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Daunorubicin-cytarabine liposome (CPX-351) in the management of newly diagnosed secondary AML: A new twist on an old cocktail

Joseph E. Maakaron, Alice S. Mims*

The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

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ABSTRACT

Initial therapy for acute myeloid leukemia (AML) remained stagnant for approximately four decades despite advances in improved understanding of pathogenesis and prognostication of the disease. Treatment has typically consisted of an anthracycline combined with continuous infusion of cytarabine for 7 days, the "7 + 3" regimen. Attempts have been made to improve on this regimen with modest improvements in response rates but no change in overalll survival, until the recent introduction of mutation-specific agents. However, the re-vamping of the delivery of both daunorubicin and cytarabine in a liposomal encapsulation, known as CPX-351, did show improvements of overall survival compared to traditional 7 + 3 in newly diagnosed secondary and therapy-related AML in patients aged 60–75. This led to the Food and Drug Administration (FDA) approval of the agent for both of these subtypes of AML in August of 2017. Herein we will review the rationale and preclinical development of CPX-351 and discuss the pivotal studies that led to its FDA approval.

A new drug is born

The cornerstone of acute myeloid leukemia (AML) treatment has historically included three days of an anthracycline (daunorubicin or idarubicin) combined with continuous infusion of cytarabine for 7 days, the "7 + 3" regimen. Several attempts have been made to improve on this regimen by dose-intensification, altering routes of delivery, changing schedules of delivery and addition of other agents. However, despite modest improvements in response rates, overall survival has not typically been improved with the exception of the addition of midostaurin to 7 + 3 in FLT3 mutated AML [1-6].

Combination chemotherapy trials are traditionally designed around the concept of maximum tolerated dose (MTD) of an agent equals improved efficacy, though this concept is a bit simplistic. In the past when designing trials with multiple agents, less attention was paid to whether drug interactions produce synergism or antagonism in a malignancy. Mayer and colleagues highlighted this concept and emphasized that while optimal drug ratios can be explored *in vitro*, applications *in vivo* would be difficult due to distinct pharmacokinetic profiles of each individual agent. To overcome this issue, a liposomal delivery system was devised and tested that would maintain the desired concentration of each drug *in vivo*. The drugs were encapsulated at the ratios of interest into multilamellar liposomes made from a 7:2:1 molar ratio of distearoylphosphatidylcholine, distearoylphosphatidylglycerol, and cholesterol. This liposomal drug delivery design was postulated to minimize first-pass metabolism, deliver synergistic ratios, and preferentially accumulate at the sites of tumor growth and if so, hopefully lead to improvements in patient outcomes. A series of experiments were

* Corresponding author. 320 W 10th Ave, A343 Starling Loving Hall, Columbus, OH, 43210, USA.
E-mail address: alice.mims@osumc.edu (A.S. Mims).

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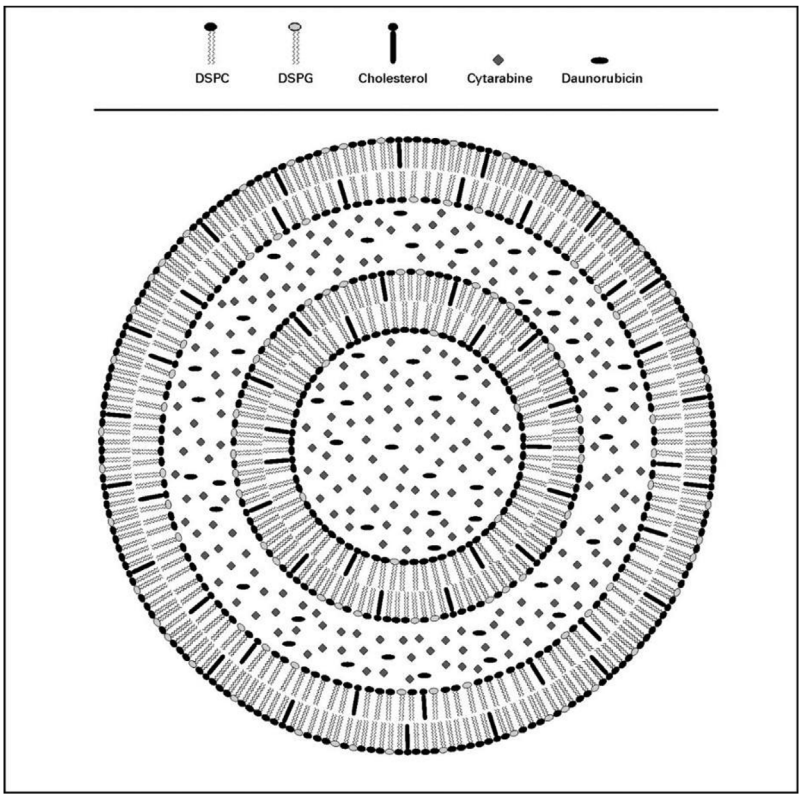

Fig. 1. Schematic representation of CPX-351 (cytarabine:daunorubicin) liposome injection. The liposomes are bilamellar with a diameter of 100 nm for the outer vesicle. The membrane is composed of desaturated phosphatidylcholine (DSPC): distearylphosphatidylglycerol (DSPG):cholesterol in a 7:2:1 molar ratio. The active agents, cytarabine and daunorubicin, are encapsulated in the aqueous space of both vesicles at a 5:1 molar ratio. The liposomes are suspended in phosphate-buffered sucrose, pH 7.4. While inside the liposome, daunorubicin is complexed with copper as copper gluconate, giving CPX-351 its characteristic purple color. The strength of CPX-351 is 5 units/mL, where 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin (base). Reproduced with permission from Feldman JE et al. *Journal of Clinical Oncology* 2011 29979-985.

performed where colorectal cell cancer, non-small cell lung cancer, and leukemia cell lines were used to test different ratios of active and commonly used cytotoxic chemotherapies. For AML, the P388 leukemia cell line was used and pre-clinical findings determined that ratios of cytarabine and daunorubicin of 1:1, 5:1 and 10:1 were similarly synergistic and exhibited 90% cell kill at increasing concentrations. Moving forward with future studies in AML, the ratio of cytarabine/daunorubicin of 5:1 was encapsulated in the liposomal formulation aforementioned (Fig. 1) and further known as CPX-351 (Vyxeos; Jazz Pharmaceuticals, Palo Alto, CA) [7]. This 5:1 molar ratio cytarabine to daunorubicin is equivalent to 1 mg cytarabine and 0.44 mg daunorubicin.

For further confirmation of findings, *in vivo* pre-clinical studies were performed with CPX-351 injected in female Rag2-M mice and drug plasma levels analyzed at various time points to ensure the ratio 5:1 was maintained. Next, the efficacy was tested by administering a dose of 50:10 μmol/kg of CPX-351 to mice inoculated with 1×10^6 P388 cells in the peritoneum. This dose was compared to liposomal formulations of the individual drugs given at their MTDs and matched doses of a 5:1 ratio given in saline. CPX-351 produced superior overall survival to both individual agent formulations with a 90% cure rate compared to 25% for cytarabine/daunorubicin in saline, 10% for liposomal cytarabine and 0% for liposomal daunorubicin. Median overall survival time for CPX-351 was 27.5 days with a log cell kill of 8.8 compared to 12 and 1.8 days for liposomal daunorubicin and 16 and 3.6 days for liposomal cytarabine. Therefore, the synergistic effect of the individual drugs in CPX-351 produced a > 2000 increase in cell kill compared to the additive effects of the individual components in liposomal formulation. CPX-351 given on a schedule of days 1, 4, and 7 was more efficacious than intravenous cytarabine given on days 1–5 at its MTD of 200 mg/kg per injection [7]. With these promising pre-clinical findings, CPX-351 moved onto further development in the clinical setting.

Bench to bedside

First-in-human phase 1 of CPX-351

A first-in-human, dose-escalation, phase I study was undertaken to evaluate the safety and MTD of CPX-351. Adults with relapsed or refractory AML, high-risk myelodysplasia (MDS), and acute lymphoblastic leukemia (ALL) with preserved organ function, left ventricular ejection fraction (LVEF) > 50%, and Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 were

enrolled. CPX-351 was administered on days 1, 3, and 5 for induction with the first cohort starting at a dose of 3 units/m^2. Single patients were treated in each cohort and doses were doubled until chemotherapy-related adverse events (AE) or reduction in bone marrow blasts or cellularity were encountered. Afterwards, cohorts included three patients and dose levels were increased by 33%. Cohorts were expanded in the cases of AEs or if patients were not evaluable. Bone marrow cellularity was assessed on day 14 and required reduction to < 20% with < 5% blasts. Otherwise, a second induction course on days 1 and 3 was allowed if deemed beneficial by the investigators. Patients who achieved a complete response (CR) were eligible for an additional consolidation cycle on days 1 and 3. An expansion cohort of AML patients in first relapse was implemented at the MTD to obtain additional safety and preliminary efficacy data [8]. In total, forty-eight patients were enrolled, 43 with AML, 3 with ALL and 2 with MDS. There was a total of 10 cohorts and 3 of 6 patients in the tenth cohort (134 units/m^2) experienced dose-limiting toxicities (DLTs). One patient experienced congestive heart failure (CHF), 1 patient had hypertensive crisis, and 1 patient had persistent cytopenias beyond 56 days. Therefore, the dose of the ninth cohort (101 units/m^2) was determined to be the MTD and moved forward as the recommended phase II dose. The dose expansion cohort included 14 additional patients at the MTD to further confirm safety and assess efficacy.

One grade 3 laboratory AE occurred each for elevated bilirubin, aspartate transaminase (AST) and alanine transaminase (ALT). A distinct maculopapular rash occurred in 71% of patients with grade 3 rash in 3 patients (6%) which resolved with topical steroids and addition of intravenous prophylactic corticosteroids [8]. In regard to serious adverse events (SAEs), 35 patients died during study or follow-up, though progressive disease was attributed for the majority in 26 patients. Two patients had clinical CHF with cumulative daunorubicin exposures of 546 and 966 mg/m^2. Regarding other evidence of therapy-related cardiac toxicity, 3 other patients whose post-exposure LVEF were available had a 10% or greater reduction in LVEF but maintained a value of greater than 50%. These patients had cumulative anthracycline exposure doses of 439, 357, and 95 mg/m^2.

Pharmacokinetic data revealed that the 5:1 molar ratio was maintained for up to 24 h on days 1 and 5 at all dose levels. Elimination half-life estimates for cytarabine ranged between 38 and 64 h for doses between 24 and 134 units/m^2. That of conventional cytarabine is about 3 h suggesting that the circulating drug remains within the liposome. The area under the curve (AUC) and half-lives were substantially greater than expected with conventional drugs. Given the safety and efficacy, the phase II dose that was recommended was 101 units/m^2 given on days 1, 3, and 5. Due to concerns for increased risk of cardiotoxicity, the decision was made to limit prior anthracycline exposure going forward [8].

Regarding outcomes in AML patients specifically, 31 (72%) of the 43 patients had been treated with prior standard 7 + 3 combination, and 8 of these patients achieved CR following CPX-351 treatment. In total, CR was achieved in 5 of 26 (19%) with AML who were ≥60 years and in 5 of 17 (29%) of patients younger than age 60. The median duration of remission was 6.9 months with 3 patients with ongoing remission of > 1 year after study completion. Seven of the patients in CR went on to receive a further cycle of consolidation with CPX-351 on days 1 and 3 [8].

Phase II and III clinical study findings

Subsequently, two multicenter, open-label, randomized, phase II studies were conducted to examine the role of CPX-351 in first relapse and newly diagnosed AML, respectively. The first trial by Cortes et al. enrolled 125 patients with AML in first relapse ages 18–65 years [9]. Patients were risk-stratified using the European Prognostic Index (EPI) which assigns patients in first relapse into one of three risk groups according to age at relapse, duration of remission, cytogenetics at diagnosis and history of stem cell transplant (SCT) [10]. Patients were then randomized in a 2:1 fashion to receive CPX-351 or investigator's choice of intensive salvage therapy. CPX-351 was given at 100 units/m^2 on days 1, 3 and 5 for first induction and on days 1 and 3 for second induction or consolidation. Two inductions and two consolidations were permitted on this study. Patients were required to have good organ function, no active CNS leukemia and ≤368 mg/m^2 cumulative daunorubicin-equivalent exposure. The primary efficacy endpoint was survival at 12-months and the study was powered to reveal trends with $P < 0.1$ considered significant. Eighty-one patients were randomized to the treatment arm with 44 patients randomized to investigator's choice. The CPX-351 group were slightly younger (median age 52 vs. 56 years), had more patients with secondary AML (12.3% vs. 6.8%), and a higher rate of prior SCT (27.2% vs. 15.9%). Ten patients (12.3%) required two inductions on the CPX-351 arm vs. 3 (6.8%) on the control arm.

In total, 30 (37%) patients achieved a CR with 10 (12.3%) additional patients achieving CR with incomplete count recovery (CRi) compared to 14 (31.8%) CR with 4 (9.1%) CRi in the control arm. Overall (OS) and event-free survival (EFS) were not significantly different with median OS and EFS for CPX-351 of 8.5 months and 4.0 months vs. 6.3 months ($P = 0.19$) and 1.4 months ($P = 0.08$), respectively. Factors that correlated with a better CR rate included a first CR duration of greater than 7 months ($P = 0.0001$) and adverse cytogenetics ($P = 0.0022$). Sub-group analysis of different EPI risk-groups showed CPX-351 achieved a higher CR (28.6% vs 20.7%) and CRi (10.7% vs 2.9%) rates in the poor-risk group. There was also a trend towards improved EFS (HR = 0.63, $P = 0.08$) and a statistically significant improvement in OS (HR = 0.55, $P = 0.02$). Survival at 12-months for this group was 28% vs 9% for control. Eighty-five percent of patients achieving CR (35/40) received consolidation (19 patients) or allogeneic SCT (15 patients). A similar number of patients from each group (24.4% vs 19%) were transplanted after induction failure. These patients had similar outcomes post-transplant with equal proportions alive > 300 days [9]. Early mortality at 30 and 60 days was similar between the groups, but 90-day deaths were less for the CPX-351 arm (21.4% vs 37.9%). Patients receiving CPX-351 had slower neutrophil (42 days vs 34 days) and platelet (45 days vs 35 days) recovery. This was associated with more bleeding and infectious complications though total grade 5 events from all causes was similar between the two arms (23.5% vs 20.5%). As mentioned, the majority (75.9%) of patients with prior SCT were randomized to the CPX-351 arm. Patients in the CPX-351 arm with prior transplant had lower response rates (36.4% vs 57.1%) and higher mortality at 30 days (18.2% vs 0) and 60 days (27.3% vs 14.3%) when compared to patients with prior transplant on the control arm [9].

The second phase II trial enrolled patients 60–75 years of age with newly diagnosed AML randomized to CPX-351 versus 7 + 3. Patients were stratified into 2 risk categories (standard- and high-risk) with the high-risk group defined as age > 70, presence of secondary AML (sAML), or complex karyotype. Secondary AML was defined as history of antecedent hematological disorder or prior cytotoxic therapy. At time of analysis, patients with high-risk cytogenetics as defined by the National Comprehensive Cancer Network criteria were also assigned to the high-risk group [11]. Non-responders on the control arm were allowed to cross over. Prior anthracycline exposure for inclusion was also capped at 368 mg/m^2. Similarly, the study had an 85% power to detect a 23% increase in the primary endpoint of response rate (CR + CRi) at a one-sided significance level of $P < 0.1$ [12].

A total of 126 patients were enrolled and randomized in a 2:1 fashion where 85 patients received at least one dose of CPX-351 and 41 received conventional 7 + 3. In total, 48.8% (41/84 vs 20/41) of both arms achieved a CR but patients treated with CPX-351 had higher CRi rates (17.9% vs 2.4%). Median duration of response was similar between the two groups (8.9 months vs 8.6 months). Among patients with high-risk cytogenetics or sAML, CPX-351 had higher response rates compared to 7 + 3 (77.3% vs 38.5%, $P = 0.03$; and 57.6% vs. 31.6, $P = 0.06$, respectively). Median OS and EFS for the overall cohort were 14.7 vs 12.9 months and 6.5 vs 2.0 months, respectively. In the sAML cohort, a preplanned subgroup analysis revealed a statistically significant OS and EFS improvement for CPX-351 with a median OS of 12.1 months vs 6.1 months ($P = 0.01$) and median EFS of 4.5 months vs 1.3 months ($P = 0.08$). Mortality by day 60 also favored CPX-351 (4.7% vs 14.6%, $P = 0.53$) but was not statistically significant. Again, noted was a delay in hematological recovery in the CPX-351 arm with an increased rate of grade 3 and 4 infections in the CPX-351 arm (70.6% vs 43.9%) but not infection-related deaths. Of note, 4 of 10 patients that crossed over from the control arm after failing induction with 7 + 3 achieved a CR [12].

These encouraging results in the subgroup analysis led to the design of a multicenter, open-label, randomized phase III study of CPX-351 vs conventional 7 + 3 in newly diagnosed patients with sAML between the ages 60 and 75 years. The primary endpoint for study was OS. For patients to be eligible, they were required to have a diagnosis of AML with antecedent MDS or chronic myelomonocytic leukemia (CMML), therapy-related AML, or de novo AML with MDS-related cytogenetic abnormalities per the 2008 WHO criteria [13]. Prior treatment with hypomethylating agents was allowed. The treatment arm was similar to prior studies – 90-min infusion with 100 units/m^2 of CPX-351 on days 1, 3, and 5 and reinduction with the same dose on days 1 and 3 if no CR/CRi was achieved after day 14 marrow assessment. Consolidation consisted of 65 units/m^2 on days 1 and 3. The control arm treatment consisted of 7 days of continuous infusion of 100 mg/m^2 daily of cytarabine with 60 mg/m^2 of daunorubicin for 3 days. Reinduction and consolidation on the control arm was 5 days of 100 mg/m^2/day of cytarabine with 2 days of 60 mg/m^2 of daunorubicin [14].

A total of 309 patients were randomized, 153 in the CPX-351 and 156 in the 7 + 3 arm. CPX-351 was found to significantly improve OS with a median of 9.56 vs 5.95 months (HR = 0.69 [0.52–0.90], $P = 0.003$). One- and two-year OS for CPX-351 vs 7 + 3 were estimated at 41.5% vs 27.6% and 31.1% vs 12.3%, respectively. More patients on the CPX-351 arm achieved remission (47.7% CR + CRi vs 33.3%, $P = 0.016$) and median EFS was also superior (2.53 months vs 1.31, HR = 0.74 [0.58–0.96], $P = 0.021$). The most frequent grade 3–5 AEs were febrile neutropenia (68.0% vs 70.9%), pneumonia (19.6% vs 14.6%), and hypoxia (13.1% vs 15.2%). Hematological recovery was delayed in patients who achieved remission with CPX-351 with a median time to recovery of neutrophils to ≥500/μL of 35 vs 29 days and of platelets to ≥50,000/μL of 36.5 vs 29 days. Infection-related events were similar between the 2 groups but there was a higher incidence of bleeding events with CPX-351 (74.5% vs 59.6%) with grade 3–5 events of 11.8% vs 8.6%. Regardless of these increased events, early mortality rates were not statistically different [14]. Fifty-two out of 153 patients (34%) on the CPX-351 arm and 39/156 (25%) proceeded to SCT. The majority were in CR or CRi with 57.7% and 19.2% for CPX-351 vs 48.7% and 12.8% for 7 + 3. An exploratory landmark overall survival analysis from the time of SCT favored CPX-351 (HR = 0.46, $P = 0.009$, Fig. 2). The 2 year OS difference between CPX-351 and 7 + 3 is markedly different at greater than 60%

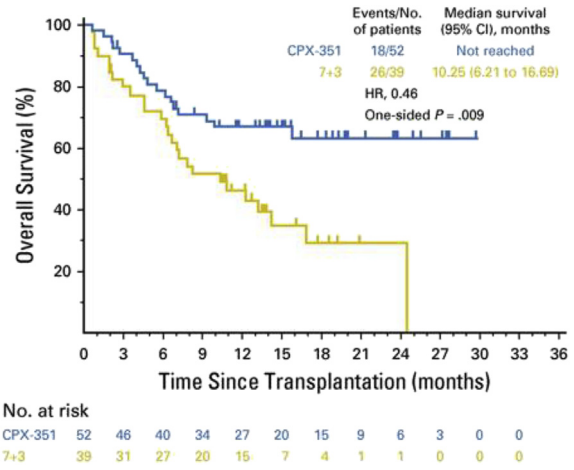

Fig. 2. Kaplan-Meier estimates of overall survival landmarked from the date of transplantation are shown for patients in the intention-to-treat population who received a hematopoietic cell transplant after induction with CPX-351 or 7 + 3. Reproduced with permission from Lancet JE *et al*; Journal of Clinical Oncology 2018 362684-2692.

versus 35%, respectively. These differences lead to further questions including if the liposomal delivery system of CPX-351 leads to deeper remissions pre-transplant or better targets leukemic stem cells. Although speculative at this point, these outcome findings in the post-transplant setting warrant further investigation. Due to meeting the primary endpoint of overall survival in this phase III study, CPX-351 was FDA approved for patients with therapy-related or secondary AML in adults ≥18 years in August 2017.

Feasibility of outpatient administration

Another interesting topic of discussion is the ability to potentially administer CPX-351 as an outpatient. Given the safety and convenience of administration of CPX-351, a recent inpatient/outpatient program (IPOP) evaluated the feasibility of administration in the outpatient setting. Patients who were deemed appropriate for outpatient administration included those with reliable transportation and caregivers, ECOG < 2, no signs and symptoms of active infections, cardiopulmonary disease or risk for tumor lysis syndrome. The patients were monitored every other day at least until count recovery. Patients who were not deemed eligible were treated inpatient (IP). A total of 12 patients were evaluated, 7 were treated IPOP and 5 IP. All patients in the IPOP program were eventually admitted; however, they were able to remain outpatient for 54% of their total days from start of induction until remission evaluation. The mean cumulative hospital days was significantly less in the IPOP program compared to IP (19 vs 31 days, $P = 0.034$). There was no difference in response rates or safety profile between the groups [15].

Discussion

In the above trials, CPX-351 was found to be safe and well-tolerated though caution needs to be taken for patients at risk for cardiac toxicity due to anthracycline exposure and in all patients due to risks of prolonged cytopenias. During the dose-escalation phase, one patient experienced heart failure at the highest dose level. That patient had a cumulative anthracycline dose of 556 mg/m^2 after treatment with CPX-351. Further investigation into patients with pre- and post-treatment LVEF measurements led to capping prior anthracycline exposure at of 368 mg/m^2. This puts the total anthracycline exposure after one induction cycle at 500 mg/m^2. In the phase III study, 2 patients on each treatment arm discontinued therapy because of cardiac complications and reduced ejection fraction [14].

Patients treated with CPX-351 in all the studies had increased myelosuppression which correlated with a higher risk of infectious complications despite no increase in infection-related deaths [8,12,14]. The longer periods of thrombocytopenia translated into a higher incidence of bleeding events although risk of fatal hemorrhage was similar between CPX-351 and 7 + 3 [14]. The investigators point out that the higher response rates with CPX-351 led to more patients receiving consolidation therapy thus prolonging the window for reporting adverse events. To adjust for that, they analyzed the number of adverse events reported per patient-year which favored CPX-351 with 75.68 vs 87.22 for 7 + 3 [14]. Vigilance should be exercised in proper infectious prophylaxis and transfusion strategies regardless. Of note, CPX-351 contains copper and due to this, patients with Wilson's disease were excluded from the previously mentioned studies; therefore, a careful estimation of the risks and benefits must be undertaken prior to treating patients with Wilson's disease.

CPX-351 is the first agent to improve overall survival in elderly patients with sAML compared to traditional 7 + 3. Clinical practice guidelines are summarized in Table 1. The recommended induction dose of CPX-351 is 100 units/m^2 for 3 doses which delivers a total dose of 300 mg/m^2 of cytarabine and 132 mg/m^2 of daunorubicin. This produced better remission rates than 700 mg/m^2 of cytarabine and 180 mg/m^2 of daunorubicin that is the traditional “7 + 3” in a population that is high-risk. Patients who failed 7 + 3 were also able to achieve remission with CPX-351. The intelligent design of this drug utilized synergistic ratios and proper delivery to target to potentiate the effects of the individual drugs [16,17]. Liposomal encapsulation allowed for longer half-lives of the drugs and a greater AUC resulting in a prolonged exposure to the leukemia cells and possibly a way of overcoming multidrug resistance in higher risk AML subtypes [8,18,19].

This new approval is another step to improve outcomes of patients with AML who traditionally had poor prognosis. Future

Table 1
Overview of administration and monitoring parameters for CPX-351 [14,20]. CNS, central nervous system. SCT, stem cell transplant.

Approved Indication	Newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes
Administration	Preferable via central line
	Premedication with steroids to avoid skin rash
	Select patients can receive outpatient therapy
Induction, cycle 1	90-min infusion of 100 units/m^2 on days 1, 3 and 5
Induction, cycle 2	90-min infusion of 100 units/m^2 on days 1 and 3
Consolidation, cycle 1 & 2	90-min infusion of 65 units/m^2 on days 1 and 3
Monitor blood counts	Institutional transfusion and infection prophylaxis policies. Prolonged cytopenias are more common with CPX-351
Cardiac function	Cardiac dysfunction has occurred with CPX-351
	Prior anthracycline exposure capped at 368 mg/m^2
	Weigh risks and benefits
CNS Leukemia	No information
Pregnancy and lactation	Not recommended
Special considerations	Might improve outcomes in patients able to move forward with SCT
	Not to be used in patients with Wilson's disease

Table 2
List of pertinent interventional trials with CPX-351 registered on clinicaltrials.gov.

Clinicaltrials.gov ID	Title	Notes
NCT03826992	Venetoclax Combined With Vyxeos (CPX-351) for Participants With Relapsed or Refractory Acute Leukemia	Phase I Pediatrics and AYA (1–39 years old) R/R acute leukemia or therapy-related AML
NCT03629171	Liposome-encapsulated Daunorubicin-Cytarabine and Venetoclax in Treating Participants With Relapsed, Refractory or Untreated Acute Myeloid Leukemia	Phase II R/R AML
NCT03575325	Vyxeos(CPX-351) in Adults w R/R Acute Lymphoblastic Leukemia	Phase II Pilot R/R ALL
NCT03572764	CPX-351 (Vyxeos™) for Transplant Eligible, Higher Risk Patients With Myelodysplastic Syndrome	Pilot Study
NCT03555955	A Trial to Evaluate the Potential Impact of Renal Impairment on the Pharmacokinetics and Safety of CPX-351	Phase I PK study for patients with moderate and severe renal impairment
NCT03844997	Palbociclib in Combination With CPX-351 for Newly Diagnosed Acute Myeloid Leukemia	Phase II Newly diagnosed AML
NCT03825796	CPX-351 and Enasidenib in Treating Patients With Relapsed Acute Myeloid Leukemia Characterized by IDH2 Mutation	Phase II R/R AML with IDH2 mutation
NCT03672539	Liposome-encapsulated Daunorubicin-Cytarabine and Gemtuzumab Ozogamicin in Treating Patients With Relapsed or Refractory Acute Myeloid Leukemia (AML) or High Risk Myelodysplastic Syndrome	Phase I CD33 $^{+}$ R/R AML

Abbreviations. R/R = relapsed/refractory, AYA = Adolescents and Young Adults, AML = Acute Myeloid Leukemia, ALL = Acute Lymphoblastic Leukemia, PK = pharmacokinetics.

endeavors should be focused on a wider application by minimizing toxicities, improving response rates with combination therapies, and expanding indications. The impact of CPX-351 treatment on minimal residual disease and subsequent SCT outcomes should also be explored. There are several ongoing trials utilizing CPX-351 in combination with targeted agents. CPX-351 is also being explored in different diseases and settings. A summary of the ongoing registered trials is available in Table 2.

Summary

Improvements in survival in AML from the standard of 7 + 3 has long been lagging. CPX-351 has prolonged survival in a subset of patients with AML with an overall dismal prognosis. Its design utilized scientific principles to maximize synergy, drug delivery, and overcome resistance. Prolonged cytopenias and cardiotoxicity should be carefully monitored. Future directions include examining the depth of response produced by more sensitive molecular techniques and utilizing drug combinations to decrease relapse rates. The cost-efficiency of outpatient administration should also be explored.

Practice points

- First-line therapy for sAML or AML-MRC based on OS improvement
- Special attention to prolonged cytopenias and resulting infections and hemorrhage with vigorous prophylactic and transfusion strategies
- Special consideration for patients at risk for cardiotoxicity
- Might be suitable for outpatient administration with close monitoring

Research agenda

- Application to broader indications, including other hematological malignancies
- Combination therapies to overcome resistance and improve response rates
- Elucidation of improved survival post-SCT and effects on leukemia stem cells

Conflicts of interest

A.M. has participated as ascientific advisory board member for Jazz Pharmaceuticals. J.M. declares no conflict of interest. This work was not supported by any external funding.

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