

In this month's Leukemia Insights newsletter, written by Yesid Alvarado, MD, and Farhad Ravandi, MD, and sponsored in part by the Charif Souki Cancer Research Fund, we discuss novel targeted therapies for the treatment of patients with acute myeloid leukemia (AML).

Novel Targeted Therapies for Patients with Acute Myeloid Leukemia (AML)

Introduction

For decades, treatment of acute myeloid leukemia (AML) has included a combination of cytarabine and an anthracycline with a long term cure rate of only around 30-40%. With increased understanding of disease biology, more effective targeted strategy for specific AML subsets such as acute promyelocytic leukemia (APL) and core binding factor (CBF) leukemias have been developed with the expectation of long term relapse free survival ranging around 85-95% in APL, and 80-85% in CBF leukemias. Furthermore, significant advances in genomic sequencing, have led to better risk classification and molecular profiling of AML subgroups. These advances in turn have led to the development of novel effective targeted therapies that are having a significant impact in the landscape of AML therapeutics. Despite the recent explosion of new available therapies, much remains to be learned about the optimal way of administering them in different combinations and for that reason all patients should be evaluated for entry into a clinical trial. At [MD Anderson Cancer Center](#), our AML research program aims to improve patient outcomes and we have several clinical trials testing on novel approaches to build on the recent progress seen in the field. Below we list and give a brief rationale about some of our important treatment priorities based on specific patient and disease characteristics.

Frontline Trials for Newly Diagnosed AML

Not APL, not CBF: Age < 65

- Cladribine + Ida + Ara-C + Venetoclax ([NCT02115295](#))
- FLAG-Ida + Venetoclax ([NCT03214562](#))
- CPX-351 + Venetoclax ([NCT03629171](#))
- Dexrazonane + CLIA + Gemtuzumab ([NCT03589729](#))

We treat younger patients with AML with novel regimens that incorporate higher-dose cytarabine, idarubicin, and a nucleoside analog in induction and consolidation. We are now exploring benefits of adding targeted therapy with a specific small molecule inhibitor, based on the patient's molecular profile (e.g. BCL-2, FLT3, IDH 1 or 2, BCR-ABL inhibitors) and a CD33 antibody drug conjugate.

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BCL-2 Inhibitor

A novel therapeutic target in AML is the intrinsic or mitochondrial pathway of apoptosis. Overexpression of the anti-apoptotic protein BCL-2 is associated with the initiation, progression and drug resistance of hematologic malignancies including AML. Venetoclax is a potent and selective small molecule inhibitor of BCL-2 with demonstrated activity against AML, both as a single agent in relapsed/refractory AML and in frontline combination therapy approaches with hypomethylating agents and low-dose cytarabine. The ability of venetoclax to reduce the apoptotic threshold makes it an ideal agent to combine with genotoxic agents which induce apoptosis, such as the FLAG-IDA or CLIA chemotherapy regimens.

FLT3 Inhibitor

Activating mutations in FMS-like tyrosine kinase-3 (FLT3) receptor tyrosine kinase are present in approximately a third of patients with AML. Activating mutations can be internal tandem duplication (ITD) of the juxtamembrane domain or point mutations in the tyrosine kinase domain (TKD) of FLT3. Several studies have demonstrated that patients with FLT3 mutated disease benefit from a FLT3 inhibitor during induction and consolidation. We have previously shown that combining sorafenib with chemotherapy in patients with FLT3-ITD mutations is both safe and efficacious. Most recently midostaurin, a type I FLT3 inhibitor that has activity against both the FLT3-ITD mutations as well as FLT3-D835 mutations, led to a significant improvement in survival and was approved in combination with chemotherapy based on the results of the phase III randomized double-blind RATIFY study. Similarly, gilteritinib is a type I FLT3 inhibitor with activity against both the FLT3-ITD and D835 mutations. [Gilteritinib was approved by the U.S. Food and Drug Administration \(FDA\) on November 28, 2018](#) based on the results from ADMIRAL study, and has demonstrated safety and tolerability in combination with chemotherapy.

IDH Inhibitor

Recurrent somatic mutations in the genes isocitrate dehydrogenase 1/2 ([IDH2](#) and [IDH1](#)) have been identified in approximately 20% of patients with AML, often seen in patients with normal karyotype and co-occurrence of FLT3 and/or NPM1 mutations. Such mutations lead to aberrant production of the oncometabolite 2-hydroxyglutarate (2-HG). This oncometabolite leads to dysregulated epigenetic function, a hypermethylated phenotype, and a block in maturation leading to leukemogenesis. Enasidenib and ivosidenib, the IDH2 and IDH1 inhibitors, have been approved by the U.S. Food and Drug Administration (FDA) on [August 1, 2017](#) and [July 20, 2018](#) for the treatment of adult relapsed or refractory (R/R) AML with IDH2 and IDH1 mutations, respectively.

BCR-ABL Inhibitor

Patients with the presence of the Philadelphia chromosome [translocation (9;22)] or the presence of the bcr-abl fusion gene (detected by PCR or FISH) such as those with CML myeloid blast phase or “Philadelphia-positive AML” may benefit from concomitant therapy with an abl tyrosine kinase inhibitor (TKI). Several orally bioavailable TKIs have now been FDA approved for Philadelphia positive CML and their selection is based on patient tolerance, comorbidities, and the presence abl kinase domain mutations.

Dexrazoxane

Dexrazoxane is a broad-spectrum metal chelator approved by the U.S. Food and Drug Administration (FDA) in 1995 for cardio protection during treatment of patients with advanced breast cancer who have already reached a cumulative anthracycline dose and who are continuing to receive doxorubicin. As demonstrated by [Emil J Freireich, MD](#), and colleagues, when dexrazoxane is combined with anthracyclines, it leads to synergistic anti-leukemic and cytotoxic responses in AML cell lines. We aim to show the feasibility of the combination of dexrazoxane with idarubicin during treatment of AML, while avoiding long-term cardiotoxicity. Dexrazoxane exerts its cardioprotective activity by interfering with site-specific iron-based oxidative damage to cardiac mitochondria. Dexrazoxane has also been extensively utilized in children with leukemia and lymphoma in order to reduce the long term cardiovascular effects of intensive anthracycline-containing chemotherapy.

Liposomal Daunorubicin and Cytarabine

CPX-351 is an encapsulated liposomal formulation of a fixed combination of cytarabine and daunorubicin in a 5:1 molar ratio that markedly increases the plasma half-life of both drugs and leads to their accumulation within leukemic blasts in the marrow. Although CPX-351 failed to increase OS when compared with “7+3” in patients 60–75 years as first line therapy, the compound showed higher response rates, it did not show an increase in 30-day treatment-related mortality, and a pre-planned analysis identified a superior CR rate and OS for CPX-351 in patients with secondary AML. CPX-351 was approved after a pivotal phase III study in patients aged 60–75 years with a history of prior cytotoxic treatment, antecedent MDS or CMML, or AML with WHO-defined MDS-related cytogenetic abnormalities, confirmed the higher CR rate and OS for CPX-351 over 7+3 (60 mg/m²daunorubicin).

Core binding factor (CBF) AML: Inversion 16 and translocation (8;21)

- **Fludarabine + Ara-C + G-CSF + Gemtuzumab/Idarubicin** ([NCT00801489](#))

Studies comparing consolidation strategies reported cure rates in CBF AML of 30–40% with one high-dose cytarabine consolidation versus 50–70% with 3–4 consolidation courses. In the MD Anderson studies, the use of fludarabine with high-dose cytarabine and GO (or idarubicin) during induction and consolidations, the application of 4–6 consolidation courses, and modifying therapy for persistent MRD resulted in cure rates of 80% in both inversion 16 and t(8;21) AML. The MRC trials using the fludarabine, high-dose cytarabine, and idarubicin combination (FLAG-Ida regimen) have reported estimated cure rates of 80–90% in CBF AML. Addition of a small dose of GO to induction and consolidation has been shown in multiple randomized trials to significantly benefit patients with CBF AML.

Acute Promyelocytic Leukemia: translocation (15;17)

- **ATRA and arsenic +/- Gemtuzumab (GO)** ([NCT01409161](#))

The non-chemotherapy regimen of ATRA plus arsenic trioxide is considered today a standard of care in patients with standard risk APL. With such regimens, the CR rates are 95–100% and the cure rates over 95%. Patients with high-risk APL, defined by high white cell count over $10 \times 10^9/L$ at diagnosis, have a worse outcome (estimated cure rate 80%) and benefit from the addition of GO or anthracycline.

1(GO)

The myeloid-lineage surface antigen, cluster of differentiation 33 (CD33), is expressed in more than 80% of leukemia isolates from patients with AML. GO is an immunoconjugate, combining an anti-CD33 monoclonal antibody to calicheamicin, a highly cytotoxic antibiotic. After binding to the CD33 antigen, the complex is internalized, the calicheamicin derivative is released inside the lysosomes of the myeloid cell and binds to DNA, which results in DNA double strand breaks and cell death. It was first reported to be effective in producing responses in about 30% of older patients with AML in first relapse. Over the next decade, several large international studies showed encouraging results, suggesting that optimization of the dose and schedules of combination regimens with GO may be beneficial in specific subsets of patients with AML. Experience from these studies led to the [FDA approval of GO on September 1, 2017](#).

Therapy for Elderly or Debilitated Patients

Age \geq 65 or patients not fit for intensive chemotherapy

Older patients experience shorter remissions, shorter relapse-free and overall survival, and considerably higher treatment-related mortality than younger patients. Patients older than 75 years in particular, are more likely to have unfavorable cytogenetics (mostly complex) and multidrug resistance, as well as poor performance status (PS), organ dysfunction, comorbid conditions, and antecedent hematologic disorders. CR is achieved in ~50% of patients aged >60 if they are treated with cytarabine + anthracycline regimens, but most patients relapse and $<10\%$ become long-term survivors. Older patients can be offered established or investigational low-intensity strategies combining epigenetic therapy with targeted agents (e.g. CD33 antibodies, FLT3 inhibitors, IDH1/2 inhibitors, and CD123 targeted agents).

Decitabine and azacitidine are pyrimidine analogs with significant antileukemic activity. Cladribine, a purine nucleoside with single-agent and combination activity in AML, was also shown to induce DNA hypomethylation, by a mechanism distinct from traditional DNA methyltransferase inhibitors. The combination of cladribine and low-dose cytarabine alternating with decitabine appears to be a safe and highly effective regimen for the treatment of elderly or unfit patients with newly diagnosed AML. Partnering these agents in a protocol that incorporates a BCL2 inhibitor could be complementary, overcoming potential resistance mechanisms, and translating into clinical benefit. Immunomodulatory strategies with checkpoint inhibitors and targeted antibodies may soon deliver therapeutic breakthroughs in AML therapy.

- **Cladribine + LD Ara-C alternating Decitabine** ([NCT01515527](#))
- **Venetoclax + cladribine + LD Ara-C alternating Azacitidine** ([NCT03586609](#))
- **Nivolumab + Ipilimumab + AZA** ([NCT02397720](#))
- **Venetoclax + DAC** ([NCT03404193](#))
- **AZA + Venetoclax + Pevonedistat** ([NCT03862157](#))
- **BP1001 + LD Ara-C** ([NCT02781883](#))
- **Ivosidenib + Aza + Venetoclax** ([NCT03471260](#))
- **Enasidenib + Aza +/- Venetoclax** ([NCT03683433](#))
- **Quizartinib + DAC + Venetoclax** ([NCT03661307](#))
- **AZA +/- Pracinostat** ([NCT03151408](#))

Other Selected Studies:

- **BP1001 + Dasatinib** ([NCT02923986](#))
- **FT-2102 +/- AZA** ([NCT02719574](#))
- **PDR001 +/- MBG453 +/- DAC** ([NCT03066648](#))

Selected Monoclonal Antibody Trials

Monoclonal antibodies targeting cluster designation (CD) surface molecules have significantly improved the outcomes in patients with lymphoid malignancies. Monoclonal antibodies may have also a significant role in the treatment of AML, as highlighted by the experience with GO. Other CD33 monoclonal antibodies are under development. The bispecific T-cell engaging antibody (BiTE) technology utilizes monoclonal antibodies that recruit CD3-effector T cells to target tumor cells. This BiTE technology has been successful in the treatment of ALL, where a CD19-CD3 engaging monoclonal antibody, blinatumomab, showed significant activity, resulting in its FDA approval for ALL. A similar approach is being investigated with other monoclonal antibodies directed against CD123, the alpha-subunit of the interleukin-3 receptor (IL-3R α). CD123 levels of normal hematopoietic stem cells are very low, but early common myeloid progenitors express higher CD123 levels and expression is greater than 95% in AML cells.

BiTE (bispecific T cell engagers):

- **AMG330 (CD33/CD3)** ([NCT02520427](#))
- **AMG673 (CD33/CD3)** ([NCT03224819](#))
- **AMV564 (CD33/CD3)** ([NCT03144245](#))
- **Xmab14045 (CD123/CD3)** ([NCT02730312](#))
- **AMG427 (FLT3/CD3)** ([NCT03541369](#))
- **MGD006 (CD123/CD3) DART** ([NCT02152956](#))
- **MCLA-117 (CLEC12A/CD3)** ([NCT03038230](#))

Antibody Drug Conjugates (ADC):

- **SL-401(CD123-Diphtheria Toxin) + Aza** ([NCT03113643](#))
- **IMGN632(CD123-DNA-alkylating agent DGN549-C) + Venetoclax +/- Aza** ([NCT04086264](#))
- **DCLL9718S [CLL-1: C-type lectin-like molecule-1 antibody linked to pyrrolobenzodiazepine (PBD)]+ AZA** ([NCT03298516](#))
- **MEDI-7247 (ASCT2). Na⁺ dependent alanine-serine-cysteine transporter 2, linked to PBD** ([NCT03106428](#))

Other:

- **HU8F4 (PR1/HLA-A2)** a novel humanized T cell receptor-like monoclonal antibody that binds to the conformational epitope of PR1 bound to HLA-A2 (PR1/HLA-A2) expressed on the surface of AML. ([NCT02530034](#))
- **Hu5f-G4 (CD47) + Aza** ([NCT03922477](#)) a humanized monoclonal antibody that blocks the anti-phagocytic signal CD47, which is highly expressed on cancer cells including AML and serves as a key immune evasion signal for cancers.

Salvage Protocols

With traditional anthracycline plus cytarabine based regimens, expected complete remission (CR) rates are 60-70% and long term cures are about 25%. Younger patients with diploid karyotypes have a CR rate of about 80% and cures rates of about 25%, while older patient and/or those with adverse cytogenetics have CR rates of 35-50% and cure rates of less than 10%. Accordingly, approximately 30% of patients do not benefit from first line therapy (primary refractory disease), and of the remaining 70% of patients who receive first line therapy and achieve CR, around 60% would be expected to experience recurrent disease, which means that almost 80% of all AML patients will experience either refractory disease or relapse after standard therapy. Survival of patients with relapsed AML is dependent on patient age and the duration of the first remission. In first relapse AML typical therapies include salvage chemotherapy, often cytarabine at various dosages and regimens, which have a second response rate around 40%, however disease recurrence is still prevalent, with reported median survival of approximately 12 months or less. Following failure of salvage therapy, patients often have multiple comorbidities with depressed bone marrow function, and their median overall survival is around 1.5 months. Treatment in a clinical trial is generally recommended for patients with relapsed AML.

- **Cladribine + Ida + Ara-C + Venetoclax** ([NCT02115295](#))
- **FLAG-Ida + Venetoclax** ([NCT03214562](#))
- **Dexrazonane + CLIA + Gemtuzumab** ([NCT03589729](#))
- **CPX-351 + GO** ([NCT03672539](#))
- **Decitabine + FIA + Ven- Followed by ALLO SCT** ([NCT02250937](#))
- **Quizartinib + DAC + Venetoclax** ([NCT03661307](#))
- **Quizartinib + DS3032b** ([NCT03552029](#))
- **Sapacitabine + Venetoclax** ([NCT01211457](#))
- **CYC-065 (CDK9 inhibitor) + Venetoclax** ([NCT04017546](#))
- **S64315 (MCL-1 inhibitor) + Venetoclax** ([NCT03672695](#))
- **Azacitidine + Venetoclax + Gilteritinib** ([NCT04140487](#))
- **Venetoclax + Quizartinib** ([NCT03735875](#))
- **AZA + PLX51107** ([NCT04022785](#))
- **AZA-Ven+ (GO/Atezo) or OX40 or GO-Glasdegib** ([NCT03390296](#))

Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress.

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