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REVIEW ARTICLE

The Role of CPX-351 in the Acute Myeloid Leukemia Treatment Landscape: Mechanism of Action, Efficacy, and Safety

Livio Pagano[1,2] · Romano Danesi[3] · Edoardo Benedetti[4] · Riccardo Morgagni[5] · Luigina Romani[6,7] · Adriano Venditti[8]

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Abstract

CPX-351 (also known as VYXEOS® or Vyxeos liposomal) is a dual-drug liposomal encapsulation of cytarabine and daunorubicin in a synergistic 5:1 molar ratio and was the first example that utilized CombiPlex®, a combination drug technology platform. Superior efficacy with CPX-351 in the pivotal phase 3 randomized clinical trial versus its conventional free-drug counterpart led to its approval for the treatment of newly diagnosed therapy-related acute myeloid leukemia (AML) or AML with myelodysplasia-related changes in multiple countries. Emerging evidence indicates that CPX-351 affords additional benefits compared with conventional chemotherapy, including protection against intestinal dysbiosis and fungal colonization, fewer infectious complications, and a lower incidence of cardiotoxicity. This review examines the mechanisms underlying CPX-351's therapeutic effects and highlights its expanding role in AML treatment by summarizing efficacy and safety data from preclinical models, the pivotal clinical trial, and real-world studies. Particular focus is given to recent findings on CPX-351's intestinal and cardioprotective properties, which together strengthen its safety and efficacy profile compared with conventional chemotherapy.

Plain Language Summary

CPX-351 is a chemotherapy treatment for acute myeloid leukemia (AML) that combines the two drugs cytarabine and daunorubicin in very small fat bubbles called liposomes. The liposomes help deliver the drugs in the best possible way, keeping them at the right balance to be most effective at killing leukemia cells. This special delivery method via liposomes releases the drugs in a controlled manner, ensuring they reach the leukemia cells while minimizing harm to healthy cells, therefore, reducing side effects. Compared with traditionally delivered chemotherapy, CPX-351 causes less damage to the intestines and less disruption to the gut bacteria, lowering infection risk and stomach issues such as diarrhea. Additionally, CPX-351 may cause less damage to the heart by limiting its direct exposure to daunorubicin. The important clinical trial that led to the approval of CPX-351 showed that CPX-351 works better than traditional chemotherapy for patients with a high-risk type of AML, with improved remission rates and survival. Subsequent studies of CPX-351 in everyday medical practice across multiple countries showed similar results. These protective effects and confirmed effectiveness in everyday practice mean CPX-351 is a safe and effective treatment option for people with high-risk AML compared with traditional chemotherapy.

✉ Romano Danesi
romano.danesi@unimi.it

1 Department of Laboratory and Hematological Sciences, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

2 Department of Diagnostic Imaging, Radiotherapy Oncology, and Hematology, Catholic University of the Sacred Heart, Rome, Italy

3 Department of Oncology and Hemato-Oncology, University of Milan "La Statale", 7, Via Festa del Perdono, 20122 Milan, Italy

4 Hematology Operative Unit (UO), Department of Clinical and Experimental Medicine, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy

5 Department of Cardiology and Interventional Cardiology, University Tor Vergata, Rome, Italy

6 Department of Medicine and Surgery, University of Perugia, P.le Lucio Severi 1, Perugia, Italy

7 Casa di Cura San Raffaele, Sulmona, L'Aquila, Italy

8 Hematology, Department of Biomedicine and Prevention, University Tor Vergata, Rome, Italy

Key Points

The liposomal encapsulation of cytarabine and daunorubicin in a synergistic 5:1 molar ratio, known as CPX-351, has shown significantly superior efficacy and comparable safety versus its conventional free-drug chemotherapy counterpart for the treatment of newly diagnosed, high-risk/secondary acute myeloid leukemia.

Recent studies suggest that CPX-351 affords additional safety benefits, including intestinoprotective and cardioprotective properties, enhancing its favorable safety profile versus conventional chemotherapy delivery.

1 Introduction

Acute myeloid leukemia (AML) is a highly heterogeneous hematological malignancy, characterized by uncontrolled proliferation of clonal and poorly differentiated hematopoietic cells, and is the most common acute leukemia [1, 2]. The greatest burden is predominantly found in older adults (median age at diagnosis, 60–70 years) who are commonly diagnosed with therapy-related AML (t-AML) or secondary AML (comprising antecedent hematological disorders) subtypes along with unfavorable genetic factors, presence of comorbidities, and impaired performance status, all of which are associated with poor clinical outcomes [2–7]. As the global population ages, the incidence and burden of AML are gradually increasing [2, 3]. Despite this, mortality rates are improving, which may be partly due to recent advancements in AML treatment, such as lower-intensity regimens and novel targeted agents [3, 8–12]. However, even with the advent of new AML treatments, 5-year survival rates remain as low as 8% for patients with secondary AML and 29% for those with de novo AML, highlighting the continued unmet need for superior treatment options [7, 13].

Intensive induction chemotherapy offers the best chance of controlling and eradicating AML by inducing a complete remission (CR) and minimal residual disease (MRD) negative status, and providing a bridge to hematopoietic cell transplantation (HCT) [8, 14, 15]. For several decades, patients with newly diagnosed AML considered fit for intensive chemotherapy have received the gold standard intensive induction "7 + 3" chemotherapy combination of 7 days of cytarabine plus 3 days of an anthracycline [8, 11, 14]. Treatment with conventional 7 + 3 combination achieves CR in approximately 60–80% of younger adults (aged < 60 years) and 30–60% of older adults (aged ≥ 60 years) [14, 16–19]. However, 7 + 3 treatment can be associated with significant systemic toxicity and treatment-related mortality [20, 21]. For patients who are not considered eligible for intensive chemotherapy, a less intensive induction combination approach with venetoclax plus hypomethylating agents (HMA) is preferred [8, 9]. Although a pivotal step in the treatment for AML, long-term data suggest this approach is non-curative and often associated with significant myelosuppression and cytopenia [22–26]. Indeed, to date, intensive chemotherapy followed by HCT remains the only potential curative treatment option for long-term disease eradication in a fixed treatment duration [8, 14]. Conventional induction chemotherapy typically consists of administering more than one therapeutic agent in a free-drug cocktail [27, 28]. Nevertheless, the inability to control drug ratios in vivo due to the unique pharmacokinetics and pharmacodynamics of each agent is a major challenge. Tumor cells are exposed to different ratios, including antagonistic ratios, resulting in dramatic differences in antitumor activity [27, 29]. Co-encapsulation of anti-cancer agents in nanoscale drug carriers provide an effective tool to aid the delivery of combined drugs previously unachievable with conventional combination free-drug delivery. Nanoscale carriers, such as liposomes, enable pharmacologic control through controlled multi-drug release at synergistic ratios for a prolonged period to target cells and tissues, maximizing efficacy with reduced systemic toxicity [28, 30, 31].

CPX-351 (also known as VYXEOS® [USA and Canada] and Vyxeos liposomal [Europe]) is a dual-drug liposomal encapsulation of cytarabine and daunorubicin in a synergistic 5:1 molar ratio and was the first example that utilized CombiPlex®, a combination drug technology platform [28, 32–35]. Primary results of the pivotal phase 3 randomized clinical trial that explored the use of CPX-351 versus 7 + 3 in adults with newly diagnosed, high-risk/secondary AML confirmed the superiority of CPX-351 versus 7 + 3 and led to its approval for the treatment of newly diagnosed t-AML or AML with myelodysplasia-related changes (AML-MRC) in adults and pediatric (aged ≥ 1 year) patients in the USA and in adults in Canada and Europe [32–38].

While the pivotal clinical trial provided important data to establish the role of CPX-351 in the treatment of secondary AML, it was conducted, as most clinical trials are, in a restricted patient population [36]. Real-world studies have since evaluated CPX-351 in routine practice across several countries and addressed important data gaps, including its use in younger adults, achievement of MRD negativity, and outcomes by mutation status [39–44].

Although numerous comprehensive reviews have summarized the efficacy and safety of CPX-351, and the reported improvement observed with CPX-351 versus 7 + 3 for overall survival (OS) and remission rates in the pivotal phase 3 trial, emerging evidence indicates that CPX-351 affords additional benefits, including protection against intestinal dysbiosis and fungal colonization, fewer infectious

complications, a lower incidence of cardiotoxicity, and a lower incidence of alopecia [42, 44–49] compared with conventional chemotherapy [50–57]. In light of these recent findings, this review delves into the underlying mechanisms that contribute to CPX-351's therapeutic effects and explores its growing significance in the AML treatment landscape by summarizing efficacy and safety data from preclinical models, the pivotal clinical trial, and real-world studies. Special attention is given to the recent safety findings on CPX-351's intestinoprotective and cardioprotective properties, which collectively enhance its safety and efficacy profile in comparison to traditional chemotherapy approaches.

2 CPX-351 Structure and Mechanism of Action

CPX-351 was developed using CombiPlex®, a combination drug technology platform designed to maintain and preferentially deliver synergistic drug ratios to tumor cells [28, 31]. The CombiPlex® approach investigates various drug combinations at the preclinical stage in a broad range of tumor cell lines to determine the most effective drug ratio with therapeutic synergy. The identified synergistic ratio is then fixed in a nanoscale formulation, using liposome or nanoscale drug carriers, which preferentially direct the encapsulated drugs to the target tumor cells, while maintaining the synergistic ratio and allowing controlled drug exposure at the tumor site [28, 31]. Through CombiPlex®, effective formulations in the preclinical stage of drug development can be translated more predictably in the clinical stage, allowing patients to benefit from combined formulations with potent therapeutic activity early on [28, 29, 31].

In a study investigating the ratiometric dosing of different anticancer drug combinations, synergistic ratios of cytarabine:daunorubicin were identified at molar ratios of 1:1, 5:1, and 10:1 in murine P388 leukemic cells in vitro [29]. To test this finding in vivo, CPX-351 was developed by encapsulating the 5:1 ratio of cytarabine:daunorubicin inside 100 nm diameter liposomes composed of a membrane of distearoylphosphatidylcholine:distearoylphosphatidylglycerol:cholesterol (7:2:1 molar ratio) at a 0.1:1 drug-to-lipid ratio (mol/mol) [28, 29]. The structure of CPX-351 is shown schematically in Fig. 1. CPX-351 was shown to maintain the ratio of circulating cytarabine and daunorubicin for over 24 h after intravenous administration and achieved a 90% cell death rate in murine models [29]. Furthermore, the antitumor activity of CPX-351 was superior to that of the cytarabine and daunorubicin combination administered in saline at their respective maximum tolerated dose and matched doses of the individual liposomal drugs [29]. Subsequently, superior antitumor activity with CPX-351 versus other liposome-formulated drug ratios of cytarabine:daunorubicin as well as the free-drug counterparts was observed, which established that a molar ratio of 5:1 exhibited the highest degree of synergy in a panel of 15 tumor cell lines in vitro, including a wide range of leukemia cell lines [58].

With the established synergistic ratio of CPX-351, further studies sought to elucidate the other mechanisms of therapeutic activity afforded by CPX-351. The pharmacodynamics of CPX-351 were investigated using Rag2-M mice engrafted with the CCRF-CEM leukemia cell line as a leukemia model [59]. CPX-351 selectively accumulated in CCRF-CEM leukemic cells, with these cells taking up approximately twice as much liposomal lipid as normal bone marrow cells, with cytarabine and daunorubicin concentrations being more than nine and two times higher, respectively. The uptake pathway of CPX-351 was shown to occur on the plasma membrane of leukemic cells, whereby as plasma-membrane associated liposomes decreased, daunorubicin accumulation in the nuclei increased, indicative of CPX-351 internalization. An ex vivo study verified that increased sensitivity of leukemia cells to CPX-351 correlated with the uptake of intact CPX-351 liposomes and intracellular drug release [60].

Since the approval of CPX-351, the advantages of its liposomal delivery continue to be further established. A study using animal models verified the controlled, coordinated, and targeted release of cytarabine and daunorubicin by CPX-351 liposomes while prolonging tissue exposure at the synergistic 5:1 ratio, with the results providing insights into the mechanisms that drive the improved efficacy of CPX-351

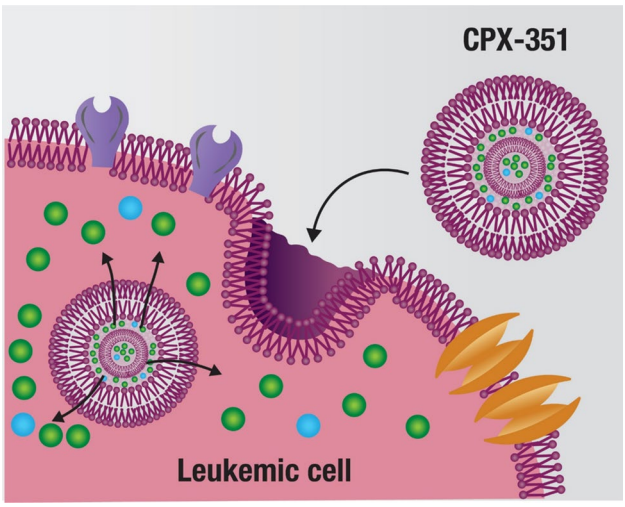

Fig. 1 Structure and mechanism of action of CPX-351. A 5:1 molar ratio of cytarabine (green circles) and daunorubicin (blue circles) is encapsulated in liposomes, composed of a distearoylphosphatidylcholine:distearoylphosphatidylglycerol:cholesterol membrane. CPX-351 is taken up via the plasma membrane of leukemic cells, maintaining the synergistic ratio and allowing controlled drug release at the tumor site

versus 7 + 3 observed in clinical trials [61]. Meaningful differences in the tissue distribution of cytarabine and daunorubicin following CPX-351 versus free-drug administration were observed, with tissue:plasma ratios generally being < 1 versus > 1, respectively. Notably, the highest CPX-351 concentrations were seen in well-perfused organs and tissues, including the bone marrow where AML is present. Therefore, CPX-351 may afford protection against toxicities associated with conventional free-drug delivery, even at the same exposure level.

3 Efficacy of CPX-351

Approval of CPX-351 was based on the primary analysis of the pivotal phase 3 trial [36–38, 62–64]. After a median follow-up of 20.7 months in 309 adults aged 60–75 years with newly diagnosed, high-risk/secondary AML randomized to receive CPX-351 (n = 153) or 7 + 3 (n = 156), treatment with CPX-351 led to significantly improved median OS (9.56 versus 5.95 months; hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.52–0.90; one-sided p = 0.003) and remission rates (CR + CR with incomplete hematologic recovery [CRi]; 47.7% versus 33.3%; two-sided p = 0.016) versus 7 + 3 without increased toxicity [36]. Long-term 5-year follow-up data reported improved median OS (9.33 months [95% CI 6.37–11.86] versus 5.95 months [95% CI 4.99–7.75]; HR 0.70; 95% CI 0.55–0.91) with CPX-351 versus 7 + 3 across the study population [37].

Various European real-world studies have since confirmed the efficacy observed with CPX-351 in the pivotal phase 3 trial that was conducted in the USA and Canada [36]. Table 1 summarizes the efficacy outcomes from the pivotal trial along with European real-world experiences with CPX-351. Overall, in the European real-world clinical setting, OS (median OS, 12–21 months; 1-year OS, 51–69%), remission rates (47–70%), and HCT rates (28–62%) were either higher or consistent with the pivotal trial (median OS, 9.56 months; 1-year OS, 41.5%; remission rate, 47.7%; HCT rate, 34%) [36, 39–44]. A recent real-world Italian study analyzed CPX-351 treatment outcomes of 513 patients and further established the efficacy of CPX-351 in a large cohort, reporting a CR/CRi rate of 66% and median OS of 16 months [43].

Despite recent advancements in front-line AML treatment options, there remains some uncertainty around the standard recommendation of intensive regimens, such as CPX-351, as opposed to less intensive treatment options, such as venetoclax plus azacitidine, for fit patients and particularly older patients who often have complex comorbidities. While data comparing the effectiveness of CPX-351 versus venetoclax plus azacitidine are lacking, a real-world study in 656 patients revealed similar median OS between the two regimens (13 months versus 11 months, respectively; HR 0.88; 95% CI 0.71–1.08; p = 0.22) [65]. Nevertheless, venetoclax plus azacitidine is indicated in unfit patients with de novo AML; therefore, the patient populations are not comparable. However, interestingly, a sensitivity analysis restricted to the population of patients eligible for the CPX-351 pivotal trial showed no significant difference in median OS. Furthermore, the study demonstrated a significantly higher proportion of patients were bridged to HCT following CPX-351 (28%) versus venetoclax plus azacitidine (10%), the difference being comparable with the HCT rates observed from their respective registrational trials (34% versus 1%) [25, 36].

4 Safety of CPX-351

4.1 Intestinal Dysbiosis

Several clinical studies have shown that the intestinal microbiota of patients with newly diagnosed AML is markedly disrupted during the 7 + 3 induction course, correlating with a higher risk of infectious complications, including bloodstream and fungal infections [50–56], and is a strong independent predictor of OS in transplanted patients and transplantation-related mortality [52, 66]. A translational study explored the impact of CPX-351 versus 7 + 3 on the intestinal microbiota [45] given the well-known association of the microbiota with intestinal homeostasis and mucosal permeability, colonization resistance, and effects on the hematopoietic system and treatment of hematologic disease [67–69]. Confirming previous findings [50], the study showed that treatment with 7 + 3 led to multiple signs of intestinal damage and pathology in mice models, including ileocolic infiltrates, activation of inflammatory pathways, immune dysregulation, and increased epithelial paracellular permeability, all of which were not observed with CPX-351 treatment [45]. In fact, CPX-351 reduced ongoing intestinal damage; stimulated anti-inflammatory pathways, including the activation of mesenteric FOXP3$^+$ regulatory T-cells; and counteracted the increased epithelial permeability, thus preventing bacterial translocation to draining lymph nodes. The study highlighted that CPX-351 offers mucosal protection via regulation of the ligand-dependent aryl hydrocarbon receptor/interleukin (IL)-22/IL-10 host pathway, a critical pathway in the maintenance of the intestinal barrier and microenvironment [45, 70]. Indeed, CPX-351 was also effective in the prevention of dextran sodium sulfate-induced colitis, a classic model of intestinal inflammation, an effect to which the liposome component likely contributed [45, 71]. The preservation of a protective intestinal microbiota during CPX-351 treatment pivotally contributed to the maintenance of the intestinal barrier function, local immune homeostasis, and prevention of infections. Different from 7

Table 1 Comparison of the pivotal phase 3 trial that led to the approval of CPX-351 versus European real-world experiences with CPX-351

Study	Country	Study population, *N*	Median age, years	Median follow-up, months	Overall survival	Remission rate (CR/CRi), *n* (%)	Patients receiving HCT after CPX-351, *n* (%)	Safety summary
Lancet et al. (pivotal phase 3 trial) [36]	USA and Canada	153	Mean age 67.8 (SD 4.2)	20.7	Median OS, 9.56 months; 1-year OS, 41.5%; 2-year OS, 31.1%	73 (47.7)	52 (34)	The most frequently reported grade ≥ 3 AEs were infection-related AEs (83.7%), febrile neutropenia (68.0%), pneumonia (19.6%), hypoxia (13.1%), and bleeding (11.8%)
Guolo et al. [43]	Italy	513	65.6 (range 19–79)	23.66	Median OS, 16.23 months	340 (66.3)[a]	166 (48.8)	NR
Legg et al. [39]	UK	353	64 [IQR 58–69]	10.9	Median OS, 12.9 months; 1-year OS, 51%; 2-year OS, 34%; 3-year OS, 32%	NR	150 (42)	NR
Rautenberg et al. [41]	Germany	188	65 (range 26–80)	9.3	Median OS, 21 months; 1-year OS, 64%	85 (47)	116 (62)	Grade ≥ 3 AEs were mainly infections (22%), pneumonia (22%), febrile neutropenia (15%), gastrointestinal (4%, including mucositis, nausea, vomiting), bleeding (4%), and renal failure (3%)
Mehta et al. [40]	UK	147	64 (range 18–83)	10.6	Median OS, 12.8 months; 1-year OS, 51%; 2-year OS, 36%; 3-year OS, 34%	73 (53)	50 (34)	The most common (occurring in ≥ 5% of patients) grade ≥ 3 TEAEs were febrile neutropenia (38.1%), bacteremia (12.9%), pneumonia (8.2%), fungal infection (8.2%), sepsis (6.8%), and epistaxis (5.4%)

Table 1 (continued)

Study	Country	Study population, *N*	Median age, years	Median follow-up, months	Overall survival	Remission rate (CR/CRi), *n* (%)	Patients receiving HCT after CPX-351, *n* (%)	Safety summary
Chiche et al. [42]	France	103	67 (range 20–83)	8.6	Median OS, 16.1 months	61 (59)	36 (35)	Most common (occurring in > 20% of patients) grade ≥ 3 AEs were sepsis (98%), febrile neutropenia (91%), pneumonia (30%), and bacteremia (24%) In total, four patients experienced grade 3 gastrointestinal AEs (vomiting in one patient and mucositis in three patients)
Guolo et al. [44]	Italy	71	66 (range 52–79)	11	1-year OS, 68.6%	50 (70.4)	20 (28.2)	AEs included FUO (28%), sepsis (28%), self-resolving diffuse skin rash (25%), pneumonia (11%), mucositis (7%), alopecia (6%), and fungal infection (4%) Most of the AEs were easily manageable and resolved completely

AE adverse event, *CR* complete remission, *CRi* complete remission with incomplete hematological recovery, *FUO* fever of unknown origin, *HCT* hematopoietic cell transplantation, *IQR* interquartile range, *NR* not reported, *OS* overall survival, *SD* standard deviation, *TEAE* treatment-emergent adverse event

[a]Only CR was reported

+ 3, CPX-351 promoted a transplantable protective microbial community capable of affording mucosal protection, limiting pathogenic inflammation, and promoting colonization resistance to fungi, as indicated by a significant decrease in both *Candida* and *Aspergillus* growth by CPX-351. These results highlight the mechanisms by which CPX-351 can provide superior safety versus 7 + 3 and its role in maintaining a functional mucosal barrier with functional microbiota.

In the pivotal phase 3 trial, CPX-351 demonstrated a comparable safety profile with 7 + 3, which reported the most frequent grade ≥ 3 adverse events (AEs) as infection-related AEs (84%), febrile neutropenia (68%), pneumonia (20%), hypoxia (13%), and bleeding (12%), with no reported grade ≥ 3 gastrointestinal events [36]. In post hoc subgroup analyses of the pivotal trial, the safety profile of CPX-351 in patients who achieved remission was generally consistent with the overall study population and that known of 7 + 3; however, the incidence of diarrhea was notably lower with CPX-351 (38%) versus 7 + 3 (73%) [72]. In a pooled safety analysis of five clinical studies comprising the CPX-351 clinical development program versus conventional chemotherapy, while the most frequent system organ class was gastrointestinal disorders at 90% versus 95%, respectively, the lower incidence with CPX-351 was driven by a lower rate of diarrhea (46%) versus conventional chemotherapy (66%), and the most frequently reported grade ≥ 3 AEs with CPX-351 were febrile neutropenia (62%), pneumonia (16%), hypoxia (10%), and bacteremia (10%) [73]. These additional studies supplement the acceptable safety profile observed with CPX-351, with no new safety signals. A summary of reported real-world safety on CPX-351 is shown in Table 1. Generally, in the real-world setting, febrile neutropenia and infections were the most commonly reported grade ≥ 3 AEs with CPX-351, whereas grade ≥ 3 gastrointestinal AEs were infrequent [40–42], consistent with results from clinical trials [36, 72, 73].

Treatment with intensive AML chemotherapy has demonstrated significant intestinal dysbiosis during treatment and persisting after the end of treatment, which may have implications for subsequent phases of curative therapy, such as HCT [52–54, 74, 75]. For example, 7 + 3 was shown to induce intestinal damage and dysbiosis, with prolonged loss of bacterial load, diversity, and function of the microbiota [50, 51]. The SEIFEM Italian study focused on the absolute infectious risk in a real-life setting of 200 patients with AML who were treated with CPX-351 and reported a total of 249 febrile events (febrile neutropenia of unknown origin [37%], microbiologically documented infections [47%], and clinically documented infections [17%; pneumonia, cellulitis/abscesses, arthritis, mucositis, and sinusitis]) [46]. Overall, infection-related mortality was low with CPX-351 (6%) despite prolonged myelosuppression, with few fungal infections (6%), which may be attributed to CPX-351's ability to increase antifungal resistance [45, 46]. The prolonged myelosuppression was to be expected due to the extended drug exposure offered by CPX-351 [61], and consistent with the pivotal phase 3 trial (median time to neutrophil [≥ 500/mL] and platelet [≥ 50,000/mL] recovery in patients who achieved CR + CRi after initial induction chemotherapy was longer with CPX-351 [35 and 36.5 days, respectively] versus 7 + 3 [29 and 29 days, respectively] in the pivotal trial [36]). In a subsequent analysis of the SEIFEM study in patients who underwent allogeneic HCT post-CPX-351 treatment and with available data ($n = 70$), low rates of HCT-related complications were observed, and low infection-related mortality was maintained [76]. These encouraging results further support a good safety profile with CPX-351 and its potential to bridge patients to HCT.

Consequently, the intestinal mucosal damage and myelosuppression caused by intensive chemotherapy regimens may lead to neutropenic enterocolitis (NEC), an uncommon but life-threatening complication with reported mortality rates of up to 50% [77, 78]. A prospective study investigated the potential damaging effects of different intensive chemotherapy regimens on intestinal mucosal injury and incidence of NEC of patients with AML [78]. As expected, treatment with CPX-351 had a lower impact on intestinal mucosal injury versus other chemotherapy regimens. Notably, there was an absence of NEC episodes in patients treated with CPX-351 during both induction and consolidation. In contrast, other chemotherapy regimens, including 7 + 3, were associated with a statistically higher incidence of NEC [78], consistent with previous reports of significant intestinal damage following 7 + 3 treatment [50, 51]. The study suggested that resulting mucosal barrier damage from chemotherapy agents was the likely mechanism of NEC rather than myelosuppression, and again, the liposomal formulation of CPX-351 was indicated in regard to affording the intestinoprotective effects, which may explain the absence of NEC.

4.2 Cardiotoxicity

Anthracyclines, such as daunorubicin, are a primary cause of cardiotoxicity, with the risk of cardiac dysfunction from anthracycline-induced cardiotoxicity increasing with higher cumulative doses of anthracyclines. However, this class of anti-cancer drugs remain critical chemotherapeutic agents, including in the treatment of AML [79–81]. The liposomal formulation of CPX-351 provides cardioprotective properties, which can yield better cardiac outcomes. Liposomes enable selective drug delivery and sequestration from organs with tight capillary junctions, including the heart, preventing excessive exposure and therefore reducing cardiotoxicity while maintaining antitumor effects [82, 83]. This is thought to be due to the polyethylene glycol coating around liposomes, which protects the molecule from phagocytosis,

resulting in a targeted, gradual release of the drug at tumor sites [82]. A study using animal models showed that the heart:plasma ratio of cytarabine and daunorubicin following CPX-351 administration in rats were 10-fold and 95-fold lower, respectively, compared with free-drug delivery, with > 99% of daunorubicin rendered pharmacologically inactive, suggesting the cardioprotective benefit afforded by CPX-351 liposomes [61]. Recently, an in vitro investigation compared the relative cardiac safety profile of CPX-351 versus its free-drug counterparts using human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) [47]. In contrast to the free-drug combination, CPX-351-treated hiPSC-CM did not result in concentration-dependent cumulative cytotoxicity after repeated exposure, suggesting that liposomal encapsulation of daunorubicin may be improving the cardiotoxicity profile of daunorubicin, indicating the cardio-protection afforded by CPX-351. Long-term clinical studies are required to corroborate the reduced cardiotoxicity observed with CPX-351 versus free-drug in the preclinical and in vitro models, but these findings provide valuable insights for patients with previous anthracycline exposure.

Clinical data have shown that CPX-351 may provide cardioprotective benefits. A phase 2 study in 26 patients with acute leukemia found no clinically meaningful effects on heart rate, QRS interval, PR interval, or QT interval corrected for heart rate using Bazett's corrected QT interval following CPX-351 administration, suggesting that CPX-351 may induce less cardiotoxicity than previously reported for conventional daunorubicin, further supporting the clinical benefit with liposomal CPX-351 versus its free-drug counterpart [84]. Given that prior anthracycline exposure is a risk factor for cardiotoxicity, it is worth mentioning that 54% of patients in the study had known prior anthracycline exposure; however, neither mean QTcB nor the frequency of prolonged QTcB (> 450 ms) significantly increased following CPX-351 treatment, except in one patient. In post hoc subgroup analyses of the pivotal phase 3 trial, lower proportions of patients treated with CPX-351 versus 7 + 3 had cardiac impairment based on echocardiogram measures of left ventricular ejection fraction (LVEF) < 53% (12% versus 31%) and global longitudinal strain (GLS) ≤ 18% (25% versus 38%) [57]. Furthermore, clinically significant changes in LVEF (> 10% decrease from baseline and LVEF < 53%) and GLS (> 12% relative decrease from baseline and GLS < 18%) were less common with CPX-351 versus 7 + 3 (9% versus 20% and 21% versus 44%, respectively). While cardiac-related toxicities have been reported infrequently in real-world studies, those studies that did assess cardiac outcomes have reported low frequencies of cardiac events (9–12%) [40, 42]. Underreporting of cardiac events in pivotal clinical trials supporting the approval of contemporary anticancer therapies has been previously documented, highlighting the importance of further studies focusing on cardiac safety and real-world studies to support trial data [85].

4.3 Alopecia

While gastrointestinal and constitutional toxicities arising from cancer treatment impact negatively on patients' quality of life, it is also important to highlight the dermatological toxicities, which are often overlooked despite their significant impacts, particularly with regard to psychological and social well-being [86, 87]. For patients, chemotherapy-induced alopecia is one of the most distressing and traumatic aspects of undergoing treatment [87, 88]. Alopecia is a well-known common adverse effect of cancer treatment, occurring in at least 65% of patients who receive cytotoxic therapies [89]. Therefore, it is notable that CPX-351 does not cause the classic alopecia seen with traditional chemotherapies such as daunorubicin, with reported rates of 100% [89]. In clinical studies, rates of alopecia with CPX-351 were reported between 12 and 33% [48, 49], and real-world studies reported even lower rates, at 5–11% [42, 44], highlighting the importance of CPX-351 from the patient perspective.

5 Conclusions

The unique mechanism of action and distinct physical and pharmacological characteristics of CPX-351 plays a crucial role in explaining its clinical efficacy and safety observed in patients with t-AML or AML-MRC. To date, CPX-351 has been reserved for fit patients with secondary AML. However, its superior efficacy versus the conventional 7 + 3 regimen combined with its favorable toxicity profile suggests that its use may be also extended to other patient populations. At the same time, CPX-351's favorable toxicity profile opens the possibility of treating high-risk patients who were previously excluded from clinical trials due to concerns about the adverse effects. This is particularly significant given the pressing need for new therapeutic options for adults with AML who are less fit for intensive treatment. For this reason, it may now be time to explore the use of CPX-351 in other high-risk populations. Indeed, there are a number of ongoing clinical trials evaluating CPX-351 versus conventional chemotherapy in high-risk groups, including patients with AML with intermediate or adverse genetics (NCT05260528; NCT03897127), with or without *FLT3* mutations (NCT04293562) and with higher-risk myelodysplastic syndrome and oligoblastic AML (NCT04061239).

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Conflict of interest L. Pagano is a board member of Basilea, Cidara Therapeutics, Gilead Sciences, Janssen, Jazz Pharmaceuticals, MSD, Novartis, Pfizer, and Stemline Therapeutics; a consultant for Cidara Therapeutics and Stemline Therapeutics; and has been a speaker for Astellas Pharma, Gilead Sciences, Janssen, Jazz Pharmaceuticals, Kyowa Kirin, MSD, Novartis, and Pfizer. R. Danesi has received speaker's bureau/advisor's fees from AstraZeneca, EUSA Pharma, Genzyme, Gilead Sciences, Ipsen, Janssen, Jazz Pharmaceuticals, Lilly, Novartis, Pfizer, and Sanofi. E. Benedetti has received speaker's bureau/advisor's fees from AstraZeneca, BeiGene, and Jazz Pharmaceuticals. R. Morgagni has no conflicts of interest to declare. L. Romani has no conflicts of interest to declare. A. Venditti has received research funding from Jazz Pharmaceuticals; he was a consultant for AbbVie, Amgen, Astellas Pharma, Astex Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, Delbert Pharma, Glycostem, Janssen, Kite-Gilead, Menarini, Novartis, Otsuka, Pfizer, Servier, and Stemline Therapeutics. All are not related to this manuscript.

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