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Real-world multicenter analysis of CPX-351 efficacy in patients aged less than 60 years with secondary acute myeloid leukemia

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Initial evidence of CPX-351 activity in patients younger than 60 years emerged from a phase I trial [1]; however, subsequent pivotal phase III trial focused on older patients (≥60 years), where CPX-351 demonstrated superiority over conventional '7 + 3' induction, in in secondary acute myeloid leukemia (sAML), including therapy-related AML (t-AML) and AML with myelodysplasia-related changes (AML-MRC), showing higher overall response rates (ORR), improved overall survival (OS) and increased haematopoetic stem cell transplantation (HSCT) rate [2].

Since CPX-351 is approved for all adult sAML, we conducted a multicentric retrospective study in patients <60. We collected data on 113 fit sAML patients (aged 18–59) treated with CPX-351 as first-line therapy across 21 Italian centers from September 2019 to October 2023. Statistical methods are detailed in the supplementary material.

Median age was 54 years; ECOG performance status (PS) was 0 in 66.4%. Thirty percent had t-AML and 70% AML-MRC. Twelve patients (6%) were previously exposed to hypomethylating agents (HMAs) before sAML diagnosis (11 for previous MDS and 1 for t-MDS). High-risk cytogenetics were seen in 47.8%, including complex karyotype (CK) in 66.7% of these. *TP53* mutations (*TP53*mut) were present in 21% of tested patients. Other mutations (*NPM1*, *FLT3*-ITD, *IDH1*/2, *DNMT3A*, *RUNX1*, *ASXL1*) were infrequent. At least one comorbidity was present in 53%. Further baseline features are summarized in Supplementary materials and Tables S1–S5.

All patients received CPX-351 induction (days 1, 3, 5), except one who received only two doses due to pneumonia onset. Disease was re-evaluated after a median of 38 days (range 21–96). ORR was 64.6% (73/113), including 62 complete remissions (CR, 54.9%), 10 CR with incomplete hematologic recovery (CRi, 8.8%), and 1 morphological leukemia-free state (MLFS, 0.9%). Thirteen patients (11.5%) achieved partial remission (PR) and 21 (18.6%) were refractory. In responders, median severe neutropenia lasted 26 days and thrombocytopenia 30 days. Reinduction was given to 19 patients (16.8%): 11 in PR (8 achieved CR, 2 failed), 6 already in CR after first induction, performed cause historical 'double induction strategy' (1 of them relapsed thereafter), and 2 refractory who remained non-responders. At the end of induction/reinduction, ORR was 70.7% (80/113), counting the patient who lost response during reinduction as resistant (Supplementary Table S1). Response correlated with ECOG PS (higher in PS 0: 73.8% vs 48.5% in PS 1-2, $p = 0.01$). Conversely, CK related with inferior ORR (55.6% vs 78.9%, $p = 0.01$). After treatment evaluation, 1 patient was lost to follow-up.

Early death (ED) occurred in 9 patients (8%): 3 (2.7%) before day 30 and 6 (5.3%) between days 30 and 60 (supplementary Table S6).

Sixty-seven patients (84.4% of responders) underwent consolidation with CPX-351, and 26 of them (38.8%) received a second cycle.

Fifty patients (62.5% of responders) underwent HSCT in first remission (supplementary Table S7). Only 8 of 20 patients with CK (40%) underwent HSCT in first remission, compared to 41 of 57 without CK (71.9%, $p = 0.01$). Similarly, patients with *TP53*mut were less frequently transplanted (2/9, 22.2%) than wild-type cases (26/37, 70.3%, $p = 0.008$). Among those with available molecular data, none of the 4 patients with *NPM1* mutations underwent HSCT, versus 48 of 70 wild-type patients (68.6%, $p = 0.005$). Reasons for not undergoing HSCT in first remission are detailed in the Supplementary File.

After a median follow-up of 29.1 months (95% confidence intervals [CI], 24.5–33.6), median OS (mOS) was 20.2 months (95% CI, 11.6–28.8), with 58 patients alive, 44 in CR.

Median relapse-free survival (mRFS), evaluated in 81 patients, including one patient who achieved CR after consolidation following a PR at the end of induction, was 16.1 months (95% CI, 4.5–27.7) (Supplementary Table S8). CK was associated with shorter mRFS than patients without CK (4.4 months vs not reached; $p = 0.005$, Fig. S2A). *TP53*mut conferred the poorest prognosis, with a mRFS of 2.9 months versus not reached in wild-type patients ($p < 0.01$, Fig. S2B). Patients transplanted in first CR had significantly longer mRFS than those who did not (not reached vs 3 months; $p < 0.01$, Fig. S2C). In univariable analysis, CK and *TP53*mut were adverse predictors of RFS, while HSCT in first CR was strongly protective. In multivariable analysis, *TP53* (HR 3.1, 95% CI 1.1–9.0; $p = 0.038$) and HSCT in first CR (HR 0.12, 95% CI 0.06–0.3; $p < 0.001$) retained independent significance, whereas CK showed only a nonsignificant trend (HR 1.9, 95% CI 0.9–3.7; $p = 0.07$). (Supplementary Table S9).

No differences in event-free survival (EFS) were observed according to clinical and laboratory parameters (Supplementary Table S10).

HSCT in first CR was the only independent predictor of OS (HR 0.2, 95% CI 0.07–0.6; $p = 0.002$; Supplementary Table S11), In multivariable analysis limited to responders, HSCT in first remission significantly improved OS (HR 0.2, 95% CI 0.09–0.4, $p < 0.001$), whereas HSCT in second remission did not (HR 1.6, 95% CI 0.4–3.6, $p = 0.7$).

CK and *TP53*mut gave the shortest mOS (9.6 and 10.7 months, respectively) in those without ($p < 0.05$; Fig. 1A, B). Treatment response had a major impact on survival: mOS was not reached for responders vs 7 months for non-responders ($p < 0.001$; Fig. 1C). Other factors did not reach statistical significance (Supplementary Table S12).

Among responders (Fig. 2A), OS was significantly longer in patients transplanted in first remission (median not reached). Those transplanted in second remission also benefited, with mOS of 22 months versus 9 months in non-transplanted responders ($p = 0.04$). In the refractory setting (Fig. 2B), patients undergoing

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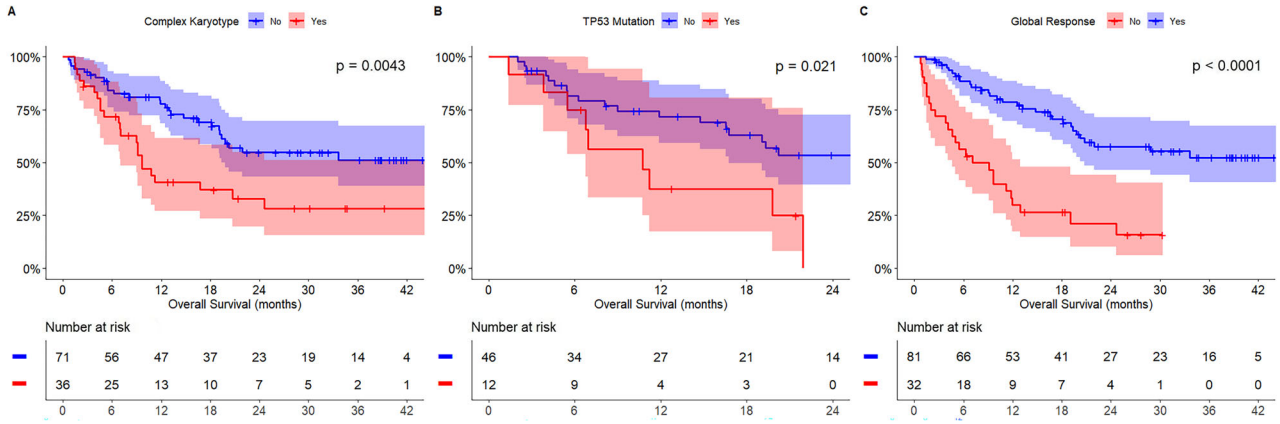

Fig. 1 Overall survival by cytogenetics, TP53 status and CPX351 response. Kaplan-Meyer plots showing the overall survival in months for: **A** patients harboring complex karyotype (red line) versus patients without (blue line); **B** patients harboring *TP53* mutations (red line) versus w.t. *TP53* (blue line) **C** patients responding to CPX351 therapy (blue line) vs refractory (red line).

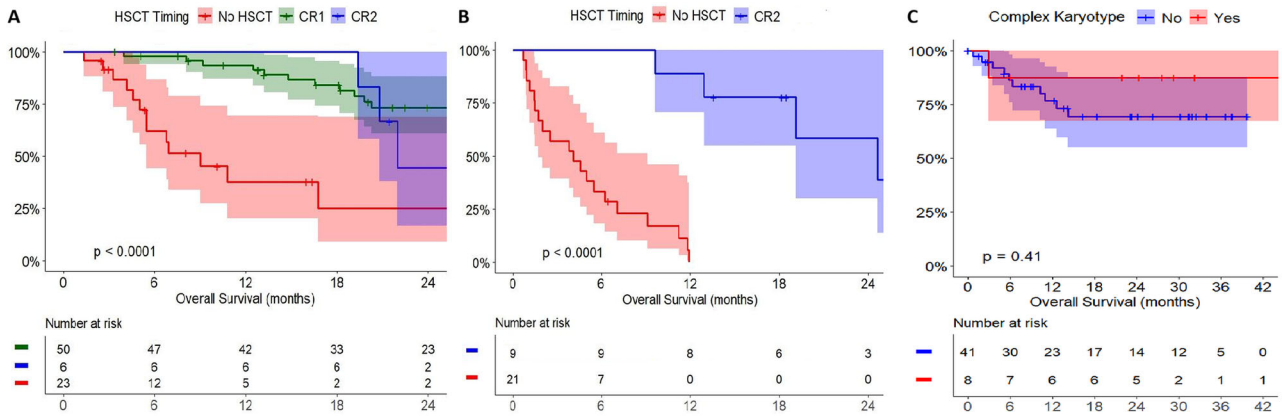

Fig. 2 Overall survival by transplant timing and cytogenetics. Kaplan-Meyer plots showing the overall survival in months for: **A** HSCT timing in patients responding to CPX351 therapy: HSCT at 1st complete remission (CR1, green line), HSCT at second CR after salvage therapy (blue line) and patients not undergoing HSCT (red line); **B** HSCT timing in patients refractory to CPX351: HSCT at second CR after salvage therapy (blue line), patients not undergoing HSCT (red line). **C** landmark OS analysis after HSCT at CR1 considering the occurrence at diagnosis of complex karyotype (red line) vs no complex (blue line). 1 patient not included cause failed cytogenetics. OS overall survival, CR1 complete remission at first line.

HSCT in second remission had significantly longer mOS compared to non-transplanted patients (25 months vs 4.1 months; $p < 0.01$). In contrast, those transplanted with active disease had poor outcomes, with mOS of 9.6 months.In the landmark analysis, patients transplanted in first CR had not reached mOS, while no significant OS differences were observed by CK presence (Fig. 2C). Adverse events were frequent but manageable, mainly febrile neutropenia (Supplementary Tables S13–S16).

In this study we validated and expanded CPX-351 effectiveness in a cohort of younger patients. not represented in the phase III trial [2]. ORR (70.7%) was markedly higher than the 48% reported in that trial, consistent with other real-life series from Italy [3] and France [4] (≈70%), while German [5] and UK [6] studies reported lower rates of 47–53%. The CREST-UK study specifically compared younger versus older patients, showing, in line with our findings, higher CR rates in younger patients (66% vs 44%) and a doubled OS [6]. However, other studies, reported modest outcomes, suggesting heterogeneity in patient selection and prior treatments [7, 8]. ED in our series (2.7% at 30 days, 5.3% at 60 days) was lower than in other real-life studies (9–17%) [9], possibly reflecting differences in baseline characteristics and supportive strategies. The Italian infection-focused study, conducted largely in older patients, reported a 30-day mortality of 14%, further highlighting the impact of age [10].

Regarding genetics, both CK and *TP53*mut were adverse prognostic factors for remission and RFS. Notably, the negative prognostic impact of *TP53mut* was lost in multivariate OS analysis, suggesting that HSCT may potentially mitigate its effect. Similar findings were reported by other groups, reinforcing the concept that achieving remission and proceeding to transplant remain the strongest determinants of outcome [4, 11]. In our cohort, RFS in responders who did not undergo HSCT was not significantly different from time-to-transplant in those who did; however, early progression was more frequent in patients with CK or *TP53*mut, potentially preventing them from undergoing transplant. This highlights the importance of optimizing timing and access to HSCT, especially in high-risk subgroups. However, *TP53* status was assessed in only a subset of patients (58/113, 58%), which restricts the robustness of these findings.

The UK NCRI AML19 trial further compared CPX-351 with FLAG-Ida in younger adults with high-risk AML/MDS, showing no OS difference but improved RFS with CPX-351, particularly in patients with MDS-related gene mutations [12]. On the other hand, although widely used in unfit patients, current evidence does not show survival advantage of HMA combined with venetoclax (HMA-VEN) over CPX-351 in this population [13]. Although HMA-VEN is active and feasible in outpatient setting, data indicate similar OS but higher HSCT rates with CPX-351, supporting its role

in achieving deeper cytoreduction and enabling curative strategies. In molecularly defined sAML, no OS advantage for CPX-351 over 7 + 3 has been found, although HMA-VEN likely benefited patients with splicing mutations, but data on patients <60 are limited [14]. Recent studies on patients ≥60 further highlighted the possible role of VEN-HMA as bridge to transplant. For example, the VEN-DEC GITMO phase II trial in fit patients demonstrated a 69% CR rate, with 83% of responders proceeding to HSCT [15]. Although interesting, these results come from single-arm study on older patients not designed for OS. A prospective randomized trial comparing CPX-351 and HMA-VEN is needed to draw stronger conclusions.

Our study confirms the efficacy and safety of CPX-351 in sAML patients <60, with high remission rates and favorable survival, particularly when followed by HSCT in first remission.

Early transplant referral is essential, while *TP53*mut and CK remain poor-risk factors. Incorporating minimal residual disease (MRD) monitoring may further refine response assessment. Overall, CPX-351 effectively bridges younger sAML patients to HSCT providing durable survival in real-world practice.

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DATA AVAILABILITY

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

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AUTHOR CONTRIBUTIONS

C.Vetro and B.Garibaldi collected aggregated clinical data, contributed to methodology design, and drafted the manuscript. F.Guolo and A.Duminuco supervised the study and contributed to data analysis. C.Vetro and F.Garibaldi coordinated the ethical approval process and managed communication across participating centers. C.Vetro, F.Grimaldi and F.Garibaldi conducted statistical analyses. F.Grimaldi and F.E.Palumbo coordinated submission processes. F.E.Palumbo, P.Chiusolo, C.Filì, C.Riva, V.Cardinali, M.Franciosa, F.Pilo, R.Palmieri, L.Esposito, D.Menotti, S.Perrone, A.Mulè, C.Alati, E.Vigna, M.Dargenio, G.De Luca, A.Sperotto, I.Tanasi, C.Papayannidis, M.Molica, M.Memoli, A. Isidori contributed to patient enrollment and data acquisition. CP, P.Minetto, G.Battipaglia, P.Salutari, L.Brunetti, E.Todisco, I.Lotesoriere, G.A.M.Palumbo, M.Annunziata, M.Gottardi, M.Gentile, M.P.Martelli, D.Capelli, M.Martino, M.Rossi, F.Ferrara, A.Venditti, C.Romani, S.Galimberti, A.Candoni, L.Fianchi, L.Pagano, G.Marconi, R.M.Lemoli, F.Di Raimondo, F. Pane, A.Billio provided critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript and agree to be accountable for the accuracy and integrity of the work.

COMPETING INTERESTS

D.Capelli: Honoraria: Jazz Pharmaceuticals; C.Papayannidis: Honoraria: Abbvie, Astellas, Servier, Menarini/Stemline, BMS, Pfizer, Amgen, Janssen, Incyte, Novartis, Advisory Board: Pfizer, Astellas, Janssen, GSK, Blueprint, Jazz Pharmaceuticals, Abbvie, Novartis, Delbert Laboratoires; A.Duminuco: Honoraria: Novartis, GSK, Incyte. Support for attending meetings and/or travel: AbbVie, J&J, AOP Health, Recordati Rare Diseases, BeiOne. Advisory board: Incyte, GSK; M.Rossi: Expert testimony: Abbvie; Astrazeneca. Support for attending meetings and/or travel: Abbvie; Johnson and Johnson; Amgen; Sobi. Advisory board: Sanofi; Amgen; L.Pagano Grants: Gilead, JAZZ, Menarini-Stemline, Beigene, Blueprint, Pfizer. Honoraria: Gilead, JAZZ, Menarini-Stemline, Beigene, Blueprint, Pfizer. Advisory Board: Pulmocide, Cidara; A.Venditti: Grants or contracts from any entity: Jazz Pharmaceuticals; AstraZeneca; Abbvie. Consulting fees: Jazz Pharmaceuticals; Abbvie; Servier; Istituto Gentili; BMS; Pfizer; Astellas; Otsuka; Janssen; Daiichi-Sankyo. Honoraria: Servier; Jazz Pharmaceuticals; Abbvie; Otsuka; Pfizer; Astellas; Astex; Janssen; Support for attending meetings: Servier; Janssen; Abbvie; Daiichi-Snkyo; Pfizer; Janssen; A.Candoni: honoraria: Astellas, Servier, JAZZ, Incyte, Abbvie; Otsuka; Support for attending meetings and/or travel: Abbvie, JAZZ, Gilead; L.Brunetti: Honoraria: Jazz Healthcare, Abbvie, Incite, Research support: Karyopharm Therapeutics Inc.; R.M.Lemoli: Travel grant and Speaker's bureau for Jazz Pharma; F.Guolo: Consultancy: Astellas; JAZZ; P.Minetto: Advisory board: Menarini-Stemline; Abbvie; C.Vetro: Honoraria: JAZZ; Astellas; Advisory Board: JAZZ; Abbvie; BMS; Astellas; Incyte; Amgen; G.Marconi: Honoraria, consulting or advisor from AbbVie Inc, Astellas Pharma, AstraZeneca, Enable life science, ImmunoGen, Janssen, Menarini Group, Pfizer, Ryvu Therapeutics, SERVIER, Syros Pharmaceuticals, Takeda; Speakers' bureau: AbbVie Inc, Astellas Pharma, AstraZeneca, ImmunoGen, Janssen, Menarini Group, Pfizer, Ryvu Therapeutics, Syros Pharmaceuticals, Takeda; Research funding from AbbVie Inc, Pfizer, Jazz Pharmaceuticals, AstraZeneca, MEI Pharma, and Daiichi Sankyo.

ETHICS APPROVAL

The study was reviewed and approved by the Institutional review board Catania 1. Mail: celct1@policlinico.unict.it. File number 52/2021/PO. Date of approval 22.02.2021.

CONSENT FOR PUBLICATION

All procedures were performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects involved in the study.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41408-025-01394-7.

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