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PROGRESS IN ACUTE MYELOID LEUKEMIA

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Abstract

Significant progress has been made in the treatment of acute myeloid leukemia (AML). Steady gains in clinical research and a renaissance of genomics in leukemia have led to improved outcomes. The recognition of tremendous heterogeneity in AML has allowed individualized treatments of specific disease entities within the context of patient age, cytogenetics, and mutational analysis. The following is a comprehensive review of the current state of AML therapy and a roadmap of our approach to these distinct disease entities.

Keywords

AML Induction; Hypomethylating; FLT3

INTRODUCTION

Acute Myeloid Leukemia (AML) is diagnosed at a rate of 18,000 new cases per hear and accounts for over 10,000 deaths annually in the United States. Many AML experts and reviews emphasize a perceived lack of progress in the standard treatment of AML, commonly referred to as "7+3", and call for more research and newer therapies. While more innovation and research are needed, important progress in diagnosis, treatment, and specialized-care of AML has occurred which has not been publicized or broadly adopted.

In this review, we present a roadmap of AML treatment - one where we (1) recognize the tremendous disease heterogeneity, (2) individualize treatment, (3) move away from "7+3" to favor regimens with higher dose cytarabine (araC) and nucleoside analogue-doublets, (4) employ targeted therapies when appropriate, and (5) cultivate a robust research program to understand the AML biology and offer investigational therapies to patients with the poorest prognoses. Recognizing the diverse approaches to AML treatment seen between specialized academic centers and community practices, and even among specialized centers, our programs are implemented through research-based clinical trials with the goal of high

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accrual, rapid knowledge acquisition and adoption, and maximal dissemination of positive therapeutic discoveries.

AML is heterogeneous and requires accurate diagnosis and consideration of pretreatment disease- and patient-characteristics prior to instituting definitive treatment. A discussion of AML treatment should begin with a discussion of the various prognostic subtypes, which are closely linked to the chromosomal karyotype present in the leukemia cells.[1-3] The leukemia karyotype allows the segregation of patients with AML into 3 broad categories of favorable, adverse, and the ill-defined intermediate prognosis. Recent discoveries of recurrent somatic mutations in AML have allowed further refinement in prognostication and, in some cases, have provided opportunities for targeted treatment. We will discuss the treatment of AML as several distinct subtypes, starting with treatment options for entities that have established, highly curative therapies, moving on to refinements of current therapies for younger and older patients, and concluding with a look at newer targets and therapies on the horizon.

TREATMENT OF FAVORABLE KARYOTYPE AML

Favorable karyotypes include t(8;21), inv(16), and t(15;17), the defining abnormality of acute promyelocytic leukemia (APL), which is discussed separately. The inv(16) chromosomal abnormality, as well as the t(16;16), lead to the formation of the CBFB/MYH11 fusion gene. This, along with t(8;21) (which leads to the formation of RUNX1/RUNX1T1 fusion gene), represent the core binding factor (CBF) leukemias. The CBF AML subtypes have high response rates to induction and consolidation chemotherapy, and the potential for excellent long-term outcome. Steady progress has been made in this subgroup, improving overall survival (OS) rates from 55% in earlier studies to current rates of 75-80%.[3-8] The CALGB studies demonstrated the benefit of adding 3 to 4 cycles of high-dose araC (HiDAC) consolidation after 7+3 (7 days of standard-dose araC; 3 days of anthracycline) induction in reducing the risk of relapse, improving disease-free survival (DFS), and improving OS rates to 50-60%.[6,7] Bradstock, et. al. investigated HiDAC-based induction followed by HiDAC consolidation vs. standard dose araC consolidation.[9] In the subset of favorable karyotype AML, they observed improved rates of relapse free survival (RFS) and OS of 76% and 88%, respectively when using HiDAC consolidation.[9] More recent studies involving fludarabine and high-dose araC (FLAG) have reported complete response rates of 94% and improved RFS.[10] The addition of gemtuzumab ozogamicin (GO) or idarubicin to FLAG further improved the cure fraction.[5,8] In the MRC AML 15 trial, Burnett and colleagues randomized 1113 patients < 60 years to one of 3 induction regimens with or without GO,[8] and reported a significant OS benefit with the addition of GO in a predetermined subset of patients with favorable karyotype. In a recent multivariate analysis, the use of GO was found to be the most significant factor associated with improved OS.[11] Similarly, a SWOG trial randomizing 595 patients to daunorubicin and araC with or without GO found, within the subgroup of favorable karyotype AML, a significant benefit in RFS and trend towards benefit in OS for patients who received GO.[12] (Table 1) A meta-analysis of 5 trials combining chemotherapy with GO in AML induction concluded that the addition of GO led to a significant benefit in OS that outweighs any increase in early mortality, particularly in patients with favorable and intermediate-risk karyotype.[13] These and other studies provide justification to reinstate approval and marketing of this important agent.

Among this favorable subset, emerging data suggests that the presence of an associated *c-KIT* mutation or the presence of persistent minimal residual disease (MRD) after induction/consolidation may identify patients with a higher incidence of relapse and inferior outcome.[14-18] Dasatinib, a *KIT* inhibitor, has been studied in combination with chemotherapy in patients with c-*KIT* mutated CBF AML, but the added benefit is not yet clear.[19] Standardization of the testing for mutations and MRD, as well as better *c-KIT* inhibitors are needed to address these high-risk cases. Since the removal of GO from the market, our approach to a patient with CBF AML is induction with FLAG-Idarubicin[20] with age- and comorbidity-adjusted dosing, followed by 6 consolidation cycles. Minimal residual disease is monitored routinely with quantitative real-time PCR and acted upon in a risk-adjusted manner.

TREATMENT OF APL

The treatment of APL is an important example of individualized treatment. The t(15;17) and variants lead to the PML-RARA fusion gene and oncoprotein. The PML-RARA protein acts as a dominant negative inhibitor of the wild-type retinoic acid receptor, leads to differentiation block and development of acute promyelocytic leukemia.[21] Discovery of the clinical activity of all-trans-retinoic acid (ATRA) in APL, and understanding its mechanism in reversing the differentiation block, have revolutionized APL treatment.[21] Initial studies of ATRA and its combination with chemotherapy have transformed the disease from one that was highly fatal to one that is now highly curable.[22] Studies have also demonstrated the activity of single-agent arsenic trioxide (ATO) in APL by a slightly different mechanism, in patients with relapsed and previous untreated disease.[23-29] Based on the activity of each these agents and on preclinical evidence of synergy, combination strategies have been tested.[30] Shen et. al. randomized 61 patients with newly diagnosed APL to ATRA, ATO, or the combination, followed by consolidation chemotherapy including anthracycline and araC.[26] They demonstrated similar high CR rates (>90%) in all 3 groups, but with a shorter time to CR and platelet recovery in the combination arm.[26] Our group conducted a study exploring a non-chemotherapy treatment in APL.[31] Patients with low-risk disease, defined as having an initial WBC of $< 10 \times 10^9$/L, received ATRA and ATO. Patients with high-risk disease additionally received GO 9 mg/m^2 IV × 1 dose on Day 1. Patients with who had developed hyperleukocytosis in response to ATRA/ATO treatment, and those with persistent or recurrent molecular evidence of disease at 3+ months in CR received GO 9 mg/m^2 IV × 1 dose. In an update of 82 patients treated, the CR rate was 92% and the 3-year OS rate was 85%.[32] A European consortium (GIMEMA, German-Austrian AMLSG) compared the above regimen of ATRA/ATO to standard therapy with ATRA/Idarubicin (Ida).[33] They randomized 162 patients with low or intermediate risk APL age < 70 years between the 2 treatment regimens in a non-inferiority study. They reported a CR rate of 100% for ATRA/ATO and 95% for ATRA/Ida.[33] With a median follow-up of 34.4 months, the 2-year event free survival (EFS) was 97% vs. 86% (p=0.02), favoring ATRA/ATO. The ATRA/ATO arm was also associated with a significantly improved OS (p=0.02), less hematologic toxicity, and fewer infections. This study established a new standard frontline APL treatment, without the routine use of cytotoxic chemotherapy, at least in patients with standard-risk disease. Our current frontline approach remains the combination of

ATRA/ATO with GO in patients with high-risk disease or hyperleukocytosis, in an ongoing clinical trial.

FLT3 MUTATED AML

The FMS-like tyrosine kinase 3 (FLT3) receptor tyrosine kinase and its ligand are important in the maintenance of normal hematopoiesis. Activating mutations in the FLT3 receptor tyrosine kinase gene are present in 20-30% of patients with AML.[34-38] The most common mutations, internal tandem duplications (ITDs) of the juxtamembrane domain, and point mutations in the tyrosine kinase domain (TKD) affecting amino acid D835, lead to ligand-independent constitutive activation of FLT3 signaling.[39,40] Both *FLT3*-ITD and *FLT3*-TKD mutations are associated with higher WBC and peripheral blast counts. *FLT3*-ITD is associated with a higher rate of relapse, and significantly inferior OS compared to that seen in wild-type (WT) *FLT3*; the data on *FLT3*-TKD is controversial.[34,35,37,38] When comparing the outcomes between *FLT3*-ITD, *FLT3*-TKD, and *FLT3*-WT, patients with *FLT3*-ITD have the worst prognosis, those with *FLT3*-WT the best, and those with *FLT3*-TKD an outcome intermediate between the other two.[34] In the context of available therapies, the presence of either mutation may have implications for small-molecule targeted treatment. The currently investigated FLT3 tyrosine kinase inhibitors (TKIs: sorafenib, quizartinib, midostaurin) are active in *FLT3*-ITD AML, but have little activity in *FLT3*-TKD mutants. Early studies suggest that development of a *FLT3*-TKD mutation may be a resistance/escape mechanism in patients treated with these drugs.[41]

In addition to the type of *FLT3* mutation, the “allelic burden” or allelic ratio of *FLT3* mutant and wild-type genes be prognostic. This term refers to the ratio of mutant *FLT3* allele to wild-type *FLT3* allele as assessed by PCR. Several groups have suggested a correlation between an increasing *FLT3* allelic burden and worse outcome. In a study by Thiede et. al[37], patients with an allelic ratio of > 0.78 had a significantly shorter OS and DFS, while those with a lower ratio had an OS and DFS similar to the *FLT3*-WT cohort. The UK MRC[42] divided patients by low (< 0.25), intermediate (0.25 – 0.5), and high (> 0.5) levels of *FLT3* mutant allelic ratios. Patients in the “high” category had a shorter OS and DFS compared with the low and intermediate groups, which had similar outcomes, but still worse than *FLT3*-WT patients.[42] In contrast, a study from Canada[43] found that the *FLT3* mutant allelic ratio did not influence outcomes. Further work is needed to standardize the methodology and classification of the allelic burden of mutant *FLT3* in AML, since future therapeutic decisions may depend on these criteria. Indeed, Pratz, et. al.[44] reported that AML samples with high *FLT3* mutant allelic ratios may represent a subset of disease that is “addicted” to the FLT3 signaling and therefore may be more sensitive to FLT3 inhibitor-based therapy.

Several small molecule TKIs have demonstrated the ability to inhibit the FLT3 kinase and have been evaluated in the treatment of *FLT3*-ITD AML. Evidence of synergy in combination with chemotherapy has prompted adding FLT3 inhibitors to induction regimens.[45] Ravandi, et. al. reported the results of a phase I/II study of sorafenib in combination with idarubicin and HiDAC in patients with AML, demonstrating an overall CR rate of 75%.[46] In patients with *FLT3* mutations, the CR rate was 93%, with a 1-yr OS rate of 74%. In a long-term follow-up, the investigators updated the CR rates to 95% vs.

84% (p=0.23) in patients with *FLT3*-mutated vs. wildtype disease and found no significant difference in OS or DFS between the 2 groups.[47] Stone et. al.[48] studied the combination of midostaurin with daunorubicin and cytarabine in patients with AML. The CR rate was 80% overall, and 92% in patients with *FLT3*-mutated AML. The OS for *FLT3*-mutated patients at 2 years was 62%, similar to that seen in patient with *FLT3*-WT, suggesting that the FLT3 inhibitor, in both studies, may have diminished the negative impact of the *FLT3* mutation. Rollig, et. al.[49] reported preliminary results of the SORAML study which randomized 276 patients aged 18 to 60 years to daunorubicin and cytarabine with or without sorafenib. They reported similar CR rates between the 2 arms, but a significant prolongation of EFS in the sorafenib arm (64% vs. 50% at 1-year, p=0.023), particularly in those with *FLT3*-ITD. Serve et. al.[50] investigated this approach in older patients with AML. Among 201 patients with a median age of 68 years (61 – 80 years) randomized to "7+3" with or without sorafenib, there was a trend towards lower CR rate (48% vs. 60%, p=0.12), higher early death (17% vs. 7%, p=0.052), and no improvement in EFS or OS for patients in the sorafenib arm.

Emerging data suggests that elevated FLT3 ligand levels are triggered by intensive chemotherapy-induced bone marrow aplasia and may hinder the action of TKIs when combined with such regimens.[51,52] Based on this, Ravandi, et. al. conducted a phase II trial of sorafenib combined with low-intensity chemotherapy in patients with relapsed *FLT3*-ITD mutated AML.[53] Patients received azacytidine 75 mg/mg^2 IV for 7 days in combination with sorafenib 400mg orally twice daily, continuously. The overall response rate (ORR) was 46% with 16% CR, 27% CR with incomplete count recovery (CRi), and 3% partial response (PR). FLT3 kinase inhibition was achieved in 64% of patients and correlated with plasma sorafenib concentrations. Also, confirming the hypothesis, FLT3 ligand levels did not increase to levels that were observed in previous studies with cytotoxic chemotherapy. This regimen is being studied in newly diagnosed patients with FLT3-ITD mutated AML.

Since the validation of FLT3 as an important therapeutic target in AML, newer more specific FLT3 inhibitors are currently in development. Following positive results of a phase I trial of the potent FLT3 inhibitor quizartinib (AC220), Cortes et. al.[54] recently presented the final results of a phase II trial of single-agent quizartinib in patients with relapsed/ refractory AML. The composite CR/CRi rate was 32% in patients without *FLT3*-ITD mutations and 54% in those with a *FLT3*-ITD mutation. The median OS in those with *FLT3*-ITD(+) AML treated with quizartinib was 25 weeks. These high response rates with single-agent quizartinib in relapsed and refractory AML were encouraging and prompted ongoing combination studies. Higher dose schedules of quizartinib (90 – 200mg daily) were associated with QTc prolongation in 40% of patients. Lower dose schedules (30 – 60mg daily) maintained the efficacy (marrow CR rates of 40-50%) and reduced the incidence of QTc prolongation to 5-20%. Our approach in patients with *FLT3*-mutated AML involves risk stratification based on *FLT3* mutation, allelic burden, and incorporation of FLT3 inhibitors into investigational treatment protocols. Newer studies with next generation inhibitors of *FLT3*-TKD mutations such as crenolanib are ongoing. (NCT01657682)

NPM1 MUTATED AML

The *NPM1* gene encodes for nucleophosmin, a nuclear phosphoprotein that shuttles between the nucleus and cytoplasm.[55] Mutations in the *NPM1* gene are the most common genetic alterations in AML and lead to aberrant cytoplasmic localization of the protein. *NPM1* mutations are found in over 50% of patients with diploid karyotype AML and in up to 60% of patients with *FLT3*-ITD mutations.[36] In the absence of concurrent *FLT3*-ITD mutations, NPM1 mutations confer a favorable prognosis, predicting for a high CR rate and favorable OS.[36,55-58] Patients with normal karyotype AML with *NPM1* mutation and without a *FLT3* mutation are classified, along with the CBF, as AML with a favorable prognosis.[1] Patients with both an *NPM1* mutation and a *FLT3*-ITD mutation have an adverse prognosis related to the effect of *FLT3*-ITD. Since the favorable prognosis of NPM1 mutations and their interaction with *FLT3* mutations have been validated, these should be routinely checked in all patients with AML. Acknowledging the distinct characteristics, the recent World Health Organization (WHO) classification of myeloid neoplasms considers these subtypes as provisional distinct entities.[59] Our approach to patients with diploid karyotype AML with *NPM1* mutation and wild-type *FLT3* is to offer them a clinical trial with intensive chemotherapy, with higher dose cytarabine based regimens, recognizing the potential for favorable outcome.

Other Subtypes

While specialized treatment programs are defined for patients who fall into the above categories, many patients with AML fall outside these categories. As new data emerge, new AML subtypes are recognized and eligible patients are offered clinical trials that exploit the new scientific data. In the remaining patients, treatment options are often decided based on patient age and comorbidities, as well as the expected morbidity and mortality associated with standard chemotherapy. Almost 55% of patients are older than 65 years at diagnosis and about a third are older than 75 years. While age in itself may not be the sole factor in determining outcome, older age is generally associated with increased comorbidities, more marginal performance status, and the presence of more adverse disease features, including dysplasia, antecedent hematologic disorder, and adverse-risk karyotype. A significant proportion of older patients will not be considered good candidates for, and may not benefit from, intensive chemotherapy. In these cases, an arbitrary age of 65 years is often used to select patients who will receive higher or lower-intensity therapy. In practice, these cohorts actually consist of the “young and fit” (including some patients ≥ age 65) or the “older and unfit” (including some < age 65). Our approach to systematically define these groups begins with a simple model that helps identify patients with a high risk for early mortality and reduced OS with intensive chemotherapy. Based on a cohort of 998 patients ≥ 65 years treated with intensive chemotherapy, we developed a model that predicted for 8-week mortality, response rate, and OS.[60] Excluding patients with CBF cytogenetics, 5 independent factors were identified: age ≥ 75 years, complex karyotype (≥ 3 abnormalities), ECOG performance status ≥2, presence of antecedent hematologic disorder (AHD) ≥ 12 months, and serum creatinine >1.3. Patients with 0, 1, 2, or ≥3 factors had a predicted 8-week mortality rate of 10%, 19%, 36%, and 65%, respectively. Median OS estimates were 16, 9, 4, and 1 month, respectively.[61] Younger patients or those with lower predicted early

mortality are offered higher intensity chemotherapy; those with a higher predicted early mortality are offered lower-intensity investigational approaches. We will examine the challenges and treatment paradigms for each of these groups separately.

For younger patients, the so called standard treatment outside of specialized centers has been "7+3". This consists of 7 days of araC at a dose of 100mg/m^2/day combined with an anthracycline (daunorubicin or idarubicin) during days 1-3, followed by 3 – 4 cycles of HiDAC consolidation. Historically, this regimen yielded a CR rate of 64% and a 4-year DFS and OS of 39% and 46%, respectively in a study by Mayer, et. al. which used 7+3 induction, 4 HiDAC consolidation cycles, and 4 additional consolidations with "5+2".[62] More recent studies have used less HiDAC consolidation, eliminated "5+2", and expanded eligibility to include older patients. These resulted in lower long-term OS rates in the range of 20-30%.[63] Many attempts to innovate on this basic backbone have led to improvements in outcome. Key areas of research have included: (1) dose of araC, (2) dose of anthracycline, (3) choice of anthracycline, (4) nucleoside analogue-doublets in 3-drug combinations, and (5) the addition of GO.

Dose of araC

AraC is the most active agent in AML and demonstrates a steep dose-response curve. High dose araC (HiDAC) typically refers to doses ≥ 1000mg/m^2. Dose-escalation of araC to doses up to 1000 to 3000 mg/m^2 has been studied in induction and consolidation to take advantage of the dose-response. Several studies have demonstrated the benefit of HiDAC in post-remission consolidation, particularly in CBF leukemias. The role of HiDAC in induction has been debated and examined in randomized studies. The SWOG randomized patients with AML <65 years between standard-dose araC (SDAC, 200 mg/m^2/d × 7) and HiDAC (2000 mg/m^2 Q12 hours × 12 doses) during induction.[64] Both groups received daunorubicin at 45 mg/m^2/d × 3 days. The rates of CR and 4-year OS were similar in both arms, in all age groups. However, the 4-year RFS was better following HiDAC induction: 33% vs. 21% in patients < 50 years, and 21% vs. 9% in patients between 50 and 64 years (p=0.049).[64] HiDAC was associated with significantly greater toxicity. Bishop et. al. randomized patients ≤ 60 years old to either HiDAC (3000 mg/m^2 Q12 hours × 8 doses) or SDAC (100 mg/m^2/day × 7), each in combination with daunorubicin and etoposide as part of induction.[65] Among 301 patients treated, there was no significant difference in CR rates, 71% with HiDAC vs. 74% with SDAC, or OS. However, there was a significant improvement in median CR duration among patients receiving HiDAC: 45 months vs. 12 months (p=0.0004). The RFS at 5 years was 49% with HiDAC vs. 24% with SDAC.[65] Kern and Estey performed a meta-analysis of 3 randomized trials of SDAC vs. HiDAC in AML induction,[66] and concluded that HiDAC in AML induction improved long term RFS and OS in patients < 60 years of age. Thus, the data from these older studies suggest that the use of HiDAC in induction and consolidation results in more durable remissions, and better rates of RFS and OS in subsets of patients. The higher toxicity profile is of concern in older patients. Optimizing the delivery of HiDAC in induction and improving supportive care could potentially translate the RFS benefit into an OS benefit.

A more recent study by the HOVON/SAKK collaborative group once again addressed the question of araC dose during induction by randomizing 858 patients with AML.[67] During cycle 1, patients were randomized to receive either HiDAC (1000 mg/m^2 q12 hours × 10 doses) vs SDAC (200 mg/m^2/day ×7). All patients received idarubicin 12 mg/m^2/day × 3. All patients on both arms, regardless of their response to cycle 1, received amasacrine and higher dose araC as part of cycle 2. Patients on the HiDAC arm received araC 2000 mg/m^2 Q12 hours × 8 doses (total dose 16,000 mg/m^2) and those on the SDAC arm received araC 1000 mg/m^2 Q12 hours × 12 doses (total dose 12,000 mg/m^2). Patients in CR after 2 cycles were then considered for 1 course of consolidation or stem cell transplant. The CR rates were similar between the 2 groups: 82% (HiDAC) vs. 80% (SDAC), and there were no differences in the rates of EFS, OS, or risk of relapse at 5 years.[67] The authors concluded that there was no benefit of HiDAC over SDAC and that an intermediate dose of araC between 100 mg/m^2 and 3000 mg/m^2 could maximize antileukemia benefit while mitigating toxicity. However, the study did not actually compare HiDAC vs. SDAC-based induction in AML, since all patients on in the SDAC arm were treated with HiDAC at a total dose of 12,000 mg/m2 during cycle 2. The lack of difference in CR, OS, and EFS could be accounted for by the exposure to HiDAC during induction in both arms.

In contrast, a recent study by the European (EORTC) and Italian (GIMEMA) Leukemia Groups found that HiDAC in induction improved outcomes in patients with AML, particularly in those ≤ 45 years and those of any age with FLT3-ITD or “very-bad” karyotype.[68] Willemze et. al randomized 1942 patients ≤ 60 years to a regimen containing daunorubicin, etoposide, and either standard araC (100 mg/m^2/day × 10) or HiDAC (3000 mg/m^2 Q12 hours × 8 doses). For patients ≤ 45 years, the CR rate (82% vs. 76%, p=0.01), 6-year EFS (44% vs. 35%, p=0.003), and 6-year OS (52% vs. 43%, p=0.009) were all superior in the HiDAC arm.[68] Even among patients > 45 years, HiDAC demonstrated a significant improvement in CR rate and 6-year EFS, with a trend for improvement in OS in those who had FLT3-ITD or “very-bad” karyotype.

Finally, the UK MRC AML 15 trial compared a HiDAC regimen FLAG-Ida (araC 2000 mg/m^2/day × 4, with fludarabine, idarubicin and GCSF) to standard-dose araC regimens, DA (araC 100 mg/m^2/day × 8-10, with daunorubicin) or ADE (araC 100 mg/m^2/day × 8-10, with daunorubicin and etoposide) and found significantly improved rates of CR and RFS with FLAG-Ida, but not an OS benefit.[69] Among patients who could tolerate 4 cycles of FLAG-Ida, the 8-year OS was 66% vs. 47% with 7+3. Among patients with favorable or intermediate risk disease who received 4 cycles of FLAG-Ida followed by 2 cycles of HiDAC consolidation, the 8-year OS was 72%.

Preclinical studies by Plunkett,et. al.[70,71] have established that higher doses up 3 g/m^2 may be beyond what is necessary to saturate araC uptake into leukemia cells. Therefore, escalation of araC may be beneficial, but up to a point that maximizes intracellular araC concentration and avoids excess toxicity. The UK MRC compared 1.5 g/m^2 to 3 g/m^2 during consolidation and found no difference in outcome.[69] A recent Korean study compared ≥ 1.5 g/m^2 to 1 g/m^2 in consolidation and reported significantly better RFS and OS with ≥ 1.5 g/m^2 of araC.[72] The ideal dose of araC in induction and consolidation continues to be

debated.[73] Clinically, a dose of 1500 – 2000 mg/m^2 may be optimal, and our practice is to incorporate araC doses in the range of 1000 to 2000 mg/m^2/d during induction.

Nucleoside analogue doublets

Since the cytotoxicity of araC is directly related to the intracellular concentration of its metabolite, araC-triphosphate (ara-CTP), modulation of its intracellular metabolism could be therapeutically beneficial. Beyond increasing the treatment dose of araC to an optimal level, methods to augment its efficient conversion to the active intracellular metabolite could lead to increased efficacy. Gandhi and Plunkett demonstrated that several purine nucleoside analogues synergize with araC by increasing intracellular ara-CTP.[74-76] These purine nucleosides act as potent inhibitors of ribonucleotide reductase and modulators of deoxycytidine kinase (the enzyme responsible for converting araC to ara-CTP). This leads to rapid depletion of intracellular deoxynucleotides, increased ara-CTP generation, and increased incorporation of these antileukemic analogues into the growing DNA strand. This preclinical rationale has been translated successfully into clinical trials combining fludarabine, clofarabine, and cladribine with araC in the treatment of AML. In an early study combining fludarabine, araC and idarubicin in AML, investigators reported a CR rate of 51% in very adverse-risk population.[77] This regimen has been adopted internationally and is one standard therapeutic option for AML induction. The UK-MRC recently reported on their large AML15 study demonstrating the advantage of this combination over other induction regimens.[69] They reported a CR rate of 77% after 1 cycle and an improved RFS of 45% over 7+3 with etoposide. Among patients who received 4 cycles of FLAG-Ida and achieved a CR, the 8-year OS was 66% vs. 47% ($p<0.001$) for patients receiving 4 cycles of 7+3 with or without etoposide.[69] The Polish Acute Leukemia Group (PALG) conducted a randomized phase III trial in 400 patients with AML comparing the combination of daunorubicin and standard dose araC with or without cladribine.[78] The CR rate (64% vs. 46%, $p=0.0009$) and LFS (44% vs. 28%, $p=0.05$) were significantly better in the 3-drug arm compared to the 2-drug arm, highlighting the benefit of adding cladribine.[78] In a follow-up study, the PALG next compared the outcomes of either fludarabine (DAF) or cladribine (DAC) added to daunorubicin and standard dose araC (DA). Compared to DA, DAC (but not DAF) was associated with a significantly higher CR rate (67.5% vs. 56%, $p=0.01$) and better 3-year OS (45% vs. 33%, $p=0.02$).[79] Our group recently reported initial results of the combination of clofarabine, idarubicin, and high-dose araC (CIA) in newly diagnosed AML.[80] In a phase II study of CIA, we reported a CR rate of 74% and an induction mortality of only 2%. With a median follow-up of 10.9 months, the median RFS and OS had not been reached.[80] These studies suggest an advantage for the 3-drug combinations over the standard doublet of araC and anthracycline. Our current approach to frontline induction therapy in younger AML incorporates high dose araC at doses of 1000 to 1500 mg/m^2 in 3-drug combinations, investigating either fludarabine, clofarabine, or cladribine.

Anthracycline

Aside from increasing the dose of araC in AML induction, intensifying the dose of daunorubicin in the standard “7+3” doublet has been debated. Several single-arm studies investigating higher doses of daunorubicin ranging from 60 to 90 mg/m^2 have suggested superior response rates. To address this question, ECOG conducted a randomized study in

582 patients ≤ 60 years of age, assigning them to either 45 mg/m^2/d × 3 or 90 mg/m^2/d × 3 of daunorubicin, each in combination with araC 100 mg/m2/day × 7.[63] The CR rate (57% vs. 71%, p<0.001) and median OS (15.7 vs. 23.7 months, p=0.003) were significantly better in the higher dose daunorubicin arm.[63] The largest benefit was observed in patients ≤ 50 years and those with intermediate-risk disease by cytogenetics. Patients ≥ 50 years and those with adverse karyotype or FLT3 mutation did not benefit. The HOVON/SAKK collaborative group asked the same question, but in patients > age 60 years.[81] Patients were randomized to 45 vs. 90 mg/m^2 of daunorubicin for 3 days, combined with araC 200 mg/m^2/day × 7. While the CR rate was higher (65% vs. 54%, p=0.002) in the higher dose arm, there was no difference observed between the 2 groups with respect to EFS, DFS, or OS.[81] The cumulative incidence of relapse was lower (54% vs. 61%) in the high-dose group, but this was offset by an increased rate of death in CR (16% vs 10%). In a post-hoc analysis, there may have been some benefit with high-dose daunorubicin in patients aged 60-65 years, with regards to CR, EFS, and OS. While these data suggest a benefit for higher dose daunorubicin in AML induction in younger patients, the question remains whether a more intermediate dose of daunorubicin of 60 mg/m^2 is sufficient to improve outcomes and avoid toxicity. To answer this, the GOELAMS group recently reported their retrospective experience comparing patients who had received 60 mg/m^2 (DNR60) vs. 90 mg/m^2 (DNR90) of daunorubicin as part of 7+3 induction for AML.[82] Among 402 patients with a median age of 49 years, 340 had received DNR60 and 62 had received DNR90. They found no difference in rates of CR (72% vs. 74%, p=0.4), induction mortality (2% vs. 5%, p=0.15), 2-year RFS (52% vs. 60%, p=0.33), or 2-year OS (48% vs. 53%, p=0.7).[82] The authors concluded that DNR60 may be equivalent to DNR90, but prospective studies are needed.

Following from the question of optimal dose of daunorubicin arises the question of choice between daunorubicin and idarubicin. There have been several comparisons between daunorubicin and idarubicin in the treatment of AML to determine the better anthracycline, including a meta-analysis of 5 trials that concluded that treatment with idarubicin produced higher rates of CR and OS.[83] Unfortunately, these analyses have been limited by dose-inequalities comparing 12 mg/m^2 of idarubicin, to the now “inferior” dose of daunorubicin. The Acute Leukemia French Association (ALFA) conducted a series of studies to further clarify this issue. Pautas et. al.[84] randomized 468 patients with AML to daunorubicin 80 mg/m^2/d × 3 (DNR) vs idarubicin 12 mg/m^2/d × 3 (IDA3) vs. idarubicin 12 mg/m^2/d x4 (IDA4), each in combination with ara-C 200 mg/m^2/d × 7. They observed that IDA3 was associated with a significantly improved CR rate (83% vs. 70%, p=0.007), and a trend for better 4-year EFS (21% vs. 12%) and OS (32% vs. 23%) when compared to DNR.[84] The improved CR rate was also seen in patients with unfavorable karyotype. There were no significant differences in induction mortality or serious AEs, except more mucositis with IDA. In a recent retrospective follow-up analysis of 2 large trials comparing idarubicin to daunorubicin, the ALFA group analyzed the outcomes of 727 patients who had received either DNR or IDA3.[85] They found that IDA3 was associated with a significantly higher CR rate (69% vs. 61%, p=0.029). They also found a significantly higher cure rate associated with IDA3 compared to DNR (16.6% vs. 9.8%, p=0.018). Finally, Mandelli, et. al. compared the efficacy of daunorubicin (50 mg/m^2/day × 3) to mitoxantrone (12 mg/m^2/day × 3) or idarubicin (10 mg/m^2/day × 3), each combined with etoposide and araC (100

mg/m^2/day × 10).[86] A total of 2157 patients (median age of 44) were randomized to one of the 3 arms. There was no difference in CR or 5-year OS rates in patients who had received an allogeneic stem cell transplant (SCT). However, compared to daunorubicin, both idarubicin and mitoxantrone were associated with a significantly better 5-year DFS (29%, 37%, and 37%, respectively, p=0.02) and OS (36%, 43%, and 45%, respectively, p=0.01) in patients who had *not* received an allogeneic SCT.[86] Based on the available data, treatment with idarubicin 12 mg/m^2/d × 3 is at least as good, if not better than high-dose daunorubicin. Therefore, our approach is to incorporate idarubicin in our programs for younger patients with AML.

Treatment of AML in Older Patients

Intensive chemotherapy with HiDAC and anthracyclines may be considered standard in most younger patients with newly diagnosed AML, but most patients with AML are ≥ 65 years and may be vulnerable to higher rates of early mortality and induction failure. In addition to an increased prevalence of comorbidities and early organ dysfunction in older patients, AML in older patients is more often associated with adverse features. Many patients have a history of an AHD, myelodysplastic syndrome, and adverse karyotypes at diagnosis – all characteristics associated with lower CR rates. With lower predicted rates of response and higher probability of toxicity, a significant proportion of older patients may not benefit from intensive chemotherapy. Kantarjian et. al.[60,61] studied the outcomes of older patients (≥ 65 yrs[60] and ≥ 70 yrs[61]) with AML treated with intensive chemotherapy at MD Anderson Cancer Center. They observed a CR rate of 45%, a median OS of 4.6 months, and a 1-year survival of 28%. The rates of 4-week and 8-week mortality were 26% and 36%, respectively. By multivariate analysis, factors that strongly influenced outcome were older age, complex karyotype, poor performance status, history of AHD, and abnormal organ function, particularly renal dysfunction. They concluded that intensive chemotherapy did not benefit most older patients with AML, with the exception of patients who were fit, with a favorable karyotype. In some cases, physicians may decide to offer palliative or supportive care, rather than risk high rates of toxicity and early mortality. However, studies have shown that patients receiving even low-intensity therapy do better than those receiving only supportive care. The UK MRC AML14 trial randomized 217 older patients to receive low-dose araC (LDAC, 20mg SQ BID × 10 days) vs supportive care and hydroxyurea.[87] Patients receiving LDAC had a significantly higher CR rate (18% vs. 1%, p=0.00006) and improved OS (odds ratio: 0.60, p=0.0009) compared to those who received supportive care. Patients who achieved CR had a better median OS compared with those who did not (80 vs. 10 weeks). In a separate study, Tilly et. al.[88] compared LDAC with “7+3” in patients older than 65 (without a previous history of AHD or MDS), reporting a CR rate of 32% for LDAC vs. 52% for “7+3”. Patients receiving “7+3” had a higher early death rate (31%), more severe infectious complications, required more transfusions, and spent more days in the hospital. Additionally, there was no significant difference in CR duration or OS between the 2 groups.

Hypomethylating agents such as 5-azacytidine (5-AZA) and decitabine are approved for the treatment of MDS and have significant activity in older patients with AML, along with an OS benefit compared to that seen with standard supportive care. Studies of 5-AZA in AML

have shown CR rates in the range of 15% - 20% and median OS ranges of 19 to 24.5 months among patients with 20-30% bone marrow blasts and less proliferative disease.[89-94] Decitabine treatment in AML has also produced similar response rates ranging from 18% to 24% and a survival benefit in responding patients (7.7 to 14.4 months).[95,96] A randomized phase III study of decitabine vs. supportive care or LDAC demonstrated a significant OS benefit (7.7 vs. 5 months, p=0.37) and led to its approval by the European Medicines Agency for the treatment of AML in patients ≥ 65 years.[96] In a recent retrospective analysis,[97] the outcomes of 671 older patients treated with intensive chemotherapy vs. hypomethylating agents were reviewed. The study reported a higher CR rate for intensive chemotherapy (42% vs. 28%), but there was no significant difference in the 2-yr RFS (28% vs. 39%) or OS (median 6.7 vs. 6.5 months). By multivariate analysis, outcome was dependent on age, cytogenetics, performance status, creatinine, but not on the type of treatment.[97] Experience from these studies with 5-AZA and decitabine suggest that they affect the natural history of the disease and prolong survival independent of achieving a CR. Therefore, the former principle of achieving a CR with intense chemotherapy in order to convey a favorable outcome may not apply to these agents and lower intensity approaches. More prolonged schedules of decitabine (20 mg/m^2/d × 10) have also been studied with a suggestion of superior response rates.[98,99] A randomized study evaluating 5 or 10 days of decitabine is currently underway at our institution.

Other lower-intensity nucleoside analogue combinations and prolonged consolidation/ maintenance strategies have been studied and provide promising leads for the treatment of older patients with AML. Faderl et. al. reported the results of the combination of clofarabine and LDAC alternating with decitabine in older patients with AML.[100] Patients were treated with clofarabine 20 mg/m^2/day × 5 in combination with LDAC for 7-10 days for three 28-day cycles. This was alternated with 3 cycles of decitabine at 20 mg/m^2/day × 5. Patients could receive up to 18 cycles of this prolonged consolidation/maintenance therapy. In 59 evaluable patients with a median age of 70, investigators reported a CR rate of 58%, a median RFS of 14.1 months, and a median OS of 12.7 months.[100] In responding patients, the median OS was 24.2 months. The combination was well tolerated with 7% early mortality at 8 weeks.

Building on this, and extending from the Polish experience with cladribine and higher doses of araC, Kadia et. al. reported the preliminary results of a phase II trial of cladribine and LDAC alternating with decitabine in older patients with AML.[101] Patients were treated with cladribine 5 mg/m^2/day × 5 combined with LDAC for 10 days for two 28-day cycles, alternating with 2 cycles of decitabine at 20 mg/m^2/day × 5. Patients could receive up to 18 cycles as long as they were deriving benefit. In 68 evaluable patients, with a median age of 69, the CR/CRp rate was 63%. With a median follow-up of 7+ months, the median OS and CR duration have not been reached. The 1-year OS estimate is 68%. The regimen was very well tolerated with 1% 4-week mortality and no treatment-related grade 3/4 nonhematologic toxicities. This ongoing study is part of our frontline lower intensity treatment program for older patients.

Recently, an investigational hypomethylating agent, SGI-110, has been studied in older patients with AML. SGI-110 is a dinucleotide of decitabine and deoxyguanosine with

distinctive pharmacokinetic properties allowing longer half-life and more extended decitabine exposure. This longer exposure was shown to have more potent hypomethylating properties and may translate into greater clinical benefit. In the phase II study of SGI-110 in patients with AML,[102] a CR/CRi rate of 53% was observed in treatment-naïve older patients with AML. Further studies with this promising agent in different dose-schedules and combinations are underway.

To improve the safety and increase the efficacy of the traditional "7+3" approach, a liposomal formulation of araC and daunorubicin at a 5:1 molar ratio was developed for the treatment of AML. After promising phase I data with this agent was presented, CPX-351 was studied in a randomized phase II trial of 126 older patients (aged 60-75 years) with AML.[103] In a planned subgroup of patients with secondary AML, the investigators reported an improved response rate (58% vs. 32%, p=0.06), improved EFS (HR: 0.59, p=0.08), and improved OS (HR: 0.46, p=0.01) for CPX-351 compared with 7+3. Further studies will determine whether this may be a safer and more effective way to deliver the combination of cytarabine and daunorubicin.

Contrasting our approach to lower-intensity treatment, a large Swedish registry study offers an important alternative perspective on the treatment of older patients with AML.[104] They reviewed the outcomes of 2767 patients with AML diagnosed in Sweden between 1997 and 2005 who may have received intensive vs. "palliative" therapy. Outcomes were dependent on age and PS, but PS was a more important determinant of outcome in each age group, including those > 70 years old. They reported higher early death rates among patients receiving palliative treatment and in those with poor PS. With intensive chemotherapy, 50% of patients ≤ 75 achieved CR. In patients with a good PS, this extended up to age 80. The authors concluded that most patients up to age 80 should be offered standard intensive therapy.

Clearly, there is a subset of fit older patients with AML with good PS, preserved organ function and more favorable disease biology that may benefit from intensive chemotherapy regimens. We agree that newer agents and regimens for these patients should be compared to standard chemotherapy. In our practice, each patient undergoes a risk-stratification based on age and other pretreatment characteristics – including comorbidities, organ function, pretreatment AML risk-classification, predicted response to chemotherapy, and patient preference/tolerance. An older patient with favorable risk AML and adequate organ function may be offered a more intensive induction with close monitoring in laminar air flow isolation. Conversely, a younger patient with adverse karyotype, organ dysfunction, poor PS unrelated to leukemia, and low predicted response to chemotherapy could be offered a clinical trial using a novel or lower-intensity approach. Evaluating these pretreatment characteristics in every patient mandates an individualized approach that also involves waiting[105,106] for appropriate cytogenetic and molecular studies before starting therapy.

Role of Allogeneic Stem Cell Transplant

Intensification of induction regimens and newer combinations have translated into higher response rates in AML, but relapses are frequent and a major source of treatment failure. Post-remission therapy is important in converting remissions into longer term cures. An

allogeneic stem cell transplant (SCT) can fulfill the goals of replacing a diseased marrow with a leukemia-free graft and establishing a lifelong graft vs. leukemia effect towards achieving a cure. However, this comes with the price of treatment-related mortality (TRM). Therefore, careful selection of the patient and donor to optimize benefit : risk is critical. Several genetically randomized studies comparing matched sibling allogeneic SCTs to consolidation chemotherapy demonstrated reduced rates of relapse and improved DFS, but no OS benefit in unselected patients with AML in first complete remission (CR1).[107-111] (Table 2) However, when these data were analyzed for benefit by cytogenetic-risk group, there was a significant benefit in DFS and OS among patients in the adverse- and intermediate-risk groups, but no benefit in patients with a favorable karyotype.[107,109,112] This was corroborated in a large meta-analysis of prospective trials of allogeneic vs. non-allogeneic therapy for AML in CR1.[113] Similar benefits were suggested for patients with *FLT3*-mutated/*NPM1*-WT cytogenetically-normal-AML (CN-AML), but not in those who had *NPM1*-mutated/*FLT3*-WT AML.[36] Retrospective studies in patients receiving allogeneic matched unrelated donor (MUD) SCTs have reported long-term OS rates of 44 – 78% and DFS rates of 43 – 70%, with a potentially greater benefit in those with adverse prognosis AML[114-117] (Table 3). TRM ranged from 17 – 24% in sibling SCTs vs. 15 – 30% in MUD SCTs. Unfortunately, allogeneic SCT is not universally available or feasible, particularly in the older population that constitutes the majority of patients with AML. Furthermore, much of the data comparing allogeneic SCT to chemotherapy does not account for the inherent bias that exists when selecting patients for transplant. With the development of novel strategies such as non-myeloablative transplant procedures, improved supportive care measures, and expansion of the donor pool (using alternative donor sources), the transplant option is also evolving.

Our approach to allogeneic SCT for patients with AML in CR1 follows a multidisciplinary, risk-adapted approach that considers age, PS, comorbidities, and AML prognosis. Patients with favorable karyotype AML or CN-AML with *NPM1*-mutated/*FLT3*-WT are not referred for SCT in CR1. High-risk patients, such as those defined as having an adverse prognosis based on karyotype, presence of dysplasia, refractory disease, or persistence of minimal residual disease (MRD), are referred early in their course for SCT consultation. Innovations in reduced-intensity conditioning and the wider use of alternative donor sources (cord blood, haploidentical transplants) have expanded the number of patients who are candidates for SCT. With the increased use of FLT3 inhibitors in patients with *FLT3*-ITD AML, and improved DFS rates with these agents, we are currently limiting SCT consideration to those patients with the lowest expected TRM (ie. excellent physical condition, fully matched sibling donor). While allogeneic SCT and the concept of lifelong immunosurveillance to reduce relapse is an important option for high-risk patients with AML, it may be a blunt instrument where more precision is needed. Advances in the research in chimeric-antigen-receptor (CAR) modified T-cells, specific monoclonal antibodies, and newer immune checkpoint inhibitors give us a glimpse of the hopeful future progress in AML.

Future of Molecularly-Based AML Treatment

The impact of recurring cytogenetic alterations on prognosis in AML has been known for decades. As mentioned, recurrent mutations in FLT3 and NPM1 also play an important role

in prognosis and treatment selection. Advances in whole genome deep-sequencing and targeted gene sequencing have uncovered several recurrent somatic mutations that begin to define the landscape of normal karyotype AML.[118] The prognostic significance of these mutations and their relation to the pathogenesis of AML are the focus of intense research endeavors.

The *DNTM3A* gene encodes DNA methyltransferase, an enzyme important in cytosine methylation and thus a key component of the cell epigenetic machinery. Ley et. al. first reported on recurrent, functionally-significant mutations in *DNMT3A* in 22% of patients with intermediate karyotype AML.[119] Mutations in *DNMT3A* were associated with concurrent mutations in FLT3 and NPM1 and were not seen in patients with a favorable karyotype. *DNMT3A* mutations were associated with an adverse prognosis among patients with a diploid karyotype, in patients with FLT3 mutation, and in all age groups. In a separate cohort of 489 patients < 60 years, Thol et. al.[120] confirmed the incidence of *DNMT3A* in 18% of cases and its adverse prognosis in diploid karyotype AML.

Similarly, whole-genome sequencing led to the discovery of recurrent somatic point mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene, and its isoform *IDH2*, in 7 – 19% cases of AML, particularly enriched in cases with a diploid karyotype. Others have confirmed the incidence of these mutations and their possible adverse prognosis, but limited to patients with normal karyotype AML who are NPM1 mutated and FLT3 wildtype.[121-128]

The recurrent mutations in the *IDH* genes are point mutations in “hotspot” regions that lead to alterations in amino acids such as R132 (IDH1) or R140 (IDH2). This prompted further research to determine their functional significance. Isocitrate dehydrogenase is normally involved in the Krebs cycle, in the metabolism of α-ketoglutarate. Mutations in these hotspot regions lead to a neomorphic activity of the enzyme that results in the aberrant accumulation of the metabolite 2-hydroxyglutarate (2HG).[129,130] 2HG is implicated in dysregulating several enzymes involved in epigenetic modulation of DNA, leading to hypermethylation, and thereby contributing to AML pathogenesis.[131] Based on this discovery, small molecule inhibitors are being developed to inhibit the neomorphic enzyme, reduce 2HG levels, and potentially have clinical benefit. After promising preclinical studies, one compound, AG-221, an orally bioavailable, reversible inhibitor of mutant IDH2, entered a phase I dose-escalation trial. Stein et. al presented early findings in 19 patients treated with AG-221 30 mg orally twice daily to 100 mg orally daily with good tolerance and no dose-limiting toxicities.[132] Pharmacodynamic studies confirmed sustained reduction in 2HG levels by up to 97%. Of 10 evaluable patients, 6 had objective responses, including 2 complete responses. Responses occurred with morphologic “differentiation” or maturation of blasts and recovery of blood counts. The study is ongoing and may represent an important breakthrough in this subset of AML.

RAS is a GTP-dependent second messenger protein that couples signals from receptor tyrosine kinases to downstream signaling networks. Mutations in RAS lead to constitutive signaling, are among the most common mutations in human cancer, are present in 10-25% of cases of AML, and are often associated with inv(16) karyotype.[133,134] The prognostic significance of RAS mutations in AML is unclear, but recent data suggest a benefit from

post remission therapy with HiDAC consolidation.[134] Since mutated RAS could be a potential driver mutation and lead to constitutive downstream activation of Mek, inhibiting this pathway could be clinically relevant. Borthakur, et. al. tested the activity of the Mek inhibitor trametinib in patients with relapsed and refractory AML.[135] In a cohort enriched for patients with activating RAS mutations, they reported a response rate of 28% including 12% CR with the single-agent. Compensatory upregulation of parallel pathways could account for resistance to single-agent Mek inhibitor treatment. Indeed, proteomic analysis of patients with RAS-mutated AML demonstrated upregulation of both the RAS-MAPK and PI3K-AKT signaling pathways, providing a rationale for combination treatment in this subset of patients.[133] A trial combining trametinib and the AKT inhibitor GSK2141795 to test this hypothesis in patients with RAS-mutated AML is currently underway (NCT01907815).

Other recurrent mutations in genes such as TET2, RUNX1 and TP53, as well as differential DNA methylation patterns have been described in AML.[118] Abnormalities in genes of histone modifying proteins such as MLL, ASXL1, KDM6A (UTX), and EZH2, imply an important role of chromatin regulation in the pathogenesis of AML. The relevance of these genetic and epigenetic changes in determining prognosis and treatment is the subject of ongoing research. As our understanding of the biology of AML increases, we will recognize even more distinct diseases entities and favor specific, individualized treatment paradigms for more AML “subtypes” over non-specific AML therapies.

Conclusion

Through collaborative research and education, important progress in the diagnosis and management of patients with AML has occurred. First, we have come to recognize AML heterogeneity – not just as a function of the underlying molecular abnormalities, but also accounting for age, comorbidities, functional performance, and patient preference. The answer to AML treatment in the current era is no longer “7+3”, but rather a risk-adapted approach, weighing patient and disease characteristics. Younger patients are offered intensive multidrug combinations for the chance to optimize remission rates and improve overall survival. Older patients with adverse-risk disease and/or not fit for intensive chemotherapy are offered clinical trials investigating low-intensity, prolonged therapy to achieve and maintain remissions. Targetable molecular abnormalities are recognized early, and targeted therapies are offered when appropriate. Specific subtypes such as APL or CBF leukemias are offered specific and intense treatment to maximize the potential for cure. The future of AML treatment is extremely hopeful. A recent renaissance of discovery in AML has revealed several clues into the underlying pathophysiology of AML and collaborative efforts are underway to translate these findings into improved therapies for patients.

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Table 1

Recent Studies in CBF AML

Study - Year	Regimen		N	Median Age	% CR/CRp	RFS / EFS	OS
Borthakur - 2008	**FLAG**		**22**	39	94	3-Yr RFS: 86% vs. 57% for FLAG vs. IA	3-Yr OS: 80% vs. 66% for FLAG vs. IA
	FA		**45**	47			
	IA +/− GCSF		**47**	36			
Borthakur - 2012	**FLAG-GO**		**50**	48	96	85%	78%
Borthakur - 2013	**FLAG-Ida**		**38**	51	98	No difference vs FLAG-GO	No difference vs FLAG-GO
Burnett - 2011	**ADE/DA 3+10/FLAG-Ida**	**+ GO**	**72**	49	85[a]	NR	79% vs. 51% in favor of + GO (p=0.001)
		− GO	**65**	49	87[a]		
Petersdorf - 2013	**Dauno 45mg/m^2 +AraC**	**+ GO**	**37**	47	78	Significantly better for +GO in CBF (p=0.043)	Trend towards benefit for CBF in +GO (p=0.12)
	Dauno 60mg/m^2 +AraC	**− GO**	**44**	48	93		

N: number of patients; CR: complete remission; CRp: CR with incomplete platelet recovery; RFS: Relapse-free survival; EFS: Event-free survival; OS: Overall survival; FLAG: Fludarabine, HiDAC, + GCSF (filgrastim); FA: Fludarabine + HiDAC; IA: Idarubicin(Ida) + HiDAC; GO: Gemtuzumab ozogamicin; ADE: araC+Daunorubicin (dauno)+Etoposide; DA 3+10: 3 days of Dauno + 10 days of araC; CBF: Core-binding factor leukemia.

[a]Represents CR in all patients, whereas other values are CR only in CBF subset; NR: not reported.

Table 2

Studies of Sibling Allogeneic SCT vs. Chemotherapy in AML in CR1

Study - Year	Age (Years)	% TRM		% Relapse Rate		% 4-year DFS		% 4-year OS	
		Allo	Chemo	Allo	Chemo	Allo	Chemo	Allo	Chemo
Zittoun - 1995	11 - 55	17	7	24	57	55	30	59	46
Harosseau - 1997	15 -50	22	3	37	55	50	43	55	59
Cassileth - 1998	16 - 55	21	3	29	61	43	35	40	52
Burnett - 2002	< 55	24	8	36	52	50[a]	42[a]	56[a]	50[a]
Cornelissen - 2007	< 55	21	4	32	59	48	37	54	46

TRM: treatment-related mortality; DFS: Disease-free survival; OS: Overall survival; Allo: Allogeneic stem cell transplantation; Chemo: Consolidation chemotherapy;

[a]Represents 7-year data.

Table 3

Studies of Matched Unrelated Donor Allogeneic SCT in AML in CR1

Study - Year	% TRM		% EFS / LFS[b]		% OS	
	MUD	Other	MUD	Other	MUD	Other
Sierra - 2000			5-yr LFS - 50			
Yakoub-Agha - 2006	29	24[c]	2-yr EFS - 55	56[c]	2-yr - 58	64[c]
Lazarus - 2006	30	6[a]	3-yr LFS - 43	53[a]	3-yr - 44	57[a]
Bashir - 2011	15		3-yr EFS - 70		3-yr - 78	

TRM: treatment-related mortality; EFS: Event-free survival; LFS: Leukemia-free survival OS: Overall survival; MUD: Matched unrelated donor allogeneic stem cell transplantation; Other: refers to either-

(b) matched sibling donor allogeneic stem cell transplant or

(c) autologous stem cell transplant;

(a) Values in this column represent EFS except where indicated.