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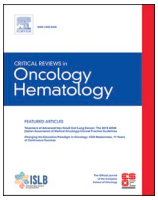

Real-world experience with CPX-351 in high-risk acute myeloid leukemia

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ABSTRACT

CPX-351, a dual-drug liposomal encapsulation of daunorubicin/cytarabine, was approved for newly diagnosed therapy-related acute myeloid leukemia (AML) and AML with myelodysplasia-related changes in adults in 2017 (US; updated to patients aged ≥1 year in 2021) and 2018 (EU/UK) based on improved survival and remission and comparable safety versus 7 + 3 chemotherapy in a randomized trial in older adults. Real-world studies have since evaluated CPX-351 in routine practice across several countries and addressed important data gaps (e.g., use in younger adults, measurable residual disease negativity, outcomes by mutation). This review discusses real-world studies of CPX-351 as AML treatment, with the aim of helping prescribers make informed treatment decisions.

1. Introduction

For several decades, cytarabine plus an anthracycline (e.g., "7 +3" regimen) remained the standard-of-care induction therapy for acute myeloid leukemia (AML), including high-risk disease such as therapy-related AML (t-AML) and AML with myelodysplasia-related changes (AML-MRC; includes AML transformed from an antecedent hematological disorder and *de novo* AML with myelodysplasia-related cytogenetic or genetic changes). Although complete remission was historically achieved in 60–80% of patients aged < 60 years with AML, treatment with conventional chemotherapy may not be well tolerated in older patients or those with significant comorbidities (Chen et al., 2019; Daver et al., 2020), which is a notable concern given that the majority of patients are aged ≥ 65 years at the time of AML diagnosis (Surveillance Epidemiology and End Results Program, 2019). Furthermore, increasing age is associated not only with a higher frequency of comorbidities, but also with development of adverse-risk mutations and cytogenetic abnormalities in AML (Appelbaum et al., 2006; Chen et al., 2019; Daver et al., 2020). t-AML and AML-MRC are often diagnosed in older patients and those with adverse and/or complex cytogenetics, mutations, or a multidrug-resistant phenotype, and these factors contribute to worse outcomes and poorer prognosis compared with many other AML subtypes (Granfeldt Østgård et al., 2015; Grimwade et al., 2010; Hulegårdh et al., 2015; Leith et al., 1997; Miesner et al., 2010). In recent years, an improved understanding of AML pathophysiology has led to the development and approval of several new therapies for the treatment of various AML subtypes, facilitating a more individualized approach to treatment.

One of these newer therapies is CPX-351 (European Union/United Kingdom: Vyxeos® liposomal; United States: Vyxeos®), a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio. CPX-351 was initially approved for the treatment of newly diagnosed t-AML or AML-MRC in adults in the United States in August 2017 (updated to patients aged ≥1 year in March 2021) and in the European Union and United Kingdom in December 2018 (European Medicines Agency, 2018; Jazz Pharmaceuticals Inc., 2022). These approvals were primarily based on efficacy and safety results from a phase 3, randomized controlled trial (RCT) conducted in North America, which evaluated CPX-351 versus 7 + 3 chemotherapy in patients aged 60–75 years with newly diagnosed, high-risk/secondary AML (Lancet et al., 2018). With 5 years of follow-up, the favorable difference in median overall survival (OS) was maintained with CPX-351 versus 7 + 3 (9.33 vs 5.95 months; hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.55–0.91) (Lancet et al., 2021). Among patients who proceeded to hematopoietic cell transplantation (HCT), median OS landmarked from the HCT date was not reached with CPX-351 versus 10.3 months with 7

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+ 3 (HR 0.51, 95% CI 0.28–0.90), and the estimated 5-year OS rate from randomization was > 50% with CPX-351 and was higher versus 7 + 3 (Uy et al., 2022). These results confirmed CPX-351 as a standard-of-care treatment for newly diagnosed t-AML and AML-MRC (Lancet et al., 2018; Lancet et al., 2021).

RCTs are considered the gold standard for establishing the safety and efficacy of therapies and are conducted in highly controlled conditions and in patients meeting prespecified criteria to generate robust data on clinical outcomes and adverse effects. In contrast, real-world studies evaluate the effectiveness of new therapies in a broader label population and during routine practice, which may vary between different regions; thus, real-world studies provide a valuable complement to RCTs. Herein, we summarize and discuss data from real-world studies of CPX-351 for the treatment of high-risk AML, with the aim of helping prescribers make informed treatment decisions. In addition to providing regional data, these studies help fill data gaps not addressed by the phase 3 RCT, such as use in younger patients (aged ≤60 years), measurable residual disease (MRD) negativity, and outcomes by mutation profile.

2. Methods

Relevant real-world studies of CPX-351 as AML treatment were identified by pragmatic, non-structured hand searching of available literature, following literature searches of PubMed and key congresses (ASCO, ASH, EHA, ESMO) conducted in May 2022 using a combination of MeSH headings and keywords for AML and CPX-351. Additional publications of real-world studies of CPX-351 known by the authors and relevant publications that emerged during manuscript development were also included. Study titles and abstracts were first reviewed followed by complete articles. Congress abstracts were not included if there was a subsequent follow-up congress abstract or manuscript that included the same endpoints. Without access to a translation service, only studies written in the English language were considered. Ultimate final article inclusion was determined by all authors.

3. Real-world evidence of CPX-351 in high-risk AML

Although the studies discussed herein all reflect the real-world use of CPX-351, there are several notable differences between them. Most of the studies are retrospective in design; however, compassionate use programs, observational studies, and case reports also contribute to the totality of real-world evidence (Supplementary Material. Table S1). Some studies collected data using national databases or healthcare systems, whereas others represent single-center or multicenter experience. The studies also reflect regional differences in routine practice—although real-world studies are conducted in accordance with a drug's labeled indication(s), regional differences in treatment decisions may lead to variations in patient populations, and differences in patient

Table 1
Comparison of CPX-351 efficacy outcomes from real-world studies versus the phase 3 RCT that led to CPX-351 approval.

Citation	CR+CRi	MRD negativity in patients with CR+CRi	OS (months)			OS (months) landmarked from HCT date	
			Median (95% CI)	1 year	HCT	Median (95% CI)	1 year
(Lancet et al., 2018, 2021)[a]	48%	NR	9.33 (6.4–11.9)	42%	35%	Not reached	NR
(Andrews et al., 2020)	50%	NR	NR	44%	36%	NR	NR
(Chiche et al., 2021)	59%	MFC/NGS/qPCR: 57% (16/28)	16.1 (range 13.1–16.7)	NR	35%	Not reached[b]	NR
(Plesa et al., 2021)	67%	MFC: 52% (12/23)	NR	NR	47%	NR	NR
(Klingler et al., 2022)	42% (50% in t-AML or AML-MRC)	NR	Not reached	NR	81%	Not reached	NR
(Rautenberg et al., 2021)	47%	MFC: 64% (23/36)	21	64%	62%	Not reached	73%
(Garibaldi et al., 2022)	75%	NR	20	NR	64%	Not reached[b]	NR
(Guolo et al., 2020)	70%	MFC: 38% (15/40)[c] WT1: 54% (21/38)[c]	Not reached	69%	28%	Not reached	100%
(Guolo et al., 2021)	80%	MFC: 45% (18/40) WT1: 55% (22/40)	19	NR	28%	NR	NR
(Bernal et al., 2022)	49%	MFC: 56% (14/25)	12.1 (7.8–NE)	NR	30%	Not reached[b]	NR
(Legg et al., 2022)	NR	NR	12.9 (10.5–17.5)	51%	51%[d]	Not reached	72%
(Murthy et al., 2021)	61%	NR	14.1 (9.0–25.9)	NR	39%	23.2 (14.1, NE)[b]	NR
(Taylor et al., 2022)	65%	45% (5/11)[e]	~24[f]	NR	62%	Not reached	NR
(Benitez et al., 2021)	48%	NR	9.1 (6.3–12.0)	NR	29%	Not reached[b]	NR
(Grenet et al., 2021)	58%	NR	17.3 (13.8–20.5)	NR	48%[g]	64[g]	NR
(Jain et al., 2021)	59%	NR	17.3	NR	30%	NR	NR
(Kim et al., 2020)	54%	NGS: 56% (14/25)	10.4	NR	33%	NR	NR
(Lee et al., 2022)	53%	NR	16	61%	54%	77[b]	NR
(Madarang et al., 2020)	36%	NR	NR	NR	39%	NR	NR
(Matthews et al., 2022)	56%	NR	13	51%	28%	NR	NR
(Przespolewski et al., 2021)	44%	NR	5.2	NR	50%	Not reached	NR
(Talati et al., 2020)	41%	NR	7.1	NR	50%	Not reached[b]	NR

Abbreviations: AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; HCT, hematopoietic cell transplantation; MFC, multiparameter flow cytometry; MRD, measurable residual disease; NE, not estimable; NGS, next-generation sequencing; NR, not reported; OS, overall survival; qPCR, quantitative polymerase chain reaction; RCT, randomized controlled trial; t-AML, therapy-related acute myeloid leukemia; WT1, wild-type 1.

[a] Phase 3 RCT is included in this table for comparison with real-world analyses. CR+CRi and 1-year OS estimate based on primary analysis; median OS, landmarked OS, and HSCT proportion was based on long-term follow-up analysis.

[b] Not specified as OS landmarked from the HCT date.

[c] MRD analysis not specified as among patients who achieved CR or CRi.

[d] Among 165 patients with ≥ 3 months of follow-up.

[e] Method of MRD assessment not specified.

[f] 50% of patients were alive at a median of 24 months after completion of CPX-351 treatment.

[g] Among a subgroup of 152 patients aged 60–75 years.

management may impact outcomes.

3.1. Achievement of CR and CRi

The achievement of a complete response (CR) or a complete response with incomplete hematological recovery (CRi) remains a key treatment goal for patients with AML, because those who achieve remission are more likely to proceed to allogeneic HCT, which improves the likelihood of achieving long-term survival. Overall, real-world studies have confirmed the high remission frequency observed in the RCT (Table 1), with real-world studies of CPX-351 reporting either higher (53–80%) (Chiche et al., 2021; Garibaldi et al., 2022; Grenet et al., 2021; Guolo et al., 2020; Guolo et al., 2021; Jain et al., 2021; Kim et al., 2020; Lee et al., 2022; Matthews et al., 2022; Murthy et al., 2021; Plesa et al., 2021; Taylor et al., 2022) or similar (44–50%) (Andrews et al., 2020; Benitez et al., 2021; Bernal et al., 2022; Klingler et al., 2022; Przespolewski et al., 2021; Rautenberg et al., 2021) percentages of patients achieving CR or CRi compared with the CPX-351 arm in the phase 3 RCT (48%) (Lancet et al., 2018).

3.2. Achievement of MRD negativity

Although assessment of MRD is routinely used in the management of other hematological malignancies, its utility in adults with AML is still emerging, and methodologies and thresholds for MRD negativity are only recently being standardized for AML (Heuser et al., 2021). Despite these challenges, studies have shown that achievement of MRD negativity is an important prognostic marker of relapse risk and OS in AML (Cluzeau et al., 2022; Ravandi et al., 2018; Schuurhuis et al., 2018; Short et al., 2020). Moreover, achievement of MRD negativity at the time of HCT has been associated with significantly improved OS and progression-free survival, as well as a lower relapse risk versus MRD-positive remission (Araki et al., 2016).

MRD was not assessed in the phase 3 RCT of CPX-351 but has been assessed in several real-world analyses of CPX-351 (Table 1). Among patients who had achieved CR or CRi, 38–64% had MRD negativity after CPX-351 treatment across studies (Bernal et al., 2022; Chiche et al., 2021; Guolo et al., 2020; Guolo et al., 2021; Kim et al., 2020; Plesa et al., 2021; Rautenberg et al., 2021; Taylor et al., 2022). The method of MRD assessment and threshold for MRD negativity varied across studies, contributing to the broad range of proportions achieving MRD negativity.

The impact on outcomes of achieving MRD negativity after CPX-351 has been assessed in five real-world studies thus far (Chiche et al., 2021; Guolo et al., 2020; Guolo et al., 2021; Kim et al., 2020; Rautenberg et al., 2021), with some variability in the findings, which may be due—at least in part—to the small patient numbers assessed for MRD status (<40 patients in each analysis). Although additional analyses are needed, achievement of MRD negativity after CPX-351 is expected to be associated with improved survival outcomes, consistent with what has been reported generally for AML.

One challenge in the assessment of MRD relates to the detection of leukemia stem cells (LSCs), which are immunophenotypically defined as $CD34^{+}/CD38^{-}$ in combination with an aberrant marker absent from hematopoietic stem cells (Heuser et al., 2021), and these cells can drive relapse. In a French retrospective study, 52% (12/23) of patients in remission after CPX-351 achieved MRD negativity, and 13% (3/23) achieved LSC negativity. At the time of the analysis, all three MRD^{-}/LSC^{-} patients remained in remission, whereas 67% (6/9) of MRD^{-}/LSC^{+} patients and 73% (8/11) of MRD^{+}/LSC^{+} patients had relapsed (Plesa et al., 2021). These findings reinforce the potential utility of detecting LSCs.

3.3. Overall survival

Historically, it is uncommon for OS to be longer in real-world studies than in RCTs, as the real-world patient population is typically more diverse, and the management and/or assessment of patients is less standardized. However, the majority of real-world studies of CPX-351 reported longer median OS values (12.1–24.0 months or not yet reached) (Bernal et al., 2022; Chiche et al., 2021; Garibaldi et al., 2022; Grenet et al., 2021; Guolo et al., 2020; Guolo et al., 2021; Jain et al., 2021; Klingler et al., 2022; Lee et al., 2022; Legg et al., 2022; Matthews et al., 2022; Murthy et al., 2021; Rautenberg et al., 2021; Taylor et al., 2022) compared with those observed in the phase 3 RCT (primary analysis: 9.56 months (Lancet et al., 2018); long-term follow-up analysis: 9.33 (Lancet et al., 2021); Table 1). Other studies reported median OS values that were similar (9.1 and 10.4 months) (Benitez et al., 2021; Kim et al., 2020) to the phase 3 RCT. In contrast, two US retrospective studies (with overlap between centers) reported shorter median OS values of 5.2 and 7.1 months (Przespolewski et al., 2021; Talati et al., 2020); however, these studies had a high proportion of patients with prior hypomethylating agent exposure (70% and 100% versus 41% in the phase 3 RCT (Lancet et al., 2018)), which is typically associated with poor outcomes.

Of note, the phase 3 RCT of CPX-351 was performed exclusively in older adults (aged 60–75 years), whereas many real-world studies were performed in patients representing broader age cohorts. However, the median age of most real-world studies of CPX-351 was 60–69 years (reflecting the median age at AML diagnosis), indicating that most patients in these studies were older adults. Several real-world studies were performed primarily (approximately ≥75% of patients) in older adults (aged ≥60 years), with median OS values ranging from 10.4 to 21 months (Bernal et al., 2022; Chiche et al., 2021; Grenet et al., 2021; Guolo et al., 2021; Kim et al., 2020; Legg et al., 2022; Rautenberg et al., 2021).

Median follow-up times varied considerably across the real-world studies (Supplementary Material. Table S1). Several studies reported a median of < 12 months of follow-up (Andrews et al., 2020; Benitez et al., 2021; Bernal et al., 2022; Chiche et al., 2021; Guolo et al., 2020; Legg et al., 2022; Przespolewski et al., 2021; Rautenberg et al., 2021), including three studies that reported a median of 6.0–6.5 months of follow-up (Benitez et al., 2021; Bernal et al., 2022; Przespolewski et al., 2021). These shorter follow-up times may have contributed to the variation in median OS values reported. For example, in the Italian Compassionate Use Program, the initial follow-up time was 11 months with a median OS not reached and an estimated 1-year rate OS of 68.6% (Guolo et al., 2020); after 22 months of follow-up, median OS was 13 months and estimated 2-year OS rate was 29% (Minetto et al., 2021).

3.4. Transplant outcomes

An important treatment goal of intensive induction therapy for patients with AML is to bridge patients to HCT, which can be associated with long-term survival and eventual cure. Treating physicians should consider multiple patient and disease factors when deciding if a patient is a candidate for HCT. Ideally, patients will have achieved a deep remission during induction therapy and remain healthy enough to undergo the HCT procedures. Although traditionally many older adults were not considered candidates for HCT based on age alone, this trend has been changing with more recent research showing that many older adults benefit from both intensive induction therapy and HCT. Advances in transplant research (e.g., reduced-intensity conditioning) have expanded the eligibility criteria for HCT candidates to include older adults with AML (Gupta et al., 2011). In addition, the development of new transplant techniques (e.g., haploidentical donor transplantation using the post-transplant cyclophosphamide approach (Ciurea et al., 2015)) means that most patients who are candidates for HCT now have a donor.

The percentage of patients proceeding to HCT in these real-world studies ranged considerably, from 28% to 81%, although the majority of studies reported percentages that were either comparable to or higher

than the phase 3 RCT (35% (Lancet et al., 2021); Table 1). Several factors may have contributed to the variation in patients proceeding to HCT. Of note, the nine studies with HCT percentages ≥ 40% included two studies conducted exclusively in younger adults. Differences in the percentages of patients proceeding to HCT also may reflect regional and center-specific differences in the decision-making process for selecting candidates for HCT. Additionally, short follow-up times may have decreased the percentage of patients proceeding to HCT in some studies, as some patients may not have had sufficient time since their diagnosis to proceed to HCT. For example, in a UK-based retrospective study, 40% (84/211) of all patients were bridged to HCT; however, some patients were newly diagnosed. When the analysis was performed on the subset of patients with ≥ 3 months of follow-up time in order to focus on patients who realistically could have proceeded to HCT, 51% (84/165) of patients bridged to HCT (Legg et al., 2022).

Patients who were bridged to HCT after receiving induction therapy with CPX-351 achieved prolonged OS after HCT. In a UK study, median OS landmarked from HCT was 23.2 months (Murthy et al., 2021), and in a US study, median OS for patients proceeding to HCT was 77 months (Lee et al., 2022); in other studies, the median OS (from diagnosis or landmarked from the HCT date) had not yet been reached (Benitez et al., 2021; Bernal et al., 2022; Chiche et al., 2021; Garibaldi et al., 2022; Guolo et al., 2020; Klingler et al., 2022; Legg et al., 2022; Przespolewski et al., 2021; Rautenberg et al., 2021; Talati et al., 2020; Taylor et al., 2022) (Table 1). In a longer-term follow-up analysis of the Italian Compassionate Use Program (median follow-up of 22 months), median OS landmarked from the HCT date was still not reached among patients who proceeded to HCT and were alive and in CR at Day 90, with an estimated 2-year OS rate of 58% (Minetto et al., 2021). These findings are consistent with the long-term analysis of the phase 3 RCT, which also reported a median OS that had not yet been reached and an estimated 3-year OS rate landmarked from the HCT of 56% (Lancet et al., 2021). Together, these data support that CPX-351 can provide a bridge to HCT with prolonged post-HCT OS in younger and older adults with AML.

Treatment with CPX-351 has also been compared with venetoclax + a hypomethylating agent in two real-world studies, although it should be noted that there were significant differences in patient characteristics between treatment cohorts in both studies. In a US retrospective study of primarily older adults, the authors attributed the observed OS advantage with CPX-351 (17.3 vs. 11.1 months; $p = 0.007$) to the larger percentage of older adults who underwent HCT following CPX-351 (48% vs. 19%; $p < 0.001$) (Grenet et al., 2021). A separate US study of patients from a multicenter group and the Flatiron Health database also noted a significantly higher proportion of patients proceeding to HCT after CPX-351 (28% vs. 10%; $p < 0.0005$); the HR was 1.27 for OS among patients proceeding to HCT after CPX-351 versus venetoclax + azacitidine, and evaluation of HCT as a time-varying covariate confirmed the impact of HCT on OS ($p < 0.0005$) (Matthews et al., 2022). It should be noted that venetoclax + azacitidine is indicated for use in patients who are not eligible for intensive chemotherapy due to age and/or comorbidities (consistent with the phase 3 study population (DiNardo et al., 2020)), and current guidelines recommend the use of intensive therapy in most eligible patients (Döhner et al., 2022; Heuser et al., 2020; Network, 2022; Sekeres et al., 2020); however, some patients eligible for intensive chemotherapy are being treated with less intensive therapy.

3.5. Safety profile

No new safety concerns were identified with CPX-351 treatment in real-world analyses. Reported adverse events (AEs), recovery of myelosuppression, and early mortality are summarized in Table 2. Across studies, most AEs were described as Grade 1 or 2 in severity and/or resolved, although a few patients experienced more severe AEs. Gastrointestinal toxicity was only rarely reported in real-world studies, despite being a commonly reported AE in the phase 3 RCT and other clinical studies (Cortes et al., 2019); the lack of reporting of

Table 2
Comparison of CPX-351 safety findings from real-world studies versus the phase 3 RCT that led to CPX-351 approval.

Citation	Summary of nonhematological AEs[a]	Median time to recovery (per μL)		Early mortality	
		Neutrophils	Platelets	30 days	60 days
(Lancet et al., 2018)[b]	Grade ≥ 3: infections (84%; pneumonia [20%]), febrile neutropenia (68%), hypoxia (13%), bleeding (12%)	35 d to ≥ 500	36.5 d to ≥ 50,000	6%	14%
(Andrews et al., 2020)	Fungal infection (20%)	32 d to ≥ 500	34 d to ≥ 50,000	4%	10%
(Chiche et al., 2021)	Grade ≥ 3: febrile neutropenia (91%), pneumonia (30%), bacteremia (24%), invasive pulmonary aspergillosis (10%) Other: GI toxicity (50%), rash (25%), mucositis (22%)	29 d to > 500	28 d to > 20,000	6%	8%
(Klingler et al., 2022)	Sepsis (23%) Grade ≥ 3: febrile neutropenia (27%), rash (27%)	NR	NR	NR	15%
(Rautenberg et al., 2021)	Grade ≥ 3: pneumonia (22%), febrile neutropenia (15%)	33 d to ≥ 500	30 d to ≥ 50,000	8%	NR
(Fianchi et al., 2021)	Infection (febrile neutropenia [71%]; microbiologically documented [55%], unknown [31%], clinically documented [14%])	NR	NR	14%	NR
(Garibaldi et al., 2022)	NR	26 d to ≥ 500	22 d to ≥ 20,000	NR	NR
(Guolo et al., 2020)	Infections (fever of unknown origin [28%], sepsis [28%]), skin rash (25%)	38 d to > 500	28 d to > 25,000	NR	7%
(Guolo et al., 2021)	NR	NR	NR	NR	6%
(Bernal et al., 2022)	NR	31 d to ≥ 500	30 d to ≥ 50,000	12%	17%
(Legg et al., 2022)	NR	NR	NR	6%	14%
(Murthy et al., 2021)	Febrile neutropenia (100%)	35 d	NR	5%	11%
(Taylor et al., 2022)	NR	31 d	37.5 d	NR	NR
(Benitez et al., 2021)	Febrile neutropenia (93%), infections (74%; pneumonia [37%], bacteremia [36%])	36 d to < 1000	38 d to < 100,000	9%	14%
(Jacoby et al., 2021)	None in ≥ 20% of patients or Grade ≥ 3 in ≥ 10% of patients Infusion-related reactions: one patient	NR	NR	NR	NR
(Jain et al., 2021)	NR	NR	NR	3%	7%

(continued on next page)

Table 2 (*continued*)

Citation	Summary of nonhematological AEs[a]	Median time to recovery (per μL)		Early mortality	
		Neutrophils	Platelets	30 days	60 days
(Kim et al., 2020)	Febrile neutropenia (85%), bacteremia (31%)	NR	NR	9%	15%
(Lee et al., 2022)	NR	NR	NR	0%	1%
(Madarang et al., 2020)	Fungal infection (42%)	47 d	NR	NR	NR
(Matthews et al., 2022)	Infection (51%) Within MC cohort[c]: febrile neutropenia (90%), infection (67%)	NR	NR	5%	10%
(Przespolewski et al., 2021)	SAEs: infections (80%), bleeding (13%)	NR	NR	9%	17%

Abbreviations: AE, adverse event; GI, gastrointestinal; MC, multicenter study; NR, not reported; RCT, randomized controlled trial; SAE, serious adverse event.

[a] AEs reported in ≥ 20% of patients and Grade ≥ 3 AEs reported in ≥ 10% of patients.

[b] Phase 3 RCT is included in this table for comparison with real-world analyses.

[c] Study included retrospective analyses from a MC cohort and the Flatiron Health database.

gastrointestinal toxicity in real-world studies may reflect a generally low severity. In the Italian Compassionate Use Program, low frequency of nonhematological toxicity (e.g., mucositis) may have contributed to the relatively low rate of peri-transplant mortality (Guolo et al., 2020).

Similar to observations from prospective clinical trials of CPX-351, including the phase 3 RCT (Lancet et al., 2018), several real-world studies noted that CPX-351 was associated with delay in neutrophil and platelet recovery of > 20 days (Andrews et al., 2020; Benitez et al., 2021; Bernal et al., 2022; Chiche et al., 2021; Garibaldi et al., 2022; Guolo et al., 2020; Madarang et al., 2020; Murthy et al., 2021; Rautenberg et al., 2021; Taylor et al., 2022). Although potentially life-threatening, myelosuppression is an expected and often manageable side effect for patients undergoing chemotherapy. Across real-world studies, the most frequently reported AEs were infections, which was not unexpected given the delay in neutrophil recovery after CPX-351. The frequency of febrile neutropenia varied widely, from 15% to 100% of patients (Benitez et al., 2021; Chiche et al., 2021; Fianchi et al., 2021; Kim et al., 2020; Klingler et al., 2022; Matthews et al., 2022; Murthy et al., 2021; Rautenberg et al., 2021), although most studies reported febrile neutropenia in the range of 71–100% of patients. Other frequently reported infections included pneumonia, bacteremia, and fungal infections. This is consistent with the phase 3 RCT, which noted Grade ≥ 3 AEs of febrile neutropenia in 68% of patients and pneumonia in 20% (Lancet et al., 2018).

Despite the prolonged myelosuppression and high prevalence of infections after CPX-351, early mortality was relatively infrequent across real-world studies (Andrews et al., 2020; Benitez et al., 2021; Bernal et al., 2022; Chiche et al., 2021; Fianchi et al., 2021; Guolo et al., 2020; Guolo et al., 2021; Jain et al., 2021; Kim et al., 2020; Klingler et al., 2022; Lee et al., 2022; Legg et al., 2022; Matthews et al., 2022; Murthy et al., 2021; Przespolewski et al., 2021; Rautenberg et al., 2021; Talati et al., 2020), with several studies reporting lower early mortality rates versus the phase 3 RCT (Day 30: 6%; Day 60: 14%) (Lancet et al., 2018). At Day 30, early mortality rates ranged from 0% to 14% (median: 6%), including seven real-world studies reporting percentages ≤ 6%. At Day 60, early mortality rates ranged from 1% to 17% (median: 10.5%), including 10 real-world studies reporting percentages ≤ 14%.

Real-world early mortality reported for CPX-351 is notable, as early mortality rates in real-world analyses are often higher versus RCTs. This is likely due—at least in part—to a broader patient population that includes patients often excluded from RCTs, as well as greater variability in approaches to patient management. Additionally, the 30-day real-world early mortality rate after CPX-351 was generally lower than that reported for conventional chemotherapy regimens. In the Cancer and Leukemia Group B 10201 study, the 30-day mortality rate in patients treated with 7 + 3 chemotherapy was 12% (Walker et al., 2021). In a Swedish registry study, the 30-day mortality rate in patients aged ≥ 50 years was markedly lower in patients who received intensive chemotherapy versus palliative therapy (8% vs. 26%) (Juliusson et al., 2009). Together, these data suggest that CPX-351 treatment is tolerable, with toxicities that are manageable in routine clinical practice.

Additionally, a prospective exploratory analysis of patient-reported outcomes suggested that patients treated with CPX-351 may have an overall better patient experience during induction versus conventional chemotherapy, using validated measures of symptom burden, quality of life, and mood (LeBlanc et al., 2020). Although CPX-351 is an intensive therapy and patients should be carefully monitored, its manageable safety profile, relatively low early mortality rate, and administration schedule (two or three 90-minute infusions per cycle) permit some patients to receive CPX-351 as outpatient therapy. Successful administration of CPX-351 in an outpatient setting requires careful patient selection, quick and easy access to providers, and established center protocols for transfusion support and symptom management (Kasner, 2019).

3.6. Outcomes in younger patients (aged < 60 years)

Prospective trials of CPX-351, including the phase 3 RCT, primarily evaluated the efficacy and safety of CPX-351 in older adults with AML, although CPX-351 is indicated for patients aged ≥ 1 year in the United States and in adults of all ages in the European Union and the United Kingdom (European Medicines Agency, 2018; Jazz Pharmaceuticals Inc., 2022). Thus, the evaluation of CPX-351 in younger adults represents a noteworthy evidence gap addressed by real-world studies.

In an Italian real-world study in nine patients aged < 60 years, CR or CRi was achieved by 75% (6/8) of evaluable patients after one or two inductions, and 63% (5/8) of these patients proceeded to HCT (Garibaldi et al., 2022). In a US-based real-world study in 66 patients aged 23–59 years, CR or CRi was achieved by 44% (27/62) of evaluable patients, with a median OS of 5.2 months, although the duration of follow-up was only 6.2 months and the study included a notable proportion of patients with *TP53* gene mutations and/or complex karyotype, which may have contributed to worse outcomes, as discussed in the following section (Przespolewski et al., 2021). Fifty percent (31/62) of patients received HCT, and median OS from the date of HCT was not yet reached. Early mortality rates were 9% by Day 30% and 17% by Day 60 (Przespolewski et al., 2021).

Two real-world studies have also compared outcomes for cohorts of younger versus older adults treated with CPX-351. In a UK-based retrospective study using data from the National Cancer Registration and Analysis Service, median OS was 18.5 months for patients aged < 60 years (n = 60) versus 11.2 months for those aged ≥ 60 years (n = 151) (Legg et al., 2022). In the cohort of patients with ≥ 3 months of follow-up, 58% (29/50) of patients in the younger group proceeded to HCT; median OS from the date of HCT was not yet reached. Early mortality rates in the younger group were 3% by Day 30% and 10% by Day 60. Overall, results were more favorable for younger versus older adults included in this study (Legg et al., 2022).

In a US-based retrospective study, there was no significant difference between patients aged < 60 years (n = 36) and those aged ≥ 60 years (n = 133) with regard to achievement of CR+CRi (47% vs. 55%, respectively), patients proceeding to HCT (53% vs. 55%), median OS (18 vs. 15 months), or median OS among those who proceeded to HCT (not reached vs. 34 months) (Lee et al., 2022).

Some other real-world studies have also included younger adults in their patient populations, although they did not report outcomes for this subpopulation separately. For example, in a real-world study conducted in Germany, a substantial percentage of patients (24%) were aged < 60 years; as a result, a large proportion of patients (62%) proceeded to HCT after CPX-351 and, of these, 71% did not require further therapy prior to HCT (Rautenberg et al., 2021).

Overall, analyses in younger adults tended to report more frequent achievement of CR+CRi, longer median OS, and lower early mortality rates versus the phase 3 RCT in older patients. Observed differences between studies may reflect the retrospective study designs, short follow-up times (especially for one of the US studies (Przespolewski et al., 2021)), small sample sizes, differences in patient populations, and regional differences in routine care. However, the European LeukemiaNet (ELN) guidelines indicate that data for CPX-351 in younger patients with newly diagnosed AML are lacking and still need to be evaluated in well-designed prospective trials (Döhner et al., 2022).

3.7. Outcomes by mutation status

With the development of several targeted agents in the past few years and an improved understanding of the prognostic implications of certain mutations in AML, the field has placed increasing importance on the role of genetic analyses in the classification of AML. The importance of genetic analyses is reflected in the 2022 updates for the diagnosis and classification of AML published by the World Health Organization (WHO) and the International Consensus Classification (ICC) (Arber et al., 2022; Khoury et al., 2022), as well as a revised ELN risk classification (Döhner et al., 2022). Some of the CPX-351 real-world studies have evaluated outcomes by mutation status; however, the numbers of patients with and without specific mutations in each study were small.

Although patients with AML and *TP53* mutations typically have a poor prognosis, the effect of *TP53* mutation status on CPX-351 treatment outcomes varied across real-world studies. In a French retrospective study, CR+CRi was achieved by 41% and 66% of patients with and without a *TP53* mutation, respectively (p = 0.04); in a univariate analysis, patients with a *TP53* mutation also had significantly worse OS (p = 0.02) (Chiche et al., 2021). In a UK retrospective study, patients with versus without *TP53* mutations had lower CR+CRi (50% vs. 60%, respectively) and shorter median OS (8.4 vs. 17.2 months; HR 2.4, 95% CI 1.08–5.25; p = 0.032) (Murthy et al., 2021). In a US retrospective study of younger patients, CR+CRi was 44% overall, and CR was 32% (6/19) in patients with a *TP53* mutation (Przespolewski et al., 2021); in another US study, CR+CRi was 53% overall and 21% in patients with a *TP53* mutation (Lee et al., 2022). A third US retrospective study also noted poorer outcomes among patients with a *TP53* mutation versus the overall population (CR+CRi: 30% vs. 58%; median OS: 10.2 vs. 17.3 months) (Grenet et al., 2021). In contrast, an Italian retrospective study observed comparable CR+CRi rates in patients with and without *TP53* mutations (77% and 75%, respectively; p = 1.0); *TP53* mutation status also had no significant effect on OS (Guolo et al., 2020). Likewise, in a German retrospective study, there were no statistically significant differences between patients with and without a *TP53* mutation for CR+CRi (54% and 47%, respectively; p = 0.77) and OS (HR 2.1, 95% CI 0.7–5.9; p = 0.07) (Rautenberg et al., 2021). Finally, in a US-based retrospective study, CR+CRi was 57% (8/14) in patients with a *TP53* mutation, including five patients with MRD negativity by next-generation sequencing assessment, which was consistent with CR+CRi in 54% of patients overall (Kim et al., 2020). Although remission rates and survival were poorer among patients with versus without *TP53* mutations in some of these real-world studies, treatment with CPX-351 nevertheless appeared to benefit some patients with *TP53* mutations.

No significant differences in CPX-351 treatment outcomes were observed between patients with versus without an *FLT3* mutation, which is consistent with preclinical data indicating that CPX-351 has activity in *FLT3*-mutated AML blasts (Gordon et al., 2017). A Canadian retrospective study found no difference in OS when stratified by *FLT3*-internal tandem duplication (ITD) status (p = 0.29) (Andrews et al., 2020). In a French retrospective analysis, CR+CRi was 67% and 60%, respectively, in patients with and without *FLT3*-ITD (*P* = 0.72), and was 50% and 60%, respectively, in those with and without a *FLT3*-tyrosine kinase domain mutation (p = 0.62) (Chiche et al., 2021). In an Italian retrospective analysis, CR+CRi was 60% and 70%, respectively, in patients with and without *FLT3*-ITD (p = 1.0); mutation status had no significant effect on OS (Guolo et al., 2020). In a German retrospective study, CR+CRi was 58% and 48%, respectively, in patients with and without *FLT3*-ITD (p = 0.45); mutation status again had no significant effect on OS (HR 0.4, 95% CI 0.2–1.1; p = 0.21) (Rautenberg et al., 2021). These results are generally consistent with those of the phase 3 RCT: the primary analysis reported that CR+CRi was achieved by 68% of patients with a *FLT3* mutation who were treated with CPX-351 (vs. 48% of the overall population) (Lancet et al., 2018), whereas the long-term analysis reported a median OS of 10.25 months for patients with a *FLT3* mutation and 8.87 months for those without (Lancet et al., 2021).

There were no significant effects of *ASXL1* gene mutation status on CPX-351 outcomes across real-world studies. A Canadian retrospective study found no difference in OS when stratified by *ASXL1* mutation status (p = 0.06) (Andrews et al., 2020). In a French retrospective study, CR+CRi was 53% and 67%, respectively, in patients with and without an *ASXL1* mutation (p = 0.28) (Chiche et al., 2021). In a German retrospective study, there were no significant differences in CR+CRi between patients with and without *ASXL1* mutations (46% and 49%, respectively; p = 0.83) and OS (HR 1.2, 95% CI 0.6–2.4; p = 0.64) (Rautenberg et al., 2021). For comparison, in the post hoc analysis of the phase 3 RCT, CR+CRi was achieved by approximately 30–35% of patients with an *ASXL1* mutation who were treated with CPX-351, with a median OS of 8.9 months (Lindsley et al., 2019).

Similarly, there was no significant effect of *RUNX1* gene mutation on CPX-351 outcomes across real-world studies. A Canadian retrospective study reported no difference in OS when stratified by *RUNX1* mutation status (p = 0.123) (Andrews et al., 2020). In a French retrospective study, CR+CRi was 57% and 66%, respectively, in patients with and without a *RUNX1* mutation (p = 0.50) (Chiche et al., 2021). A German retrospective study reported no significant differences between patients with and without a *RUNX1* mutation in CR+CRi (57% and 45%, respectively; p = 0.37) or OS (HR 1.1, 95% CI 0.5–2.3; p = 0.93) (Rautenberg et al., 2021). These real-world results again compare favorably with those from the post hoc analysis of the phase 3 RCT, in which CR+CRi was achieved by approximately 35–40% of patients with a *RUNX1* mutation who were treated with CPX-351, with a median OS of 8.9 months (Lindsley et al., 2019).

Lindsley's classifier, which is based on groupings of mutations for AML, also provides important prognostic information (Lindsley et al., 2015). Of note, Lindsley's secondary-type mutations are included in the 2022 ICC and WHO classifications of AML with myelodysplasia-related gene mutations (Arber et al., 2022; Khoury et al., 2022). In a French real-world study of 103 patients with newly diagnosed t-AML or AML-MRC, CR+CRi was achieved by 86% of patients with *de novo* AML, 56% with secondary-type mutations, and 41% with *TP53*-mutated AML. Median OS was not yet reached in patients with *de novo* AML and secondary-type mutations, and was 8.5 months in patients with *TP53*-mutated AML (Chiche et al., 2021). These results are favorable compared with a post hoc analysis of the phase 3 RCT conducted by Lindsley and colleagues, which reported a median OS of 7.0 months for patients with activated signaling mutations, 10.1 months for those with secondary-type mutations, and 5.7 months for those with *TP53*-mutated AML (Lindsley et al., 2019).

Ongoing and future studies are evaluating outcomes for CPX-351 in patients with common mutations, as well as the benefit of combining CPX-351 with targeted agents.

4. Summary and future perspectives

Real-world studies of CPX-351 reported high CR and/or CRi rates, prolonged OS, larger percentages of patients bridged to HCT, post-HCT OS that was typically not yet reached, low early mortality rates, and a manageable safety profile with no new safety signals. Despite considerable variability in some reported outcomes, in general, the findings from these real-world studies compared favorably with those from the phase 3 RCT of CPX-351 versus conventional 7 + 3 chemotherapy (Lancet et al., 2018; Lancet et al., 2021). The observed variability across studies may be due to differences in study design and patient populations, data collection methods, provision of routine care, and follow-up times. In addition to confirming the efficacy and safety of CPX-351 in everyday clinical practice, data from these real-world studies provide important insights into the use of CPX-351 in younger adults, who were not included in the phase 3 RCT.

It remains uncertain as to which patients should receive CPX-351 over less intensive therapy options such as venetoclax + azacytidine, and if CPX-351 should be recommended for older adults who often have complex comorbidities and are ineligible for transplant. Although a comparative, prospective trial is lacking, a real-world study comparing the effectiveness of CPX-351 vs venetoclax + azacytidine in 656 patients with newly diagnosed AML demonstrated similar OS with CPX-351 as venetoclax + azacytidine (Matthews et al., 2022). These results were replicated when the analysis was restricted to AML patients eligible for the CPX-351 registration trial. However, it should be kept in mind that patients treated with venetoclax + azacytidine in this study were older, often treated in community hospitals and diagnosed with *de-novo* AML in a higher percentage. The study also demonstrated that 10% of AML patients receiving venetoclax + azacytidine proceeded to allogeneic HCT vs 28% following CPX-351 treatment, and HCT significantly improved survival outcomes.

The assessment of MRD has gained recognition as an important outcome for AML and can be used not only to determine the depth of remission but also to predict treatment response and monitor patients for potential relapse (Schuurhuis et al., 2018). Although MRD is used routinely in other leukemias, its use in AML is still being standardized, and many RCTs conducted in AML, including the phase 3 RCT of CPX-351, have not included MRD as an endpoint. Several real-world studies reported data on the achievement of MRD negativity after CPX-351, which varied from 38% to 64% across studies (Bernal et al., 2022; Chiche et al., 2021; Guolo et al., 2020; Guolo et al., 2021; Kim et al., 2020; Plesa et al., 2021; Rautenberg et al., 2021; Taylor et al., 2022), possibly reflecting differences in the methods and thresholds used (Cluzeau et al., 2022). Additional prospective studies and RCTs are warranted to further standardize MRD assessment for AML and evaluate the achievement of MRD negativity with CPX-351.

Real-world studies provide a valuable complement to RCTs and other prospective clinical trials, reflecting the use of CPX-351 in routine clinical practice across different countries, as well as different regions within the United States. Real-world studies evaluate the safety and effectiveness of CPX-351 in a diverse patient population that is more representative of the full label population, including patients who were excluded from the RCT due to age or comorbidities. Real-world studies also provide an opportunity to evaluate outcomes not included in RCT protocols and thus fill important data gaps, such as the achievement of MRD negativity.

Nevertheless, real-world studies are not intended to be substitutes for RCTs, as they have several important limitations. There can be substantial differences in study designs/methodology, patient populations, patient monitoring, outcome assessments, and statistical analyses; these differences make it difficult to compare data across studies and to control certain biases. AML-MRC (other than patients with an antecedent haematological disorder) can be difficult to diagnose in routine clinical practice, particularly in smaller regional and community centers, as diagnostic confirmation requires cytogenetic and molecular genetic testing; this hinders the identification and inclusion of these patients in retrospective real-world analyses. Real-world studies may also include smaller patient numbers and have shorter follow-up times than RCTs. These characteristics can affect the accuracy and reliability of real-world outcomes. Finally, most real-world studies do not include comparison of outcomes versus other standards of care.

The 2022 ICC and WHO recently provided a new framework for AML classification, with the purpose of identifying homogeneous groups of patients (Arber et al., 2022; Khoury et al., 2022). Here, we did not discuss the AML diagnosis/classification in detail because they have only recently been published, how they will impact clinical practice is not yet clear, and this discussion is not the focus of this review article. Indeed, the real-world studies themselves do vary in their description of AML subtypes and we need to reflect the data as reported in the study publications.

Ongoing and future prospective clinical trials and real-world studies will continue to evaluate and explore the benefits of CPX-351 for AML patients. Together, these complementary study designs will provide researchers and clinicians with a more complete view of the experience and outcomes with CPX-351 worldwide, which can help to guide treatment decisions in different settings and for diverse patient populations.

CRediT authorship contribution statement

All authors contributed to the conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization and writing (including original draft, review & editing, and approval of final draft) of this manuscript.

Declaration of Competing Interest

RML has served as an advisor for Jazz Pharmaceuticals. PM has served as a consultant for and has received speaker honoraria and research funding from Jazz Pharmaceuticals. AJ has no conflicts of interest to disclose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2023.103984.

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