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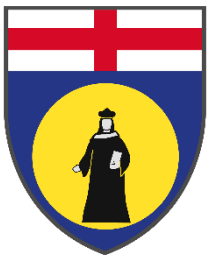

COMPARING OUTCOMES BETWEEN CPX-351 AND FLUDARABINE-BASED INDUCTION IN SECONDARY ACUTE MYELOID LEUKEMIA IN THE REAL-WORLD SETTING: THE PROGNOSTIC ROLE OF MEASURABLE RESIDUAL DISEASE

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Summary

Abstract

Secondary acute myeloid leukemia (s-AML) is associated with inferior outcomes with conventional chemotherapy and fludarabine combinations (FLAG-Ida) have been tested to improve results.

More recently, CPX-351 resulted superior to conventional 3+7 in s-AML patients.

In the UK NCRI AML19 trial, AML patients were randomized to receive either FLAG-Ida or CPX-351. Overall, the two treatments showed similar results in terms of complete remission (CR) and overall survival (OS), but subgroup analysis revealed better OS with CPX-351 in patients with MDS-related gene mutations. Unfortunately, minimal residual disease (MRD) was evaluated only in a minority of patients.

The aim of this study was to further disclose the mechanisms of higher efficacy of CPX-351 in s-AML, with a focus on MRD.

We analyzed 183 consecutive s-AML elderly patients (median age 69, range 60-77) treated with CPX-351 (n=82) or receiving FLAG-Ida (n = 101).

Complete remission (CR) rate and MRD negativity probability were higher among patients receiving CPX-351 (MRD negative CR rate of 40/64, 62.5%, compared to 25/55, 45% in patients who received FLAG-Ida, $p<0.05$). Extra-hematological toxicity was lower in CPX-351 arm, and 30 days mortality was 3.6% and 8% in patients receiving CPX-351 or FLAG-Ida, respectively. Notably, 21/64 (32.8%) CR patients treated with CPX 351 underwent allogeneic stem cell transplantation (HSCT), compared to 5/55 with FLAG-Ida (9%, $p<0.05$). Overall, CPX-351 treatment resulted in higher OS (median OS 17.7 vs 11.2 months with FLAG-Ida, $p<0.05$).

The better outcome of CPX-351 compared to FLAG-Ida in our cohort may be explained by a greater probability of MRD negativity, alongside with an improved tolerance, enabling more s-AML patients to undergo HSCT.

Introduction

Acute Myeloid Leukemia: biology and prognostic factors

Acute Myeloid Leukemia (AML) is a disease of the bone marrow characterized by the clonal expansion of immature myeloid precursors, resulting in impaired hematopoiesis and bone marrow failure.[1-2]

Genomic sequencing studies have brought about great insights into the mechanisms of leukemogenesis, a multistep process involving the serial acquisition of somatic mutations, dysregulation in epigenetic factors and gain of cytogenetic alterations in hematopoietic stem cells, which ultimately result in the acquisition of self-renewal capacity and propagation of the neoplastic clone.[3-4]

The better understanding of the molecular basis of AML allowed to identify mutations in critical genes, not only providing an extended panorama of the biological heterogeneity of the disease, but also deeply refining AML classification and prognostic prediction.

Before the "genomic era", for several years AML has been classified on the basis of clinical ontogeny in 3 distinct clinical subgroups, defined by the presence of: an antecedent hematological disorder such as MDS or MPN (secondary AML, s-AML); a previous leukemogenic exposure (therapy-related AML, t-AML); or the absence of both (de novo AML).[5]

Moving from the advances in understanding of AML ontogeny, in the last years the definition of s-AML has progressively moved from a clinical to a molecular characterization, as it is reflected by the recent WHO 2022 classification [2], where s-AML is hierarchically defined by:

1. the presence of myelodysplasia (MDS) related gene mutations, consisting in the mutation of at least one among: *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR*, *STAG2*;
2. the presence of MDS-related cytogenetic aberrations if no MDS-gene mutations are found;
3. the anamnesis of an antecedent history of MDS.

The WHO 2022 definition of s-AML steps significantly forward from the previous 2016 edition, where s-AML were defined either by the presence of MDS-related cytogenetic aberration, by a clinical history of MDS, or by the presence of morphological marrow dysplasia.[6]

While the importance of clinical definition of s-AML and t-AML is somehow reduced in the refined genetic-based classification of AML, the importance of an antecedent hematological disorder or cytotoxic treatment is still recognized as a diagnostic qualifier.

From a prognostic point of view, s-AML and t-AML are biologically characterized by the high incidence of high-risk cytogenetics and molecular aberrations, and, as a consequence, are historically considered as high-risk disease due to the dismal prognosis following conventional chemotherapy. The adverse leukemia-related factors together with older age at diagnosis are mainly responsible of the high toxicity and low efficacy of conventional treatment in s-AML, thus hampering the possibility to proceed to allogeneic-stem cell transplantation consolidation, which represents the only curative approach for fit patients.[5]

Acute Myeloid Leukemia: treatment

Combination chemotherapy remains the standard of care for intensive AML induction therapy in fit patients; treatment regimens typically consist of a multi-day infusion of cytarabine in combination with an anthracycline, mainly daunorubicin, in a scheme called "3+7". This regimen has remained unchanged for over 40 years, but is limited by low complete remission (CR) rates in the context of high risk-disease, as s-AML, and by high relapse incidence if no further treatment is administered.[2]

Given the unsatisfactory prognosis with conventional chemotherapy, allogeneic hematopoietic stem cell transplantation (HSCT) represents the only curative option for fit patients with high-risk AML, but it's mostly effective if performed in CR, especially if patients achieve negative measurable residual disease (MRD) status, which is unlikely to be achieved with conventional treatments.[2]

In an effort to enhance the efficacy of standard chemotherapy, new combination strategies have been tested. Following the observation that fludarabine increases the concentration of Ara-C triphosphate, the active metabolite of Ara-C, in leukemia cells, fludarabine combinations (FLAG-Ida) have been investigated as induction strategies, and proved to have good antileukemic effect with superior remission rate and reduced risk of relapse. However, the treatment is burdened by significant toxicities which limit its feasibility in elderly AML patients.[7- 8]

In the last few years, several new drugs for specific AML subsets have been introduced.

CPX-351 has been approved by the US Food and Drug Administration (FDA) in 2017 and by the European Medicines Agency (EMA) in 2018 for the treatment of adults with newly diagnosed t-AML, s-AML or AML with morphologic myelodysplasia-related changes (MRC-AML).[9]

CPX-351 is a dual-drug liposomal encapsulation of cytarabine and daunorubicin that was designed to improve efficacy compared to the traditional 3+7 chemotherapy regimen. The liposome is able to maintain an optimal synergistic 5:1 molar ratio of cytarabine and daunorubicin and protects the drugs from metabolism and elimination. The preferential uptake of liposomes by leukemia cells may

also bypass P-glycoprotein-based efflux pumps, which are important mediators of chemotherapy resistance, and reduces the exposure of healthy tissues to the drug, thus reducing extra-hematological toxicity.[10-11]

The efficacy and safety of CPX-351 have been assessed in a randomized phase III trial, enrolling 309 patients aged 60-75 years with newly diagnosed high-risk or s-AML. CPX-351 demonstrated a significantly improved median overall survival (OS; 9.56 vs 5.95 months) and a higher CR rate versus the conventional 7+3 chemotherapy (48% vs 33%), both in patients receiving HSCT consolidation or not. The safety profile of CPX-351 resulted manageable and consistent with the known safety profile of 7+3, albeit the median time to neutrophil and platelet recovery was longer following treatment with CPX-351.[10]

After a 5-years follow-up, improved median OS and long-term remission with CPX-351 versus 7+3 was maintained in older patients with newly diagnosed high-risk/s-AML.[11]

Subsequent real-world evidences (RWE) confirmed the efficacy of CPX-351 in s-AML, showing similar results compared to the phase III trial.[12-15]

In the UK NCRI AML19 trial, 189 patients affected by high risk AML were randomized to receive either CPX-351 or FLAG-IDA as induction treatment.[15] Overall, CPX-351 and FLAG-IDA showed similar results in terms of CR and OS in high risk AML, but further subgroup analysis revealed better OS with CPX-351 in the 59 patients who had MDS-related gene mutations, suggesting a higher anti-leukemic activity with deeper responses in this setting. Unfortunately, in the latter subgroup analysis, numbers were too small to perform a precise characterization of the reasons behind the increased CPX-351 efficacy. Furthermore, MRD analysis was not an endpoint of the study and was available in only 59/84 CR patient, with conflicting results.[15]

Moreover, also in the RWEs published so far only incomplete data is available.[12-15]

As a consequence, the reasons of the better results achieved with CPX-351 in the s-AML setting are not completely elucidated yet.

Aims

The aim of this study is to compare the probability of achieving MRD negativity and its prognostic significance in a cohort of 183 consecutive elderly patients (median age 69, range 60-77) affected by s-AML treated with CPX-351 (n=82) or receiving an age-adjusted FLAG-Ida regimen (FLAI, n=101) in our Center.

Material and methods

Study cohort and risk assessment

The study included 183 consecutive elderly patients (median age 69, range 60-77) affected by s-AML treated with CPX-351 (n=82) or receiving an age-adjusted FLAG-Ida regimen (FLAI, n=101).

Patients treated before January 2019 received FLAI. All 82 patients treated after January 2019 received CPX-351. All patients had s-AML as defined by the 2016 WHO classification.[6]

All patients provided written informed consent in accordance with the Declaration of Helsinki.

Diagnostic workup was performed as per internal standard in all patients and included cytogenetic analysis with conventional q-banding and molecular assessment consisting in RT-PCR for NPM1, FLT3-ITD and TP53 mutational status.

Leukemia risk score was graded according to European LeukemiaNet (ELN) 2017 classification, since the 2017 edition was in use at the time of patient treatment.[16]

Treatment

CPX-351 was administered according to the EMA approval, consisting in an induction cycle with a CPX-351 dose of 44 mg/sqm (daunorubicin 44 mg/sqm plus cytarabine 100 mg/sqm) administered on day 1, 3 and 5. Patients failing to achieve at least CRi after the first induction cycle were allowed to receive a second induction course with the same dose of the drug given on day 1 and 3. Post-remission therapy consisted of up to two consolidation cycles with a CPX-351 dose of 29 mg/sqm (daunorubicin 29 mg/m2 plus cytarabine 65 mg/m2) administered on day 1 and 3.

The age-adjusted FLAI regimen consisted in an induction cycle with Fludarabine 30 mg/sqm, Cytarabine 1 g/sqm and Idarubicin 8 mg/sqm on days 1–3. Patients achieving CR were given a second identical induction course, according to standard clinical practice in our Center. Consolidation chemotherapy consisted in intermediate dose Cytarabine (1g/sqm daily on day 1-3).

In the whole cohort, eligible patients proceeded to allo-HSCT consolidation as per internal guidelines and clinical evaluation.

Response and MRD assessment

Treatment responses were defined according to the recommendations of the European LeukemiaNet 2017. **(16)** Specifically, CR was defined as an absolute neutrophil count of more than 1000 cells per cubic millimeter, a platelet count of more than 100.000 per cubic millimeter, red-cell transfusion independence, and less than 5% blasts in the bone marrow. CRi was defined as all the criteria for CR, except for neutropenia (absolute neutrophil count ≤500 per cubic millimeter) or thrombocytopenia (platelet count, ≤100,000 per cubic millimeter). Partial response (PR) was defined by a count recovery with a marrow blast count between 5% and 25% and decrease of pretreatment bone marrow blast percentage by at least 50%. All others were considered non-responders (NR). Relapse was defined by either bone marrow blast count $\geq$ 5% in patients who have been in CR previously, reappearance of blasts in the blood or development of extramedullary disease.[16]

MRD assessment was performed in all patients achieving morphological CR/CRi using multicolor flow cytometry (MFC) on post-treatment bone marrow aspirate samples. MRD was evaluated in all patients at the same timepoint: after each cycle of CPX-351 or FLAI and before and after HSCT.

A positive MFC-MRD in the follow-up samples was defined by the presence of no less than 100 clustered leukemic cells/10^5 total events (threshold of 0.1%) and a number of acquired events of at least 100.000, ideally with the goal of acquiring 500.000 events. Both leukemia associated immunophenotype (LAIP) and different from normal (DfN) approaches have been applied.[2,17]

Study Endpoints and Statistical Methods

The outcomes for effectiveness were the complete remission rate (CR), the overall survival (OS), defined as the time from the 1st day of treatment to death from any cause or time of last follow-up, and the event-free survival (EFS) defined as the time from the 1st day of treatment to treatment failure, disease relapse or death from any cause, whichever occurs first.[2]

Statistical analysis was performed as previously recommended.[18]

Univariate analysis of dichotomous variables was performed using the Chi square test, or, whereas necessary, Fisher's exact test. Continuous variables were compared using Student's T test, or, if normal distribution could not be confirmed, by Wilcoxon's rank test. A logistical regression analysis

including only variable with a p value <0.1 in the early univariate analysis was performed for multivariate analysis.

Survival curves were built using the Kaplan Meier method and compared using the Log Rank test. A landmark analysis including only patients alive and in remission at day 30 was performed in order to evaluate the impact of transplantation on OS.

Multivariate survival analysis was performed using the proportionate risk Cox regression model, including only variables that respected the proportional risk assumption.[18]

All two tailed p values <0.05 were considered statistically significative.

All statistical analysis was performed using IBM SPSS v22 running on a Debian (Linux) operating system.

Results

Patients' characteristics

A total of 183 consecutive elderly patients (median age 69, range 60-77) affected by s-AML were included in this study. Patients were divided in two cohorts based on the treatment received: 82 patients were treated with CPX-351, whereas 101 patients received an age-adjusted FLAI regimen. Overall, the two treatment cohorts were well matched for age and ELN risk.

In the CPX-351 arm, 20 patients were affected by t-AML (24%) and 62 by MRC-AML (76%). Thirty-five patients had high risk cytogenetics according to ELN criteria and among them 28 patients (34%) showed a complex karyotype. Twenty-two patients (27%) had TP53 mutation, whereas NPM1 and FLT3-ITD mutations were found in 9 (11%) and 3 patients (4%), respectively. Ten patients (12%) previously received hypomethylating agents (HMA) for myelodysplastic syndrome. ELN 2017 risk was favourable, intermediate or adverse in 7 (8%), 32 (39%) and 43 (53%) patients, respectively.

Among patients receiving FLAI, 18 (18%) had t-AML and 83 (82%) had MRC-AML. Two patients had already received HMA for MDS (2%). Thirty-four patients (33%) showed a complex karyotype and ELN risk score was favourable, intermediate and adverse in 11 (11%), 49 (49%) and 41 (40%) patients, respectively. NPM1 and FLT3-ITD mutations were found in 6 (6%) and 3 patients (3%), respectively.

A detailed overview of patients' characteristics is provided in Table I.

Table I: Patients' characteristics

		OVERALL (n=183)	CPX-351 ARM (n=82)	FLAI ARM (n=101)	*p*
Median Age		69 (60-77)	68 (60-77)	69 (60-75)	n.s.
ELN 2017	**Favourable**	18 (10%)	7 (8%)	11 (10%)	n.s.
	Intermediate	81 (44%)	32 (39%)	49 (49%)	
	Unfavourable	84 (46%)	43 (53%)	41 (41%)	
Karyotype Risk Group	**Low**	5 (3%)	0 (0%)	5 (5%)	n.s.
	Intermediate	102 (55%)	47 (57%)	55 (55%)	
	High	76 (42%)	35 (43%)	41 (40%)	
WHO 2016	**t-AML**	38 (21%)	20 (24%)	18 (18%)	n.s.
	MRC-AML	145 (79%)	62 (76%)	83 (82%)	
Previous HMA	**YES**	12 (7%)	10 (12%)	2 (2%)	<0.05
	NO	171 (93%)	72 (88%)	99 (98%)	

Table legend: ELN= European LeukemiaNet; WHO= World Health Organization; HMA= hypomethylating agents; MRC= Myelodisplasia Related Changes

Response to treatment and MRD evaluation

After first induction cycle, a total of 119 patients (65%) achieved CR. Among patients treated with CPX-351 CR rate was 64/82 (78%), significantly higher when compared to patients receiving FLAI (55/101, 54.5%, $p<0.05$).

Thirty-day mortality was 3/82 (3.6%) and 8/101 (8%) in CPX-351 and FLAI treated patients, respectively. Severe mucositis was observed in 1 (1%) and 8 (8%) patients in the CPX and FLAI arm, respectively ($p<0.05$).

In the CPX-351 arm, CR rate was not affected by karyotype, presence of TP53 mutation, ELN risk, age, previous HMA treatment or WHO classification, whereas in the FLAI arm it was lower among ELN 2017 high risk patients ($p<0.05$).

In the whole cohort, among CR patients, a total of 65 (54.6%) achieved MFC-MRD negativity. MFC-MRD negativity probability was higher among patients receiving CPX-351 (MFC-MRD negative CR rate of 40/64, 62.5% and 25/55, 45% in patients who received CPX-351 or FLAI, respectively, $p<0.05$, Fig. 1).

Among CPX-351 treated patients, MFC-MRD negativity was not affected by any of the analyzed variables. In the FLAI cohort, MFC-MRD negativity rate was significantly lower among ELN 2017 adverse risk patients ($p<0.05$).

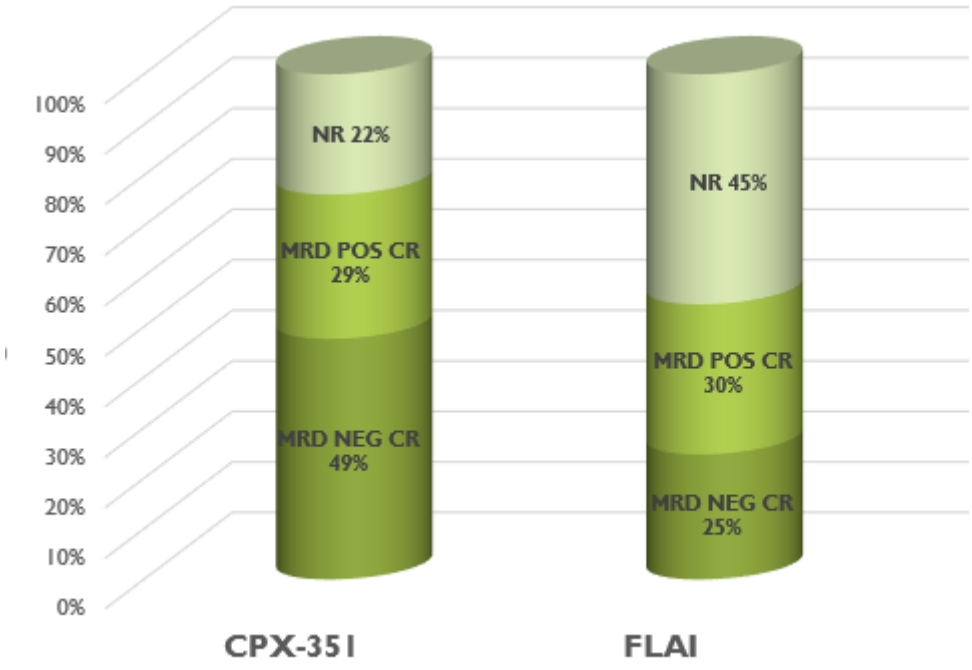

Figure 1: MRD negativity rate according to treatment

Survival analysis

Median follow-up was 20.7 months (CI 95% 16.49-26.37) for CPX-351 treated patients and 58 months (CI 95% 34.97-72.98) in the FLAI cohort.

Overall, median OS was 13.4 months (CI 95% 8.04-16.97). CPX-351 resulted in higher OS if compared to patients receiving FLAI (median OS 17.7 vs 11.2 months, respectively, $p<0.05$, Fig. 2).

With the limitation of the relatively small cohort, the presence of *TP53* mutation did not impact on OS in the CPX-351 arm.

In multivariate analysis, MRD was the strongest prognostic factor for OS, with a 2-year OS of 35% and 79% in patients with or without residual MFC-MRD after induction, respectively ($p<0.05$). MRD retained a strong prognostic value on OS regardless of treatment received: patients treated with CPX-351 and achieving MRD negative CR had a 2-year OS of 58% (median not reached) compared to 13% (median 10.6 months) for patients with residual MFC-MRD ($p<0.05$), whereas in the FLAI cohort the 2-year OS was 33% (median 16 months) and 17% (median 16 months) in patients with or without residual MFC-MRD, respectively ($p<0.05$, Fig. 3).

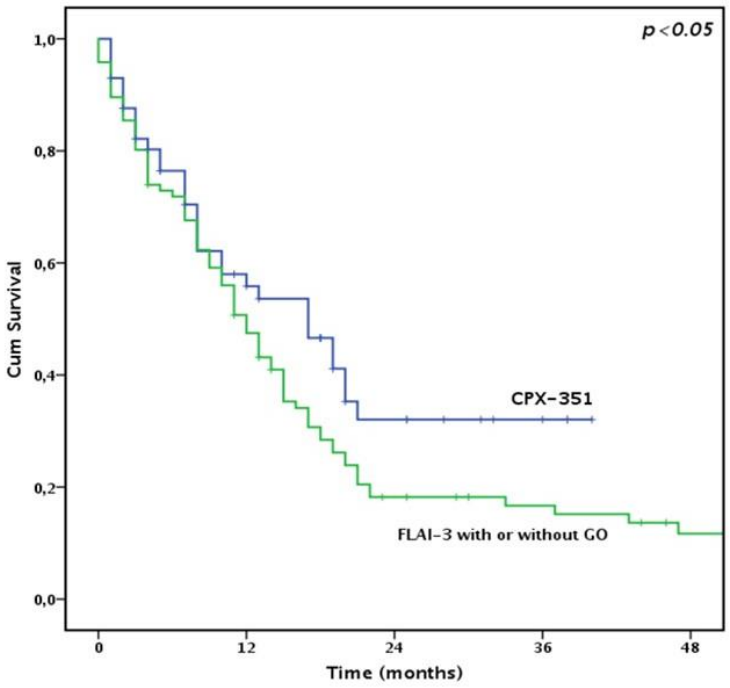

Figure 2: Overall Survival according to treatment arm

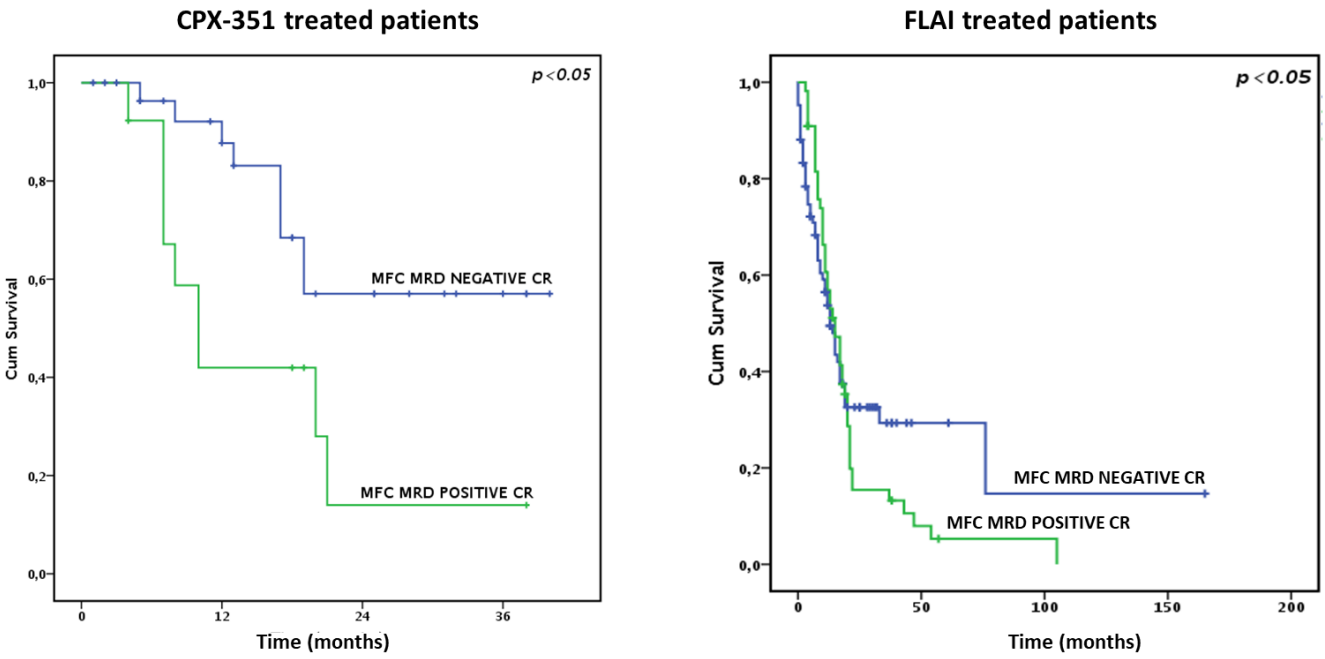

Figure 3: OS according to MRD in patients treated with CPX-351 or FLAI

Role of HSCT

In the CPX-351 cohort, 21/64 (33%) CR patients underwent HSCT, compared to 5/55 (9%) CR patients treated with FLAI (p<0.05). Considering patients achieving CR but not proceeding to HSCT, in the CPX-351 cohort 17/43 (39%) were considered ineligible to transplantation, 15/43 (35%) lost transplant opportunity due to early relapse, 6/43 (14%) refused HSCT, and 5/43 (12%) developed treatment-related toxicity (mainly infective complications), which prevented them from receiving HSCT. In the FLAI cohort, among the 50 CR patients who did not receive HSCT, 12/50 (24%) were considered ineligible, 19/50 (38%) relapsed before HSCT, 2/50 (4%) refused the procedure and 17/50 (34%) experienced treatment related toxicity, hampering the transplant opportunity (Fig. 4).

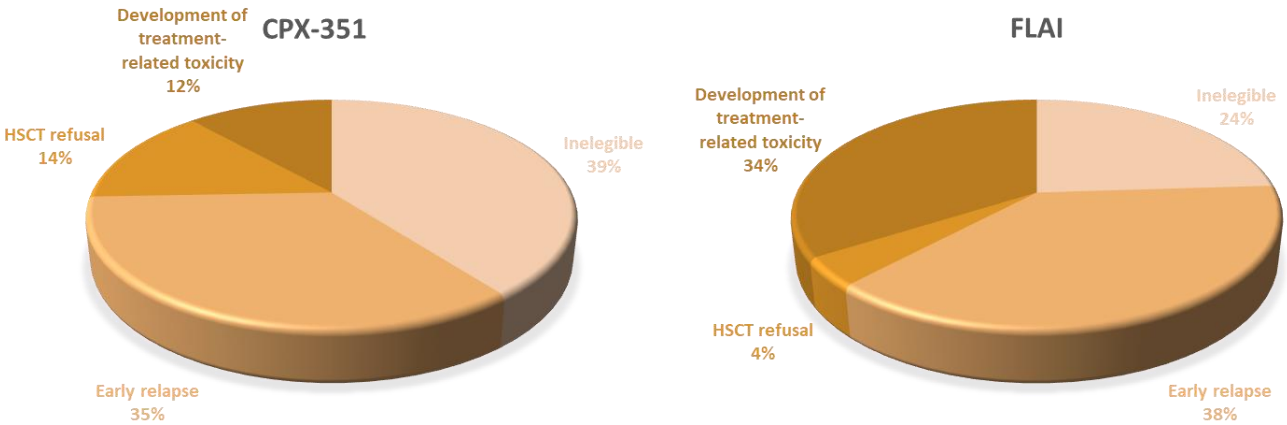

Figure 4: CR patients not proceeding to HSCT

In the whole cohort, relapse incidence was 77/119 CR patients (65%), 39/64 (61%) and 48/55 (87%) in the CPX-351 and FLAI cohorts, respectively. In the CPX-351 arm, 7/64 CR patients (11%) died without relapsing, 2 because of transplant-related mortality (TRM), 2 because of SARS-CoV-2 infection and 3 because of concomitant solid neoplasia. In the FLAI arm, 2/55 CR patients (4%) died without relapsing, 1 because of TRM and 1 because of severe infection.

In a landmark analysis including only patients achieving CR and alive at day 30, consolidation with HSCT was the strongest predictor of survival, both in uni- and multivariate analysis (median OS not reached, $p<0.05$). Specifically, the best results were achieved in the 13 patients who received HSCT within 3 months after achieving CR, with a 3-year OS of 68% (Fig. 5).

In the whole cohort, 3 patients died because of transplant related complications, 2 patients in the CPX arm and 1 patient in the FLAI arm. TRM at 1 year was 18%.

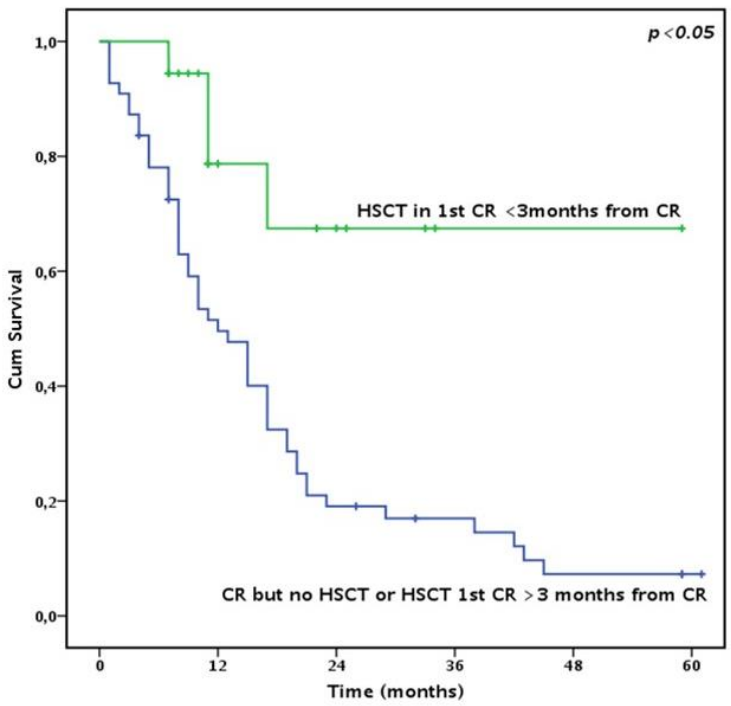

Figure 5: OS according to HSCT timing (landmark analysis)

Discussion

For several decades, the standard chemotherapy induction for AML has been the 3+7 regimen, but outcome has always been unsatisfactory, especially in the context of high-risk disease, where low CR rates and high relapse incidence are often observed.

Based on a randomized comparison with 3+7 chemotherapy, CPX-351 has recently been approved for the treatment of adults diagnosed with t-AML or MRC-AML, defined by the previous WHO 2016 classification, and its efficacy has subsequently been confirmed in multiple real-world experiences.[12-14]

Fludarabine-based regimens have historically shown good antileukemic effects, but are burdened by significant toxicities, which limit their feasibility in elderly patients.

Recently, the UK NCRI AML19 trial provided for the first time a randomized comparison between FLAG-Ida regimen and CPX-351, demonstrating no significant difference in CR rate and OS between the two arms. As expected, the main differences observed in the trial within the two groups were toxicities, being the risk of relapse higher among CPX-351 treated patients and risk of non-relapse death higher in the FLAG-Ida 5 days arm.[15]

Overall, our results confirm, in the real-world setting, the higher efficacy of CPX-351 for s-AML patients, also in comparison to a fludarabine-based regimen, extend the results reported by the UK NCRI AML19 trial, and provide some novel insights.

In our study, all patients were aged more than 60, with a median age of 69 years (range 60-77), compared to the UK NCRI AML19 trial where only about one third of patients were above 60 years. As a consequence, in our FLAI cohort a dose reduction was necessary in all patients, whereas, given the good tolerability, no dose adjustment was required in patients receiving CPX-351. This translated into an acceptable treatment-related mortality in the FLAI arm, but hampered the antileukemic activity of the treatment.

Nevertheless, thirty-day mortality remained lower in the CPX-351 arm, where a significantly lower extra-hematological toxicity was also observed. This finding is consistent with a recent evidence that the liposomal formulation of CPX-351 reduces the damage inflicted to the gut mucosal barrier, reducing the risk of life-threatening infections.[19]

Regarding the efficacy of the two treatments, in our study almost 50% of CPX-351 treated patients achieved MRD negative CR, significantly more than patients receiving FLAI induction (25%).

While response to treatment has historically been evaluated with bone marrow morphological assessment, the prognostic relevance of measurable residual disease (MRD) evaluation has become evident.[17,20] However, most information on MRD assessment derives from younger AML patients receiving conventional intensive chemotherapy, whereas only few data in elderly AML patients receiving more modern induction regimens are available.[2,17,21]

Focusing on CPX-351 treated patients, in the UK NCRI AML19 trial MRD was evaluated only in a minority of patients, providing conflicting results, and only incomplete data is available from RWEs, so that the reasons of the better results achieved by CPX-351 are not completely elucidated yet.[12-15]

In our study MRD assessment was performed in all patients, and results confirmed that MRD retains high prognostic value on OS also in the setting of elderly high-risk AML patients, regardless of treatment received.

From a clinical standpoint, the reduced toxicity and the higher MRD negative CR rate translated in a higher number of elderly AML patients undergoing HSCT in the CPX-arm. CR patients proceeding to HSCT had the best prognosis, as median survival was not reached. Unfortunately, due to the relatively small sample size, we were not able to perform MRD stratification among HSCT patients.

Due to the retrospective nature of the study there are some limitations to be disclosed. Several unmeasured confounding factors may be present, such as comorbidities and other patient-related factors that may have influenced survival outcomes. However, as the cohorts were overall similar from a biological point of view and were both constituted by consecutive patients, the impact from those bias should have been minimized.

Conclusions

In conclusion, our data confirm the efficacy of CPX-351 for the treatment of s-AML and t-AML.

MRD confirms to retain high prognostic value also in this particular setting of patients, regardless of treatment received.

With the limitation of a retrospective study, in the setting of elderly s-AML and t-AML patients, CPX-351 appears to have a greater anti-leukemic activity if compared to an age-adjusted FLAG-Ida regimen, with a higher probability of MRD negativity. The enhanced efficacy of CPX-351, alongside with an improved tolerance, enabled more patients to undergo HSCT, ultimately resulting in a better long-term OS.

In elderly s-AML patients, CPX-351 induction appears to be a reasonable choice, allowing to achieve a good efficacy without the excess of toxicity observed with fludarabine-based induction, and consequently could substitute conventional chemotherapy as a backbone in order to test the addition of new targeted drugs.

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