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REVIEW

Reformulating acute myeloid leukemia: liposomal cytarabine and daunorubicin (CPX-351) as an emerging therapy for secondary AML

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Abstract: Despite increasing understanding of the pathobiology of acute myeloid leukemia (AML), outcomes remain dismal particularly for patients over the age of 60 years, a population enriched for therapy-related AML (tAML) and secondary AML (sAML). For decades, the standard of care for AML has been the combination of cytarabine and daunorubicin, typically delivered in combination as "7 + 3" induction. In 2017, a liposomal-encapsulated combination of daunorubicin and cytarabine (CPX-351, Vyxeos) was approved by the US Food and Drug Administration (FDA) for use in the treatment of newly diagnosed tAML or AML with myelodysplasia-related changes (AML-MRCs). CPX-351 was designed to deliver a fixed 5:1 molar ratio of cytarabine and daunorubicin, respectively, based on the hypothesis that ratiometric dosing may be more effective than the delivery of either drug at their maximum tolerated dose. In a Phase III trial of older patients with sAML aged 60–75 years, CPX-351 was compared to "7 + 3" and was associated with a higher overall survival, event-free survival, and higher rates of complete remission (CR) and CR with incomplete hematologic recovery (CRi). These data were the basis for the approval of this new drug for use in the treatment of AML, but questions remain regarding how to best administer this agent across AML subgroups. Future directions include evaluating dose intensification with CPX-351, combining this agent with targeted therapies, and better understanding the mechanism of improved responses in tAML and AML-MRC, two entities that are historically less responsive to cytotoxic agents. In summary, CPX-351 offers an exciting new change to the landscape of AML therapy.

Keywords: acute myeloid leukemia, AML, liposome, liposomal, Vyxeos, CPX-351, cytarabine, daunorubicin

Introduction

Acute myeloid leukemia (AML) is a cancer of hematopoietic progenitor cells, which is characterized by a proliferation of blast cells and loss of normal hematopoiesis. It predominantly impacts older adults with a median age of diagnosis of 68 years.[1] In spite of substantial gains in the pathobiology of AML, outcomes remain poor at the population level. In particular, survival is dismal among patients diagnosed with AML over the age of 60 years, who also represent the majority of AML cases. This may be, in part, because this older group of patients is enriched for AML developing out of preceding myeloid malignancies (secondary AML, sAML) and AML arising after prior radiation or chemotherapy (therapy-related AML, tAML). The poor outcomes seen in older patients may also reflect excess toxicity of existing cytotoxic regimens among these patients as well as less frequent and shorter treatment responses. CPX-351 (Vyxeos, Jazz Pharmaceuticals), a liposomal formulation of cytarabine and daunorubicin in a

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5:1 molar ratio, has emerged as a new treatment option for AML.[2] The current review discusses the current treatment landscape of AML, specific challenges related to the subgroup of patients with sAML, and then focuses on the preclinical and clinical data supporting the use of CPX-351.

Current treatment landscape of AML

Induction chemotherapy for AML

For decades, the standard of care for treating AML has been the combination of the nucleoside analog, cytarabine, with an anthracycline, typically daunorubicin or idarubicin.[3] Most often, these agents are administered using a 7-day continuous infusion of cytarabine with idarubicin or daunorubicin administered on days 1, 2, and 3, a combination typically referred to as "7 + 3." Dosing schedules of "7 + 3" underwent a number of adjustments through trials run by the Cancer and Leukemia Group B (CALGB), eventually resulting in a dose of daunorubicin of 45 mg/m^2 per day for 3 days and cytarabine at a dose of 100 mg/m^2 per day via continuous infusion for 7 days. This was superior to 2 and 5 days of each respective drug and superior to 10 days of daunorubicin.[4,5] The "7 + 3" resulted in remission rates of 60%–80% of younger adults (those under the age of 60 years) and 40%–60% of older adults (typically defined as patients over the age of 60 years).[6]

Many attempts to improve upon "7 + 3" have failed to conclusively supplant this regimen. The Southeastern Cancer Study Group compared idarubicin at 12 mg/m^2 to daunorubicin for induction among younger patients, suggesting that idarubicin is similarly active in AML induction.[7] Dose intensification of daunorubicin, at 90 mg/m^2 compared to 45 mg/m^2, results in higher remission rates and improved survival among younger patients but not older patients with AML.[8,9] Variations on the administration of cytarabine and anthracycline, including substituting the continuous infusion of cytarabine with high-dose cytarabine, have been explored.[9] Although some studies suggested a possible improvement in disease-free survival with high-dose cytarabine, there was no significant benefit in complete remission (CR) rate and overall survival (OS) and at a cost of more significant hematologic side effects.[10,11] Thioguanine with a double induction protocol, or the addition of etoposide to induction, also failed to show significant improvements in CR rates or disease-free survival.[12,13] More recently, encouraging responses were reported with the histone deacetylase (HDAC) inhibitor, vorinostat, added to the idarubicin and Ara-C (IA) backbone;[14] however, this also failed to improve upon "7 + 3" in a Phase III study.[15]

Advances in targeting specific AML subgroups

Recent advancements in AML induction chemotherapy have largely been within specific, well-defined AML subpopulations, often characterized by recurrent, targetable genetic mutations. The clinical development of targeted therapies in AML is most advanced for agents targeting *FLT3*- or *IDH*-mutated proteins. For patients whose AML harbors mutations in FLT3, either an internal tandem duplication (ITD) or a tyrosine kinase domain (TKD) mutation, a Phase III trial of midostaurin added to standard "7 + 3" resulted in improved OS (HR for death, 0.78; one-sided $p = 0.009$) and event-free survival (EFS; HR for event or death, 0.78; one-sided $p = 0.002$).[16] These findings led to the approval of this agent during induction and the first targeted therapy to alter induction therapy in decades. For *IDH2*-mutated AML, enasidenib, a selective *IDH2* inhibitor, has also shown impressive responses in relapsed and refractory *IDH2*-mutated AML.[17] Of the patients receiving enasidenib, 19% of those with relapsed/refractory AML achieved CR, while the overall response rate was 40%. Median OS was 9.3 months, and for those patients who had received at least 2 treatment regimens for AML prior to enasidenib, the median survival was 8.0 months. While these agents are shaping the standard of care for the subsets of patients with these mutations, the vast majority of AML patients do not harbor such mutations, and new, more effective therapies are desperately needed.

sAML: an unmet need for new therapies

Many of the gains seen in AML have been in younger patients,[18] while patients over the age of 60 years at diagnosis have had minimal improvement in overall dismal survival outcomes.[18,19] One reason may be the underlying genetic features of AML in older adults: sequencing of the disease of older patients with AML shows an increased frequency of complex mutation patterns and a greater proportion of unfavorable mutations than are seen in younger patients. Many of these mutations are similar to those seen in secondary AML (sAML), which develop from a preexisting hematologic neoplasm such as myelodysplastic syndrome (MDS) or a myeloproliferative neoplasm (MPN), or therapy-related AML (tAML), which arise following chemotherapy or radiation.[20] Patients with "secondary-like" AML according to the mutational profile have worse outcomes than patients with de novo AML lacking such mutations.[21] Regardless of mutation profile, the overall outcomes of patients with sAML, accounting for cytogenetics and age, are worse than the de novo AML population.[22]