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Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Use of Menin Inhibitors for Acute Leukemia

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H&O What is the mechanism of action of menin inhibitors?

GI Menin inhibitors are a new class of drugs for patients with acute leukemia that work by epigenetic modulation. Menin is a critical protein for some genes that cause leukemia; we can think of it as important for a type of software that is responsible for leukemia development. Menin inhibitors create a wedge between the key and the engine that turns on the software, turning off the software and allowing leukemia cells to revert to normal cells.

H&O What are the indications for treatment with menin inhibitors?

GI The US Food and Drug Administration (FDA) approved revumenib (Revuforj, Syndax) for use in *KMT2A*-rearranged acute leukemia in November 2024 and for use in *NPM1*-mutant acute myeloid leukemia (AML) in October 2025; in both cases, the drug was indicated for use in relapsed or refractory disease in patients aged 1 year and older. Ziftomenib (Komzifti, Kura Oncology) received FDA approval in November 2025 for use in adults with relapsed or refractory AML with *NPM1* mutations who have no satisfactory alternative treatment options. Ziftomenib is also being studied for use in *KMT2A*-rearranged leukemias (NCT06930352).

H&O How many patients with AML are now eligible for treatment with a menin inhibitor?

GI The most common mutation in adults with AML is the *NPM1* mutation, which occurs in approximately 25% to 30% of adults with AML. In approximately 70% of these patients, the disease is cured with chemotherapy alone, so relapsed or refractory disease develops in only a fraction of patients with an *NPM1* mutation, and they may benefit from revumenib or ziftomenib. *KMT2A* rearrangements are less common, occurring in 5% to 10% of adults and 80% of infants with newly diagnosed AML. Because leukemia with *KMT2A* rearrangements does not respond to initial treatment with chemotherapy in 40% to 50% of cases and is usually resistant to any other chemotherapy we would use, these patients could benefit from the use of revumenib.

H&O Could you discuss your study that led to the approval of revumenib?

GI Revumenib received approval on the basis of the AUGMENT-101 study. This started as a phase 1 dose escalation study that established the dose of revumenib. Revumenib is affected by CYP3A enzymes in the liver that decrease the amount of medication in the bloodstream. As a result, the initial phase 1 study had 2 arms: one with strong CYP3A inhibitors, which increase the levels of revumenib in the bloodstream, and one without CYP3A inhibitors. We were able to determine a recommended dose of revumenib for use in both these settings. We also saw very early activity of revumenib against acute leukemia.

The open-label phase 2 study that led to approval was separated into 2 cohorts: one for *KMT2A*-rearranged acute leukemia[1] and one for *NPM1*-mutant AML.[2]

The 94 patients in the *KMT2A*-rearranged cohort, who ranged in age from 1 year to 75 years, received a 163-mg revumenib pill twice a day (with lower dosing for patients weighing <40 kg), plus a strong cytochrome P450 inhibitor, in 28-day cycles. The rate of complete remission or complete remission with partial hematologic recovery (CR/CRh) among the 57 efficacy-evaluable patients was 23%, which is higher than the historical rate of less than 10%. The overall response rate, which was based on a reduction in the bone marrow blast level to less than 5%, was 63%. These results led to FDA approval of revumenib in patients with *KMT2A*-rearranged acute leukemia.

Accrual took longer in the *NPM1*-mutated cohort because more options are available for these patients. For example, some patients were able to benefit from targeted therapies for comutations or were still able to respond to chemotherapy. In addition, most of the patients in the *NPM1*-mutated cohort were adults who were heavily pretreated. A total of 84 patients received revumenib at the same dosage as in the *KMT2A*-rearranged cohort. The CR/CRh rate among the 64 patients in the efficacy-evaluable population was the same as in the earlier cohort, at approximately 23%, and the overall response rate was lower, at approximately 47%. The median duration of CR/CRh was 4.7 months. These findings led to the FDA approval of revumenib for adults with *NPM1*-mutant AML.

H&O Could you discuss the study that led to the approval of ziftomenib?

GI KOMET-001 was an open-label, single-arm trial in 112 adults who had relapsed or refractory AML with an *NPM1* mutation.[3] A total of 92 patients aged 33 to 84 years received a 600-mg ziftomenib pill once daily. The CR/CRh rate was 22% and the overall response rate was 33%, with a median duration of response of 4.6 months. These findings led to the FDA approval of ziftomenib for adults with *NPM1*-mutant AML.

H&O What adverse events are seen with menin inhibitors?

GI The biggest concern we have with menin inhibitors is differentiation syndrome, which is something that occurs in acute leukemia or acute promyelocytic leukemia treated with effective targeted agents. Leukemia cells have a differentiation block, which means they should have differentiated and reverted to a normal state, but instead they are stuck in a zombie state in which they retain immature features. Menin inhibitors work by reversing the differentiation block, but for reasons we do not understand, the reversal can lead to an overreaction of the cytokines that is similar to a cytokine storm. This inflammatory state can affect the lungs or the kidneys, can cause chest or bone pain, and can cause pleural or pericardial effusion that has the potential to be fatal. The early use of corticosteroids can reverse this syndrome and allow patients to resume treatment, so it is important to recognize differentiation syndrome early and address it right away. I tell my patients to be on the alert for symptoms such as fever, chest pain, muscle aches, bone aches, and new rash, any of which should prompt a phone call. In the visit, we do blood tests to check for an increase in the white blood cell count and chest radiography to look for fluid around the lung or heart.

A newer type of next-generation sequencing based on RNA sequencing can pick up more *KMT2A* rearrangements.

Approximately 15% of patients who take revumenib require hospitalization for differentiation syndrome. Another class-related adverse event is myelosuppression affecting the platelet count, which may necessitate a blood transfusion. Myelosuppression occurs in approximately 30% of patients taking a menin inhibitor.

An adverse event that is more specific to revumenib is QT prolongation, which also occurs to a lesser extent with ziftomenib and can lead to an abnormal heart rhythm and even cardiac arrest if levels of electrolytes are low, such as low potassium or magnesium. As a result, we monitored patients with multiple electrocardiograms while they were receiving revumenib. If an abnormal heart rhythm is detected, the medicine should be held while it is confirmed that the potassium and magnesium levels are normal and that the patient is not receiving any other medication that could prolong the QT interval. After the QT interval has normalized, the medication can be reintroduced at a lower dose.

The other side effects of revumenib or ziftomenib are less concerning. Approximately 30% of patients taking a menin inhibitor experience nausea or vomiting, but this is usually well controlled with medications such as ondansetron. There is also a theoretical risk that the medication could affect the parathyroids or the thyroid because menin is the protein involved in multiple endocrine neoplasia type 1 (MEN1) syndrome, but we have not seen this in

patients or in the laboratory. An additional adverse event that has been seen with ziftomenib is mild itching.

H&O How do menin inhibitors promote the use of hematopoietic stem cell transplant?

GI AML is difficult to manage because it tends to contain multiple clones. Even if you target one mutation, another one can develop and cause resistance, which is especially common with *NPM1* mutations. As good as menin inhibitors are, the chances of a cure are minimal without a stem cell transplant. At our center, we use revumenib when appropriate to control the leukemia well enough to get the patient to stem cell transplant. In most cases, we resume revumenib after transplant to make sure that leukemia does not come back. This is not an FDA-approved indication, but it is what we do in our practice.

H&O What genetic testing is required before treatment?

GI The standard procedure in any AML workup, even before revumenib and ziftomenib were approved, was next-generation sequencing to look at mutations and common genes in AML, particularly *NPM1,* because this knowledge informs the prognosis and next treatment steps. Next-generation sequencing is even more important now that we have more therapies to target these genetic alterations. We also check for mutations in *FLT3* and *IDH*, both of which have targeted therapies.

The standard genetic testing that we do to detect *KMT2A* rearrangements is fluorescence in situ hybridization, which picks up most cases. A newer type of next-generation sequencing based on RNA sequencing can pick up more *KMT2A* rearrangements, but this test is not in common use right now in the United States.

H&O What research is continuing to examine menin inhibitors?

GI Although the AUGMENT-101 study showed that revumenib works in 2 subtypes of AML, we also found that the duration of response can be limited and resistance can occur. Our next step is to improve on what we have done by lengthening the duration of response, such as by combining revumenib with other drugs that can improve efficacy, hopefully without increasing the risk of adverse events. The biggest leap is in newly diagnosed AML. For example, a phase 3 trial is looking at revumenib in combination with intensive chemotherapy in participants with newly diagnosed *NPM1*-mutated AML; this study includes overall survival at up to 5 years as one of its secondary endpoints (NCT07211958). Phase 2 trials are looking at revumenib in combination with venetoclax (Venclexta, AbbVie/Genentech; NCT06284486) and in combination with chemotherapy (NCT05761171). We also need to learn more about the mechanisms of resistance to revumenib so that we can design medications or devise combination treatments that would overcome these resistance mechanisms. In addition, revumenib is being investigated in less common subtypes of leukemia, such as *NUP98*-rearranged leukemia, which is probably underrecognized in adults. Although revumenib has not received approval for use in *NUP98* rearrangement, it has shown excellent activity in these patients. Many of the trial designs that are being done with revumenib are also being done with ziftomenib.

H&O What other menin inhibitors are being developed?

GI Johnson & Johnson is developing the menin inhibitor bleximenib for use in patients who have AML with *KMT2A* or *NPM1* alterations (NCT05453903), and Sumitomo is developing a menin inhibitor called enzomenib for use in patients with *NPM1*-mutated acute leukemia (NCT04988555). In addition, Servier Pharmaceutics has acquired worldwide rights to the menin inhibitor BN104 from BioNova Pharmaceuticals in China. Servier is expected to start clinical investigation in the United States soon. Finally, we have reached the era of second-generation menin inhibitors; AstraZeneca is about to launch clinical trials with AZD3632 (NCT07155226).

Disclosures

Dr Issa has received research funding from Merck, Kura Oncology, Cullinan Oncology, Syndax Pharmaceuticals, Astex Pharmaceuticals, Novartis, Pupil Bio, Sumitomo, Daiichi Sankyo, and Crossbow Therapeutics; has served as a consultant or on the advisory board for AbbVie, Novartis, Sanofi, AstraZeneca, Syndax, Kura Oncology, Biostate AI, and Crossbow; and has served on the scientific advisory boards of Pupil Bio and Biostate AI.

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