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In this month's Leukemia Insights newsletter, written by Alexandre Bazinet, M.D., and Farhad Ravandi, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we outline clinical trials offered for patients with myeloproliferative neoplasms. Learn more about our Leukemia program.

Acute myeloid leukemia therapy in older adults: A shift towards highly effective targeted oral therapies

1. Introduction

Acute myeloid leukemia (AML) demonstrates an increased incidence in older patients, with a median age at diagnosis of 68 years.[1] It is the most common acute leukemia in adults and responsible for considerable morbidity and mortality. Standard therapy for AML is generally based on intensive chemotherapy composed of cytarabine and anthracyclines. Older patients with AML (usually defined as aged 60 years and above) have inferior outcomes compared to younger patients due to adverse disease biology and increased toxicity from therapy.[2] Historically, therapies for older patients with AML ineligible for standard chemotherapy consisted of hypomethylating agents (HMAs) alone (azacitidine, decitabine), low-dose cytarabine, or best supportive care. These were generally poorly effective and resulted in short survival.[3]

The development of the oral BCL-2 inhibitor venetoclax has dramatically altered the therapeutic landscape for older patients with AML. AML blasts leverage BCL-2 to sequester pro-apoptotic proteins, thus evading apoptosis, a process referred to as "priming". Release of these pro-apoptotic proteins by venetoclax results in leukemic cell apoptosis.[4] As monotherapy, venetoclax demonstrates limited activity in AML.[5] However, the combination of venetoclax with low-intensity chemotherapy such as HMAs or cytarabine is effective in inducing remissions and prolonging survival in AML.[6, 7] In 2020, the randomized VIALE-A study established the superiority of azacitidine plus venetoclax over azacitidine alone in terms of remission rates and overall survival (OS).[6] This defined a new standard of care in patients with AML ineligible for intensive chemotherapy. Multiple retrospective studies have shown that low-intensity therapy such as azacitidine plus venetoclax compares favorably to intensive chemotherapy in terms of the risk-benefit ratio in older patients with AML.[8, 9] In addition, a

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randomized study comparing low-intensity versus intensive chemotherapy in patients potentially eligible for both is ongoing (NCT04801797).

Azacitidine plus venetoclax requires parenteral administration of the azacitidine component, generally consisting of 7 days of infusion clinic visits or subcutaneous injections. This makes the regimen less portable, is inconvenient in an older and/or frail population and poses a strain on caregivers. Fully oral regimens are generally preferred by patients and caregivers.

ASTX727 (decitabine/cedazuridine) is an oral formulation of the HMA decitabine with demonstrated area-under-curve (AUC) equivalence.[10] With the advent of oral HMAs such as ASTX727, effective fully oral combination regimens are now a possibility for the treatment of AML.

2. ASTX727 (decitabine/cedazuridine) plus venetoclax: A new backbone on which to build

We evaluated the fully oral combination of ASTX727 plus venetoclax in 49 patients with newly diagnosed AML at MD Anderson Cancer Center in a phase 2 study. The combination was generally well tolerated and resulted in an overall response rate of 64% and a median OS of 11.5 months in the frontline setting. When excluding patients with treated secondary AML to obtain a population comparable to VIALE-A, the median OS was 13.5 months, similar to that obtained with parenteral azacitidine plus venetoclax in VIALE-A (14.7 months).[11] Although our practice is to admit patients during the induction cycle for close monitoring, consolidation cycles can be given in the outpatient setting with close monitoring of blood counts, prophylactic antibiotics, and transfusion support if needed. This oral regimen is convenient for patients and caregivers. This study is open for further recruitment at MD Anderson.

The benefit of ASTX727 plus venetoclax is not uniform across AML subgroups. In patients with AML, risk stratification has traditionally been performed using the ELN classification, which is validated in patients treated with intensive chemotherapy. However, the ELN risk stratification performs poorly in patients treated with HMA plus venetoclax doublets. Recently, a novel system has been proposed to predict the expected benefit with HMA plus venetoclax based on the mutational status of 4 genes (FLT3-ITD, NRAS, KRAS, and TP53). Patients without any such mutations are expected to derive the most benefit. Patients with FLT3-ITD and/or N/KRAS mutations derive an intermediate benefit while patients with TP53 have a low benefit.[12] In our study of ASTX727 plus venetoclax, patients with high, intermediate, and low predicted benefit using the above system had a median OS of 16.2, 9.1, and 2.0 months, respectively.[11]

3. Building on the ASTX727 plus venetoclax backbone with targeted agents: Fully oral triplet combinations

AML is a genetically heterogeneous disease. Numerous chromosomal and genetic alterations have been described, many of which are amenable to direct targeting using oral small molecule inhibitors. We established previously that 44% of patients with AML aged 60 years and over had a targetable genetic abnormality, namely FLT3-ITD or TKD, IDH1, IDH2, NPM1, or KMT2A rearrangements.[13] In patients harboring these genetic changes, the addition of a third targeted agent to ASTX727 plus venetoclax (within oral triplet regimens) is an attractive strategy to potentially enhance efficacy.

3.1 FLT3-mutated AML

FLT3 mutations, consisting of either internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutations are one of the most common genetic lesions in AML. They are identified in approximately 20% of older patients with AML.[13] FLT3-ITD confers an adverse prognosis, with shortened remissions and OS.[14] FLT3-ITD mutations are also an adaptive resistance mechanism to venetoclax-based therapy.[15]

Gilteritinib is a small molecule FLT3 inhibitor active in both FLT3-ITD and FLT3-TKD. In the phase 3 LACEWING study, the addition of gilteritinib to azacitidine did not improve OS compared to azacitidine alone, although this study was not blinded and many patients in the azacitidine arm went off study early and subsequently received gilteritinib.[16] Given the synergy between FLT3 inhibitors and venetoclax,[17] triplet regimens consisting of HMA plus venetoclax plus a FLT3 inhibitor are currently being investigated. In a phase 1/2 study, the combination of azacitidine, venetoclax, and gilteritinib was evaluated in 52 patients with FLT3 -mutated AML (30 frontline, 22 relapsed/refractory). The triplet combination demonstrated very high response rates (90% complete remission [CR], 6% CR with incomplete blood count recovery [CRi]). The 18-month OS and relapse-free survival (RFS) were 72% and 71%, respectively. Additive toxicity is a concern with the administration of an increasing number of drugs. Therefore, venetoclax duration was limited to 14 days in induction (assuming bone marrow blast clearance on day 14) and to 7 days in consolidation.[18]

An oral adaptation of this regimen consisting of ASTX727, venetoclax, and gilteritinib is currently available as a clinical trial at MDACC. Early results of this study in relapsed/refractory AML (n=15) showed an overall response rate of 53%.[19] This study is currently open for enrollment in patients with newly diagnosed FLT3-mutated AML who are age ≥ 75 years or ineligible for intensive chemotherapy.

3.2 IDH1 and IDH2-mutated AML

Mutations in IDH1 and IDH2 are respectively identified in 8% and 13% of older patients with AML.[13] Mutated IDH enzymes generate the oncometabolite 2-hydroxyglutarate (2-HG), which leads to DNA hypermethylation and alterations in gene expression and differentiation.[20] Importantly, these cellular effects are reversible with elimination of 2-HG.[21] The IDH1 inhibitor ivosidenib and IDH2 inhibitor enasidenib are both active as single agents in IDH-mutated AML.[22, 23] In addition, the combination of the IDH1 inhibitor ivosidenib with azacitidine has been shown to result in superior rates of CR/CRi and longer OS compared to azacitidine alone in a phase 3 randomized trial.[24] The addition of enasidenib to azacitidine was shown to improve overall response rates compared to azacitidine alone in a phase 1b/2 trial.[25] Furthermore, AML with IDH1 or IDH2 mutations display heightened sensitivity to venetoclax.[15, 26] Therefore, triplet regimens incorporating an HMA, venetoclax, and the appropriate IDH inhibitor are emerging strategies in IDH1 and IDH2-mutated AML ineligible for intensive chemotherapy.

Early data evaluating the combination of azacitidine, venetoclax, and ivosidenib in IDH1-mutated myeloid neoplasms (n=19) demonstrated an overall response rate of 100% and 12-month OS of 85%.[27] The azacitidine, venetoclax, and enasidenib triplet was evaluated in 7 patients with relapsed/refractory IDH2 -mutated AML and showed a CR/CRi rate of 86% and 6-month OS of 70%.[28]

By replacing azacitidine with oral ASTX727 as the HMA backbone, an oral triplet combination comprising ASTX727 plus venetoclax plus either ivosidenib or enasidenib has been developed and is currently being evaluated at MDACC in a phase 1b/2 trial. In the 50 frontline patients currently enrolled and evaluable for response, the CR/CRh/CRi rate is 96% and the median OS is not yet reached.[29]

3.3 NPM1-mutated and KMT2A-rearranged AML

NPM1 mutations are identified in 20% of older patients with AML. *KMT2A* (formerly *MLL*), located on chromosome 11q23, is rearranged (*KMT2A*r) more commonly in younger patients (12%) compared to older patients (3%).[13] Acute leukemias with *NPM1* or *KMT2A*r depend on an aberrant *HOX-MEIS1* gene expression

program. The protein menin is a key co-factor for this gene expression program and is susceptible to inhibition by oral small molecule inhibitors.[30] Of note, many other AML genotypes are predicted to rely on this *HOX-MEIS1* gene expression program and may also exhibit sensitivity to menin inhibition. This is an active field of research.[30]

Although many menin inhibitors are currently in clinical development, SNDX-5613 (revumenib) is currently the most studied. As a single agent in relapsed/refractory AML with *NPM1* or *KMTA*r, treatment with revumenib resulted in an impressive overall response rate of 53%.[31]

The phase 1/2 study SAVE is currently evaluating the triplet oral combination of ASTX727, venetoclax, and revumenib in relapsed/refractory AML. Early results of this study have shown an overall response rate of 100% in the first 7 patients treated.[32] This study protocol was recently amended to allow the enrollment of patients with newly diagnosed AML and is currently recruiting at MD Anderson.

4. Maintenance therapy

Consolidative allogeneic stem cell transplantation (SCT) is recommended in most patients with non-favorable risk AML if they are appropriate candidates. Older patients may not be eligible for allogeneic SCT due to frailty, comorbidities, or extremes of age. In addition, some patients may be unable to complete the originally planned therapy due to emergent toxicities or complications. In these cases, prolonged administration of low-dose oral chemotherapy is of interest as a strategy to prevent or delay relapse.

Oral azacitidine (CC-486) is currently approved by the FDA as maintenance therapy in patients with AML in first remission who are ineligible for SCT. We recently published our experience in combining low-dose parenteral azacitidine plus venetoclax as maintenance therapy in AML. In this phase 2 study, maintenance therapy led to a RFS of 56% at 2 years. In patients with genetically sensitive disease (NPM1, IDH1, or IDH2 mutated), RFS was 79% at 2 years.[33]

Given a fully oral regimen is preferable in the maintenance setting for prolonged outpatient administration, we have developed a multi-arm phase 1b study evaluating a maintenance regimen consisting of an ASTX727 backbone combined with physician's choice of a targeted agent (venetoclax, gilteritinib, ivosidenib, or enasidenib) selected based on the individual patient's genetic profile. At the most recent update including 23 patients, the median RFS and OS were not reached in any of the treatment arms.[34]

5. Conclusions

Convenient fully oral regimens are an emerging therapeutic strategy in older or chemotherapy-ineligible patients with AML. Increasing knowledge of the genetic landscape of AML allows these regimens to be personalized to the individual patient via addition of targeted agents. Currently available studies at MD Anderson discussed in this article are summarized in **Table 1**.

Table 1: Clinical trials available at MD Anderson evaluating fully oral regimens in patients with newly diagnosed AML who are ineligible for intensive chemotherapy due to age or comorbidities.

Study ID	Target population	Fully oral regimen
NCT04746235	Any AML	ASTX727 + venetoclax
NCT05010122	*FLT3*-ITD or *FLT3*-TKD mutated	ASTX727 + venetoclax + gilteritinib
NCT04774393	*IDH1*-mutated	ASTX727 + venetoclax + ivosidenib
NCT04774393	*IDH2*-mutated	ASTX727 + venetoclax + enasidenib
NCT05360160	*NPM1*-mutated *KMT2A*-rearranged Other emerging genotypes (NUP98, others)	ASTX727 + venetoclax + revumenib
NCT05010772	Any in remission (maintenance)	ASTX727 + physician's choice (venetoclax, gilteritinib, ivosidenib, or enasidenib)

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