A acute myeloid leukemia (AML) is a rare but deadly cancer. In 2018, approximately 19,500 new cases of AML were estimated to be diagnosed in the United States and more than 10,600 people to die from the disease.1 Clinical trials data show that up to 70% of adults with AML have disease that completely responds to initial treatment with cytotoxic chemotherapy.1 However, the 3-year survival rate for patients with AML remains poor, at approximately 25%.1,2

The management of AML in adults has undergone a major shift since 2017.3,4 In addition to cytogenetic testing, the measurement of minimal residual disease is now recognized to have prognostic value.3 Furthermore, after 40 years of no new drug approvals for AML, the US Food and Drug Administration (FDA) approved several novel targeted agents in 2017 for patients with specific subtypes of AML; these drugs include midostaurin (Rydapt), an FLT3 inhibitor; enasidenib (Idhifa), an isocitrate dehydrogenase (IDH) 2 inhibitor; daunorubicin and cytarabine liposome (Vyxeos), a 2-drug chemotherapy combination encapsulated in liposomes; and gemtuzumab ozogamicin (Mylotarg), an antibody drug conjugate.5-7

Despite advances in our understanding of molecular mechanisms and their impact on disease prognosis, the treatment of AML remains a challenge. The optimal use of new drugs for AML continues to be explored in clinical trials.4

**Ivosidenib Approved for AML with IDH1 Mutation**

On July 20, 2018, the FDA approved ivosidenib (Tibsovo; Agios Pharmaceuticals), an oral targeted therapy that inhibits IDH1, for the treatment of adults with relapsed or refractory AML and a susceptible IDH1 mutation, as detected by the FDA-approved test, the Abbott RealTime IDH1 assay.8,9 Data from the large phase 1 clinical trial Study AG120-C-001 supported the approval of ivosidenib.8-10

“Tibsovo is a targeted therapy that fills an unmet need for patients with relapsed or refractory AML who have an IDH1 mutation. The use of Tibsovo is associated with a complete remission in some patients and a reduction in the need for both red cell and platelet transfusions,” said Richard Pazdur, MD, Director of the FDA’s Center for Drug Evaluation and Research.8

**Mechanism of Action**

Ivosidenib is a small-molecule inhibitor that targets a mutation in the IDH1 enzyme. The most common susceptible IDH1 mutations are R132H and R132C substitutions.9 Blood samples from patients with IDH1 mutation–positive AML showed that ivosidenib decreased 2-hydroxyglutarate levels, reduced blast counts, and increased the percentages of mature myeloid cells.9

**Dosing and Administration**

Patients with relapsed AML should be selected for ivosidenib therapy based on the presence of IDH1 mutations in the blood or bone marrow. Because a mutation in the IDH1 gene can emerge during treatment and at relapse, patients who did not have an IDH1 mutation at diagnosis should be retested at disease relapse.9

The recommended dose of ivosidenib is 500 mg taken orally once daily until disease progression or until unacceptable toxicity. Ivosidenib should be used for a minimum of 6 months to allow time for clinical response, unless disease progression or unacceptable toxicity occurs first.9

Ivosidenib can be administered with or without food.
Because of an increase in the concentration of ivosidenib, the drug should not be used with a high-fat meal.9

**Pivotal Clinical Trial: Study AG120-C-001**

The efficacy of ivosidenib was evaluated in 174 adults with relapsed or refractory AML and an IDH1 mutation, which was identified or confirmed by the Abbott Real-Time IDH1 assay.9,10 The dose of ivosidenib was 500 mg given orally once daily until disease progression, unacceptable toxicity, or performance of hematopoietic stem-cell transplant.9

The median age of patients in Study AG120-C-001 was 67 years (range, 18-87 years).9 Patients received a median of 2 previous therapies (range, 1-6). Overall, 63% of patients had refractory disease and 33% had secondary AML.9

The study primary end point was the combination of complete remission rate and complete remission plus partial hematologic recovery (CRh) rate. CRh was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts.9

Ivosidenib demonstrated a complete remission plus CRh rate of 32.8%, with a median duration of 8.2 months (Table).9 Among the 110 patients who were dependent on red blood cell and/or platelet transfusions at baseline, 37% became transfusion independent during any 56-day postbaseline period. Overall, 12% of the 174 patients in the study had a transplant after treatment with ivosidenib.9

**Adverse Events**

The safety profile of ivosidenib monotherapy was evaluated in 179 patients with AML who received ivosidenib 500 mg daily.9 Patients were exposed to ivosidenib for a median of 3.9 months (range, 0.1-39.5 months). Overall, 19% of patients had differentiation syndrome, a condition associated with the rapid proliferation and differentiation of myeloid cells and can be fatal if not treated.9

The most common (≥20%, any grade) adverse reactions reported with ivosidenib were fatigue (39%), leukocytosis (38%), arthralgia (36%), diarrhea (34%), dyspnea (33%), edema (32%), nausea (31%), mucositis (28%), electrocardiogram QT prolongation (26%), rash (26%), pyrexia (23%), cough (22%), and constipation (20%).9

Serious adverse reactions that occurred at a rate of ≥5% were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolongation (7%).9

Adverse reactions that led to the permanent discontinuation of ivosidenib included Guillain-Barré syndrome (1%), rash (1%), stomatitis (1%), and elevated creatinine levels (1%).9

Ivosidenib has no contraindications.9

---

**Table**

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Ivosidenib 500 mg/day (N = 174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission, %</td>
<td>24.7 (95% CI, 18.5-31.8)</td>
</tr>
<tr>
<td>Median duration of response, mo</td>
<td>10.1 (95% CI, 6.5-22.2)</td>
</tr>
<tr>
<td>CRh, %</td>
<td>8.0 (95% CI, 4.5-13.1)</td>
</tr>
<tr>
<td>Median duration of response, mo</td>
<td>3.6 (95% CI, 1-5.5)</td>
</tr>
<tr>
<td>Complete remission+CRh, %</td>
<td>12.8 (95% CI, 8.5-21.3)</td>
</tr>
<tr>
<td>Median duration of response, mo</td>
<td>8.2 (95% CI, 5.6-12)</td>
</tr>
</tbody>
</table>

*Complete remission was defined as <5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and ANC >1000/microliter).

*Duration of response was defined as time since first complete remission or CRh to disease relapse or death, whichever was earlier.

*CRh was defined as <5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

*Complete remission+CRh rate was consistent across all baseline demographic and baseline disease characteristics, except for the number of previous regimens.

ANC indicates absolute neutrophil count; CI, confidence interval; CRh, complete remission plus partial hematologic recovery.

Source: Tibsovo (ivosidenib tablets) prescribing information; July 2018.

---

**Drug Interactions**

When strong cytochrome (CY) P3A4 inhibitors are given concurrently with ivosidenib, the dose of ivosidenib should be reduced.9

Ivosidenib therapy should be avoided concomitantly with strong CYP3A4 inducers, sensitive CYP3A4 substrates, and corrected QT (QTC)-prolonging drugs. If coadministration with QTC-prolonging drugs is unavoidable, patients should be assessed for increased risk for QTc interval prolongation.9

**Use in Specific Populations**

Women should not breastfeed during treatment with ivosidenib and for at least 1 month after the final dose.9

The safety and effectiveness of ivosidenib have not been established in children.9

Among the 179 patients who received ivosidenib in clinical trials, 63% were aged ≥65 years. The efficacy and safety of ivosidenib were similar between these patients and younger patients.9

**Warnings and Precautions**

The prescribing information for ivosidenib includes a boxed warning about the risk for differentiation syndrome, which can be fatal if not treated.9 If differentiation syndrome is suspected, corticosteroid therapy and hemodynamic monitoring should be started until symptom resolution.9

In Study AG120-C-001, 19% of 179 patients had differentiation syndrome.9 In patients who received ivosidenib, symptoms of differentiation syndrome included noninfectious leukocytosis, peripheral edema,
pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and increased creatinine levels. Differentiation syndrome occurred as early as 1 day and up to 3 months after starting ivosidenib therapy, and has been observed with or without concomitant leukocytosis. The majority (79%) of the 34 patients who had differentiation syndrome recovered after treatment or after dose interruption of ivosidenib.9

The FDA approval of ivosidenib represents the first treatment option that targets the IDH1 mutation specifically.

Patients who receive ivosidenib can have QTc prolongation and ventricular arrhythmias. Study AG120-C-001 excluded patients with baseline QTc of ≥450 milliseconds (unless QTc ≥450 milliseconds was attributed to a preexisting bundle branch block) or patients with a history of long QT syndrome or uncontrolled or significant cardiovascular disease.9

Patients taking ivosidenib should be assessed for new signs or symptoms of motor and/or sensory neuropathy. Ivosidenib should be permanently discontinued in patients with Guillain-Barré syndrome.9

Conclusion

Ivosidenib, a novel oral inhibitor of IDH1, demonstrated durable remissions and good tolerability in patients with relapsed or refractory AML with IDH1 mutation. Although several new treatments have been approved by the FDA for the treatment of AML, the FDA approval of ivosidenib represents the first treatment option that targets the IDH1 mutation specifically. This approval provides a new treatment option for patients with relapsed or refractory AML whose disease is associated with the IDH1 mutation.9

References