A acute myeloid leukemia (AML) is a rare but deadly cancer. Approximately 21,400 new cases of AML were diagnosed in 2017 in the United States, and nearly 10,600 people died from the disease.¹ Approximately 60% to 70% of adults with AML respond to initial treatment with cytotoxic chemotherapy.¹ However, the 5-year survival rate for patients with AML remains poor at approximately 27%.²

The treatment of AML in adults has undergone major changes in 2017.³,⁴ To supplement cytogenetic testing, measuring minimal residual disease (MRD) is being integrated into clinical practice based on the value of MRD as a prognostic factor.³ In addition, after 40 years of no new drugs for AML, the US Food and Drug Administration (FDA) approved several novel targeted drugs, including midostaurin (Rydapt; an FLT3 inhibitor), enasidenib (Idhifa; an IDH inhibitor), and gemtuzumab ozogamicin (Mylotarg; an antibody drug conjugate), for the treatment of AML.⁵-⁷

Vyxeos Approved for High-Risk AML

On August 3, 2017, the FDA granted an accelerated approval for the new combination of daunorubicin and cytarabine liposome (Vyxeos; Jazz Pharmaceuticals), an intravenously infused drug, for the treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes.⁵,⁸,⁹ The FDA granted this drug breakthrough therapy and orphan drug designations for this indication.⁸ Full FDA approval is contingent on additional evidence from clinical trials. Both drugs are already available as individual chemotherapies.

“This is the first approved treatment specifically for patients with certain types of high-risk AML. Vyxeos combines two commonly used chemotherapies into a single formulation that may help some patients live longer than if they were to receive the two therapies separately,” said Richard Pazdur, MD, FDA’s Director of Oncology Center of Excellence.

Mechanism of Action

This new combination of daunorubicin plus cytarabine is a liposomal formulation at a fixed molar ratio of 1:5. This molar ratio of daunorubicin to cytarabine is synergistic in killing leukemia cells in vitro and in animal models.⁹

Daunorubicin is antimitotic and cytotoxic: it forms complexes with DNA, inhibits topoisomerase II activity, inhibits DNA polymerase activity, affects the regulation of gene expression, and produces DNA-damaging free radicals. Cytarabine affects cells only during the synthesis phase of cell division by inhibiting DNA polymerase.⁹

Dosing and Administration

For the first cycle of induction, the recommended dose is daunorubicin 44 mg/m² and cytarabine 100 mg/m² liposome, administered via an intravenous (IV) infusion for 90 minutes on days 1, 3, and 5.³ For patients who do not achieve remission with the first induction cycle, a second cycle can be administered 2 weeks to 5 weeks after the first, presuming no unacceptable toxicity. The recommended dose for the second induction cycle is daunorubicin 44 mg/m² and cytarabine 100 mg/m² liposome, administered via a 90-minute IV infusion on days 1 and 3.³

The first consolidation cycle should be given 5 weeks to 8 weeks after the start of the last induction cycle. The recommended dose for each cycle of consolidation therapy is daunorubicin 29 mg/m² and cytarabine 65 mg/m² liposome via a 90-minute IV infusion on days 1 and 3.³

Treatment consolidation cycles should not be given until the absolute neutrophil count recovers to >0.5 G/L and the platelet count recovers to >50 G/L, in the absence of unacceptable toxicity. The second consolidation cycle should be administered 5 weeks to 8 weeks after the start of the first consolidation cycle and no evidence of disease progression or unacceptable toxicity.³

Pivotal Clinical Trial

The efficacy of the daunorubicin plus cytarabine liposome formulation was evaluated in a randomized, multicenter, open-label, phase 3 clinical trial that compared this novel combination with a standard combination of...
cytarabine and daunorubicin (7+3) in patients aged 60 to 75 years with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes. Patients were randomized and stratified by age and by AML subtype.9,10

Overall, 309 patients were randomized to receive the liposome formulation (N = 153) or the standard formulation (N = 156).9,10

At least 1 cycle of induction was given to all the patients in the liposome formulation arm and to 97% of patients in the standard arm.9 Overall, 32% of patients in the liposome arm and 21% in the standard arm received at least 1 cycle of consolidation.9 The rate of hematopoietic stem-cell transplantation (HSCT) in first complete remission was 20% in the liposome arm versus 12% in the standard arm. The overall rate of HSCT was 34% versus 25%, respectively.9

The efficacy of the liposome formulation was established on the basis of overall survival data from the date of study randomization to death from any cause. The median overall survival was 9.6 months in the liposome formulation arm versus 5.9 months in the standard formulation arm (hazard ratio, 0.69; 95% confidence interval, 0.52-0.90; P = .005; Table).9,10

The complete remission rate was 38% versus 26%, respectively (P = .036).9

Adverse Reactions

Overall, 9 (6%) patients in each study arm had fatal adverse reactions unrelated to disease progression while receiving treatment or within 30 days of therapy.9 Among recipients of the liposome formulation, these adverse events included infection, central nervous system hemorrhage, and respiratory failure.9 All-cause day-30 mortality was 6% with the liposome formulation versus 11% with the standard formulation.9 During the first 60 days of the study, 14% of patients died in the investigational arm compared with 21% of patients in the standard treatment arm.9

The most common (≥5%) serious adverse reactions with the liposome formulation were dyspnea, myocardial toxicity, sepsis, pneumonia, febrile neutropenia, bacteremia, and hemorrhage. Treatment discontinuation because of adverse reactions occurred in 18% of the new formulation recipients versus 13% of the standard formulation recipients.9 Adverse reactions leading to treatment discontinuation included prolonged cytopenias, infection, cardiotoxicity, respiratory failure, hemorrhage, renal insufficiency, colitis, and generalized medical deterioration. Common adverse events were less frequent during the consolidation phase than in the induction phase. Incidence rates of chills, dizziness, and pyrexia were similar between the induction and consolidation cycles.9

Table Efficacy of Daunorubicin plus Cytarabine Liposome Formulation in High-Risk Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Novel liposome formulation: daunorubicin + cytarabine (N = 153)</th>
<th>Standard combination: daunorubicin + cytarabine (N = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>Hazard ratio 0.69 (95% CI, 0.52-0.90)</td>
<td>5.9 (95% CI, 5.0-7.8)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.69 (95% CI, 0.52-0.90)</td>
<td>5.9 (95% CI, 5.0-7.8)</td>
</tr>
<tr>
<td>Complete response</td>
<td>58 (38)</td>
<td>41 (26)</td>
</tr>
</tbody>
</table>
| P value (2-sided) | .036                                                          | for patients with mild or moderate kidney dysfunction or in patients with bilirubin levels ≤3 mg/dL.9

Women of childbearing potential should use effective contraception during treatment with the new formulation and for 6 months after the last dose.9

Warnings and Precautions

The new liposome formulation of daunorubicin and cytarabine contains a boxed warning stating that the dose and schedule recommendations for this combination are distinct from those for daunorubicin hydrochloride injection, cytarabine injection, daunorubicin citrate liposome injection, and cytarabine liposome injection. The drug name and dose should be verified before its preparation and administration. Other preparations of daunorubicin or cytarabine should not be substituted for the new formulation.9

Serious or fatal hemorrhagic events with associated prolonged thrombocytopenia have occurred with the new formulation.9

The new combination therapy is not recommended in patients with impaired cardiac function. The medication should be discontinued in patients with poor cardiac function, unless the benefit of continuing treatment outweighs the risk. It should also be discontinued if a severe or life-threatening hypersensitivity reaction occurs.9

A reconstituted daunorubicin and cytarabine combination contains elemental copper.9

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Daunorubicin has been associated with local tissue necrosis at the site of drug extravasation.9

Conclusion

The novel liposome-encapsulated formulation of 2 previously available chemotherapy agents, daunorubicin and cytarabine, has demonstrated efficacy and low all-cause 30-day mortality in patients aged 60 to 75 years with high-risk, newly diagnosed therapy-related AML or AML with myelodysplasia-related changes. This novel combination therapy is the first treatment approved specifically for this patient population and may become a new standard of care for older patients with these forms of high-risk AML.

References