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RESEARCH

Feasibility of allogeneic stem cell transplantation (HSCT) in patients with acute myeloid leukemia previously treated with CPX-351: report from a single center

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Abstract

The increased use of CPX-351, a liposomal formulation of cytarabine and daunorubicin, in association with reduced intensity conditioning regimen and new strategies of GvHD prophylaxis such as PTCY, allows to proceed with HSCT in older patients or previously heavily treated, improving outcomes. Of 55 patients with s-AML treated with CPX-351 from February 2019 till December 2023, at our center, all 28 patients with an indication to proceed with HSCT, underwent to transplant to consolidate the obtained response. The median age was 62 yrs (range 43–69). They were all in complete remission except two. The median HCT-CI was 4 (range 0–7). The main conditioning regimen was the association of Thiotepa, Busulfan, and Fludarabine. A Prophylaxis Gvhd regimen was performed with cyclosporine and mycophenolic acid, and PTCY. Engraftment was reached in all patients treated with CPX-351, except one. Eight patients developed acute GVHD. 1 year's OS was 66%. Comparing data with 59 patients, previously treated with 7 + 3 standard induction therapy, we found differences in terms of median age ($p < 0.00001$), HCT-CI ($p = 0.01$), and in terms of median CD34 + stem cells, which are significantly higher in the younger comparison population ($p = 0.0002$), with similar outcomes. The growing use of CPX-351 appears to be a safe and effective bridge therapy for HSCT in patients with a poorer prognosis, reproducing outcomes similar to younger populations.

Keywords Secondary acute myeloid leukemia · Allogeneic stem cell transplantation · CPX-351

Abbreviations

GVHD	graft versus host disease
HCT-CI	hematopoietic cell transplantation- comorbidities index
HSCT	hematopoietic stem cell transplantation
MRC-AML	Acute myeloid leukemia with myelodysplasia-related changes
PTCY	post-transplant Cyclophosphamide
t-AML	therapy-related acute myeloid leukemia

Introduction

Secondary acute myeloid leukemia (s-AMLs) including AML with myelodysplasia-related changes (AML-MRC) and therapy-related AML (t-AML) are generally associated with a poor prognosis [1].

The sAMLs are more frequent in older patients and their prognosis is often worsened by adverse/complex cytogenetics, high-risk molecular abnormalities, multidrug-resistance phenotype, and the presence of comorbidities [2].

In this setting of patients, standard treatment can induce less than 40% short-term complete remissions and allogeneic

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stem cell transplantation (HSCT) is the only curative therapeutic option [3]. New recent advances in the transplant setting such as the use of reduced intensity regimens, the use of alternative donors (haploidentical donors), and the use of post-transplant cyclophosphamide (PTCY) allow to proceed with HSCT in older and/or previously heavily treated patients, improving outcomes [4].

However, HSCT feasibility and overall results are impaired by the low efficacy of available induction therapies, and the high median age and comorbidity burden of the majority of these patients.

CPX-351 is a liposomal formulation of cytarabine and daunorubicin in a fixed 5:1 molar ratio, approved for the treatment of t-AML or MRC-AML by FDA in August 2017 and by EMA in December 2018, based on the results from a phase 3, randomized controlled trial (RCT), which showed a superior overall response rate (ORR) and overall survival (OS) of CPX-351 compared with classical 7+ 3 (cytarabine and daunorubicin) intensive chemotherapy (IC), in the treatment of patients aged 60–75 years with newly diagnosed, high-risk/secondary AML [5, 6]. The safety profile was comparable between the 2 arms, except for prolonged myelosuppression in the CPX-351 arm. The data were also confirmed in the 5-year follow-up study [7].

Despite the significant prolongation of neutropenia, with a higher rate of serious infections (32% vs. 21%), particularly of bacteremia, in the CPX-351 arm, this difference did not translate into a higher rate of discontinuation of the study treatment or overall AE-related mortality [5, 6, 8].

The "3 +7" regimen which represents the gold standard for the treatment of AML contributes to increasing the risk of infection in AML patients due to the toxicity induced at the level of the intestinal mucosa. Some previous studies analyzed the impact of induction chemotherapy on the intestinal barrier in patients with AML [9, 10]. In AML patients, they have demonstrated a profound impairment of the intestinal barrier, with transient epithelial damage resulting in prolonged loss of microbiota diversity and function. Recently the study on the mouse model highlighted a qualitative dysbiosis and a deterioration of the physical barrier that facilitates bacterial translocation. CPX-351, unlike the "7 +3" combination, showed a protective barrier effect, preserving microbial composition and function in the intestine [11].

The reduced toxicity induced by the CPX 351 induction treatment translates into better tolerability of the treatment with reduced incidence of adverse events which potentially makes CPX 351 an optimal bridge to transplant therapy for elderly patients and/or patients previously treated for other pathologies, resulting in a probable lower rate of infections and development of intestinal GVHD post-transplant, compared to patients treated with standard 3+ 7 therapy.

Aim of the study

Our study aims to assess the feasibility of HSCT in patients with s-AML and t-AML treated with CPX-351, comparing clinical data with patients with AML submitted to HSCT, previously treated with 7+ 3 induction chemotherapy.

Materials and methods

In our retrospective study, we collected clinical data on 28 patients submitted to HSCT at our center from February 2019 to December 2023. In this aim, we compared clinical data with 59 patients with AML submitted to HSCT, previously treated with 7+ 3 induction chemotherapy from January 2019 to December 2023. GVHD prophylaxis was performed with cyclosporine, mycophenolic acid, and cyclophosphamide at days +3 and +5 after HSCT.

The study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome as part of the TOHP (Transplant Outcome in Hematological Patients) study (protocol number 0030921/20). All patients signed informed consent before proceeding with chemotherapy and allogeneic stem cell transplantation.

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Policlinico Universitario A.Gemelli, Rome, Italy.

Statistical analysis was performed using NCSS 19 Statistical Software −2016 (NCSS, LLC, Kaysville, Utah, USA; ncss.com/software/ncss). Data were presented as median and range for continuous variables and as the number and proportion of patients for categorical variables.

For the statistical analysis, the following variables were evaluated: patient's age and gender, response to induction treatment, disease status at transplant, hematopoietic stem cell transplantation comorbidity index (HCT-CI), conditioning regimen, graft versus host disease (GvHD) prophylaxis, granulocyte, erythrocyte and platelet engraftment, sepsis, incidence of acute and chronic GvHD, comparing the two populations.

For comparison between the two groups, the Chi-square test was used in univariate analysis for categorical variables and the Mann-Whitney test for continuous variables.

The non-relapse mortality (NRM) and the relapse incidence were evaluated with the cumulative incidence and the differences between curves were examined with the Gray test.

The overall survival (OS) and the disease-free survival (DFS) were evaluated with Kaplan-Meier curves and the differences between curves were examined with the log-rank test.

Results

Of 55 patients with sAML treated with CPX-351 from February 2019 to December 2023 at our center, all 28 patients with indication to proceed with HSCT, underwent to transplant as consolidation. There were 20 patients with t -AML and 8 patients with AML-MRC. There were 14 males and 14 females, with a median age of 62 years (range 43–69). Thirteen patients had complex cytogenetics, eleven patients had normal karyotype and in the remaining four patients cytogenetic was not evaluable. Twelve patients underwent to one chemotherapy cycle, nine patients to two cycles, and seven patients to three cycles. All but five patients obtained CR, so these refractory patients were treated with reinduction chemotherapy based on the association of venetoclax and hypomethylating agents. Thus, all but 2 patients were in CR, at the time of transplant. The median HCT-CI was 4 (range 0–7). The main conditioning regimen was the association of Thiotepa, Busulfan, and Fludarabine, modulating the busulfan dose according to the patient's comorbidities and performance status, defined by HCT-CI. Thus twenty-one patients received a myeloablative conditioning regimen and the remaining seven patients received a reduced-intensity conditioning regimen. Eighteen patients received grafts from unrelated donors, nine patients from haploidentical donors, and one patient from a sibling donor. Stem cell source was peripheral blood in 24 pts, bone marrow in 3 pts, and CBU in 1 patient. The median $CD34^+$ cell dose was 4×10^6/kg (range: 0.1–12.7). Engraftment was reached in all but one patient receiving CBU. The median time of neutrophil and platelet engraftement was 20 (range: 13–34) and 24 (range: 12–47) days respectively.

Sepsis was identified in 7 patients out 28 (25%). There were 4 patients with Gram negative sepsis and 3 wih Gram positive sepsis.

Eight patients (28%) developed acute GVHD. Five patients presented skin involvement (three with grade II and two with grade I); a patient with skin and pulmonary involvement (Grade II) and two patients with skin and gut involvement (one with grade II and one with grade III) [12].

Eighteen patients are alive (64%): six patients died after AML relapse and four patients due to TRM: two patients for GVHD (one patient for acute GVHD with gut involvement and one for chronic Gvhd with pulmonary involvement), one for post-transplant lymphoproliferative disease (PTLD), and one for engraftment failure.

During the same time interval the patients treated with 7 + 3 induction chemotherapy were 32 males and 27 females, with a median age of 52 years (range 24–68). In this group, we have 12 patients with complex karyotype, 12 with karyotype not evaluable, and 31 patients with normal karyotype; Moreover 35 patients presented genetic abnormalities (18 patients with normal karyotype, 7 patients with karyotype not evaluable and 10patients with complex Karyotype.

Forty-eight patients were in complete remission after the first induction therapy, so the eleven refractory patients underwent to a second-line chemotherapy and only six patients reached the CR and the remaining 5 patients were not in complete remission at the time of transplant. The median HCT-CI was 3 (range 0–8). Forty-nine patients received a myeloablative conditioning regimen and the remaining ten patients received a reduced-intensity conditioning regimen. The donors were twenty-nine unrelated donors, fourteen haploidentical donors, twelve sibling donors, and four cord blood units. Stem cell's source was peripheral blood in 45 pts, bone marrow in 10 pts and CBU in 4 patients. The median $CD34^+$ cell dose was 6.3×10^6/kg (range: 0.09–13.27). All patients reached engraftment. The median time of neutrophil and platelet engraftement was 20 (range: 14–40) and 23 (range: 13–60) days respectively.

Sepsis was identified in 30 patients out 59 (51%). There were 13 patients with Gram negative sepsis and 17 wih Gram positive sepsis.

Twenty-four (40%) patients developed acute GvHD: twelve patients with grade I, seven patients with grade II, four patients with grade III, and one patient with grade IV. Eleven patients presented gut involvement: one patient with grade I, six patients with grade II, three patients with grade III, and one patient with grade IV.

Forty-one patients are alive (69%): twelve patients died of relapse disease and six patients of transplant-related mortality (three due to acute Gvhd grade IV with gastrointestinal involvement, and three due to other causes such as cerebral hemorrhage, renal impairment, and neurodegenerative disease).

The comparative analysis between the two populations showed no difference in terms of gender, disease status at transplant, donor type, donor gender, stem cell source, conditioning regimen, GVHD prophylaxis, sepsis occurrence, median time of engraftement and GVHD incidence. A significant difference was found in terms of median age ($p < 0.00001$), HCT-CI ($p = 0.01$) as expected, and in terms of median CD34 $\times 10^6$/kg stem cell infused ($p = 0.0002$). In particular, patients treated with CPX-351 were significantly older than patients treated with 7 + 3 chemotherapy induction, and they had a higher HCT-CI, due to the comorbidities burden and medical history. Another significant finding was that patients in the younger population received a higher

median number of CD34 × 10^6/kg stem cells, as reported in Table 1. We found no difference in terms of OS, DFS, TRM, and GVHD cumulative incidence (Fig. 1a-b-c-d).

Discussion

Allogeneic HSCT can be considered a therapeutic option in elderly patients, if they achieve complete remission, according to their age, comorbidities, and performance status, evaluated through HCT-CI [13]. For several decades, the 7 + 3 regimen has been the standard induction therapy for AML; in recent years, the introduction of new drugs such as gemtuzumab ozogamicin and FLT3 inhibitors, the improved alloHSCT outcomes and the use of post-transplant maintenance therapies led to better survival rates [1, 2, 14, 15]. Despite these improvements, less of than 40% of patients achieve short-term complete remission, with poor tolerability. In such cases, alloHSCT remains the only potentially curative option, albeit in a challenging setting [16–18].

Table 1 Patients'characteristics

	CPX-351	7 + 3 induction	$p > 0.05$
Patients	28	59	
Gender male/female	14/14	32/27	$p = 0.1$
Median age (range)	62 (43–69)	52 (24–68)	***p* =< 0.00001**
n° treatment lines	**1**: 23 (71%)	**1**: 48 (81%)	
	2: 5 (29%)	**2**: 6 (10%) **3**: 5 (9%)	***P* = 0.6**
Disease status at transplant CR/Refractory	26/2	54/5	$p = 0.2$
Median HCT-CI (range)	4 (0–7)	3 (0–8)	***p* = 0.01**
Donor type			
MUD 8/8	11	21	$p = 0.2$
MUD 7/8	6	8	
Sibling donor	1	12	
Haploidentical donors	9	14	
CBU	1	4	
Donor gender male/female	21/8	44/15	$p = 0.8$
Stem cell source			
PBSC	24	45	$p = 0.5$
BM	3	10	
CBU	1	4	
Conditioning regimen			$p = 0.08$
Myeloablative	21	49	
Reduced intensity regimen	7	10	
Median CD34 cell dose x10 ^{6} /kg (range)	4 (0.1–12.7)	6.3 (0.09–13.27)	***P* = 0.0002**
Median neutrophil engraftment (range)	20 (13–34)	24 (12–47)	$P = 0.7$
Median platelets engraftment (range)	20 (14–40)	23 (13–60)	$P = 0.5$
GvHD prophylaxis			*p = 0.6*
PTCY	27	54	
OTHER	1	0	
Gvhd Incidence n°(%)	8/28 (28%)	24/59 (40%)	$p = 0.1$
Sepsis n°(%)	7/28 (25%)	30/59 (51%)	$p = 0.1$
Relapse n°(%)	6/28 (21%)	16/59 (27%)	$p = 0.5$
Alive/death	18/10 (64%)	41/59 (69)	$p = 0.6$
Overall Survival n°(%)	66%	76%	$p = 0.2$

The introduction of CPX-351 led to an improvement in the management of these patients with poor prognosis [5].

In vitro studies have demonstrated that cytarabine and daunorubicin efficacy depend on the molar ratio of the 2 drugs, with the highest proportion of synergy and the lowest level of antagonism occurring at a 5:1 molar ratio [19], which allows a prolonged drug exposure, with an increased leukemic cell killing relative to free drug [20, 21], and with an increased capacity to overcome drug resistance mechanisms [22].

Real-life studies have confirmed the higher rate of remission, observed in the previous studies, with a range between 40 and 80% of patients reaching complete remission [23–26]. Despite the more prolonged cytopenia and the increased rate of serious infections, this seems to have no impact on overall survival. In particular, patients submitted to HCT, after induction therapy with CPX-351, achieved prolonged OS after alloHCT. In the study of Lee et al., treatment with CPX-351 led to similar OS rates in elderly and younger populations; in particular, for patients submitted to alloHSCT, the median OS was 77 months. Similar results were reported in a UK study, with a median OS landmarked from HCT OF 23.2 months [27]. In a subanalysis of the Italian Compassionate Use Program, the 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% [28].

Focusing on nonhematological adverse effects, gastrointestinal toxicity was only rarely reported in real-world studies [29]. The low frequency of non-hematological toxicity (e.g., mucositis) may have contributed to the relatively low rate of peri-transplant mortality, as suggested by a previous study by Guolo et al. [24].

A French retrospective multicenter study by Chiche et al. recently reported that while 50% of patients experienced some grade of gastrointestinal toxicity, only 4 out of 103 AML patients treated with CPX-351 had grade 3 gastrointestinal toxicity [23]. Additionally, Hueso et al. investigated the mechanism of mucosal damage from the 7 + 3 regimen with daunorubicin and their impact on bloodstream infections, reporting intestinal barrier impairment, as determined by citrulline levels, and deep modifications of intestinal microbiota combining a dramatic loss of overall bacterial load and alpha and beta diversities [30]. A recent study conducted in a murine model has provided insights into the pathophysiological mechanism responsible for the

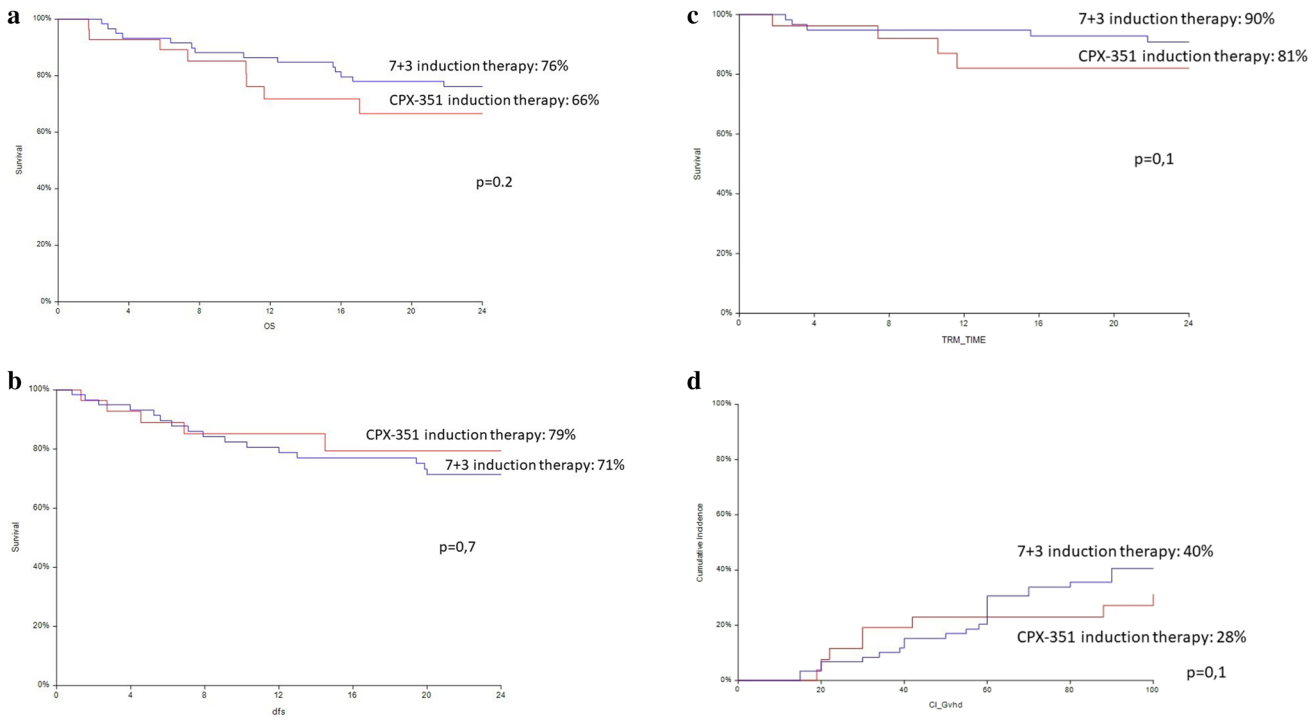

Fig. 1 **a** Overall survival according to induction therapy. **b** Disease free survival according to induction therapy. **c** Transplant related mortality according to induction therapy. **d** Cumulative Incidence of acute gvhd according to induction therapy

diminished mucosal damage observed in liposomal formulations [11]. These findings are consistent with previous observations reported [31, 32].

In our monocentric retrospective study on 55 patients with s-AML treated with CPX-351, from February 2019 to December 2023 at our center, all 28 patients with an indication to proceed with HSCT, evaluated on the basis of age, comorbidities, and performance status, underwent transplant.

Comparing clinical data with a population of patients submitted to transplant for AML, previously treated with standard 7 + 3 regimen induction therapy, we found no clinical difference, except for age, HCT-CI, and median number of CD34 + stem cells infused. As expected, patients treated with CPX-351 were significantly older, with a higher HCT-CI, reflecting their comorbidities and previous treatment. A difference was found also in terms of the median number of CD34 + x10^6/kg stem cells infused, which resulted in significantly higher in the younger population. This probably may be due to the donor's type and/or donor's age, but we found no significant difference comparing the data in the two populations.

We found no difference in terms of outcomes, in particular on OS, DFS, NRM, sepsis, and incidence of GvHD. These data confirm the real-life experience with the use of CPX-351, which showed efficacy, safety, and good tolerability, as previously reported [33, 34]. As highlighted in our monocentric experience, CPX-351 treatment allows to proceed with transplant in older patients, with a higher HCT-CI, reflecting the comorbidities burden, using the same transplant platform, and reaching the same results, in terms of outcomes. This profile makes CPX-351 treatment a feasible bridge to transplant, in particular for older and/or previously heavily treated patients.

Interestingly in the CPX-351 patients group, only two patients developed GVHD with gut involvement, compared to eleven patients in the 7 + 3 induction group. This data did not reach a significant statistical difference, probably due to the small number of patients, but it reflects the insight, already reported in the literature, of reduced gastrointestinal toxicity, comparing two homogeneous study populations, in terms of donor type, stem cell source, conditioning regimen and GVHD prophylaxis. The efficacy and the good tolerability of the CPX-351 expose patients to fewer infections, fewer antibiotics, and reduced mucosal damage, which could positively influence post-transplant complications [35].

These data are very interesting and encouraging, especially for patients with a worse prognosis but it is necessary to underline that the data are preliminary, due to the small number of patients and it is necessary to confirm the findings in a larger cohort of patients, minimizing the heterogeneity of the population.

G. Uy et al. conducted a study in 92 patients as part of a prospective phase 3 randomized trial. Among them, 53 patients received CPX-351 while 39 patients received 3 + 5

and proceeded to HSCT. The population treated with CPX-351 showed (NRM) and a lower risk of relapse. It is noteworthy that despite a higher proportion of patients aged over 70 years in the CPX-351 group, there was a reduction in NRM among transplanted patients receiving CPX-351. This observation suggests the potential importance of treatment tolerability and overall health in this older population. The difference in NRM did not seem to be influenced by variations in graft-versus-host disease (GVHD) [36].

AlloHSCT outcomes elucidated in this study suggest enhanced disease management with CPX-351, increasing alloHSCT rates and notably, enhanced tolerability with reduced NRM. These findings lay the foundation for planned randomized trials investigating CPX-351 in high-risk AML populations where alloHSCT is the preferred post-remission strategy. Furthermore, OS is positively influenced, with a median OS of 10 months observed in the 3+ 7 group, whereas the CPX-351 group did not achieve a median survival at 60 months [25, 36].

Conclusion

Our monocentric experience showed data in line with those reported in the literature. The growing use of CPX-351 appears to be a safe and effective bridge therapy for HSCT. The association with reduced intensity conditioning regimen and new strategies of GvHD prophylaxis such as PTCY, allows to proceed with HSCT in older patients or previously heavily treated, reproducing outcomes similar to younger population.

Author contributions SG analyzed data and wrote the paper; EM, MAL, and FS participated in the performance of the research, FF and LDM collected clinical data; PC, LP, and SS revised the manuscript.

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Data availability The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Policlinico Universitario A.Gemelli, Rome, Italy.

Declarations

Competing interests The authors declare no competing interests.

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