Efficacy and toxicity of midostaurin with idarubicin and cytarabine induction in *FLT3*-mutated acute myeloid leukemia

Among patients able to tolerate intensive induction, standard acute myeloid leukemia (AML) induction therapy is a regimen commonly referred to as "7+3," consisting of 7 days of intravenous cytarabine and 3 days of daunorubicin (DNR) or idarubicin (IDA).[1] Depending on patients' genetic markers, targeted therapies may be added to the 7+3 backbone; in the pivotal trial establishing midostaurin as part of the standard of care for induction in fms-like tyrosine kinase 3 (*FLT3*)-mutated AML (RATIFY trial[2]), DNR 60 mg/m^2 was the anthracycline used. Although dose equivalence of IDA compared to DNR has not been definitively established, IDA 12 mg/m^2 is considered equivalent to DNR 90 mg/m^2. DNR 60 mg/m^2 was the anthracycline dose selected for the RATIFY trial, despite data supporting benefit of DNR 90 mg/m^2 over 60 mg/m^2 in *FLT3*-internal tandem duplication (ITD)-mutated AML.[3-5] Few published data exist assessing efficacy or toxicity of midostaurin in combination with an IDA-based 7+3 AML induction regimen. This multicenter, retrospective study assessed efficacy and toxicity associated with midostaurin and IDA-based 7+3 induction. Complete remission (CR) was attained in 83 of 114 patients (73%) receiving midostaurin and IDA-based 7+3 induction. Event-free survival (EFS) was 11.7 months, and no unexpected toxicity signals were noted.

Data regarding the use of midostaurin with IDA-based 7+3 induction are limited. Two small, retrospective studies examining the use of IDA-based 7+3 with midostaurin reported outcomes similar to those seen with DNR-based induction. A midostaurin expanded access program of 32 patients given IDA-based 7+3 induction reported higher rates of diarrhea and hypophosphatemia with IDA and midostaurin compared to DNR and midostaurin, but rates of other non-hematologic adverse events were similar, and rates of hematologic adverse events by induction anthracycline were not reported.[6] A single-center retrospective review of 20 patients with *FLT3*-mutated AML given midostaurin in addition to IDA-based 7+3 induction found a higher incidence of rash compared with the RATIFY results, with higher CR rate and shorter duration of neutropenia; however, all patients in this small study received granulocyte colony-stimulating factor 14 days after starting induction, which likely contributed to the shorter duration of neutropenia.[7]

In order to assess the midostaurin/IDA-based 7+3 induction regimen, we performed a multicenter, retrospective study of patients who received midostaurin and 7+3 with IDA as the anthracycline. The primary objective was CR rate after induction with midostaurin and IDA-based 7+3. CR was attained if patients met all of the following criteria: less than 5% blasts in the marrow, absence of extramedullary leukemia, an absolute neutrophil count of ≥1,000/μL, a platelet count of ≥100,000/μL, and the absence of blasts in the peripheral blood. The secondary objective was EFS, defined as time to relapse, mortality, or failure to achieve CR by day 60. Secondary objectives included assessment of hematologic and non-hematologic toxicities during induction. Adverse events were graded per CTCAE version 4.03. We performed *post hoc* analyses assessing efficacy and toxicity in those patients 60 years of age and older as those patients would have been excluded from the RATIFY trial, and sub-group analyses of EFS stratified by FLT3 and NPM1 mutation status.

At each study institution, a report was generated through the electronic medical record identifying patients who initiated IDA-based 7+3 with midostaurin induction therapy for AML between April 1, 2017 and December 31, 2020. Patients under the age of 18 years, incarcerated patients, pregnant patients, patients who received midostaurin as part of a clinical trial, and patients receiving midostaurin for systemic mastocytosis were excluded. Data collected from eligible patients' charts were recorded in a REDCap database hosted by the University of Utah. At each institution, research was exempt by the respective Institutional Review Boards and Ethics Committees; written informed consent was waived due to the retrospective nature of the study.

In all, 114 patients were included across five academic centers in the US. Baseline characteristics (Table 1) show a median age at induction of 56 years (range, 19-74), with 35 patients (31%) 60 years or older. The median duration of follow-up was 18.1 months (range, 0.5-51.3). Thirty-two patients (28%) carried *FLT3*-tyrosine kinase domain, and 87 (76%) carried *FLT3*-ITD mutations. Eighty-eight patients (78%) completed a 14-day midostaurin course. Eleven of 114 (9%) received midostaurin dose reduction due to drug-drug interactions and 2 (1.8%) received dose reduction due to toxicity. Twenty-four (21%) received growth factor during induction after day 14. Seventy-nine (69%) of patients proceeded to consolidation chemotherapy, and midostaurin was given during consolidation to 74 patients (64.3%), with 14 (12.2%) continuing maintenance midostaurin (*Online Supplementary Figure S1*). Seventy-four (64.3%) proceeded to allogeneic stem cell transplant, and four patients received maintenance midostaurin post-transplant.

Of the 114 patients who underwent induction with midostaurin and IDA-based 7+3, 83 (72.8%) achieved CR, with a relatively higher CR rate in the age under 60 years subgroup (Table 2). Median time to CR was 34 days. Median duration of neutropenia was 25 days, and median duration of thrombocytopenia was 27 days (Table 2). Median duration of follow-up was 18.1 months. Median EFS was 11.7 months (95% confidence interval [CI]: 9.8-24) (Figure 1) with median EFS of 13.4 months (95% CI: 10.3-not reached [NR]) in the age under 60 years subgroup and 10.8 months (95% CI: 5.1-NR) in the age over 60 years subgroup (*Online Supplementary Figure S2*). Censoring for transplant, median EFS was 9.8 months (95% CI: 7.9-NR). Among the *FLT3*-ITD- mutated population, there was a trend toward improved EFS with mutated *NPM1* compared to wild-type, with median EFS not reached in the *NPM1* mutant population and 6.9 months in the wild-type population (*Online Supplementary Figure S2*).

Table 2 shows rates of grade 3 or higher adverse events during induction. In both the under the age of 60 years and over the age 60 years subgroups, IDA-based 7+3 induction with midostaurin appeared to have a similar toxicity profile to DNR-based 7+3 induction reported in the RATIFY trial.

This multicenter, retrospective study found an overall CR rate of 72.8% with use of IDA in 7+3 induction with midostaurin in patients with *FLT3*-mutant AML, including patients 60 years of age or older. The CR rate was 77.2% and 62.9%, in patients younger and older than 60, respectively. Although a direct comparison to the RATIFY study is not possible, these rates stand favorably in comparison to the RATIFY trial, in which a 58.9% CR rate was achieved in patients younger than 60 years.

The high CR rate observed in this work could in part be due to the IDA dose of 12 mg/m^2; whereas the RATIFY study used DNR 60 mg/m^2. Previous studies in patients

Table 1. Baseline characteristics and patient disposition.

Baseline characteristics	All patients, N=114
Median age at induction in years (range)	56 (19-74)
Female sex, N (%)	53 (46.5)
ECOG performance status, N (%)	
0	40 (35.1)
1	50 (43.8)
2	9 (7.9)
3	2 (1.8)
Not reported	13 (11.4)
FLT3 mutation subtype, N (%)	
TKD	32 (28.0)
ITD-high[a]	19 (16.7)
ITD-low	29 (25.4)
ITD allelic ratio not quantified	39 (34.2)
2017 ELN classification, N (%)	
Favorable	17 (14.9)
Intermediate	57 (50.0)
Adverse	38 (33.3)
Unknown	2 (1.8)
Median WBC on day 1, x10^3/μL (range)	21.3 (0.2-301)
Median platelets on day 1, x10^3/μL (range)	39 (8-247)
Median ANC on day 1, x10^3/μL (range)	1.1 (0-22.2)

[a]Defined as FLT3 ITD ratio greater than 0.7. ECOG: Eastern Cooperative Oncology Goup; TKD: tyrosine kinase domain; ITD: internal tandem dublication; ELN: European Leukemia Net; WBC: white blood cell count; ANC: absolute neutrophil count.

Table 2. Complete remission summary and summary of grade 3 or higher adverse events during induction.

	All patients N=114	Age <60 years N=79	Age ≥60 years N=35
Protocol-specified CR, N (%)	83 (72.8)	61 (77.2)	22 (62.9)
Did not attain protocol-specified CR, N (%)	28 (24.6)	16 (20.2)	12 (34.2)
Remission assessment data missing, N (%)	3 (2.6)	2 (2.5)	1 (2.8)
Median time to CR in days (range)	34 (23-56)	34 (23-66)	35 (24-56)
Median duration of ANC <500x10^3/μL in days (IQR)	25 (21-30)	25 (22-31)	25 (21-30)
Median duration of platelets <100x10^3/μL in days (IQR)	27 (24-35)	27 (23-35)	28 (26-50)
Adverse events, grade 3 or higher, N (%)			
Febrile neutropenia	101 (89)	73 (92)	28 (80)
Other infection	32 (28)	20 (25)	12 (34)
Mucositis	15 (13)	9 (11)	6 (17)
Nausea	5 (4)	4 (5)	1 (3)
Diarrhea	19 (17)	9 (11)	10 (29)
Pneumonitis	1 (1)	0 (0)	1 (3)

CR: complete remission; ANC: absolute neutrophil count; IQR: interquartile range.

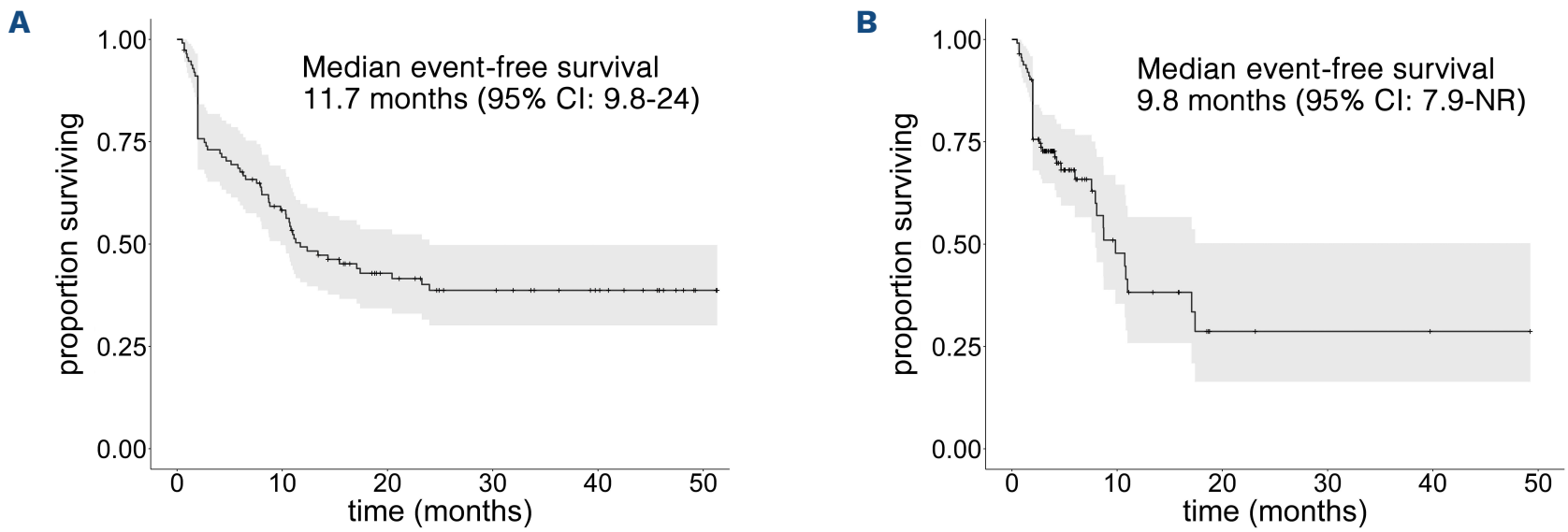

Figure 1. Kaplan-Meier curves of event-free survival. (A) Event-free survival in the overall study population and (B) overall study population censoring at time of transplant. NR: not reached.

with the *FLT3*-ITD mutation found an overall survival benefit using high-dose DNR (90 mg/m^2) rather than lower DNR doses (60 or 45 mg/m^2)[3-5] or IDA 12 mg/m^2.[8] For patients with *FLT3*-mutated AML, high-dose DNR equivalence to IDA in combination with midostaurin remains an open question.

Overall survival was not assessed in this study, due to the short median follow-up of 18.1 months. However, in a trial-level analysis of eight randomized studies of intensive chemotherapy in newly-diagnosed AML, an association was noted between EFS and overall survival, suggesting EFS may serve as a valid surrogate endpoint for initial AML treatment.[9] A favorable EFS of 11.7 months was observed across our study population, with a high proportion of patients who proceeded to transplantation. Between the younger than 60 years and 60 years and older subgroups, EFS was comparable, with EFS of 13.4 months and 10.8 months respectively. Subgroup analysis of patients with *FLT3*-ITD mutations showed improved EFS with mutated *NPM1* compared to unmutated *NPM1*.

The toxicity profile of IDA-based 7+3 with midostaurin was comparable to data reported with DNR-based 7+3 induction. We observed a low rate of grade 3 or higher infection, likely due to high rates of posaconazole or voriconazole use as antifungal prophylaxis during induction (87% of patients), with only two patients (1.8%) contracting a fungal infection. Other toxicities noted, such as those observed with mucositis, diarrhea, and pneumonitis were limited by small numbers and the nature of retrospective chart review.

In conclusion, this study describes the largest series of *FLT3*-mutated AML patients treated with midostaurin and IDA in 7+3 induction. Midostaurin and IDA in 7+3 induction demonstrated excellent efficacy and a safety profile similar to that of midostaurin with DNR as the induction anthracycline, in both the age below 60 years and the age of 60 years and older subgroups. Limitations of this work include the retrospective nature and short follow-up, but these results suggest IDA 12 mg/m^2 is a suitable alternative anthracycline to DNR 60 mg/m^2 in 7+3 with midostaurin in newly-diagnosed *FLT3*-mutated AML.

Authors

Julia S. Lee,[1] Charlotte B. Wagner,[1] Stacy Prelewicz,[1] Heena P. Kurish,[2] Robert Walchack,[2] Danielle A. Cenin,[2] Seema Patel,[2] Mimi Lo,[3] Danielle Schlafer,[4] Belinda K. T. Li,[4] R. Donald Harvey III,[4] Bestis Wasef,[5] Jian Ying[6] and Tibor Kovacsovics[7]

[1]Department of Pharmacy, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; [2]Department of Pharmacy, Cleveland Clinic Foundation, Cleveland, OH; [3]Department of Pharmaceutical Services, University of California San Francisco, San Francisco, CA; [4]Department of Hematology and Medical Oncology, Winship Cancer Institute/Emory Healthcare, Atlanta, GA; [5]Department of Pharmacy, Oregon Health and Science University Hospital, Portland, OR; [6]Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT and [7]Division of Hematology, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT, USA

Correspondence:
J. LEE - julialee@stanfordhealthcare.org

https://doi.org/10.3324/haematol.2022.281967

Received: December 15, 2022.
Accepted: June 15, 2023.
Early view: June 22, 2023.

Disclosures

RDH reports financial relationships with Abbisko, AbbVie, Actuate, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Boston Biomedical, Genmab, GlaxoSmithKline, Infinity, InhibRx, Janssen, Merck, Mersana, Meryx, Nektar, Novartis, Pfizer, Regeneron, Sanofi, Sutro, Takeda, Turning Point Therapeutics and, Xencor. HK reports honoraria from Market Access Transformation. ML reports consultancy with Oncopeptides and EUSA Pharma. TK reports research funding from Abbvie, Caelum, Gilead, Glycomimetics, Janssen, Jazz Pharmaceuticals and Syndax; honoraria from Novartis and Kite. All other authors have no conflicts of interest to disclose.

Contributions

CW, SPr and TK conceived the study question. JSL designed the data collection form, cleaned and analyzed the data, and drafted the letter. JSL, CW, SPr, DC, HK, SPa, RW, ML, DS, BL and BW collected data. JY assisted with statistical analysis. All authors reviewed and provided input on the manuscript.

Funding

Use of REDCap was supported by NIH/NCATS grant UL1TR002538.

Data-sharing statement

The REDcap study database is not available per the protocols approved by the participating institutions' Institutional Review Boards. The data collection form will be made available upon request to the corresponding author.

References

1. National Comprehensive Cancer Network. Acute myeloid leukemia (Version 3.2023). https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf Accessed June 6, 2023.
2. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454-464.
3. Burnett AK, Russell NH, Hills RK, United Kingdom National Cancer Research Institute Acute Myeloid Leukemia Study Group. Higher daunorubicin exposure benefits FLT3 mutated acute myeloid leukemia. Blood. 2016;128(3):449-452.
4. Choi EJ, Lee JH, Lee JH, et al. Comparison of anthracyclines used for induction chemotherapy in patients with FLT3-ITD-mutated acute myeloid leukemia. Leuk Res. 2018;68:51-56.
5. Luskin MR, Lee JW, Fernandez HF, et al. Benefit of high-dose daunorubicin in AML induction extends across cytogenetic and molecular groups. Blood. 2016;127(12):1551-1558.
6. Roboz GJ, Strickland SA, Litzow MR, et al. Updated safety of midostaurin plus chemotherapy in newly diagnosed FLT3 mutation-positive acute myeloid leukemia: the RADIUS-X expanded access program. Leuk Lymphoma. 2020;61(13):3146-3153.
7. Azzi J, Cirrone F, Abdul Hay M, et al. Midostaurin in combination with idarubicin and cytarabine (3+7) induction for FLT3 positive AML - very high complete response rates and transition to allogeneic transplantation. Blood. 2018;132(Suppl 1):S5216.
8. Lee JH, Kim H, Joo YD, et al. Prospective randomized comparison of idarubicin and high-dose daunorubicin in induction chemotherapy for newly diagnosed acute myeloid leukemia. J Clin Oncol. 2017;35(24):2754-2763.
9. Norsworthy KJ, Gao X, Ko CW, et al. Response rate, event-free survival, and overall survival in newly diagnosed acute myeloid leukemia: US Food and Drug Administration trial-level and patient-level analyses. J Clin Oncol. 2022;40(8):847-854.