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To cite this article: Christoph Abé, Jaana Keto, Mathias Lilja, Mie Konradsen, Johan Mesterton, Martin Höglund, Vladimir Lazarevic, Sören Lehmann & Gunnar Juliusson (2024) Cytarabine dose intensification improves survival in older patients with secondary/high-risk acute myeloid leukemia in matched real-world versus clinical trial data, *Leukemia & Lymphoma*, 65:10, 1493-1501, DOI: [10.1080/10428194.2024.2363430](https://doi.org/10.1080/10428194.2024.2363430)

To link to this article: <https://doi.org/10.1080/10428194.2024.2363430>



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Published online: 11 Jun 2024.



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Cytarabine dose intensification improves survival in older patients with secondary/high-risk acute myeloid leukemia in matched real-world versus clinical trial data

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ABSTRACT

Since 1980's, the established/standard treatment of acute myeloid leukemia (AML) is cytarabine infusion with anthracycline (7+3 regimen). We compared the 7+3 regimen in older secondary/high-risk AML patients from a clinical trial with a matched population from the Swedish AML Registry treated with an increased cytarabine dose in induction and consolidation as recommended in the Swedish National Guidelines since 2005. After successful propensity score matching, 104 patients per group were included. The primary outcome was overall survival (OS), and standard dosed patients had a median OS of 6.4 versus 10.7 months with increased dose intensity (hazard ratio: 0.69, $p=0.012$), with 5-year OS of 8.7% and 18.1%, and remission rates of 36% and 60%, respectively ($p<0.001$). Median OS after allogeneic hematopoietic cell transplantation (in 27.9% per group) was 10.4 and 20.7 months, respectively. We conclude that the more intensive cytarabine schedule seems to provide improved outcomes in the investigated AML patient group.

ARTICLE HISTORY

Received 3 April 2024
Revised 28 May 2024
Accepted 29 May 2024

KEYWORDS

Conventional 7+3 regimen; hematopoietic cell transplantation; external control arm; real-world data; overall survival; standard of care


Introduction

Acute myeloid leukemia (AML) is characterized by aberrant proliferation of neoplastic clonal myeloid stem and progenitor cells [1]. The median age of patients at diagnosis is 72 years [2,3]. The majority of cases arise *de novo*, however, a subset of patients develops secondary AML (sAML) from a pre existing myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasia or following prior chemotherapy and/or radiation therapy for another cancer [4–6]. Secondary AML accounts for approximately one quarter of all AMLs, has a worse prognosis than *de novo* AML, occurs more frequently with advancing age, and has higher rates of adverse risk/complex cytogenetics, adverse mutations, and multidrug resistance phenotype associated with poor outcomes [5–10].

Standard treatment for AML since the 1980's consisted of cytarabine [11] and an anthracycline, most commonly daunorubicin [12]. The current cytarabine schedule with

seven days of continuous infusion of 100mg/m²/day was derived from a randomized Cancer and Leukemia Group B study reported in 1981 [13], where, however, the daunorubicin dose was 45mg/m² bolus infusion daily for three days. More recently, a daunorubicin dose of 90mg/m² was found to be superior in patients up to 60 years [14], and subsequently a study conducted in United Kingdom found similar outcomes with a dose of 60 and 90mg/m² [15]. Thus, the 2017 and 2022 European LeukemiaNet (ELN) guidelines recommend a regimen consisting of seven days of continuous infusion cytarabine (100–200mg/m²) and three days of an anthracycline, i.e. daunorubicin at least 60mg/m², idarubicin 12mg/m², or mitoxantrone 12mg/m², as induction therapy for all ages [1]. Furthermore, as a crucial step in the post-remission management of AML, many patients with AML who achieve remission receive allogeneic hematopoietic cell transplantation (HCT) as an effective consolidation strategy to prevent disease relapse [1].

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 Supplemental data for this article can be accessed online at <https://doi.org/10.1080/10428194.2024.2363430>.

This article has been corrected with minor changes. These changes do not impact the academic content of the article.

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There has been no study focusing on optimal dosing of standard 7+3 in secondary and high-risk AML. However, adual-drug liposomal encapsulation of daunorubicin and cytarabine powder at a fixed 1:5 molar ratio (CPX-351) was found to be superior to standard 7+3 in a prospective randomized phase III study in older patients conducted in North America (in the following referred to as the 301-trial) [16,17]. The liposomal preparation [18–21] was thus approved by the United States Food and Drug Administration and the European Medicines Agency for the treatment of adults with newly diagnosed high-risk AML, defined as therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC) [16].

The 301-trial findings have been updated with a recently published study with a 5-year follow-up [17]. A recent study compared CPX-351 and the FLAG-Ida regimen, which comprised a higher dose of cytarabine ($2\text{g}/\text{m}^2$), in younger adults with adverse karyotype AML and high-risk MDS and showed a significantly longer relapse-free survival with CPX-351 (22.1 versus 8.4 months; 95% CI: 0.36–0.95), but no statistical difference in OS (13.3 versus 11.4 months), indicating the feasibility of higher dose regimens. Notably, there was a significant improvement in OS with CPX-351 (median = 38.4 months) in a sub-group of patients with MDS-related gene mutations compared to FLAG-Ida (16.3 months) with HR of 0.42 ($p=0.05$; 95% CI: 0.21–0.85), however, the overall response rate was similar ($p=0.5$; 70% versus 62%) with no differences in relapse (3-year CIR, 19% versus 20%) [22].

Since 2005, Swedish National Guidelines recommend higher cytarabine dosages for patients at all ages, i.e. the Swedish Standard of Care (SoC), based on an Australian study [23], pharmacokinetic considerations [24], regional experiences, and known outcomes in Sweden through the Swedish AML Registry [3,25].

The aim of the present retrospective study was to assess if higher cytarabine dosing in induction may provide a benefit in older patients with secondary and high-risk AML compared with the standard 7+3 regimen. This was done using an external control arm constructed by propensity score matching of patients from the 301-trial population and patients from the population-based Swedish AML Registry. The primary endpoint was OS, and secondary endpoints were early mortality, response rate and duration, and OS after HCT.

Methods

Study design and population

This was an observational cohort study utilizing previous phase III clinical trial data, i.e. the 301-trial, on

patients with secondary or high-risk AML aged 60–75 years at diagnosis conducted across 39 centers in the United States and Canada [17], and data from the national Swedish AML Registry, selected using the similar inclusion criteria as the clinical trial study. See [Supplementary methods](#) for more details.

The 301-trial protocol (ClinicalTrials.gov ID: NCT01696084) was approved by the independent ethics committee or institutional review board at each involved study site, and use of Swedish AML Registry data for the present study received approval from the ethics review board in Sweden (reference number 2021-00947). All patients who participated in the 301-trial have provided written informed consent. Patient consent is not required in any Nordic country for using register-based data.

The study population consisted of two cohorts –the Conventional 7+3 cohort and the Swedish SoC cohort:

Conventional 7+3 cohort

Patients who received conventional cytarabine and daunorubicin (7+3) treatment regimen as part of the 301-trial ($n=156$) were included. The induction course contained cytarabine $100\text{mg}/\text{m}^2$ by 7-day continuous infusion and daunorubicin bolus injection $60\text{mg}/\text{m}^2$ on Days 1 to 3. The second induction course and post-remission consolidation courses consisted of cytarabine at $100\text{mg}/\text{m}^2$ by 5-day continuous infusion with daunorubicin at $60\text{mg}/\text{m}^2$ on Days 1 and 2. HCT was performed at the discretion of the treating physician. Only patients with available primary endpoint data and available baseline variables required for matching were included in the study ($n=135$). The enrollment period in the 301-trial was from December 2012 to October 2014, with a follow-up of five years post randomization, starting 30 days after completion of the last induction or consolidation course. Information on complete remission (CR) and/or CR with incomplete neutrophil or platelet recovery (CRi) (hereafter referred to as 'CR/CRi') and relapse was available until three years after randomization [16].

Swedish SoC cohort

Patients who received the Swedish SoC, met the inclusion criteria for the 301-trial, and were diagnosed between 2007 and 2020 were included ($n=695$). The Swedish SoC consists of cytarabine at $1\text{g}/\text{m}^2$ in two-hour infusion twice daily for five days, with daunorubicin at $60\text{mg}/\text{m}^2$ in eight-hour infusion for three days, with an identical course as consolidation, and subsequent HCT if feasible. See [Supplementary](#)

methods for specific inclusion and exclusion criteria for both cohorts and Figure 1 for a study design scheme. Definitions of index date and time periods are summarized in Supplementary Table S1.

Propensity score (PS) matching

The patient cohorts were matched on specific and clinically relevant baseline characteristics to ensure comparable groups, using PS matching with a 1:1 matching ratio using a nearest-neighbor algorithm without replacement and a caliper width of 0.2 of the standard deviation (SD) of the propensity score logit. Covariance balance was assessed by calculating the standardized mean difference (SMD) with a SMD <0.2 indicating a satisfactory match [26–28]. The following variables were used as matching variables: age, sex, Eastern Cooperative Oncology Group/World Health Organization Performance Status (ECOG/WHO-PS), AML subtype, creatinine levels, white blood

cell count, and cytogenetic risk according to ELN 2017. To maximize sample size, the following were omitted as matching variables: bone marrow blast counts (correlated with white blood cell count), FMS-like tyrosine kinase 3 internal tandem duplication mutation status (correlated with cytogenetic risk), and prior hypomethylating agent (HMA) exposure (not available for the Swedish SoC cohort). Note that sensitivity analyses have been conducted to address the latter (see below).

Study outcomes

To assess and compare relative effectiveness, the following outcomes were compared between the Conventional 7+3 cohort and the Swedish SoC cohort:

The primary outcome, OS, was defined as the risk of all-cause mortality which was estimated based on the time from treatment start (index date) to the date of death or censoring. Patients were censored at the date of last available data, which was October 2019 for the Conventional 7+3 cohort and December 2021 for the Swedish SoC cohort. Patients from the Conventional 7+3 cohort were also censored if they were lost to follow-up. This was not needed for the Swedish SoC cohort since data regarding cause of death and date of death have complete population coverage in Sweden.

Secondary outcomes were OS within 30 and 60 days from treatment start (early mortality), and OS after HCT in patients who underwent HCT (with date of HCT as index date), using the same censoring rules as defined for the primary analysis.

Given limitations of recording practices and data availability in the Swedish AML Registry, the following outcomes were compared in exploratory analyses: incidence of CR/CRi, incidence of relapse following CR/CRi, time to CR/CRi (time from index date to date of achieved CR/CRi within three years of treatment start), and remission duration (time from CR/CRi to relapse within three years from treatment start). In cases where formally registered relapse data was missing, death after CR/CRi was considered a relapse, assuming death was due to relapse.

Statistical analyses

All analyses were conducted in R (version 4.2.2) [29]. The primary and secondary outcomes were assessed using the nonparametric Kaplan-Meier method for estimating survival probabilities on the PS matched cohorts. A semi-parametric Cox proportional hazards [30] model was used to compare the difference in survival between cohorts (reference cohort: Conventional

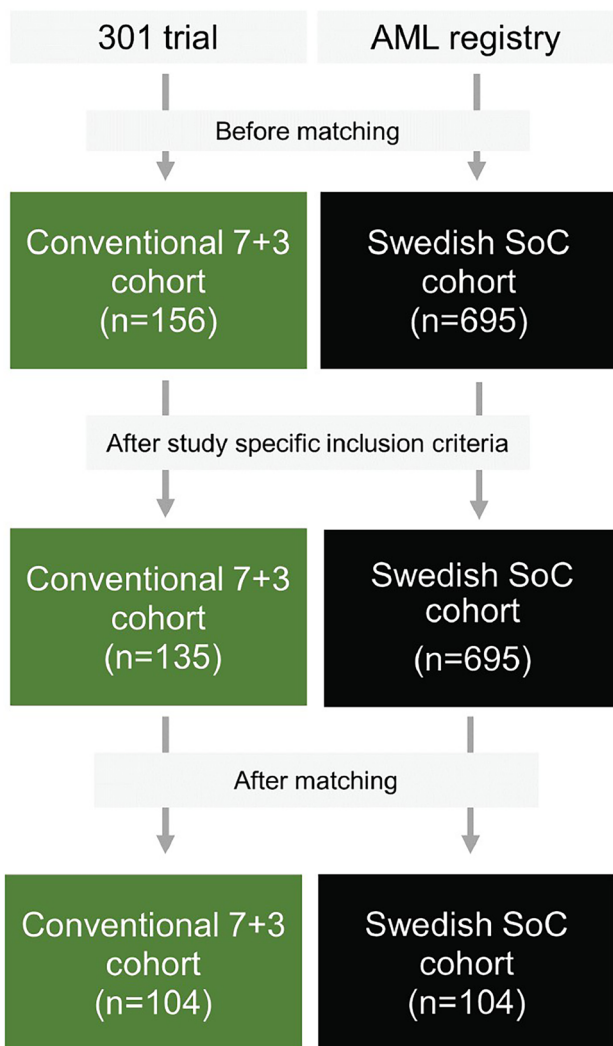


Figure 1. Study design scheme.

7+3). Kaplan-Meier survival probabilities and Cox proportional hazards models were estimated using the survival package in R [31]. Univariate models were estimated for the primary and secondary objectives, and hazard ratios (HRs) with 95% confidence intervals (CIs), and *p*-value for the Wald-tests were presented.

Depending on the nature of the outcome measure, exploratory outcomes were compared using t-tests, Wald-tests, and Chi-squared tests (Supplementary methods). Continuous variables were described by either mean and standard deviation (SD) or median, and 25th, and 75th percentiles. Categorical variables were described by the proportion and frequency. All statistical tests were two-sided and considered significant at the 5% significance level.

Sensitivity analyses

Several sensitivity analyses were conducted to both investigate potential limitations of the study design and to improve interpretability of the results. Sensitivity analyses focused on the potential effects of the matching method, potential remaining variable imbalance, differences of inclusion periods between cohorts, HCT, prior treatment with HMA within the Conventional 7+3 cohort, and AML subtypes on the outcomes in the primary objective. Methodological details for these sensitivity analyses are described in the Supplementary methods.

Results

Patient population

Before matching, there were 135 eligible patients in the Conventional 7+3 cohort (males: 61.5%; age: 67.8 [SD: 4.2] years) and 695 eligible patients in the Swedish SoC cohort (males: 56.3%; age: 67.9 [4.4] years) (Supplementary Table S2). Matching resulted in 104 patients in each cohort with satisfactory matching quality indicated by absolute SMDs between 0.01 and 0.18 for all matching variables (Figure 1 and Supplementary Figure S1).

After matching, the Conventional 7+3 cohort comprised 58.7% (*n*=61) males and had a mean age of 68.0years (SD: 4.3). ECOG/WHO-PS ranged from 0–2, with the majority (55.8%; *n*=58) of patients having a score of 1. Most patients in the Conventional 7+3 cohort exhibited adverse/poor or intermediate genetic risk. AML subtyping revealed a diverse distribution, encompassing various subtypes such as *de novo* AML (28.9%), chronic myelomonocytic leukemia (CMMoL) transformed to AML (1.0%), MDS transformed to AML (51.0%) and tAML (19.2%). Similarly, in the Swedish SoC

Cohort, 50.0% (*n*=52) were male with a mean age of 68.0years (SD: 4.4). The AML subtype and genetic risk distributions were similar to those in the Conventional 7+3 cohort.

Patient characteristics after matching are presented in Table 1. Even though matching was deemed of sufficient quality, sensitivity tests were conducted adjusting for matching variables with SMD >0.1 (Supplementary results).

Study outcomes

Primary outcome

Kaplan-Meier analyses on OS (Figure 2) showed a median survival time of 6.37months in the Conventional 7+3 cohort and 10.70 months in the Swedish SoC cohort. Comparative Cox regression showed an HR of 0.69 (*P*=0.012, CI: 0.51–0.92). The 3-year survival probability, based on the Kaplan-Meier survival function, in the Conventional 7+3 cohort was 8.7%, while it was 18.1% in the Swedish SoC cohort.

Table 1. Patient characteristics after matching.

Patient characteristics at baseline (index date)	Swedish SoC cohort	Conventional 7+3 cohort	Absolute SMD
Number of patients; <i>n</i>	104	104	–
Males; <i>n</i> (%)	52 (50.0)	61 (58.7)	0.18
Age, years; mean (SD)	68.0 (4.4)	68.0 (4.3)	0.00
ECOG/WHO-PS; <i>n</i> (%)			
0*	29 (27.9)	33 (31.7)	0.08
1**	59 (56.7)	58 (55.8)	0.02
2***	16 (15.4)	13 (12.5)	0.08
Creatinine, µmol/l; median (25 th –75 th percentiles)	72.5 (63.0–86.5)	79.6 (67.6–88.4)	0.18
WBC, ≥20 10 ⁹ /l; <i>n</i> (%)	14 (13.5)	14 (13.5)	0.00
BM blast, %; median (25 th –75 th percentiles)	37.0 (24.0–56.5)	37.0 (24.0–60.0)	–
Genetic risk; <i>n</i> (%)			
favorable/better	1 (1.0)	3 (2.9)	0.12
intermediate	40 (38.5)	41 (39.4)	0.02
adverse/poor	63 (60.6)	60 (57.7)	0.06
AML subtype; <i>n</i> (%)			
<i>De novo</i> AML	31 (29.8)	30 (28.9)	0.02
CMMoL AML	3 (2.9)	1 (1.0)	0.09
MDS AML	49 (47.1)	53 (51.0)	0.08
t-AML	21 (20.2)	20 (19.2)	0.03
FLT3-ITD; <i>n</i> (%)	10 (9.6)	8 (7.7)	–

Note: See Supplementary results for patient characteristics before matching.

*0: Fully active, able to carry on all pre-disease performance without restriction.

**1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).

***2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

AML, acute myeloid leukemia; BM, bone marrow; CMMoL, chronic myelomonocytic leukemia; ECOG/WHO-PS, Eastern Cooperative Oncology Group/World Health Organization Performance Status; FLT3-ITD, FMS-like tyrosine kinase 3 internal tandem duplication mutation; MDS, myelodysplastic syndrome; PB, peripheral blood; SD, standard deviation; SMD, standardized mean difference; t-AML: therapy related AML; WBC, white blood cell.

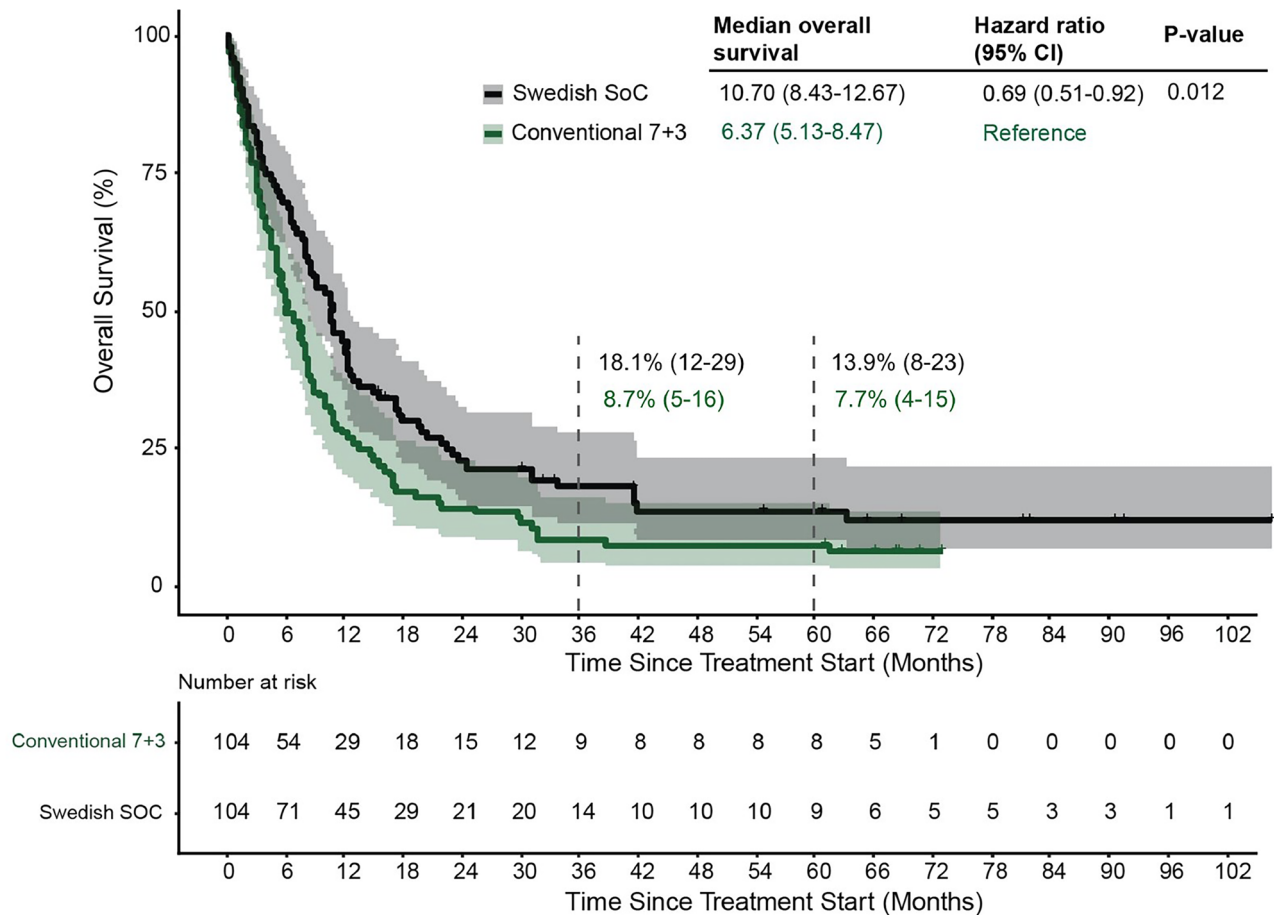


Figure 2. Overall survival in the conventional 7+3 (green) and the Swedish SoC cohort (black). Corresponding survival probabilities at 3 and 5 years are indicated.

Similarly, the 5-year survival probability was 7.7% in the Conventional 7+3 cohort and 13.9% in the Swedish SoC cohort (Figure 2).

Secondary outcomes

For early mortality within 30 and 60 days, Cox regression revealed an HR of 0.89 (CI: 0.35–2.32) and 0.73 (CI: 0.36–1.45), respectively. Neither analysis indicated a significant difference between the two cohorts ($p=0.819$ and $p=0.362$).

A total of 29 (27.9%) patients underwent HCT in each cohort (Supplementary Table S3). Kaplan-Meier analyses on OS landmarked from HCT date yielded a median survival time of 10.37 months (CI: 6.67–24.60) in the Conventional 7+3 cohort and 20.73 months (CI: 14.37; median survival not reached for upper CI) in the Swedish SoC cohort. Cox regression revealed an HR of 0.60 (CI: 0.31–1.14), but no statistically significant difference between the cohorts ($p=0.120$). The 3-year and 5-year post-transplant survival rates in the Conventional 7+3 cohort were equivalent (24.1%), while the survival rates were 45.8% and 40.7% in the

Swedish SoC cohort at 3 years and 5 years, respectively (Figure 3).

Exploratory outcomes

Exploratory analyses revealed that more patients in the Swedish SoC cohort, compared with the Conventional 7+3 Cohort, achieved CR/CRi (60 versus 36; $p<0.001$). There were no differences with respect to incidence of patients who relapsed from CR/CRi, time to CR/CRi, or remission duration (Supplementary results).

Sensitivity analyses

See Supplementary results for detailed statistical results for all sensitivity analyses. In brief, except for HCT-related factors, where analyses yielded ambiguous results (discussed below), sensitivity analyses did not indicate that the results in the primary objective were influenced by the matching method, potential remaining variable imbalances, differences in study period, or prior treatment with HMA within the Conventional 7+3 cohort, nor seemed the results to be driven by any particular AML sub-type investigated.

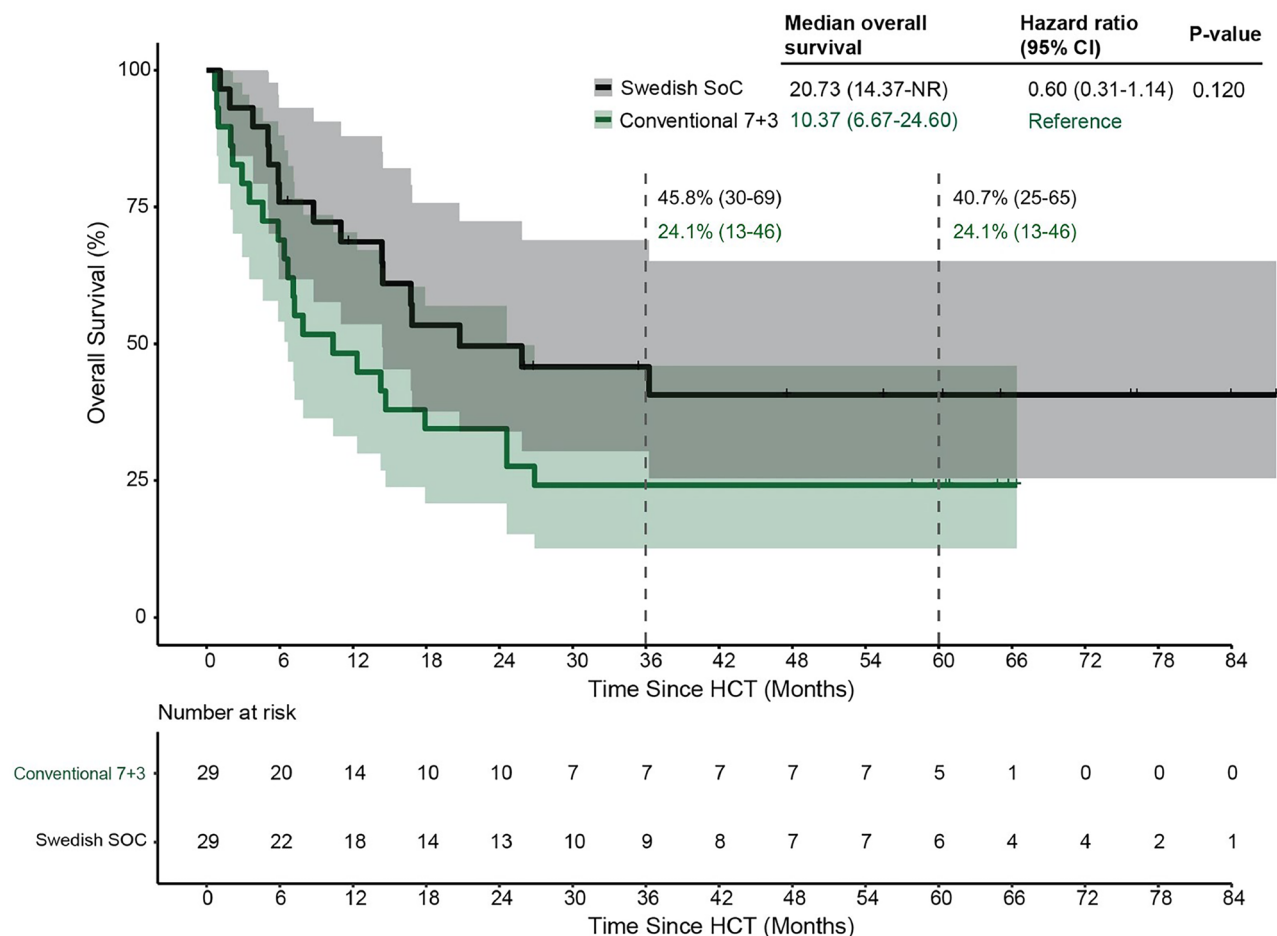


Figure 3. Overall survival in the conventional 7+3 (green) and the Swedish SoC cohort (black) who underwent HCT, using HCT date as index date. Corresponding survival probabilities at 3 and 5 years are indicated.

Discussion

Secondary and high-risk AML in older patients is common and has poor prognosis, and few studies have focused on this unmet need [5,6,17]. Currently, only CPX-351 is specifically approved for the treatment of this adverse subset of AML [17]. Here, we have utilized real-world registry data and propensity score matching with clinical trial data to broaden the view of potential therapeutic options.

Thus, an indirect comparison using an external control arm was performed between the Conventional 7+3 and the Swedish SoC, utilizing data from the 7+3 arm in the CPX-351 301-trial [16,17] and data from the Swedish AML Registry. Matching on various clinical characteristics was conducted to increase the similarities between cohorts.

First, matching was satisfactory and outcomes obtained for the matched Conventional 7+3 cohort were comparable to those obtained previously [16,17], indicating that the matched Conventional 7+3 cohort investigated in this study largely represents the characteristics

of the full 301-trial 7+3 cohort. Comparing Conventional 7+3 and Swedish SoC, the main results indicated a statistically significant difference in OS between the cohorts with favorable OS outcomes in the Swedish SoC cohort. This result may potentially be driven by OS differences during the first year of treatment, where they are most pronounced. The results were further supported by the exploratory observations that more patients in the Swedish SoC cohort achieved CR/CRi, with a mean time to CR/CRi of 1.6 months.

Results from sensitivity analyses indicated that the main results were not influenced by the matching method, potential remaining variable imbalances after matching, differences in inclusion periods, or prior treatment with HMA nor seemed the results to be driven by a particular AML subtype. Sensitivity analyses addressing the potential effects of HCT yielded ambiguous outcomes. When HCT was considered as competing event or censoring event, no significant differences between the cohorts were observed ($p=0.300$ and $p=0.056$, respectively). However, the point estimates from the competing risk analysis were still suggestive

of short-term OS differences within the first year of induction treatment start (index date). Furthermore, the cause-specific HR of death obtained when defining HCT as censoring event (HR = 0.73), was comparable to that in the primary analysis (Supplementary results). In addition, there were no statistically significant differences between the cohorts in the number of patients undergoing HCT or in the time from index date to HCT. When excluding patients with HCT, the difference in OS between the cohorts remained significant. Although, overall, these results favor the notion that differences in HCT-related factors do not explain the OS differences observed in the primary objective, they shall be interpreted with caution. Thus, it remains to be investigated whether some HCT-related factors, e.g. regional differences in patient selection, procedures, or success rates, play an explanatory role.

Thus, while the exact mechanisms remain to be investigated, a conceivable explanation for the positive outcomes in the Swedish SoC cohort may be attributed to the treatment variation, specifically, the higher dose of cytarabine used may result in a more profound, deeper, and enduring remission when compared to the Conventional 7+3 regimen [24].

The secondary objective of the present study assessed differences in early mortality and in OS after undergoing HCT. The two cohorts did not differ with respect to early mortality (within 30 and 60 days). Intriguingly, in patients undergoing HCT, there was no statistical difference in OS post-transplant between the cohorts. While this finding suggests that both treatments are associated with similar OS outcomes after HCT, this interpretation assumes that HCT-related factors, e.g. patient selection and transplant procedure outcomes, are comparable across countries, which, however, remains unknown. Therefore, this result should be interpreted with caution, especially given the small samples size included in this secondary analysis and the numerical differences in point estimates (larger 3- and 5-year survival probabilities; HR = 0.60) and longer median survival in the Swedish SoC cohort. However, although not statistically significant ($p=0.120$), this notion shall be treated with caution, given that point estimates still indicate higher risk of death in the Conventional 7+3 cohort, and the sample size in this secondary analysis was small ($n=29$ in each group). Moreover, it should be noted that the median survival time was longer in the Swedish SoC cohort (20.7 months) compared with the Conventional 7+3 cohort (10.4 months). The numerical value obtained for the Conventional 7+3 cohort is consistent with what has previously been reported in the 301-trial, where the 3-year survival was 23% and the median

survival time after HCT was determined to be 10.3 months in the Conventional 7+3 arm, while in the experimental arm (CPX-351) arm, the 3-year survival was 56% and the median survival was not reached [16,17].

Strengths and limitations

One strength of this study is its study design, where the applied matching methodology used to create an external control arm enabled comparisons between a clinical trial arm and high-quality high-coverage real-world data. Such an approach can partially compensate for the sparsity of real phase III trial data. The matching on many relevant clinical and demographic variables reduced potential biases due to confounding variables.

Some limitations should be mentioned. First, the Conventional 7+3 cohort is a selected clinical trial patient population from North America, whereas data from the Swedish SoC cohort stems from a Swedish population-based registry with almost complete coverage of the national population. The different nature of data collection for a prospective clinical trial versus a real-world registry is bound to leave a possibility of unknown imbalances. There might be differences in the recording of the diagnosis, treatment description, available follow-up time, and other variables. Although there were differences in variable assessment procedures, most outcomes and eligibility criteria were successfully harmonized. Safety outcomes were not assessed in the present study, as they were not satisfactorily available in the Swedish AML Registry, which is typical for real-world datasets. Hence, future studies could focus on safety outcomes to more comprehensively understand the treatment's overall impact and patient risk profiles. The potential confounding effect of patient and disease characteristics was minimized through propensity score matching, allowing comparison of treatments for which a head-to-head trial has not been conducted. However, as prior HMA exposure data was not specified in the Swedish AML Registry, it was not possible to distinguish between MDS-AML with/without prior HMA exposure. Although sensitivity analyses performed within the Conventional 7+3 cohort did not indicate that prior HMA exposure influenced the outcomes within the Conventional 7+3 cohort, a level of uncertainty remains in how differences in prior HMA exposure affected the results between the two cohorts. Similarly, *FLT3* mutation status was not available for patients in the AML Registry, but *FLT3*-ITD status could be assessed. While the cohorts could not be fully matched for the mutational profile in accordance with the ELN 2022 risk stratification,

FLT3 mutation relates closely to cytogenetic risk in the ELN 2017 risk grouping, on which the cohorts were successfully matched.

Furthermore, there were differences in the inclusion periods between cohorts, which may affect the study outcomes. However, results from sensitivity analyses with aligned inclusion periods indicated that the outcomes were not affected by differences in study periods. This is further supported by the reportedly stable OS outcomes over time observed in a Swedish AML registry study where patients had similar OS across a 20-year study period (1997–2016) [2]. Matching resulted in exclusion of some 7+3 patients and in the fact that the matched cohort did not reflect an intention-to-treat population. However, the applied procedure enhanced comparability between cohorts and therefore treatments which was the aim of the present study. Lastly, some results, especially for some secondary and sensitivity analyses might be limited by a small sample size, and therefore need to be interpreted with caution. This includes exploratory outcomes, such as relapse incidences, which might have been under reported in the AML Registry.

Despite these limitations, the study provided robust outcomes for the primary objective and thereby valuable insights into OS in patients treated with Conventional 7+3 and the Swedish SoC.

Conclusion

We successfully matched a clinical trial cohort with data from a Swedish population-based registry enabling the synthesis of an external control arm for real-world effectiveness estimations. Our results suggest that intensified cytarabine dosing during induction, similar to what has been used in FLAG-Ida, is feasible also in high-risk older AML patient without increased early mortality and with beneficial long-term OS. The robustness of our findings was supported by various sensitivity analyses, suggesting that the observed differences in OS were likely attributable to the difference in treatment regimen and/or unknown factors not assessed in this study. Future studies assessing more comprehensive safety outcomes and designed to determine factors and mechanisms underlying the observed differences are warranted.

Acknowledgements

We would like to thank Eugenia Priedane, PhD, for her contributions to the study design, Nalina Dronamraju, PhD, for her support with the CPX-351 301-trial data and Kripi Syal, PhD, Quantify Research for providing writing support.

Authors' contributions

All authors contributed to the study design and to writing the manuscript. CA, ML, and MK carried out the analyses and all authors critically reviewed the manuscript.

Disclosure statement

JK is an employee of Jazz Pharmaceuticals. CA, ML, MK, and JM are employees of Quantify Research. MH, VL, SL and GJ do not have any competing financial interests.

Funding

This study was supported by Jazz Pharmaceuticals Nordics ApS. The Swedish AML group activities are sponsored by grant from Cancerfonden (21 1894Pg/2021).

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