Cytotoxic therapy in acute myeloid leukemia: not quite dead yet

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Given the recent approvals of new agents for acute myeloid leukemia (AML), a clinical trial pipeline stocked with novel therapies, and the rapid integration of imaginative approaches in diseases like acute lymphocytic leukemia and chronic lymphocytic leukemia, it is reasonable to ask whether treatment of AML might finally depart from the classical cytotoxic induction therapy that has been employed since the 1970s. However, for better or worse, in 2018, cytotoxic induction regimens remain the standard of care for most patients. Indeed, the future likely lies in combinations of therapies that act with a spectrum of mechanisms. Using a case-based format, this review will outline current treatment expectations for patients according to karyotypic risk and familiarize readers with the basis for common induction choices. Relapsed/refractory disease may be especially amenable to interventions with novel agents or clinical trials; however, there are still some patients who most benefit from intensive chemotherapy. This review will outline risk systems that help the practitioner identify those with the best chances for response and survival. Finally, clinical tools, including geriatric assessments and comorbidity calculators, may help clinicians recognize patients for whom disease risk and comorbidity tip the balance against classical chemotherapy, a frequent challenge for those who treat this devastating disease.

Learning Objectives

- Learn the appropriate options for induction therapy in patients with acute myeloid leukemia
- Review risk stratification systems that can help predict response and overall survival after salvage regimens
- Understand that both geriatric assessments and calculators of treatment-related mortality should be employed when choosing therapy in patients who are physiologically vulnerable or who have adverse-risk disease features
- Understand that progress in AML will likely occur not by dichotomizing patients into intensive or less intensive modes of care, but rather by developing panels of treatments that work rationally and take advantage of layered mechanistic effects

Introduction

A fundamental shift is under way in the treatment of malignant blood diseases. Acute promyelocytic leukemia can be cured without the use of anthracyclines. Soon, classical cytotoxic chemotherapy may not be a routine component of therapy for chronic lymphocytic leukemia, multiple myeloma, or perhaps even some cases of acute lymphocytic leukemia. In the last 2 years, at least 5 new treatments for acute myeloid leukemia (AML) have become more widely available: CPX-351, a liposomal form of daunorubicin and cytarabine; midostaurin, a multikinase inhibitor with potency against AML with mutations in the FMS-like tyrosine kinase 3 (FLT3) gene; gemtuzumab ozagomicin (GO), the humanized monoclonal antibody-drug conjugate; and enasidenib and ivosidenib, oral inhibitors of isocitrate dehydrogenase-2 (IDH2) and IDH1, respectively. At the time of this writing, bubbling up through clinical trial pipelines are inhibitors of the BCL2 and MDM2 pathways, hedgehog inhibitors, second-generation hypomethylating agents, highly potent and selective FLT3 inhibitors, and bispecific T-cell engaging (BITE) antibodies targeting antigens like CD123.[1] Early hints of efficacy from these agents, coupled with remarkable progress in acute promyelocytic leukemia, chronic lymphocytic leukemia, and multiple myeloma, have led some to pose to the optimistic question: does cytotoxic therapy still have a place in the management of AML?

Addressing such a question requires reviewing several key aspects of AML treatment:

1. What are the appropriate expectations for response and survival that are associated with cytotoxic therapy in the upfront setting?
2. Which patients with relapsed/refractory disease benefit from traditional reinduction regimens?
3. When is it appropriate to withhold cytotoxic therapy in favor of novel or experimental therapies?

This review will provide a critical appraisal of these questions, using case examples to outline the role for traditional induction regimens in patients with both newly diagnosed and relapsed/refractory disease. The review will conclude with recommendations on identifying patients for whom the benefits of such therapies may outweigh the risks.

A few caveats should be noted first. It is a fallacy to draw too bright a line between targeted agents and cytotoxic therapy. Classical cytotoxic therapies are targeted. Early chemotherapeutic agents were

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Off-label drug use: Off-label drug use will be indicated in text.

initially employed because of their ability to select and impair rapidly dividing cells rather than the relatively quiescent normal cells of the host organism.[2] This explains their efficacy. Secondly, many agents are too complex to dichotomize their mechanism as either targeted or not. For example, GO conjugates a highly toxic antitumor antibiotic to cells expressing CD33. Finally, synergism of agents, like midostaurin combined with an anthracycline and antimetabolite, may provide benefit when we consider the heterogeneous and chaotic stem-cell landscape of AML.

This review will recommend therapeutic choices based on results from large, generally well-conducted clinical trials. However, these trials have implicit selection bias.[3,4] As is well known to this audience, far too many patients are not enrolled in clinical trials, for a myriad of reasons. Selection bias not only limits generalizability of the results, but also means that the results likely overestimate success, such as it is.[3,5] Complete remission rates and long-term survival estimates from studies likely represent best-case scenarios. One needs to regularly remind oneself that population-based survival data serve as a closer version of the truth of the impact of this disease.

Finally, in trying to ascertain whether a patient's disease will respond to therapy, we often turn to prediction models, statistical constructs that use historical results, including patient data, to forecast outcomes. Several of these have been published, and these may be useful when appropriately contextualized during a patient discussion. There is a tendency to believe that if we can completely characterize a patient's disease and clinical variables, we can accurately predict therapeutic resistance, event-free survival (EFS), and overall survival (OS). This is hubris. However, there are a number of sources of uncertainty in trial data.[6] Even models that take into account multiple patient- and disease-based variables fail to predict the future of a given patient ~20% to 25% of the time.[7-9]

Most of us make induction decisions with incomplete data. However, when a patient presents, urgent examination of the peripheral smear, along with fluorescence in situ hybridization (FISH) testing for common translocations or deletions, flow cytometry, and bone marrow aspirate and/or biopsy, should confirm the diagnosis and permit classification of the patient into a favorable-risk or adverse-risk karyotype. Typically, results of FLT3 mutation status should be available within 4 to 7 days. Testing for mutations in IDH1 and IDH2 should provide results in a similar timespan. The discussion here aims to reflect the realities of clinical practice, where decisions on medications and doses need to be made before completion of a full molecular panel and complete risk stratification.

Expectations for cytotoxic therapy in newly diagnosed disease

Favorable-risk karyotype

> A 59-year-old otherwise healthy man presents with a sore throat, mild cervical and posterior jugular lymphadenopathy, flu-like symptoms, and fatigue. Manual review of a complete blood count and differential demonstrates AML with leukocytosis, anemia, and thrombocytopenia. FISH performed on peripheral blood the day after diagnosis demonstrates inv(16)(p13q22). Bone marrow biopsy is performed, and a limited, AML-specific panel of molecular studies are sent off and pending at the time that induction is initiated.

AML with inv(16), as is present in this patient, is considered favorable risk by both the US and European risk-stratification systems (Table 1).[10-12] Favorable-risk disease is more common in younger patients and is defined as such because of sensitivity to traditional chemotherapeutic approaches and likelihood of a sustained remission after administration of induction and consolidation. CBF AML is cytogenetically identified by the presence of t(8;21)(q22;q22), which creates the *RUNX1/RUNX1T1* (AML1-ETO) gene, or inv(16)(p13q22) or t(16;16)(p13;q22), which results in the *CBFB/MYH11* fusion gene. Each disrupts the CBF complex, a master regulator of definitive hematopoiesis. The t(8;21) and inv(16) subtypes of AML are usually grouped and reported together in clinical studies. Although they may represent distinct biologic and clinical entities, they are both categorized as favorable cytogenetic risk.[13] Notably, a number of molecular mutations have been identified as frequent secondary mutations in CBF AML. Indeed, secondary chromosomal alterations are found in almost 90% of AMLs with t(8;21) and >90% of AMLs with inv(16).[14-17] From a prognostic standpoint, the most important of these may be mutations in c-KIT, because several retrospective studies have linked the presence of *KIT* mutations to adverse outcome, although this seems to be abrogated by elimination of minimal residual disease.[11]

Even practitioners advocating for moving away from cytotoxic therapy in AML are not ready to embrace such a strategy in patients with favorable-risk disease.[18] In patients treated in clinical trials, complete remission rates of up to 80% to 90% and long-term survival of 60% to 65% have been reported.[19] As discussed, study results likely overestimate benefit. Population-based data would estimate a 5-year OS for patients between the ages of 18 and 60 years to be ~40%,[4] although most population-based data are not specific enough to report cytogenetic findings.

GO

Since late 2017, we have used GO in the induction regimens of patients with CBF leukemia based on the preponderance of data that supports an OS benefit in this subset of patients (Figure 1). This drug, a monoclonal antibody that deposits calicheamicin into cells that express the CD33 cell-surface receptor, was originally available in May 2000 as monotherapy for advanced disease but was voluntarily withdrawn from the US market in 2010. Although gemtuzumab has been consistently available to European practitioners, the drug was only reapproved by the US Food and Drug Administration (FDA) in 2017 for treatment of adults with newly diagnosed AML whose tumors express the CD33 antigen.[20] For more than a decade, there has been significant interest in how to optimize the agent, and several large trials[21-25] refined dosing to minimize toxicity and verified benefit in patients with good-risk and intermediate-risk disease. Among these was the ALFA-0701 trial, which administered GO in a fractionated dose of 3 mg/m^2 alongside 7 + 3 induction therapy (daunorubicin 60 mg/m^2 and continuous IV cytarabine 200 mg/m^2 for 7 days) to patients between the ages of 50 and 70 years.[24] These patients were all newly diagnosed and did not have evidence of a prior hematologic disorder. GO improved EFS from 9.5 to 17.3 months.

The Medical Research Group also examined this drug in a large study of younger patients, where a single 3-mg/m^2 dose of GO was added to the first induction cycle (in patients randomized to receive daunorubicin/cytarabine, daunorubicin/cytarabine/etoposide, or fludarabine/cytarabine/idarubicin/granulocyte colony-stimulating factor).[21] They reported improved survival for patients with favorable cytogenetics who received GO and showed a trend for benefit in intermediate-risk patients in a predefined analysis. In the SWOG

Table 1. Prognostic risk systems in AML

Risk Status	2017 ELN Criteria[11]	NCCN Guidelines Version 1.2018[10]	
	Genetic abnormality	Cytogenetics	Molecular Abnormalities
Favorable-risk	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low} Biallelic mutated CEBPA	Core binding factor: inv (16) or t(16;16) or t(8;21) t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or presence of FLT3-ITD^{low} or isolated biallelic (double) CEBPA mutation
Intermediate-risk	Mutated NPM1 and FLT3-ITD^{high} Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low} (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse	Normal cytogenetics t(9;11) Other non-defined	Core binding factor with KIT mutation Mutated NPM1 and FLT3-ITD^{high} Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low} (without poor risk genetic lesions)
Adverse-risk	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* −5 or del(5q); −7; −17/abn(17p) Complex karyotype, monosomal karyotype Wild-type NPM1 and FLT3-ITD^{high} Mutated RUNX1 Mutated ASXL1 Mutated TP53	Complex (>2 clonal chromosomal abnormalities) Monosomal karytotype -5, 5q-, -7, 7q- 11q23- non t(9;11) Inv (3), t(3;3) t(6;9) t(9;22)	Normal cytogenetics: With FLT3-ITD mutation TP53 mutation Mutated RUNX1 Mutated ASXL1 Wild-type NPM1 and FLT3-ITD^{high}

Full annotation of these criteria is available in the original source documents. These annotations provide important caveats for the molecular and cytogenetics listed here., The original sources should be consulted for clinical practice.
CBF, core binding factor; ELN, European LeukemiaNet; ITD, internal tandem duplication; NCCN, National Comprehensive Cancer Network.

S0106 study,[22] analysis of the outcomes by pretreatment cytogenetics identified a significant benefit for favorable-risk patients who received GO. Attempting to integrate and interpret these trials, a meta-analysis using patient-level data was performed and published in 2014.[26] This analysis demonstrated that the addition of GO to induction therapy reduced the risk of relapse (odds ratio, 0.81; 95% confidence interval, 0.73-0.90; $P = .0001$) and improved OS at 5 years (odds ratio, 0.90; 95% confidence interval, 0.82-0.98; $P = .01$). Although this benefit was seen most strikingly in patients with favorable-risk cytogenetics, those with intermediate-risk disease also benefited.

For the entire population of GO-treated patients in the ALFA-0701 study, the complete response (CR)/pathologic CR rate was 81%, with an estimated 2-year EFS of 40.8% and 2-year OS of 53.2%. In the meta-analysis of patients with favorable-risk cytogenetics treated in the study with a GO-containing regimen, the CR/pathologic CR rate was 91%, with an EFS at 2 years of 47.1% and 2-year OS of 64.5%. In inducing this patient according to the ALFA-0701 study, one needs to remember that prolonged cytopenias and liver toxicity are occasionally of concern. I discuss with patients that the induction death rate is generally 5% to 10%. Given favorable-risk cytogenetics, transplantation would not typically be considered in first CR (CR1).

Intermediate-risk karyotype

> A 41-year-old teacher with a history of obesity and hypertension presents with anemia, thrombocytopenia, and leukocytosis. Her white blood cell count (WBC) is measured at 13×10^9/L, and there are 67% circulating myeloid blasts. She is clinically stable and is started on hydroxyurea, allopurinol, and fluids. A bone marrow biopsy is performed, and FISH studies demonstrate no evidence of favorable- or adverse-risk translocations or deletions. AML with maturation is diagnosed. Her peripheral blood is sent off for molecular studies. On day 4, testing results show no FLT3-ITD or –tyrosine kinase domain (TKD) mutations.

Patients treated with 7 + 3 should receive at least 60 mg/m^2 of daunorubicin or equivalent. In this situation, we would induce according to the intensive arm of the phase 3 E1900 study from the Eastern Cooperative Oncology Group and American College of Radiology Imaging Network Cancer Research Group, which administered 90 mg/m^2 of daunorubicin for 3 days and 7 days of continuous infusion IV cytarabine at a dose of 100 mg/m^2.[27,28] In this trial, patients between 18 and 60 years of age were randomized to this higher daunorubicin dose (n = 327) or 45 mg/m^2 daily for 3 days (n = 330). Data from this study demonstrated a significant increase in CR rate (71% vs 57%; $P < 001$) and median OS (24 vs 16 months; $P = .003$) for the dose-intense arm. Importantly, there were no significant differences in the rates of grade 3 to 5 toxicities, including cardiac effects, and the death rates during induction therapy were similar. In the initial analysis of the E1900 study, benefit of the high-dose arm seemed to be restricted to patients age <50 years or those with mutant DNMT3 or NPM1 or MLL translocations. The most recent update,[28] after a median of 80 months of follow-up among survivors, supports that 90 mg/m^2 of daunorubicin is superior to 45mg/m^2 in nearly all subgroups of patients, including those between the ages of 50 and 60 years with FLT3-ITD or NPM1 mutations. Of note, the landmark study by the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology, German AML Study Group (AMLSG), and Swiss Group for Clinical Cancer Research Collaborative Group also tested 90 mg/m^2 of daunorubicin (although with a different second course), but eligible patients were age >60 years.[29] Daunorubicin at a dose of 45 mg/m^2 should not be relied upon for induction outside of a clinical trial.[10,29,30]

Anthracycline dose and intensity

Notably, there has not been a definitive determination that 90mg/m^2 of daunorubicin is superior to 60 mg/m^2 when used in a single-induction strategy, nor is there proof that 90 mg/m^2 is more toxic. Comparison among studies is challenging because of differences in design, control arms, consolidation therapy, and parameters guiding reinduction. For example, the design of the UK National Cancer Research Institute AML17 trial randomized patients to either 90 or 60 mg/m^2 on days 1, 3, and 5 for their first cycle of induction and required that all favorable- and intermediate-risk patients receive

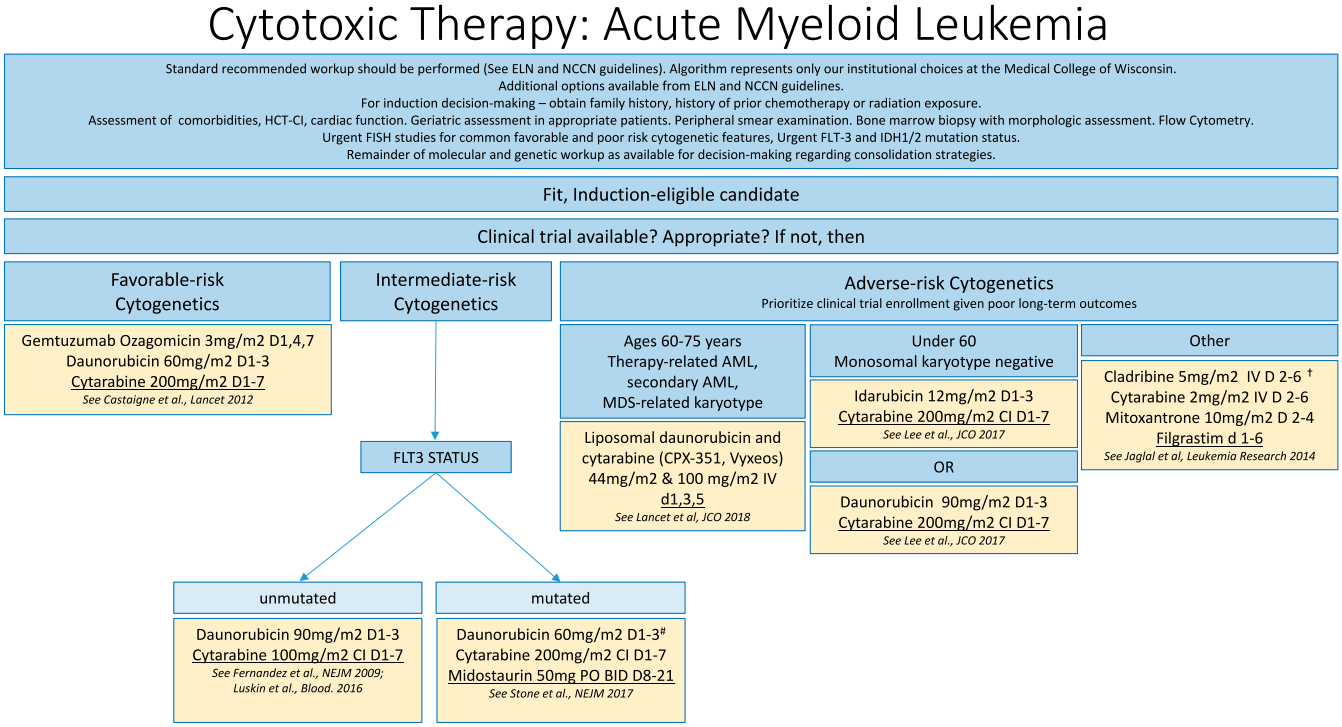

Figure 1. Cytotoxic therapy for AML. *Backbone dosing comments provided in article text. †No prospective data on this regimen in newly diagnosed patients; patients enrolled in institutional prospective trial of this regimen based on retrospective data. HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index; MDS, myelodysplastic syndrome.

a second induction cycle of 50 mg/m^2 of daunorubicin on days 1, 3, and 5.[31] Given no difference in CR rates or 2-year OS (although a later 28-month follow-up demonstrated that the high-dose arm benefited patients with an FLT-ITD mutation[32]), it might be tempting to conclude that all patients can be treated with the lower dose. However, the design actually tested 420 vs 330 mg/m^2 of anthracycline, and this should be taken into account when recognizing that toxicity was increased in the higher-dose arm, and there was a subsequent abrogation of benefit.

Cytarabine dose intensification

One question that has been raised multiple times is whether to intensify the cytarabine dose during induction. The preponderance of evidence is that increasing the dose of cytarabine does not benefit patients.[33] Although the full results have not been published, data were presented in late 2016 from the SWOG S1203 study. In this trial, newly diagnosed patients age ≤60 years received idarubicin (12 mg/m^2 daily for 3 days) administered with 24-hour continuous infusion of cytarabine at a dose of 1.5 mg/m^2 daily for 4 days (with and without vorinostat, a histone deacetylase inhibitor). The control arm was traditional 7 + 3 with daunorubicin at 90 mg/m^2 and cytarabine at 100 mg/m^2. Data showed no improvement in CR, EFS, relapse-free survival, or OS rate with higher levels of cytarabine with induction. In fact, favorable-risk patients had improved outcome if they were randomized to the control arm, perhaps because they were consolidated with 4 cycles of high-dose cytarabine rather than an attenuated redosing of the induction regimen.

Adding a nucleoside analog

What about the addition of a purine analog? Two large, relatively recent studies are worthy of analysis.[34] Investigators from the Polish Acute Leukemia Group study have long been interested in the use of cladribine for relapsed/refractory disease.[34] In a study of newly diagnosed patients, they randomized 652 patients age ≤60 years to receive daunorubicin (60 mg/m^2 on days 1-3) and cytarabine (200 mg/m^2 continuous infusion on days 1-7) alone or in combination with either cladribine or fludarabine administered on days 1 to 5. Cladribine, but not fludarabine, was associated with improved survival vs the control arm. In fact, the addition of this agent did seem to benefit patients with poor-risk cytogenetics or patients age ≥50 years.

There are 2 aspects of this study that have impeded universal adoption: the control arm outcomes were disappointing (reporting just a 56% CR rate and 33% 3-year OS rate), and the method of assessing disease response was not in keeping with common practice, at least not in the United States, because patients did not have early bone marrow aspirates (midinduction) performed and were therefore not eligible for accelerated reinduction options. Although this is an induction option based on consensus from the National Comprehensive Cancer Network guidelines,[10] it is not one we routinely use in patients with intermediate-risk cytogenetics. A single-arm, phase 1/2 study of a cladribine-based regimen in newly diagnosed patients was published earlier this year and provides additional provocative support for research into cladribine for this disease.[35]

Clofarabine, a purine nucleoside antimetabolite, gained traction as an AML drug based on data showing that monotherapy demonstrated substantial response rates in relapsing or refractory patients, as well as in newly diagnosed patients of older age who were considered unsuitable for intensive chemotherapy. Hoping to prove this could be an efficacious and safe option for older patients, the Eastern Cooperative Oncology Group and American College of Radiology Imaging Network Cancer Research Group led an intergroup study, E2906, that compared this agent with daunorubicin at 60 mg/m^2 in

the typical 7 + 3 regimen in patients age >60 years.[36] This study was terminated early for lack of efficacy in the investigational arm. The HOVON-102 study, published in 2017, also sought to capitalize on the efficacy of clofarabine.[37] In this trial of double-induction therapy, 795 newly diagnosed patients between 18 and 65 years of age were randomized to receive clofarabine in addition to idarubicin and cytarabine. They then underwent a second cycle of induction using amsacrine and cytarabine, again with or without clofarabine. CR rates (89%) did not differ but were attained faster with clofarabine (66% vs 75% after cycle 1). However, the addition of clofarabine increased toxicities and delayed hematologic recovery. At a median follow-up of 36 months, OS and EFS were equivalent. There was a markedly reduced relapse rate (44% ± 3% vs 35% ± 3%) in favor of clofarabine but also an increased probability of death in remission (15% ± 2% vs 22% ± 3%). Notably, a post hoc subgroup analysis found that in the 31% of patients classified as intermediate 1 by the ELN 2010 criteria, there was a benefit to the addition of the third agent; particularly for patients with a normal karyotype and neither the NPM1 nor the FLT3-ITD mutation present in their malignant clone. This subgroup had a CR rate of 88% to 90%, with a 4-year OS of 50%. This regimen has limited applicability in the United States because of the double-induction strategy and because amsacrine is not commercially available. Nevertheless, where available, it would be an option for relatively robust patients who meet the designation of intermediate 1 by the ELN 2010 criteria.[38]

FLT3$^+$ disease

> A 33-year-old teacher presents to urgent care with a worsening cough and shortness of breath. She has tachycardia, tachypnea, and ecchymosis of the extremities. She has a leukocytosis with a WBC of 130 × 10^9/L, with 88% circulating blasts. She is stabilized and undergoes emergent cytoreduction. On the peripheral blood, karyotyping shows t(6;11)(q27;q23) present in 19 of 20 metaphase cells. FLT3-ITD mutation is identified, with a ratio of mutant/wild-type alleles of 0.8 (high allelic ratio).

Approximately 30% of the time, mutations in the FLT3 gene are present in patients with newly diagnosed AML. This occurs either by ITDs of the juxtamembrane domain or via a point mutation in the TKD. The ITD mutations carry a poor prognosis and have prompted the evaluation of tyrosine kinase inhibitors in this AML subset. In late 2016, results from the Cancer and Leukemia Group B 10603 trial (RATIFY) were announced and led to approval of midostaurin, a multitargeted inhibitor with activity against FLT3-TKD and -ITD mutations. Early-phase studies showed only minimal single-agent activity. However, in RATIFY, the drug was combined with intensive induction[39,40]; 360 of 717 patients between the ages of 18 and 59 years were randomized to receive, in addition to 60 mg/m^2 of daunorubicin and 200 mg/m^2 of cytarabine, midostaurin at 50 mg orally twice daily from days 8 through 21. The investigative arm demonstrated a statistically significant 22% decrease in the risk of death.

Several notable points emerge from this data. On the basis of the early separation and later plateau of the survival curves, the advantage from midostaurin seems to accrue to patients early on in treatment (ie, because it intensifies induction as a result of FLT3 inhibition or because of its relatively promiscuous kinase profile). This time-dependent impact is in keeping with the drug pharmacokinetics[41]; early research showed that the plasma levels are highest during the first few weeks of treatment. This is also an example of where a so-called targeted agent works better when combined with cytotoxics and speaks to the need to layer mechanisms rather than depend on single-pronged approaches.[42] Interestingly, the European Medicines Agency approved midostaurin for both induction and maintenance, whereas the FDA limited approval to the early phases of treatment. In late 2017, at the American Society of Hematology meeting, study authors presented results of the maintenance component of the trial, concluding that, although safe, there was no significant difference in disease-free survival.[43] Midostaurin need not be included in maintenance therapy.

Secondly, a key benefit was likely the ability of the agent to induce deeper remissions for patients who proceeded to transplantation. Although this benefit might have been a result of the addition of the kinase agent, it might well merely have resulted from dose intensity. The control arm incorporated just 60 mg/m^2 of daunorubicin. Would higher doses of daunorubicin have accomplished the same?[31,44] Fit patients with FLT3-ITD and -TKD mutations should be promptly evaluated for allogeneic stem-cell transplantation in CR1. Data from this study would optimistically predict 4-year survival rates of up to 70%. However, we are vigorous in recommending participation in clinical trials posttransplantation that evaluate the use of kinase inhibitors in posttransplantation maintenance, given the historical rates of relapse (this trial was registered at www.clinicaltrials.gov as #NCT02997202).

There is 1 additional note on using midostaurin. Although there has been no systematic assessment of safety when combined with 90 mg/m^2 of daunorubicin and 100 mg/m^2 of cytarabine, not all patients can wait the 3 to 7 days is takes to get FLT3 testing back, and clinicians may need to make a decision on anthracycline dose level before knowing FLT3 results. Combining midostaurin with other variants of the 7 + 3 backbone remains an individual institution decision. I have, when a patient could not wait on treatment, combined it with a higher dose of anthracycline and a lower dose of infusional cytarabine than was used in the published study. I discuss with the patient that I do not have safety data on this combination, a point of discomfort but a clinical reality.

Although regulatory agencies have approved midostaurin without an age limit, providers should be aware that toxicities of tyrosine kinase inhibitors can be problematic, as evidenced by the clinical experience with sorafenib. In a multicenter randomized phase 2 trial, addition of sorafenib to standard induction and postremission chemotherapy reduced the risk of relapse and improved EFS in younger adults despite increased toxicity in the experimental arm.[45] However, in a similar trial in older adults age 61 to 80 years, addition of sorafenib led to higher treatment-related mortality (TRM), lower CR rates, and a lower chance of proceeding to postremission consolidation.[46] Patients age ≥60 years, who would not have met eligibility criteria for the RATIFY study, should have midostaurin added to their induction only with caution and after a full consideration of the risks and possible benefits.

Adverse-risk karyotype

> A 72-year-old woman has had rheumatoid arthritis treated with azathioprine for >8 years. She participates in water aerobics 3 times per week and powerwalks

at her local indoor mall. She has no comorbidities. Workup for pancytopenia demonstrates therapy-related AML. Karyotype shows t(3;3)(q21.3;q26.2), leading to a juxtaposition of the RPN1 gene with the EVI1(MECOM) gene. She has 7 younger siblings, 6 of whom are in good health.

This is an example of a patient for whom the choice of cytotoxic induction chemotherapy is particularly challenging. However, the clinical picture of a relatively fit older patient with adverse-risk disease is among the most frequent encountered by clinicians and likely to become more so as long-term remissions after adjuvant therapy for prior cancers become increasingly common. At the current time, the decision about therapeutic intensity is typically dichotomized around the patient's health status, with less intense agents, often including clinical trials of novel agents, reserved for patients not considered fit for induction by a variety of metrics. The downstream effect of this enrollment and eligibility culture is that fit patients are not included in studies of novel agents unless they include 7 + 3 or its equivalent, and those patients who are considered frail do not receive the benefits, such as they are, of cytotoxic therapy. A full exploration of the extent of this conundrum is beyond the scope of this article, but the reader is referred to reviews on this topic.[47-50]

In a case like this one, the patient's disease biopsy (EVI1 gene aberrations) should prompt serious consideration of clinical trials of novel agents. With traditional chemotherapy, the likelihood of CR as reported by clinical trials is optimistically in the range of 40%[30,51]; long-term disease remission is only in the single digits,[52] and median OS does not usually surpass 12 to 18 months.[48] In older patients with AML, historical rates of CR are between 45% and 65%, but they are worse when age is combined with adverse-risk cytogenetic or molecular features. Outcomes from population-based studies, which are much closer to true, are even dimmer. For example, in a study of individuals from The Netherlands, the relative 1-year survival rates for patients age >70 years were only 15%.[4] The best hope for cure is with allogeneic stem-cell transplantation, and even this is plagued by relapse.[53] A recent review[54] of >1300 patients with a complex karyotype undergoing transplantation between January 2000 and December 2015 demonstrated a 51% relapse rate, which increased in older patients and those with deletion of chromosome 5 or 7, among other features. With a patient like this, I would have a frank discussion about the poor outcomes associated with her disease biology and carefully consider her for any available innovative clinical trials. However, she is fit, and based on current data, her best chance of long-term remission remains allogeneic stem-cell transplantation. Many patients are still eager to try for cure, even with lean odds.[47] Additionally, as mentioned, too many studies of novel or less intense agents require patients to be not suitable for intensive induction based on physical fitness, a narrow-minded approach given the preeminence of disease biology in the response rates of AML.

If considering induction therapy and subsequent allograft consolidation, I would choose treatment with the liposomal form of a fixed molar ratio of daunorubicin and cytarabine, CPX-351. In August 2017, CPX-351 received FDA approval for newly diagnosed therapy-related AML or AML with myelodysplasia-related changes.[55] Approval was based on a phase 3 randomized study,[56] where the control arm was 7 + 3, with daunorubicin at a dose of 60 mg/m^2. Eligibility for the 309 patients, all between ages 60 and 75 years, included therapy-related, secondary, or cytogenetically high-risk AML. The investigational agent resulted in higher remission rates (48% vs 33%) and led to a survival benefit, with a median OS of 9.56 months in the CPX-351 arm and 5.95 months among those who received 7 + 3. Subgroup analyses were interesting, showing no OS difference in those who had been treated previously with hypomethylating agents. The drug seems well tolerated despite a longer period of cytopenias. Improvement in median OS from ~6 months to ~10 months is not a homerun, so we generally use this drug with the intention of proceeding to consolidative transplantation. Of the 156 patients in the control arm, 39 were taken to transplantation, and these individuals had a median OS of ~10 months, with roughly 2 years of follow-up. Of the 153 patients in the investigational arm, 52 proceeded to transplantation, and among these patients, the median OS was not reached. Clearly, follow-up has been short, and this is a small number of patients. However, to many of us, the results underline the importance of the deepest possible remissions when proceeding to stem-cell transplantation, no matter how a patient gets there, especially in a cohort where reduced-intensity conditioning is anticipated.

We were relatively strict at our center in limiting use of CPX-351 to only those patients who met eligibility criteria for the phase 3 trial, rather than those for whom it was granted FDA approval, which was a wider population. In younger patients with poor-risk cytogenetics, we employ 7 + 3 using 1 of the 2 regimens published by researchers from South Korea in August of 2017.[30] This study, although aimed at delineating a difference between 12 mg/m^2 of idarubicin and 90 mg/m^2 of daunorubicin, did not find significant differences between the 2 arms. However, the authors did report respectable results in patients with poor-risk cytogenetics, although not in those with a monosomal karyotype (Table 2). For individuals with a monosomal karyotype, we have written a trial that incorporates cladribine into induction, because of the benefit of the cladribine, cytarabine, filgrastim, and mitoxantrone regimen in patients with relapsed/refractory disease.[57,58] Like all practitioners, we are eager to see novel agents or combinations enter this niche, a space where cytotoxic therapies seem to be particularly limited in efficacy.

Which relapsed/refractory patients benefit from traditional salvage regimens?

A 58-year-old flight attendant with AML achieves CR1 after induction with idarubicin and cytarabine. At diagnosis, his disease demonstrated no karyotypic abnormalities but did show mutation of the NPM1 gene. After achievement of CR, he undergoes 3 cycles of high-dose cytarabine complicated by *Escherichia coli* septic shock after the final cycle. Additional therapy is deferred. He has been in CR1 for 21 months when he presents with circulating blasts, anemia, and thrombocytopenia. Bone marrow biopsy is performed, and karyotype is normal. Mutation panel shows no evidence of NPM1, FLT3-ITD, or IDH1/2.

Once CR is achieved, ~50% of patients age <60 years and up to 90% of patients older than that age will relapse despite consolidation strategies.[59,60] Refractory disease, depending on the definition applied, occurs in 20% to 25% of patients with AML,[61] and failure to respond to intensive treatment is a major unfavorable prognostic

factor.[11] In patients without a transplantation option, cure is not a realistic outcome. Indeed, although we do not have definitive data, posttransplantation outcome is likely optimized by disease control before this procedure, so a majority of patients proceed to reinduction or salvage therapy if they have the fitness and desire to pursue transplantation.[61]

Scoring systems in relapsed/refractory disease

There are several helpful systems to identify which patients with relapsed/refractory disease are likely to achieve CR/CRi; all of them are based on trials of cytotoxic salvage regimens[59,62-64] (Table 3). A meta-analysis based on 667 patients age ≤60 years was among the first to be widely disseminated. This study by Breems et al[62] outlined the European Prognostic Index score and describes a system predicting 1- and 5-year OS for relapsed/refractory disease that can be as good as 70% and 46% or as poor as 16% and 4%, respectively, based on CR1 duration, diagnostic cytogenetics, age at relapse, and whether hematopoietic stem-cell transplantation was performed before relapse. Since that publication, several other studies have corroborated key factors. The Spanish study group (PETHEMA) looked at patients in its trials and published a prognostic score that also included the molecular marker FLT-ITD.[65] Another recent addition to the literature is the finding by Japanese researchers that clonal evolution between diagnosis and relapse independently predicted a significantly lower chance of complete remission.[64]

In 2017, the German-Austrian AML Study Group published a simple scoring system based on a logistic regression model of 1307 patients in 5 clinical trials who relapsed after achieving CR1.[59] The authors were interested in pretreatment characteristics and the type of salvage therapies that were related to optimal outcomes. The result was a scoring system that tallies a total based on CR duration >18 or <18 months, presence or absence of CEBPA biallelic mutation, CBF AML, presence of the FLT-ITD mutation (any allelic level), and adverse cytogenetics. With these metrics, the likelihood of CR/CRi with salvage therapy can be calculated as low (25%), intermediate (36%), or high (54%). The authors concluded that there is a low probability of achieving CR2 with standard intensive salvage therapy in patients with an FLT3-ITD mutation, reinforcing the notion that presence of this mutation at relapse dictates an approach that incorporates a tyrosine kinase inhibitor or a clinical trial. However, the data also support that intensive reinduction therapy followed by allogeneic stem-cell transplantation can be curative in a subset of patients. As mentioned, whether patients with relapsed/refractory disease should be taken directly to transplantation or whether transplantation should be a consolidative therapy after salvage is a critical clinical question in this population that has yet to be definitively answered.

Options for salvage treatment

The choice of cytotoxic regimen in relapsed/refractory disease is often dictated by institutional habit. Data-driven decisions are limited by the absence of large randomized studies. Given that there is no standard of care, enrollment in clinical trials of novel agents is encouraged, although long-term success with these treatments, especially if the goal is to proceed to stem-cell transplantation, is largely unknown.

Regimens are often chosen based on the patient's prior exposures. A robust systemic review of salvage regimens was recently published. In this report, the authors extracted data from 157 source articles on conventional chemotherapy for relapsed/refractory adult AML patients and reported CR rates.[66] They looked at clusters of studies, including those with cytarabine as monotherapy, those that combined an anthracycline and cytarabine or used that combination plus a third agent, those that incorporated a purine analog, and those with other intensive or nonintensive approaches. Of note, this systemic analysis confirmed that salvage was more likely to be effective in patients with late relapse vs those with early relapse or refractory disease. The authors concluded that, although some regimens achieved relatively high CR/CRi rates, there is insufficient understanding of the long-term impact, including duration of CR or posttransplantation survival. They were unable to make uniform recommendations because of the paucity of comparative studies, but they did identify several regimens as having a good balance between likelihood of CR and likelihood of early death. They recommended regimens including: amsacrine plus cytarabine; mitoxantrone, etoposide, and cytarabine; GO, cytarabine, and mitoxantrone; fludarabine, cytarabine, and granulocyte-colony stimulating factor with or without idarubicin; and clofarabine plus cytarabine. For example, the combination of high-dose cytarabine and fludarabine with or without granulocyte-colony stimulating factor leads to CR rates between 30% to 50%.[67,68]

In the patient example, using the German-Austrian AML Study Group scoring system, his duration of complete remission gives him a score of 0.5, putting him in the category of high CR/CRi probability (54%). This score may be helpful in decision making when meeting with the patient and discussing options, including salvage reinduction vs novel agents. If willing and eligible, he should move to allogeneic stem-cell transplantation, which, as mentioned, is the only likely cure available for relapsed AML. At our institution, our standard reinduction regimen is a combination of cladribine, high-dose cytarabine, and mitoxantrone, absent an available clinical trial. However, in patients with a long relapse-free interval like this patient, we would also discuss retreatment with his induction regimen and would use that regimen if there had been no cytogenetic evolution or additional mutations discovered. HLA typing should be completed as soon as possible for allografting in CR2. For patients with $FLT3^+$ disease, especially if it occurs after stem-cell transplantation, we treat with sorafenib, typically in combination with a hypomethylating agent, or in a clinical trial of an investigative tyrosine kinase inhibitor. In a phase 2 study of relapsed/refractory FLT3-ITD–mutated AML, the combination of sorafenib and the hypomethylating agent azacitidine yielded a response rate of 46%.[69] There is a paucity of data on how to manage fit patients with relapsed FLT3-mutated disease; although several early-phase studies exist,[70,71] no large studies including targeted agents in conjunction with classical chemotherapy have been published. For patients with poor-risk cytogenetics, cytogenetic evolution, or high-risk molecular features, we always prefer a clinical trial of a novel agent but will also employ cladribine, cytarabine, filgrastim, and mitoxantrone for fit patients who we are trying to get to transplantation.

Which patients should not receive cytotoxic therapy?

In patients with significant comorbidities, poor performance status, or disease that is not likely to respond to therapy, the physician must make a decision between cytotoxic therapy and less intensive strategies, knowing that age alone does not guide the decision and that, in fact, there are hints in the medical literature that older, medically fit patients may benefit more from cytotoxic therapies than from supportive or nonintensive approaches. The decision about whether to induce with traditional anthracycline and cytarabine–based induction requires a clear assessment of 2 key factors: the patient's

Table 2. Select recent studies of induction for newly diagnosed disease: results by karyotypic risk

Study	Arms						Comments
E1900[27,28] Fernandez et al., NEJM 2009; Luskin et al., Blood. 2016	Daunorubicin 45mg/m2 d1-3 + 100mg/m2 Cytarabine CI d1-7			Daunorubicin 90mg/m2 d1-3 + 100mg/m2 Cytarabine CI d1-7			Ages 17-60 yrs Data after Median F/U: 80.1 mo for survivors 90mg/m2 of daunorubicin vs 45mg/m2 benefits AML patients with favorable and intermediate cytogenetics and with FLT3-ITD, NPM1, and DNMT3A mutations.
	n:330			n:327			
	CR:	4-y OS:		CR:	4-y OS:		
All Patients	59%	31%		71%	39%		
Karyotype							
Favorable Risk	84%	46%		80%	64%		
Intermediate Risk	56%	35%		77%	45%		
Adverse Risk	44%	14%		57%	19%		
PALG Induction Study[35] Holowiecki et al., JCO 2012	Daunorubicin 60mg/m2 d1-3 + 200 mg/m2 Cytarabine (DA)		DA + Cladribine 5 mg/m2 d1-5		DA + Fludarabine 25mg/m2 d1-5		Ages 16-60 yrs Median F/U: 2.8 yrs Disease response assessment inconsistent with US practice DAC arm increased 3-yr OS by 12% vs DA Unfavorable karyotype, patients over 50 and those with high WBC appeared to benefit in cladribine arm.
	N:211		n:222		n:219		
	CR:	3-y OS:	CR:	3-y OS:	CR:	3-y OS:	
All Patients	56%	33%	67.5%	45%	59%	35%	
Karyotype							
Favorable Risk		50%		83%		59%	
Intermediate Risk		36%		44%		34%	
Adverse Risk		20%		36%		37%	
ALFA 0701[24] Castaigne et al., Lancet 2012	Daunorubicin (60 mg/m2 on days 1 to 3) + cytarabine (200 mg/m2)			DA + gemtuzumab ozogamicin (3 mg/m2 d1,4,7)			Ages 50-70 Excluded secondary and treatment-related disease EFS, OS, and RFS were significantly improved in the gemtuzumab ozogamicin group at 2 years in this study.
	N: 139			N: 139			
	CR/CRi	2-y OS		CR/CRi	2-y OS		
All Patients	75%	41.9%		81%	53.2%		
Favorable/Intermediate Risk	82.5%	51.5%		91.5%	64.5%		
Adverse Risk	50%	20.1%		50%	N/A		
HOVON Study Group[38] Lowenberg et al, Blood 2017	Cycle 1 Idarubicin (12mg/m2 d1,2,3) + cytarabine (200 mg/m2) d1-7 Cycle 2 Cytarabine 1000mg/m2 BID d 1-6 + amsacrine 120mg/m2 d 4,5,6			Cycle 1 IC + clofarabine 10mg/m2 d1-5 Cycle 2 CA + clofarabine 10mg/m2 d1-5			Ages 18-65 AML or RAEB 36-month follow up Higher toxicity to clofarabine arm offset any benefit to earlier remission rate and reduction in relapse. No net benefit in survival for the entire patient population. Post-hoc analysis showed improved survival in subset of AML with Intermediate Risk by ELN 2010 criteria
	N=402			N=393			
	CR/CRi	4-y OS		CR/CRi	4-y OS		
All Patients	88%	43%		90%	44%		
ELN 2010 RISK							
Favorable		70%			66%		
Intermediate I		29%			50%		
Intermediate II		54%			44%		
Adverse		15%			16%		
Lee et al. JCO 2017[43]	Idarubicin (12mg/m2 d1,2,3) + cytarabine (200 mg/m2) d1-7 (Control arm)			daunorubicin 90mg/m2 (d1,2,3) + cytarabine (200 mg/m2) d1-7			Ages: 15-65 years Powered for non-inferiority No difference between Idarubicin and Daunorubicin arms with regard to CR, OS. High-dose daunorubicin was more effective than idarubicin for patients with FLT-ITD mutation
	N=149			N=150			
	CR/CRi	4-y OS		CR/CRi	4-yr OS		
All Patients	80.5%	51.1%		74.7%	54.7%		
Cytogenetic Risk Group							
Good	88.9%	85.2		100%	90.7		
Intermediate	84.5%	53.1		75.3%	49		
Poor, monosomal karyotype neg	58.3%	25.0		61.3%	40.8		
Poor, monosomal karyotype pos	44.4%	0		30.0%	24.0		

CI, continuous infusion; iCR, immunophenotypic CR; N/A, Not applicable; RAEB, refractory anemia with excess blasts; RFS, relapse-free survival.

tolerance for therapy and the likelihood that the disease will respond.[72,73] Research has demonstrated a steep decline in the use of intensive therapy after the age of 65 years.[74,75] There are few randomized trials comparing more intensive therapy with less intensive therapy. Epidemiologic studies support the use of some form of chemotherapy (vs palliative or supportive therapy alone) in most AML patients up to age 80 years, although these are of course subject to selection bias.[76-78] Similarly, an analysis of >1000 adults treated at 5 US institutions showed that intensive therapy was associated with a better long-term survival in older patients, including patients considered at higher risk for treatment complications and failure based on age, comorbidities, and cytogenetics.[79] In addition, we know that over the last decades, TRM in intensive clinical trials is generally decreasing.[80]

To date, the most commonly used less intensive therapies are the hypomethylating agents. The hope has been that, in the frail patient, treatment with either azacitadine or decitabine might strike a balance between efficacy and intensity. In 1 of the largest prospective studies of hypomethylating agents to date, >480 patients age >65 years with newly diagnosed AML, preserved performance status, and either poor- or intermediate-risk cytogenetics were randomized to receive either decitabine at 20 mg/m^2 for 5 days every 4 weeks or an option between supportive care or subcutaneous cytarabine for 10 days every month. Median OS for the decitabine and treatment choice arms were 7.7 and 5.0 months, respectively, a difference that did not, in the overall population, meet clinical significance. In the AZA-001 trial,[81] physicians were instructed to decide a priori if randomized to a control arm whether their patient would receive: best supportive care, low-dose cytarabine, or intensive chemotherapy; all of these were considered conventional care regimens. Patients were then randomized to either a conventional care regimen or azacitadine therapy. Fewer than 20% of patients in the conventional care regimen arm were enrolled in intensive chemotherapy, so one can infer that the overall frailty of the enrolled population was high. As in previous attempts to study this population, physicians seemed to be hesitant to randomize any patient who was a true candidate for cytotoxic therapy to a less intensive therapy. The 87 patients who were preselected for intensive chemotherapy had improved outcomes compared with those preselected for best supportive care or low-dose cytarabine, as one might expect. In this group, patients had a similar median OS of 13.3 months in the azacitadine arm and 12.2 months in the intensive chemotherapy arm, although the CR plus CRi rate was just 27.8% in the azacitadine arm and 47.7% in the intensive chemotherapy arm. Of note, patients were not enrolled if they could be considered for stem-cell transplantation, which means that 1 of the key consolidation therapies was not available for participants. In fact, for 70% of the patients in the study, this was the last and only therapy they received for their AML.

We can conclude that there is insufficient prospective data on which patients benefit from receiving hypomethylating agents rather than

Table 3. Select systems for assessing likelihood of CR/CRi or OS with salvage therapy

Study	Variables	Score	Interpretation
Schlenk et al. Leukemia 2017[60]	CR duration >18 months	+0.5	Score <0, low CR/CRi probability: 25% Score=0, intermediate CR/CRi probability: 36% Score>0, high CR/CRi probability: 54%
	Biallelic CEBPA mutation	+1	
	CBF-AML	+1	
	FLT3-ITD	-1	
	Adverse Cytogenetics	-1	
European Prognostic Index score Breems et al., 2005[63]	CR1 duration>17 months	0	Score: 1-6 points. Favorable. OS of 70% at 1 year, 46% at 5 years Score: 7-9 points. Intermediate. OS of 49% at 1 year and 18% at 5 years Score: 10-14 points. Poor. OS of 16% at 1 year and 4% at 5 years
	CR1 duration 7-18 months	3	
	CR1 duration <7 months	5	
	Cytogenetics at diagnosis: t(16;16) or inv 16	0	
	Cytogenetics at diagnosis: t(8;21)	3	
	Cytogenetics at diagnosis: Other	5	
	Age at Relapse: <36 years	0	
	Age at Relapse: 36-45 years	1	
	Age at Relapse: >45 years	2	
	Prior SCT: No	0	
	Prior SCT: Yes	2	
GOELAMS Score Chevallier et al., 2011[64]	CR duration: >11 months	0	Score: 0 points. Favourable 2 yr EFS 45%; 2 yr OS: 58% Score: 1 points. Intermediate. 2 yr EFS 31%; 2 yr OS: 38% Score: 10-14 points. High Risk 2 yr EFS 12%; 2 yr OS: 12%
	CR duration <12 months	1	
	FLT3-ITD negative	0	
	FLT3-ITD positive	1	
	Cytogenetics by MRC Criteria[36]: Favorable/Intermediate	0	
	Cytogenetics by MRC Criteria: High Risk	1	

MRC, Medical Research Council; SCT, stem-cell transplantation.

intensive chemotherapy. A comprehensive review of epigenetic therapies in AML was published 1 year ago,[48] and readers are referred to that article for a more in-depth discussion. We can also say that the balance should tip away from cytotoxic therapies as alternative regimens improve, most urgently in patients with poor-risk karyotype, mutations of p53, or adverse molecular risk. It should be mentioned that, at the time of this writing, there is increasing excitement around the possible benefit of combining the BCL-2 inhibitor venetoclax with either azacitadine or low-dose cyatarabine in patients with newly diagnosed AML. This is addressed in the companion article on targeted therapy in this issue.[82]

When should we advise against intensive induction? There are available tools that can help identify patients in whom comorbidities are too severe to allow them to tolerate the month-long period of severe cytopenias associated with classical cytotoxic induction regimens. One is the TRM score, which uses data from 1000s of patients treated with intensive therapy to develop a simplified score composed of 8 factors (performance status, age, platelet count, serum albumin, type of AML [secondary vs de novo], WBC, peripheral blood blast percentage, and serum creatinine). An online calculator is available to compute and interpret this tally.[83] Additionally, one can itemize comorbidities using either of the most commonly used indices: the Charlson Comorbidity Index or the HCT-CI. Both indices have supporting data in AML patients.[84,85] In a retrospective study of 177 patients age >60 years receiving induction chemotherapy, patients with an HCT-CI score of 0 had an early death rate of 3%, those with a score of 1 or 2 had an early death rate of 11%, and 29% of those with a score of ≥3 died within 28 days of initiating therapy; OS was 45, 31, and 19 weeks, respectively.[85] Notably, these studies are >10 years old. Since that time, supportive care has improved, and TRM is less likely, at least in patients in clinical trials.[80]

A second key tool is the geriatric assessment (GA). This clinical endeavor has been described in detail in important review articles,[49,86,87] and published studies demonstrate that it may help predict outcomes by accounting for patient characteristics such as physical function and cognition in a manner missed by performance status assessments or simply age.[88,89] For example, in the prospective study by Klepin et al,[89] 2 GA measures, objectively measured physical performance and cognitive impairment, were independently associated with OS after accounting for tumor and clinical characteristics. Patients with low physical performance at baseline had shorter OS (6.0 vs 16.8 months). Individuals with poor cognitive function at baseline had a median OS of 5.2 vs 15.6 months for those who scored higher on the cognitive test. Notably, chronologic age, performance status, and comorbidity burden were not associated with OS. With these data in mind, I typically discuss epigenetic therapy as a serious recommendation in patients with an HCT-CI score of >3, a high TRM score, or a GA revealing high-risk features, including poor cognitive function.

If a patient is fit, is the disease likely to respond to cytotoxic therapy?[12,90,91] As discussed earlier, even patients with adverse karyotype may achieve CR with induction or even at relapse with salvage therapy. At our institution, patients with adverse karyotype, including those with monosomal karyotype or TP53 mutation, are first considered for clinical trials of novel agents, if eligible. If there is frailty or comorbidity that would preclude them from stem-cell transplantation, our preference is a clinical trial or, even off study, hypomethylating agents including decitabine, based on provocative early data of these agents in patients with TP53 or adverse cytogenetic risk.[48,89] If fit, we proceed with intensive induction and transplantation if they achieve CR1 (Figure 1).

Conclusions

Cytotoxic therapy for AML has been the standard of care since the early 1970s, and despite certain limitations, it remains the optimal option for achieving complete remission, prolonging life, and, in certain cases, proceeding to allogeneic stem-cell transplantation for potential cure. In newly diagnosed patients, refinements to 7 + 3 continue, the latest of which include the addition of GO or midostaurin or the use of a liposomal formulation of cytarabine and daunorubicin. In fact, the choice between targeted agents and cytotoxic therapy is likely a false choice,[42] because the future is likely to see combinations of these therapies. Although much attention has been paid to the development of novel agents that target molecular mutations in AML, it is worth noting that improvements in our clinical trial design, including support for randomizing patients to intensive vs nonintensive strategies, lag behind. If the challenge of the last decade was translating laboratory discoveries about this heterogeneous disease into imaginative treatments, the challenge for the next 10 years is how to rationally

test these treatments so that all patients can capitalize on potential benefits without losing out on what has been gained to date.

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