial effect of a MUD transplant have been in patients with unfavorable risk AML. Historically, the hesitation to offer an alternative donor transplant was based on the higher morbidity and mortality compared with sibling transplants, possibly altering unfavorably the risk-benefit balance for AML patients in first CR. Recent publications of an almost identical outcome following an 8/8 MUD transplant, that is confirmed also by molecular high-resolution typing, are encouraging. However, such data need to be cautiously interpreted since they likely reflect a selection bias in that the eligibility criteria for a MUD
transplant are significantly more stringent than for a sibling donor transplant. Furthermore, although there is a perception, based on a sound rationale, that immunologic graft-versus-leukemia (GvL) effect may be particularly potent using MUD due to a higher likelihood of allelic disparity at minor histocompatibility antigens, a recent study from the Center for the International Blood and Marrow Transplant Research (CIBMTR) described somewhat surprising results regarding the outcome of myeloablative MUD transplants as well as a well-matched cohort of HLA-identical sibling transplants. There was an increased relapse rate in MUD transplants for AML patients in first CR and the leukemia-free survival was also significantly improved for patients receiving a sibling transplant. Unexpectedly, while the presence of graft-versus-host disease (GvHD) is associated with reduced relapse of AML, it does not appear that such an effect is dependent on the degree of genetic disparity and the best donor remains the most closely matched donor. It is of interest that similar observations were recently reported in chronic myeloid leukemia (CML) and in a CIBMTR study of reduced intensity HCT in older patients with AML.

In the absence of a sibling donor, this high-risk patient would be offered the option of a transplant from a fully matched unrelated donor, although there are no prospective data that establish this as standard of care. In the absence of the FLT3-ITD mutation the patient who does not have a sibling donor would receive post-remission therapy without allogeneic transplantation. There is much controversy regarding the optimal post-remission therapy, including the number of cycles of intensive chemotherapy, the best agent and even regarding the preferred doses. In our opinion, a patient not on a clinical study would receive 2 cycles of consolidation therapy with high-dose cytarabine followed by an autologous transplant. The rationale for using an autologous transplant is based on the fundamental concept that the optimal approach to post-remission therapy is based on the regimens with the most potent anti-leukemic activity, provided this effect is not abrogated by unacceptably high mortality. In the majority of major prospective studies published over the past decade a lower relapse rate was reported for patients undergoing an autologous
transplant compared with chemotherapy. In a meta-analysis of 6 trials, including 4,410 patients, auto HCT was associated with modest improvement of 10-18% in DFS\textsuperscript{37}. The hesitation to use an autologous transplant was the relatively high treatment-related mortality reported in older studies that in most instances used bone marrow as the source for hematopoietic cells\textsuperscript{38,39}. Currently, the mortality rate associated with an autologous transplant, in experienced centers using hematopoietic cells collected from the peripheral blood, is less than 2%\textsuperscript{40,41}, which offers a compelling argument for adding autologous transplantation to chemotherapy-based consolidation.

Although for the majority of patients a MUD transplant is the preference when a sibling donor is not available, there are other alternatives for which data are available. In experienced centers a transplant from a genetically haploidentical donor can be performed with overall results that are similar to those reported for MUD transplantation\textsuperscript{42}. An important advantage with this form of transplant is the almost universal availability of a donor, with minimal delay to transplant. Similarly, the use of double unrelated umbilical cord transplantation is increasingly employed and rapidly accumulating data suggest that this is also an option when a sibling donor or MUD is not available\textsuperscript{43}.

| The decision for induction or post-remission therapy should be based on cytogenetic and molecular determinants and is not altered by the presentation with the monocytic variant morphology or by the fact that remission was only achieved after 2 cycles of induction. |
| As post-remission therapy this patient should be referred for a matched unrelated donor transplant. |
| In the absence of FLT3-ITD mutation, or other high-risk feature, this patient with a normal karyotype would receive 2 cycles of consolidation therapy with high-dose cytarabine followed by an autologous transplant. |
Patient 3.

A 43-year-old man presents with a one-week history of weakness and progressive dyspnea. His WBC at presentation is 260,000/μL; the hemoglobin is 8g% and the platelet count is 32,000/μL. Cytogenetic analysis reveal t(8;21)(q22;q22) and molecular analysis reveals only the presence of the c-KIT mutation. What is the best emergent management? Is standard induction appropriate? Is CNS prophylaxis recommended? What is the appropriate post-remission therapy?

This patient presents with a very high WBC count, where apart from any long-term prognostic considerations, there are emergent issues. Hyperleukocytosis in AML is associated with leukostasis with potentially lethal central nervous system and pulmonary complications. The optimal emergent management is uncertain and one approach is to initiate immediate induction therapy. An alternative strategy consists of daily leukapheresis with the concurrent administration of hydroxyurea at doses of 2-6g/day. Although not substantiated by any data, it is customary in our institutions to continue this approach and wait for the initiation of induction therapy until the WBC has fallen below 40,000-50,000/μL. It is presumed, but not proven, that this increases the likelihood of achieving CR with a single cycle of chemotherapy. Once induction therapy is initiated, standard doses should be given with no modification.

The issue of prophylaxis for central nervous system is controversial in any patient with AML and is often considered in a patient who presents initially with a high WBC. While there are theoretic considerations for administering prophylaxis, in our institutions this is not customarily performed for any patient with AML, in the absence of any symptoms related to the central nervous system.

This patient presents with t(8;21)(q22;q22) karyotype. Although frequently described as associated with a favorable prognosis, this is a misnomer, considering that the long-term survival rate of
patients is less than 50% in series reporting large numbers of patients.\textsuperscript{45} (Figure 4). Despite this prognosis, multiple prospective studies as well as meta-analyses have not established any benefit to an allogeneic transplant in patients with t(8;21)(q22;q22)\textsuperscript{13,46,47}. The reduction in relapse is abrogated by the transplant-related mortality. This recommendation probably is not altered by the presence of other cytogenetic abnormalities\textsuperscript{10,48}. However, there are increasing number of reports that have suggested that patients with core-binding factor translocations with mutations in \textit{c-KIT}, have a very high relapse rate, almost comparable to patients with unfavorable risk cytogenetics\textsuperscript{49-51}. For this reason it is important to routinely obtain all the common molecular markers, which would also include \textit{FLT3-ITD}, \textit{NPM1} and \textit{CEBPA}.

The high WBC count has also been reported to be associated with \textit{c-KIT} mutations, especially in patients with t(8;21).\textsuperscript{52} These reports in adult patients need to be cautiously interpreted due to the small numbers and it should be noted that a recent publication in pediatric patients could not confirm the poorer prognosis for patients with \textit{c-KIT} mutations\textsuperscript{53}. Never-the-less, given the preponderance of data in adults, this patient would be referred for a matched sibling transplant or an alternative donor transplant in the absence of an available HLA-matched sibling.

\begin{quote}
\textbf{The patient should receive urgent leukapheresis together with hydroxyurea until the WBC is below 50,000/\mu L. At that point standard induction therapy should be given.}
\end{quote}

\begin{quote}
\textit{CNS prophylaxis is not routinely administered.}
\end{quote}

\begin{quote}
\textit{For post-remission therapy the patient should be referred for an allogeneic transplant from an HLA-identical sibling or from an alternative donor.}
\end{quote}
**Patient 4.**

A 70-year-old woman presents with AML. At diagnosis her WBC is 2,400/μL; her hemoglobin is 10.2g% and the platelet count is 17,000/μL. Cytogenetic analysis was not available. **What is the optimal induction and post-remission therapy for this patient? How would cytogenetics affect the management of such a patient?**

This patient presents with what is probably the most important challenge in managing patients with AML. Given that the median age is 72 years, this is a group with a much higher incidence of AML and among whom the overall survival remains approximately 10%, at best. There has been much discussion, controversy and a lack of accurate data, given the widely disparate treatment approaches for such patients. Less than 10% of younger AML patients are referred for cooperative group trials and among older patients the number is far below 5%. In addition, patients referred to a tertiary cancer center and then entered on clinical trials, are a highly select subgroup. In a recent elegant population-based study from the Swedish Acute Leukemia Registry a compelling case is made for the administration of standard intensive therapy for all fit older patients rather than adopting a purely palliative approach. The approach in our center is unequivocal in offering all AML patients induction therapy, unless presenting with prohibitive co-morbidities. There are several important principles in the management of such an older patient. Once the decision is made to treat, then standard doses of induction should be given. Attenuation of induction is contraindicated. A low dose will not reduce the toxicity, and is more likely to lead to ineffective therapy with a similar degree of myelosuppression. Fit older adults tolerate chemotherapy at least as well as younger patients; but they do not tolerate prolonged aplasia. A recent randomized trial from the HOVON/SAKK Collaborative Group confirmed the safety of higher doses of daunorubicin, up to 90 mg/m² for 3 days in older adults. In one report, two sequential studies of older patients were compared. No significant survival benefit was reported in the study that included post-remission
therapy compared to the study that offered no such therapy.\textsuperscript{56} The reticence by many to treat older adults with standard doses of induction chemotherapy has often been based on a mistaken perception that such doses could not be tolerated. In the HOVON/SAKK study, the higher dose of daunorubicin led to a more rapid initial response as well as a higher response rate than a more conventional dose of 45 mg/m\textsuperscript{2}, although there was no significant improvement in the overall survival (Figure 2c). For this reason, this patient would receive a dose of 60 mg/m\textsuperscript{2} for 3 days as induction recognizing that higher doses may be preferable and may in time become the standard of care. The achievement of CR remains of paramount clinical significance and this is an important endpoint also in older patients\textsuperscript{57}, particularly when considering quality of life\textsuperscript{1}.

Several suggestions have been made how to treat patients who are above 75 years of age with a suboptimal performance status. Our own approach would be to avoid using an arbitrary age cutoff and offer standard induction therapy to any patient who we think will tolerate intensive induction chemotherapy. In line with Juliusson et al (Ref. # 1; Blood, 2009), we would not withhold induction therapy for any patient based on age alone. The presence of co-morbidities encompasses a broad spectrum, ranging from those that should be treated with supportive care only which comprises the administration of blood products and antibiotics, to therapy with hydroxyurea and escalating to low-dose cytarabine or some of the new hypomethylating agents, the farnesyltransferase inhibitors or, preferably always, a clinical trial exploring an investigational agent.

There is enormous uncertainty and controversy regarding the optimal post-remission therapy in older patients. In contrast to younger adults, the value of post-remission therapy has never been unequivocally established for older patients\textsuperscript{58}. Despite this, it is common practice and virtually every published clinical trial for older patients with AML includes one or more courses of consolidation therapy. The Medical Research Council (MRC) in Great Britain conducted a large study of 1,314 older patients that attempted to determine whether the addition of multiple cycles of consolidation is superior to a single cycle. In this study patients received standard induction therapy
and, if in remission, received the identical course of induction as their first course of consolidation therapy. Patients were then randomized to receive 3 further cycles of consolidation or only observation. The outcomes in both groups were identical, demonstrating that there is no particular value in intensifying post-remission therapy beyond a single course of consolidation. \(^{59}\) (Figure 5). However, the MRC study did not address whether or not any consolidation is required in older adults. This important issue remains open.

There is information from prospective trials regarding cytogenetics that may also affect the decision regarding the optimal post-remission therapy. Between 25% and 30% of patients who present with unfavorable cytogenetics can achieve a CR \(^{60,61}\). However, despite the administration of intensive consolidation therapy, the 5-year survival is less than 5%. \(^{60-62}\) (Figure 6) Therefore, for such patients it is hard to justify the administration of consolidation and a strong case can be made for putting such patients on a clinical trial of novel investigational therapies. Despite this, most current investigations which include older patients prescribe post-remission therapy, irrespective of the cytogenetics at presentation.

It is clear that older patients cannot tolerate the same doses of consolidation therapy that is administered to younger patients, often due to gastrointestinal toxicity and, if high-dose cytarabine is used, central nervous system toxicity. Typically, doses are decreased for patients between 55 and 70 years and are further reduced for those over 70, although there is considerable arbitrariness in such a recommendation.

The advent of RIC regimens as preparative regimens prior to allogeneic HCT may, for the first time in decades, make a significant impact on the long-term survival of such patients with AML. \(^{63}\) While there is a paucity of prospective data regarding RIC transplants, recent studies emphasize the feasibility of this procedure, the curative potential and tolerability in older patients \(^{35,63-67}\). Despite reports that more than one third of patients can achieve a long-term survival with this regimen \(^{35}\), prospective data are needed to establish the true long-term survival rates in a non-select population.
Indeed, very few older patients ultimately undergo such a procedure even in sophisticated centers. Reduced intensity conditioning transplantation has become common practice in many centers but attempts at accruing a significant number of patients into prospective clinical studies of RIC have fallen short. Whenever possible, patients should be entered on a clinical trial that prospectively evaluates the role of RIC transplantation. Never-the-less, given the emerging data, in our centers and others, patients not entered on a clinical study would be offered a RIC transplant, from either a matched sibling donor or MUD.

Several issues are completely unresolved when considering such an approach. First, should any consolidation be administered prior to RIC transplantation? While for patients receiving standard ablative conditioning allogeneic transplantation there are data suggesting that there is no benefit for the administration of any prior consolidation in CR, no such data exist for patients undergoing RIC transplantation. Although a strong rationale exists for administering some form of intensification prior to RIC, in an attempt to minimize the leukemia burden and allow time for generation of the graft-versus-leukemia effect, in practice the design of cooperative group studies is not uniform. In a recently published HOVON study for older patients, RIC was offered after one cycle of consolidation, whereas in a newly designed study by the ECOG, RIC allogeneic transplantation is offered after successful achievement of CR prior to any consolidation. This is the approach taken by us which, although unproven, is driven by an attempt to reduce the transplant-related toxicity.

A second unresolved issue is whether RIC should be offered also to patients with unfavorable cytogenetics. This is the group that even among younger AML patients has a poor prognosis. There are almost no data on RIC transplants performed in patients with unfavorable cytogenetics, since younger patients with unfavorable cytogenetics almost always undergo myeloablative conditioning. In practice, in very experienced centers, an older patient with a good performance status who achieved a CR would be referred for a RIC transplant, but for these patients we
administer one course of consolidation therapy acknowledging that there are no published data to support such an approach.

This woman should receive induction therapy with a dose of daunorubicin that is not less than \(60 \text{ mg/m}^2\) for 3 days. Cytogenetics would not alter the initial attempt to achieve CR. As post-remission therapy, she should then receive 1 cycle of consolidation therapy, using an attenuated high-dose cytarabine regimen. If an HLA-matched donor is available, the patient should be offered a RIC HCT in CR1, without any prior consolidation; an exception is for patients with unfavorable cytogenetics.

**Patient 5.**

A 52-year old woman presented with AML with the following chromosomal abnormalities: del(5q); del(7q); del(12p) and abn(11q;p3). The patient has a long history of prior chemotherapy given for diffuse large cell lymphoma. She was last treated with autologous transplantation 4 years previously and is now free of lymphoma. **What is the appropriate induction and post-remission therapy?**

**How is this affected by cytogenetics?**

The patient presents with therapy-related AML. In general, the management of this type of AML is fraught with uncertainty because, among other reasons, most early studies included small numbers of patients and were retrospective. There have been no prospective randomized studies specifically directed at the treatment of therapy-related leukemias. Furthermore, the published data often included patients with myelodysplastic syndromes (MDS). Finally, the data are confounded owing to variable definitions. Until recently, the term "secondary leukemia" broadly included any AML.
with a history of prior malignancy as well as patients with any antecedent hematologic disorder and in some series any patient that presented with unfavorable cytogenetics. Among therapy-related AML patients 70% present with abnormalities of chromosome 5 or 7 which is the most typical presentation following the exposure to alkylating agents and/or ionizing radiation\textsuperscript{69}. Another important group, recognized only in the 1990s and accounting for about 30% of therapy-related AMLs, are those that arise after treatment with topoisomerase-2 inhibitors\textsuperscript{70}.

Historically it was presumed that every patient with therapy-related leukemia had an adverse prognosis and that standard induction therapy was inappropriate; high-dose cytarabine was suggested in one report\textsuperscript{71}. However, there is no evidence that any induction therapy is superior to the standard 3+7 regimen. Among young adults, quite remarkably, prospective studies report an almost identical CR rate of 55-60% for patients treated with recognized unfavorable cytogenetics and there are no reports that anything is better than this (Table 2). Therefore, this patient should be treated with standard induction therapy assuming, of course, that there are no co-morbidities related to her prior therapies that preclude the administration of anthracyclines.

This presence of a complex karyotype classifies this patient in unfavorable risk category, irrespective of whether or not she has received prior therapy. It is still somewhat controversial whether therapy-related AML has a prognosis that is intrinsically worse than \textit{de novo} AML, independent of cytogenetics. In a very large database, the National Cancer Research Institute (former MRC) in Great Britain reported a significantly worse outcome for therapy-related AML than \textit{de novo} AML, within each cytogenetic risk group. This was based on an analysis from the MRC's AML 10, 12 and 15 trials\textsuperscript{10,72} (Figure 7). The caveat here is that the impact of prior therapy or organ damage is impossible to reliably ascertain. Furthermore, it is not known whether molecular determinants now recognized to be so crucially important in the prognosis of AML, such as \textit{FLT3-ITD}, \textit{NPM1} and \textit{CEBPA}, are more or less frequent in therapy-related AML and how this may account for differences between \textit{de novo} and therapy-related AML.
The management of patients with therapy-related AML should be guided by the cytogenetic and molecular features. Although there is a perception that any patient with therapy-related AML should be considered at high risk and referred to an allogeneic transplant, there is no evidence that the long-term outcome for patients who present with a favorable karyotype, with no adverse molecular features is different than in patients with *de novo* AML. Thus, such patients should not be referred to an allogeneic transplant in CR1.

**Patient 6.**

A 48-year old man presents with relapsed AML. He receives induction therapy and chemotherapy consolidation with high-dose cytarabine. Fifteen months after achieving CR1, his CBC was normal apart from a platelet count of 92,000/µL, but his bone marrow has 18% blasts. The patient has an HLA-matched sibling. **Should this patient undergo an immediate allogeneic transplant without an attempt at reinduction? If induction is used, what are the best drugs?**

Several authors have attempted to define the prognosis of relapsed AML patients. Irrespective, the only cure for an adult with relapsed AML is a transplant and it is clear that this patient will be referred for an allogeneic transplant from his HLA-compatible sibling. However, this patient raises three important questions. The first is whether this patient should receive a transplant in untreated relapse rather than undergo reinduction therapy? Although a

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*This patient should be treated with standard induction therapy.*

*Post-remission therapy should be guided by cytogenetic and molecular determinants. Patients with favorable cytogenetics and no adverse molecular features should not undergo an allogeneic transplantation in CR1.*

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transplant can be performed safely in early relapse with an outcome that is probably not significantly inferior to performing this in CR2\textsuperscript{76,77}, in this particular patient, given the long duration of CR1, there is a greater than 50% chance of achieving CR2\textsuperscript{78-81}. As it is always preferable to undergo a transplant while in CR2, our own choice in this patient would be to attempt reinduction prior to transplant. If, on the other hand, the duration of CR1 would be less than 6 months, where the likelihood of achieving CR2 is no greater than 20\%\textsuperscript{74,78,79,82}, the equation will change such that, given the immediate availability of an HLA-compatible sibling, we would elect to proceed to an allogeneic transplant in untreated first relapse. The issue becomes more complex for older individuals, aged >60-65 years, in whom RIC conditioning is the preferred option for an allogeneic transplant. There are absolutely no prospective data or established guidelines in such a scenario and clinical practice varies enormously. Despite some hesitation, given the low likelihood of a cure when transplanting a patient with 18% blasts with RIC conditioning, our own preference in this case would be to administer one cycle of induction therapy in an attempt to obtain a better control of the disease prior to transplant.

The second issue relates to the choice of regimen to use for reinduction. There is no evidence that any given regimen is superior and much of standard practice is guided by unsubstantiated opinion. While in theory the use of a non-cross-resistant agent has intuitive appeal, there is no evidence that the efficacy of high-dose cytarabine as a salvage regimen is lessened by the prior use of this agent in consolidation, particularly after a long CR1\textsuperscript{83}. Furthermore, although commonly used with or without anthracyclines, etoposide, mitoxantrone, fludarabine, amsacrine, or asparaginase, there is no information collected prospectively to indicate that this is more efficacious than high-dose cytarabine alone\textsuperscript{83-87}. Somewhat lower doses of cytarabine may be equally effective\textsuperscript{88}. Regimens that do not include cytarabine are equally effective for relapsed patients and the use of mitoxantrone with etoposide is a well tolerated regimen with published data that are at least as good as cytarabine used alone or in combination\textsuperscript{79,89}. 
Our preference is to use mitoxantrone with etoposide. With this regimen, close to 60% of patients with a long CR1 can expect to achieve CR2, although similar results can be achieved with cytarabine-containing regimens.

The third issue is, once the patient has achieved CR2, should consolidation be administered prior to transplantation. For a patient in CR2 some investigators would add consolidation prior to an allogeneic transplant if the patient is medically fit, even if this is not the practice in CR1. Our own practice would be, also in CR2, to proceed directly to transplant, with the primary consideration being to reduce transplant-related toxicity.

<table>
<thead>
<tr>
<th>Boxed Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>This patient should be reinduced with mitoxantrone and etoposide. After achievement of CR2 this patient should be referred for an allogeneic transplant without any additional consolidation. If a sibling were not available, an alternative donor transplant in CR2 is recommended.</td>
</tr>
</tbody>
</table>

**CONCLUSION**

New insights into the pathogenesis of AML have demonstrated that we are treating patients with ever-increasing disease heterogeneity with different clinical manifestations, genetic abnormalities and outcome with current therapies. New treatment strategies generate genuine excitement about the future. The care of patients with AML has become increasingly complicated, but remains remarkably gratifying.
Author Contribution Statement:

Jacob M. Rowe, MD – wrote the paper

Martin S. Tallman, MD – wrote the paper

The authors have no conflict of interest to disclose.
References


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40. Cassileth PA, Lee SJ, Litzow MR, et al. Intensified induction chemotherapy in adult acute myeloid leukemia followed by high-dose chemotherapy and autologous peripheral blood stem cell


57. Walter RB, Kantarjian HM, Huang X, et al. Effect of complete remission and responses less than complete remission on survival in acute myeloid leukemia: a combined Eastern Cooperative


Table 1. Suggested indications for allo-HSCT among young adults with AML in first complete remission

<table>
<thead>
<tr>
<th>Cytogenetic Risk Factors</th>
<th>HLA-matched sibling</th>
<th>MUD / haplo / cord</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favorable, all except</strong></td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td><em>c-KIT</em></td>
<td>YES</td>
<td>Possible</td>
</tr>
<tr>
<td><strong>Intermediate, all except</strong></td>
<td>YES</td>
<td>Possible</td>
</tr>
<tr>
<td><em>NPM</em>⁺/ <em>FLT3</em>-ITD⁻</td>
<td>Possible</td>
<td>NO</td>
</tr>
<tr>
<td>biallelic <em>CEBPA</em>⁺/ <em>FLT3</em>-ITD⁻</td>
<td>Possible</td>
<td>NO</td>
</tr>
<tr>
<td><em>FLT3</em>-ITD⁺</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td><strong>Unfavorable</strong></td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Adapted from Rowe JM, Hematology 2009³⁶
Table 2: Results of Induction Therapy in Adults < 60 years with AML – by Cytogenetics

<table>
<thead>
<tr>
<th></th>
<th>Favorable</th>
<th>Intermediate</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
<td>CR</td>
<td>N</td>
</tr>
<tr>
<td>MRC, 1998</td>
<td>90%</td>
<td>84%</td>
<td>130</td>
</tr>
<tr>
<td>ECOG / SWOG, 1998</td>
<td>84%</td>
<td>76%</td>
<td>184</td>
</tr>
<tr>
<td>GOELAMS, 1997</td>
<td>87%</td>
<td>76%</td>
<td>36</td>
</tr>
</tbody>
</table>

Adapted from Appelbaum FR et al, Hematology 2001
Figure legends:

Figure 1. Overall survival from diagnosis for younger adults with AML.

Recent publications/presentations from four cooperative oncology groups.

A. CALGB 9222
Reproduced with permission from Moore, JO. et al. Blood 2005

B. ECOG 1900

C. German AML Cooperative Group
Reproduced with permission from Buchner T, et al, J Clin Oncol, 2009

D. SWOG 0106

Figure 2. AML: Intensifying induction therapy: Overall survival from diagnosis.

Randomized study conducted by ECOG in adults < 60 years comparing daunorubicin (DnR) 45 vs 90 mg/m² for 3 days, both with cytarabine 100 mg/m² for 7 days.

A. All patients on study

B. Patients with favorable and intermediate cytogenetics.


C. Similar randomized study conducted by HOVON/SAKK in older adults > 60 years.

Reproduced with permission from Lowenberg B et al, N Engl J Med, 2009
Figure 3. AML: Survival from relapse – by age. Data based on 2441 patients entered on 8 consecutive ECOG studies\textsuperscript{22}

Reproduced with permission from Rowe JM et al, ASH 2005\textsuperscript{22}

Figure 4. Long-term survival from diagnosis for AML patients with t(8;21)

Adapted with permission from Appelbaum FR et al, Br J Haematol, 2006 \textsuperscript{45}

Figure 5. Overall Survival from Post Remission Randomization: AML >55 years.

Randomization after induction and 1 cycle of intensification to 3 cycles of consolidation(long) versus observation (short)

Adapted with permission from Goldstone AH et al, Blood 2001\textsuperscript{59}

Figure 6. AML in Older Adults >60 years. Long-term survival for patients with unfavorable cytogenetics.

Patients received induction and consolidation therapy on trial and were randomized to receive either TAD-HAM or HAM-HAM with results that were superimposable.

Reproduced with permission from Büchner T et al, J Clin Oncol, 2006\textsuperscript{62}

Figure 7. AML < 60 years. Survival, by karyotype, of de novo and therapy-related (t-AML) AML. MRC/NCRI AML Trials: Overall Survival.

Adapted with permission from Grimwade, D. et al. Hematology 2009 \textsuperscript{10}
Fig. 1

Overall survival – AML < 60 years

A
CALGB 9222
n = 473

B
ECOG 1900
n = 657

C
German AML Cooperative Group
[TAD-HAM]
n = 356

D
SWOG 0106
n = 598
Fig 2

A. Overall Survival (%)

- All patients
- DNR 90 n=327
- DNR 45 n=330

p = .003

Months

B. Overall Survival (%)

- Favorable & Intermediate Cytogenetics
- DNR 90 n=178
- DNR 45 n=180

p = .004

Months

C. Overall Survival (%)

- All patients
- DNR 90 n=402
- DNR 45 n=411

p = .16

Months
Fig 3.

- Young AML (≤ 55 years)
- Older AML (> 55 years)

n=570 5 yr survival - 11%
n=171 5 yr survival - 6%
Fig 4

![Graph showing percent over years with n = 174 at the end.]
Fig 5
Fig 6

Overall survival (%)

Years

n = 253
How I treat acute myeloid leukemia

Jacob M. Rowe and Martin S. Tallman