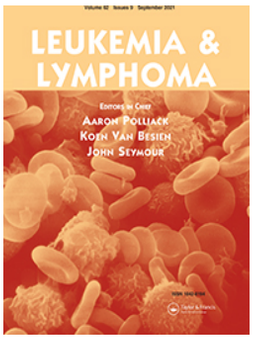

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ORIGINAL ARTICLE

Multicenter comparison of high-dose cytarabine-based regimens versus liposomal daunorubicin and cytarabine (CPX-351) in patients with secondary acute myeloid leukemia

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ABSTRACT

Liposomal daunorubicin/cytarabine (CPX-351) gained FDA approval for secondary AML after demonstrating improved outcomes over daunorubicin and cytarabine (7 + 3). A number of study limitations prompted a comparison of safety/efficacy of CPX-351 against regimens containing a purine analogue and high-dose cytarabine (HIDAC). This retrospective study compared complete response rates with/without count recovery (CR/CRi) between HIDAC-based regimens and CPX-351 in 169 patients with newly diagnosed sAML. The CR/CRi rate was 62.7% in the HIDAC-based therapy arm vs. 47.9% in the CPX-351 arm ($p = 0.002$ [one-sided for non-inferiority]). Median time to absolute neutrophil and platelet count recovery was shorter after HIDAC-based therapy (18 and 23 days, respectively) compared to CPX-351 (36 and 38 days; $p < 0.001$). Median overall survival was 9.8 months in the HIDAC-based group and 9.14 months in the CPX-351 group. 30-day mortality was greater with CPX-351 (8.5%) compared to HIDAC-based (1.3%; $p = 0.039$). These results reveal comparable efficacy and favorable safety with HIDAC-based regimens.

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CPX-351; cytarabine; secondary AML; Vyxeos; FLAG; oncology stewardship

Introduction

Acute myeloid leukemia (AML) is most frequently diagnosed in patients over the age of 65 years. It is associated with a high risk of mortality and a 5-year overall survival of 28% [1]. Secondary AML (sAML) is a subset of the cases that arise after prior chemotherapy or radiation or prior antecedent hematologic disorders. It comprises 25–35% of all cases of AML and carries a particularly adverse prognosis, with historical long-term survival rates of only 5–10% [2]. The particularly poor prognosis of sAML may be explained by a number of patient and disease-related factors, some of which include older median age and preexisting comorbidities as a result of prior disease and/or therapies, as well as high risk disease features, including poor risk cytogenetic and molecular abnormalities [3]. Together, these characteristics contribute to poor tolerability of intensive chemotherapy as well as high rates of relapse with the traditional '7 + 3' induction strategy.

Since 1973, the standard of care induction chemotherapy regimen for AML has been a combination of an anthracycline, daunorubicin or idarubicin, administered once daily for 3 days and cytarabine given continuously for 7 days (7 + 3) [4]. In a randomized phase III trial comparing liposomal daunorubicin and cytarabine (CPX-351) to 7 + 3 in patients 60–75 years old with sAML, CPX-351 was associated with higher complete remission (CR), event-free survival (EFS), and overall survival (OS) [5]. There are several issues with this trial that limit the applicability of this data in sAML, including the choice of re-induction and consolidation therapy in the control arm ('5 + 2' rather than high-dose cytarabine consolidation), approximately 1/3 of patients requiring 2 inductions to attain remission, and the high rate of hematologic toxicity, with a median duration of neutropenia and thrombocytopenia of 35 and 37 days, respectively. These concerns, combined with the high cost of $50,000 to $120,000 for induction (depending on body surface area and number of inductions), limit the use of CPX-

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351 in elderly sAML patients despite the FDA approval [5,6].

Several retrospective studies conducted in this patient population suggest that high-dose cytarabine and purine-analogue combination (HIDAC-based) regimens may be a safe, efficacious induction [6,7]. Given these findings and its potential as a cost-effective alternative (approximately $2,000–10,000 for induction) to CPX-351 in the treatment of sAML, a head-to-head comparison of these regimens in the management of newly diagnosed sAML is warranted [8]. While the gold-standard comparison would be a randomized clinical trial, the high acquisition cost of CPX-351, its recent FDA approval, and rarity of sAML cases limits the likelihood a prospective comparison of these two regimens will be conducted. The purpose of this study is to retrospectively compare clinical outcomes between patients with sAML receiving CPX-351 and HIDAC-based regimens.

Methods

This was a multi-center, retrospective cohort study including patients treated at Michigan Medicine, MD Anderson Cancer Center, Barnes Jewish Hospital, University of North Carolina Medical Center, Huntsman Cancer Institute, University of Rochester, and Indiana University. Adult patients ($\geq$18 years of age) with newly diagnosed sAML between January 2013 and January 2019 were divided into 2 cohorts based on induction regimen as follows: HIDAC-based regimen–induction regimen containing $\geq$1000 mg/m^2/day of cytarabine; CPX-351–patients receiving induction with CPX-351 monotherapy at FDA approved dose and labeled indication as standard of care or as part of clinical trials NCT01696084 and NCT02286726 [9]. This study protocol was reviewed and IRB approved at each site.

Secondary AML was defined as patients with a prior antecedent hematologic disorder (AML-AHD), treatment related AML (tAML), or AML with MDS-related cytogenetic abnormalities as defined by the World Health Organization [10]. Patients with AML-AHD who had received prior treatment with hypomethylating agents (HMA) were included in the analysis. Patients were excluded for the following reasons: receipt of high-dose cytarabine based regimens that included an anthracycline (e.g. FLAG-IDA, CLAG-M), diagnosis of active CNS leukemia, incomplete records that would result in an inability to assess outcomes, AML with myelodysplasia-related changes (AML-MRC) based only on multi-lineage dysplasia, patients receiving experimental cancer therapies other than CPX-351, or any targeted therapies in combination with CPX-351 or HIDAC-based therapy. AML-MRC based only on multi-lineage dysplasia was excluded, as these patients were not included in the phase III trial of CPX-351, and data suggests AML-MRC is only associated with a poor prognosis in cases with MDS-related cytogenetic abnormalities [11]. Disease-related characteristics including cytogenetics and molecular mutations identified at baseline were collected, and cytogenetic risk by NCCN was reported [12].

Endpoints and statistical analysis

The primary endpoint of this study was the composite of complete remission rate and complete remission with incomplete count recovery (CR/CRi) after induction chemotherapy. Induction chemotherapy was defined as up to two cycles of CPX-351 or HIDAC-based therapy. Patients failing to achieve a response and proceeding to an alternative re-induction strategy were deemed induction failures. Secondary efficacy endpoints included CR, CRi, morphologic leukemia free state (MLFS), and long-term efficacy outcomes including event-free survival and overall survival. CR was defined as a blast percentage $<$5% in the post-treatment bone marrow biopsy with count recovery, as evidenced by an absolute neutrophil count greater than 1000 μL^{-1} and platelet count $>$100,000 μL^{-1} without transfusion [13]. Patients who met criteria for blast clearance with residual neutropenia (ANC $<$1000 μL^{-1}) or thrombocytopenia (platelet count $<$ 100,000 μL^{-1}) achieved a CRi. MLFS was defined as blast clearance without hematologic recovery. Safety outcomes of interest included: time to neutrophil and platelet recovery after induction (counted from Day 1 of induction until the first of two consecutive measurements $>$ 1000 μL^{-1} for absolute neutrophil count (ANC) and 100 K/μL for platelets (PLT)); incidence of febrile neutropenia, confirmed infections, and intensive care (ICU) admission during induction; change in cardiac function; 30- and 60-day mortality; induction mortality (defined as mortality occurring any time after treatment began and before a treatment response was assessed); and other induction treatment-related complications. Baseline echocardiogram (echo) results were compared to echo results after induction chemotherapy but prior to alloHCT to assess for changes in cardiac function.

A power calculation was conducted with respect to the primary endpoint of induction CR/CRi. The previously published CR/CRi rates of 47.7 and 65% for CPX-

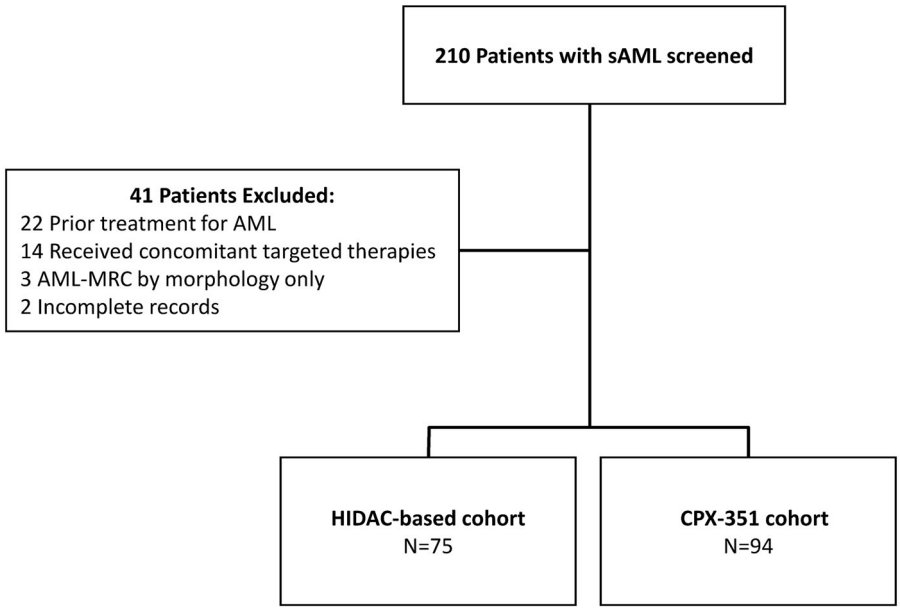

Figure 1. CONSORT diagram.

351 and fludarabine and high dose cytarabine with myeloid growth factor (FLAG) respectively, were chosen for this calculation and a margin of non-inferiority of 7.5% was defined [5,7]. Based on these values, a total sample of 96 patients was established *a priori* as necessary to demonstrate non-inferiority of HIDAC-based regimens with 5% alpha and 80% power (equivalent to a 90% CI in a two-sided analysis).

Dichotomous data were analyzed using chi squared tests or Fisher's exact test as indicated. Continuous data were analyzed using either the Student's unpaired *t*-test or Mann–Whitney *U* test based on normality. Kaplan–Meier analysis with log-rank test was performed to estimate event-free survival (EFS) and overall survival (OS). All statistical analyses were performed using SPSS statistical software (version 26.0; IBM Corporation, Armonk, NY, USA), and the power calculation was performed using Sealed Envelope Ltd.2012 [14].

Results

Patient characteristics

A total of 210 patients with sAML were screened across all institutions between January 2013 and January 2019, of which 169 patients were included for analysis (HIDAC-based: $n = 75$; CPX-351: $n = 94$). The distribution of patients from each institution was as follows: Michigan Medicine $n = 73$, MD Anderson Cancer Center $n = 27$, Barnes Jewish Hospital $n = 22$, University of North Carolina Medical Center $n = 21$, Huntsman Cancer Institute $n = 9$, University of Rochester $n = 9$, Indiana University $n = 8$. The most common reason for exclusion was prior treatment for AML (Figure 1). Thirty (31.9%) patients in the CPX-351 arm were treated as part of a clinical trial, whereas none of the HIDAC-based cohort were treated on a clinical trial. Regimens used in the HIDAC-based cohort included fludarabine, cytarabine ± G-CSF (FLAG) ($n = 73$) and clofarabine, cytarabine ± G-CSF (GCLAC) ($n = 2$).

The median age of patients was 67 years (range, 27–82), and was similar in both cohorts. The proportion of patients over the age of 65 years was also comparable between the HIDAC-based and CPX-351 cohorts (60 vs. 52% respectively, $p = 0.351$). Baseline patient characteristics were well balanced between the cohorts (Table 1), with the exception of a higher median Charlson Comorbidity Index in patients who received HIDAC-based therapy (6 vs. 5; $p = 0.025$). Disease characteristics were well balanced in general. AML arose after an AHD in 56% of patients receiving HIDAC-based regimens and in 53.2% of those receiving CPX-351 ($p = 0.716$). Therapy related AML (t-AML) was the second most common component of sAML, comprising 32% of patients in the HIDAC-based cohort and 28.7% in the CPX-315 cohort ($p = 0.645$). AML-MRC by MDS-related cytogenetic abnormalities was the least common type of sAML among both groups ($p = 0.276$). High risk disease according to cytogenetics was identified in 53 patients (72.6%) in the HIDAC-based cohort and 59 (64.1%) in the CPX-351 cohort ($p = 0.314$). A significantly higher proportion of patients tested in the HIDAC-based cohort had

mutations in *TP53* or deletion of chromosome 17p (del 17(p)/*TP53*) (20/34 (58.8%) vs. 21/67 (31.3%), $p = 0.010$), while a higher proportion of patients in the CPX-351 cohort had prior HMA-based therapy for their MDS (40.4 vs. 26.7%, $p = 0.061$).

Efficacy

The primary endpoint of induction CR/CRi (Table 2) was numerically higher and statistically non-inferior with HIDAC-based therapy (62.7%) compared with CPX-351 (47.9%), a 14.8% observed difference between HIDAC and CPX-351 (95% CI −0.1 − 29.7%, $p = 0.002$; one-sided for non-inferiority). Re-induction with the original regimen chosen was employed based on initial induction response in one patient in the HIDAC-based cohort and 26 patients (27.7%) in the CPX-351 cohort. The rates of CR were similar with HIDAC-based therapy (49.3%) and CPX-351 (41.5%) ($p = 0.352$), as were the rates of CRi (13.3 vs. 6.4% respectively, $p = 0.125$). MLFS attainment after induction was higher in patients who received CPX-351 (14.9%) compared HIDAC-based therapy (1.3%) ($p = 0.002$). A similar number of patients proceeded to alloHCT in first CR, 23 (30.7%) with HIDAC-based regimens and 27 (28.7%) in the CPX-351 arm.

The primary endpoint was evaluated in a series of subgroups of interest defined by age, type of sAML, presence of a FLT-3 mutation, cytogenetic risk, presence of del 17(p)/*TP53*, and the prior use of HMA for AHD. No difference in probability of achieving induction CR/CRi with CPX-351 vs. HIDAC-based therapy was observed in any subgroup evaluated including del 17p/TP53 status and prior HMA exposure (Figure 2). Given baseline differences in the incidence of del 17p/TP53 and prior HMA exposure between the cohorts, the effects of these variables on attainment of CR/CRi were further evaluated in a multivariate analysis also including induction strategy (Table 3). Prior HMA use was the only variable found to be an independent predictor of not attaining a CR/CRi in the study population. As such, we performed an analysis of non-HMA pretreated patients to eliminate this variable as a driver of the observed difference in CR/CRi attainment. In patients without prior HMA treatment ($n = 56$), CPX-351 resulted in 56% CR/CRi attainment whereas HIDAC-based induction ($n = 55$) resulted in 70% CR/CRi attainment ($p = 0.239$).

Table 1. Baseline characteristics.

	HIDAC-based ($n = 75$)	CPX-351 ($n = 94$)	p
Age, yrs[a]	67 (27–82)	67 (31–80)	0.919
>65 yrs[b]	45 (60)	49 (52)	0.351
Gender, female[b]	31 (41.3)	32 (34)	0.330
Charlson Comorbidity Index[a]	6 (0–14)*	5 (1–13)**	**0.025**
Disease/Treatment characteristics			
sAML etiology[b]			
AHD	42 (56)	50 (53.2)	0.716
t-AML	24 (32)	27 (28.7)	0.645
AML-MRC without AHD	9 (12)	17 (18)	0.276
Cytogenetic Risk[b,α]			
Favorable	1/73 (1.4)	3/92 (3.3)	0.631
Intermediate	19/73 (26)	30/92 (32.6)	0.394
Adverse	53/73 (72.6)	59/92 (64.1)	0.314
Molecular Characteristics[b]			
FLT3-ITD	2/60 (3.3)	2/70 (2.9)	1.000
FLT3-TKD	5/63 (7.9)	6/68 (8.8)	1.000
NPM1	3/55 (5.5)	3/70 (4.3)	1.000
CEBPα	1/53 (1.9)	0/67 (0)	0.442
IDH1	3/59 (5.1)	4/67 (6)	1.000
IDH2	8/60 (13.3)	9/67 (13.4)	1.000
cKIT	2/47 (4.3)	0/62 (0)	0.184
Del17p/TP53	20/34 (58.8)	21/67 (31.3)	**0.010**
Prior HMA use[b]	20 (26.7)	38 (40.4)	0.061
Median HMA cycles[a,†]	5 (1–40)	5 (1–23)	0.936
HIDAC-based regimen	FLA/G $n = 73$ G/CLAC $n = 2$	–	–

[a]median (range); [b]n (%); *$n = 71$; **$n = 72$; [α]per NCCN Version 1.2015; [†]if received for AHD.
Bold values are statistically significant at p-value < 0.5.
FLA/G: Fludarabine, high-dose cytarabine ± granulocyte growth colony-stimulating factor.
CLA/G: Clofarabine, high-dose cytarabine ± granulocyte growth colony-stimulating factor.

Table 2. Response rates and post induction disposition.

	HIDAC-based ($n = 75$)	CPX-351 ($n = 94$)	p-value
CR/CRi[b]	47 (62.7)	45 (47.9)	**0.002 (one-sided for non-inferiority)**
CR	37 (49.3)	39 (41.5)	0.352
CRi	10 (13.3)	6 (6.4)	0.125
MLFS	1 (1.3)	14 (14.9)	**0.002**
No response	27 (36)	35 (37.2)	0.869
AlloHCT in CR/CRi[b]	23 (30.7)	27 (28.7)	0.866
Chemotherapy Consolidation[b]	($n = 47$)	($n = 45$)	N/A
CPX-351	0	22 (48.9)	
HIDAC	25 (53.2)	7 (15.6)	
HMA	2 (4.26)	4 (8.89)	
Other	2 (4.26)	2 (4.44)	
Unfit to receive further therapy	3 (6.67)	1 (2.22)	
None, direct AlloHCT	15 (31.9)	10 (22.2)	

[b]n (%). Bold values are statistically significant at p-value < 0.5.

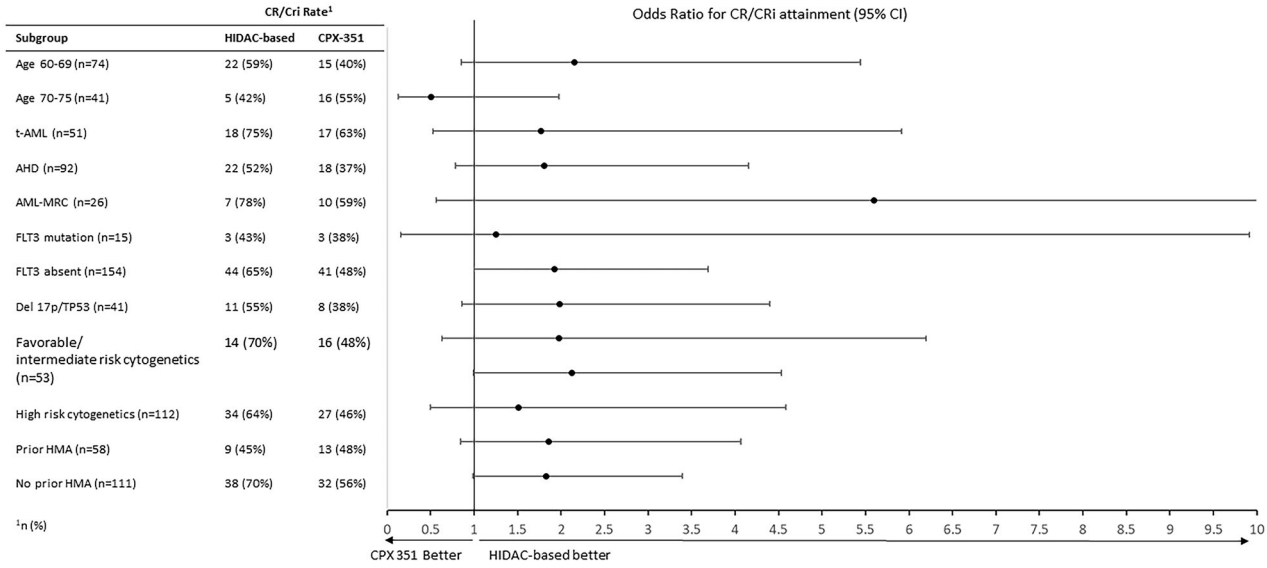

Figure 2. CR/CRi Rates in subgroups analyzed by baseline patient characteristics.

Table 3. Effect of disease characteristic on primary endpoint attainment.

	Univariate analysis			Multivariable analysis	
	CR/CRi	No CR/CRi	*p*-value	OR (95% CI)	*p*-value
Del 17p/TP53 status	19/41 (34.1)	22/41 (53.7)	0.687	0.607 (0.255-1.447)	0.260
Prior HMA	23/58 (39.7)	35/58 (60.3)	**0.004**	0.398 (0.170-0.933)	**0.034**
HIDAC-based therapy	47/75 (62.7)	28/75 (37.3)	0.063	1.739 (0.712-4.247)	0.312

Bold values are statistically significant at p-value < 0.5.

The median follow-up for the entire study population was 7 months; a median of 8 months (range, 1-60 months) for HIDAC-based therapy and a median of 6.5 months (range, 1–62 months) for CPX-351. Median OS was 9.8 months (95% CI 6.87 – 12.73) in the HIDAC-based cohort compared to 9.1 months in the CPX-351 cohort (95% CI 6.32 – 11.96) ($p = 0.88$) (Figure 3(a)). Within the subgroup of patients that proceeded to alloHCT in first CR/CRi, the median OS was 28.1 months (95% CI 8.1 – 47.2) compared to not-reached in the CPX-351 cohort ($p = 0.65$) (Figure 3(b)). Median EFS was also similar at 5.56 months vs. 4.11 months with HIDAC-based regimens compared to CPX-351, respectively (Figure 3(c)). Within the subgroup of patients that proceeded to alloHCT, the median EFS was also similar (Figure 3(d)).

Safety

Median time to ANC and PLT count recovery were significantly shorter in the HIDAC-based therapy group compared to CPX-351 (ANC: 18 vs. 36 days; $p < 0.001$; PLT: 23 vs. 38 days; $p < 0.001$) (Table 4). Thirty-day mortality was significantly lower with HIDAC-based therapy (1.3 vs. 8.5%, $p = 0.039$), while sixty day (10.7 vs. 13.8%, $p = 0.536$) and overall induction-related mortality were similar between the groups. The rate of confirmed infections during induction was lower with HIDAC-based induction (56%) compared to CPX-351 (74.5%, $p = 0.012$). Within the infections identified, pneumonia was more common in patients who received CPX-351 (37.2 vs. 21.3%, $p = 0.025$), whereas urinary tract infections were more common in patients who received HIDAC-based therapy (8.8 vs. 1%, $p = 0.025$). The incidence of new onset left ventricular ejection fraction reduction to <50% after treatment was 11.7% with CPX-351 vs. 5.3% with HIDAC-based therapy ($p = 0.148$), as anticipated considering the lack of anthracycline in the HIDAC-based group. The rates of other complications were similar between the cohorts (Table 4).

Discussion

Improving outcomes in secondary AML is a major unmet clinical need, and the optimal treatment strategy is yet to be defined. While CPX-351 is currently FDA approved for such patients, our study has observed similar efficacy with HIDAC-based therapy, with a more favorable safety profile. The patient population studied here parallels that of the phase III CPX-351 trial with a similar median age and distribution of

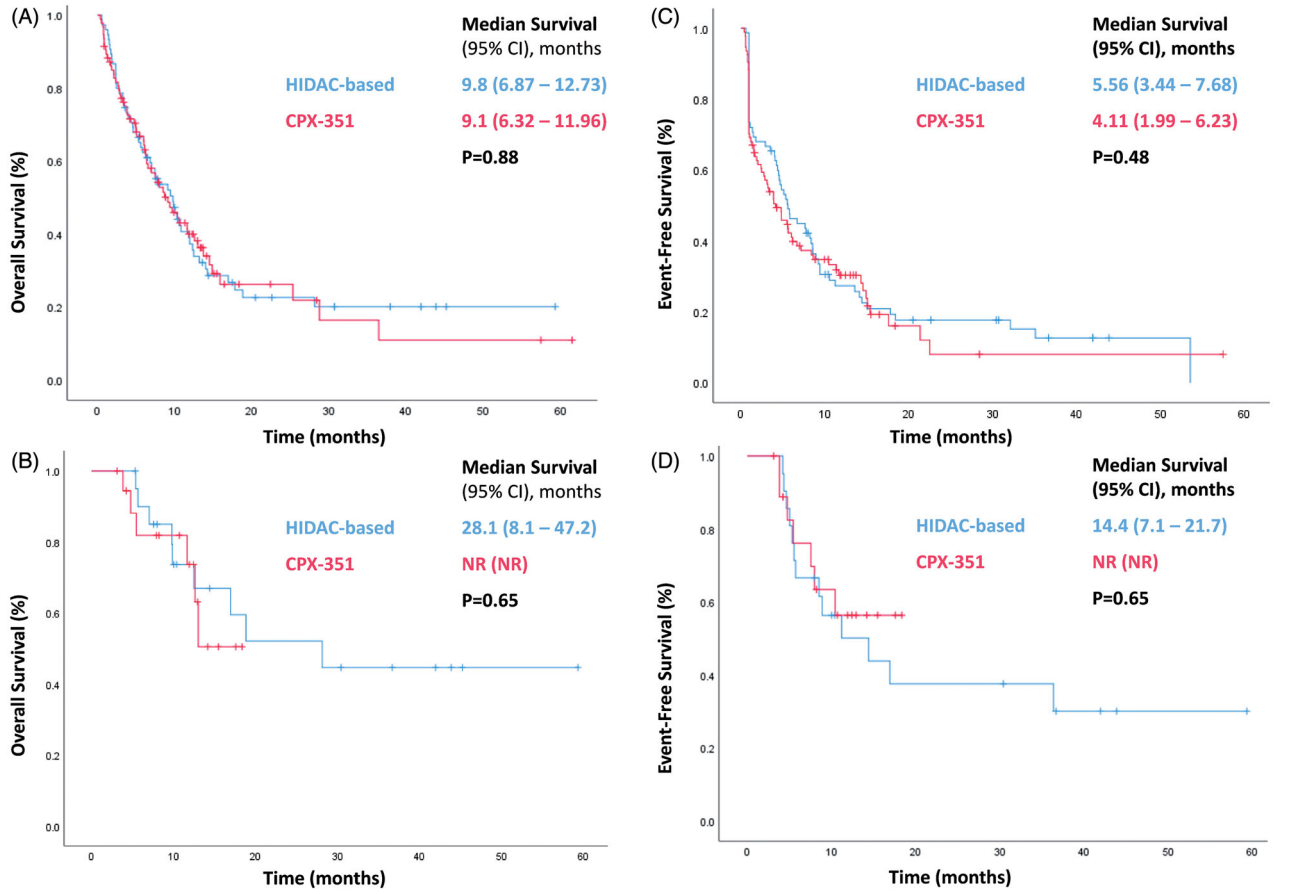

Figure 3. Long-term outcomes. (A) Overall survival estimate for all patients, (B) overall survival estimate for patients who proceeded to AlloHCT in first CR/CRi, (C) event-free survival estimate for all patients, (D) event-free survival for patient who proceeded to AlloHCT in first CR/CRi.

Table 4. Count Recovery and Toxicities.

	HIDAC-based ($n = 75$)	CPX-351 ($n = 94$)	p-value
Days to ANC recovery (1000) in CR/CRi[a]	18 (9-67)	36 (25-95)	**<.001**
Days to PLT recovery (100) in CR/CRi[a]	23 (17-112)	38 (25-95)	**<.001**
ICU admission in induction[b]	11 (14.7)	23 (24.5)	0.114
Mortality during induction[b]	5 (6.7)	11 (11.7)	0.267
30-day mortality[b]	1 (1.3)	8 (8.5)	**0.039**
60-day mortality[b]	8 (10.7)	13 (13.8)	0.536
Neutropenic fever during induction[b]	64 (85.3)	87 (92.6)	0.131
Confirmed infection in induction[b]	42 (56)	70 (74.5)	**0.012**
Bacteremia	25 (33.3)	34 (36.2)	0.701
Urinary tract infection	6 (8)	1 (1.1)	**0.025**
Pneumonia	16 (21.3)	35 (37.2)	**0.025**
Colitis	3 (4)	5 (5.3)	0.688
Other†	6 (8)	8 (8.5)	0.905
New onset LVEF $< 50\%$[b]	4 (5.3)	11 (11.7)	0.148
AKI[b,α]	9 (12)	13(13.8)	0.750

[a]Median (range); [b]n (%); [α]according to the RIFLE criteria.
†Included *C. difficile*, sinusitis, soft-skin tissue infections, and viral infections.
Bold values are statistically significant at p-value < 0.5.
ANC: absolute neutrophil count; PLT: platelet; ICU: intensive care unit; LVEF: left ventricular ejection fraction; AKI: acute kidney injury.

patients with AHD, t-AML, and AML-MRC based on cytogenetics [5]. Similar to the Lancet et al. study, we excluded patients with AML-MRC based only on multilineage dysplasia, given the heterogeneity of this diagnosis based on pathology interpretation and emerging evidence to suggest these patients do not carry the same poor prognosis as those who have MDS-defining cytogenetic abnormalities [11].

The rates of CR/CRi after induction were comparable and statistically non-inferior in the HIDAC-based cohort compared to the CPX-351 cohort. The validity of these results is substantiated by the comparable 47.7% CR/CRi rate observed in the phase III trial [5]. Similarly, while never studied prospectively, several other retrospective studies have reported comparable CR/CRi rates with HIDAC-based therapy to our findings [15–17]. Of particular interest is a recently published, retrospective, multi-center study by Talati et al. that demonstrated a 53% CR/CRi rate with another HIDAC-based regimen, CLAG ± mitoxantrone (CLAG/M), in patients with sAML who had failed prior HMA. In patients with less than 4 prior cycles of HMA, the CR/CRi rate was significantly higher with CLAG/M compared to CPX-351 (50 vs. 25%, $p = 0.0068$). These CLAG/M response rates are comparable to the 62.7%

CR/CRi seen with the HIDAC-based regimens (without anthracycline) in our study, although the inclusion of the anthracenedione mitoxantrone may have contributed to a higher 30-day mortality (12%) compared to our study (1.3%).

Because FLAG had been shown to be safe and effective in a prior single-center retrospective study, with a much lower cost and favorable safety profile, a non-inferiority design was chosen for the primary efficacy endpoint [7]. While our study allowed for a 7.5% lower CR/CRi attainment in the HIDAC-based arm to be tolerated in the non-inferiority design, HIDAC-based therapy resulted in a 14.8% higher probability of CR/CRi attainment with the lower bound of the 95% confidence interval for the difference being −0.1%. An assessment of superiority would have required a larger number of patients than was feasible given the low incidence of AML and this particular subtype and the length of time CPX-351 has been available. However, the large numerical increase in CR/CRi rate with FLAG (62.7 vs. 47.9%) is certainly hypothesis generating, and lends support to the consideration of a randomized trial to compare these two regimens in this population.

Long-term outcomes were found to be no different in patients treated with HIDAC-based therapy compared to CPX-351 (Figure 3). Overall survival estimates in this study for CPX-351 closely resemble that seen in the phase III trial (median 9.1 months vs. 9.56 months, respectively). Consistent with prior knowledge about the importance of alloHCT as a consolidative strategy in this patient population, the overall survival probability was higher in patients who proceeded to alloHCT in first CR/CRi (Figure 3B). Because a similar number of patients in both arms proceeded to transplant in first CR/CRi, it is not surprising overall survival was also similar in patients who received HIDAC-based therapy compared to those who received CPX-351 ($p = 0.65$).

The safety profile of HIDAC-based therapy was favorable when compared to CPX-351 with a shorter time to count recovery, which possibly contributed to a lower number of confirmed infections (Table 4). By combining high-dose cytarabine with a purine-analogue (e.g. fludarabine, clofarabine, cladribine), the HIDAC-based regimens in this study take advantage of the synergy between the two agents, resulting in a higher concentration of the active ara-CTP and a lower concentration of the neurotoxic ara-U metabolite for a given dose of cytarabine [18–20]. This allows for a decreased dose of cytarabine compared to the original high-dose cytarabine monotherapy regimens, resulting in a much more tolerable regimen for older patient populations. This is of particular interest given the older median age of diagnosis for patients with sAML. In this cohort the median age was 67, including 94 (55%) patients >65, and patients had a median baseline Charlson Comorbidity Index score of 6. This represents the typical sAML population, which tend to be older with more comorbidities, possibly related to a history of prior malignancies and therapy. Utilization of effective, intensive therapy is often limited in this population due to higher rates of induction mortality in patients >60 years of age. HIDAC-based therapy was associated with low 30-day mortality supporting its tolerability, in addition to efficacy, in this difficult to treat patient population.

There are some limitations to this study that must be acknowledged. Due to the retrospective nature of this study, unmeasured confounding variables cannot be excluded. Additionally, the timing of bone marrow assessments did not follow a defined protocol and therefore intra- and inter-institutional differences existed. Baseline and disease characteristics were collected to identify any large imbalances between the cohorts and minor differences were noted. First, patients treated with HIDAC-based therapy were more commonly found to have del17(p)/*TP53* mutations occurring in 20 of 34 evaluable patients (58.8%) compared to 21 of 67 evaluable patients (31.3%) in the CPX-351 cohort ($p = 0.010$). TP53 mutated AML has been associated with a lower CR rate, shorter EFS, and inferior OS [21]. It is important to note that only 101 of the 169 patient were tested for del 17(p)/TP53 ($n = 34$ in the HIDAC-based cohort and $n = 67$ in the CPX-351 cohort) limiting the information about the entire sample with regards to this mutation and its distribution amongst the cohorts. Second, more patients previously received HMA for an AHD in the CPX-351 cohort (40.4 vs. 26.7%, $p = 0.061$). Previous receipt of an HMA, particularly >4 cycles, is a predictor for worse outcomes in patients receiving CPX-351. A minority of patients in our study, 21% ($n = 20$) of those in the CPX-351 cohort, and 14.7% ($n = 11$) in the HIDAC-based arm received >4 cycles of HMA for AHD. To explore the effect of *TP53* mutations and prior HMA exposure on outcomes, we evaluated CR/CRi rates in these subgroups and did not find a difference in CR/CRi with either induction strategy. Thus these imbalances did not seem to influence the primary study outcome.

Additionally, the majority of patients receiving HIDAC-based regimens originated from a single institution (92% from Michigan Medicine). The institutional

standard of care for patients with sAML who are treated at Michigan Medicine is FLAG based on previously published data demonstrating efficacy and tolerability in this population [7]. Additionally, similar response rates have been previously reported by several other institutions [15–17]. Adverse events of interest related to thrombocytopenia, such as major bleeding events, were not collected. Given the significantly shorter time to PLT count recovery observed with HIDAC-based regimens, not accounting for these adverse events would likely only improve the safety outcomes of this arm. Differences between the diagnostic and antimicrobial prophylaxis strategies across institutions limit an extensive analysis of infectious complications. Furthermore, with a short median follow up, limited conclusions can be drawn regarding long-term outcomes, however the median OS observed in this study is similar to what has been reported with CPX-351 [5].

Despite these limitations, this study has notable merits. This is a real-world, multi-center study with a sample size comparable to the trial which led to FDA approval of CPX-351. This study attempts to build on the field of oncology stewardship with a goal of enhancing patient health outcomes while reducing financial toxicity. The arsenal for the treatment of AML has increased dramatically in the last 3 years. Despite this, there is still sizeable opportunity for improvement in long-term outcomes. Furthermore, the cost of newly approved medications ranges from $20,000 per month for oral agents to upwards of $100,000 per course for intravenous therapies. HIDAC-based regimens have been utilized in the management of sAML with success and low toxicity, and as a result they represent an equally important part of the arsenal.

This real world multi-center study demonstrated that similar rates of CR/CRi can be attained with HIDAC-based regimens with a lower infection rate in induction, and that those responses translate to similar longer-term outcomes for these patients. A randomized clinical trial would be the gold standard to compare these two regimens; nonetheless, the likelihood of such a study taking place is low. Given the non-inferior efficacy, favorable tolerability, and lower impact on healthcare resources, HIDAC-based regimens, such as FLAG, could be considered as an alternative to CPX-351 in patients with sAML.

Author contributions

All authors contributed to the study design, data collection and analysis, and preparation of the manuscript.

Disclosure statement

Jeff Klaus, PharmD serves on the speakers bureau for Jazz Pharmaceuticals and has attended an advisory board for Jazz Pharmaceuticals. Stephen Clark, PharmD is a consultant for Elliott Benson Research. Kristen Pettit, MD provides advising for the following companies: Kura Oncology, PharmaEssentia, CTI Biopharma. Tapan Kadia. No potential conflict of interest was reported by the author(s).

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