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ORIGINAL ARTICLE

Midostaurin in combination with intensive chemotherapy is safe and associated with improved remission rates and higher transplantation rates in first remission—a multi-center historical control study

Tamar Berger[1,2] · Uri Rozovski[1,2] · Yakir Moshe[2,3] · Shilo Yaari[4,5] · Avraham Frisch[4,5] · Ilana Hellmann[2,6] · Arie Apel[7] · Adina Aviram[2,8] · Maya Koren-Michowitz[2,7] · Moshe Yeshurun[1,2] · Ron Ram[2,3] · Pia Raanani[1,2] · Yishai Ofran[4,5] · Ofir Wolach[1,2]

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Abstract

The addition of midostaurin, a FLT3-inhibitor, to intensive chemotherapy (IC) was previously shown to improve outcome of younger patients with FLT3-mutated AML. The toxicity and efficacy of adding midostaurin to IC in patients not originally included in the RATIFY study or with intensified daunorubicin dosing are unknown. We conducted a retrospective, multi-center, historical-control study to characterize the safety and efficacy of adding midostaurin to IC in a "real-world" setting. Sixty-nine adult patients were included in the analysis (midostaurin $n = 34$, historical controls $n = 35$) with a mean follow-up of 18.4 (± 15) months. Median age of patients was 60 (range 26–82) years; 32% and 20% of patients were > 65 and 70 years, respectively. No differences in baseline characteristics were noted between the groups. Midostaurin was administered with 90 mg/m^2 daunorubicin in 29% of patients; One-third of patients experienced dose reductions/interruptions during midostaurin therapy. Overall toxicity was comparable between the midostaurin and control groups.CR/CRi rates were higher in patients treated with midostaurin compared with controls (80% vs. 57%, $p = 0.047$) and significantly more patients in the midostaurin group were transplanted in first remission (95% vs. 68%, $p = 0.04$).Median OS and DFS were higher in the midostaurin vs. control group (not reached vs. 11 months ($p = 0.085$) and 13 vs. 6 months ($p = 0.09$), respectively). In our analysis, midostaurin was not associated with increased toxicity including in older patients, in those with secondary AML or when administered with intensified daunorubicin dosage. Higher remission rates in the midostaurin group and increased transplantation rates in first CR were associated with a trend towards better outcomes.

Keywords Acute myeloid leukemia · Midostaurin · FLT3 mutation

✉ Ofir Wolach
owolach@gmail.com

[1] Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel

[2] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[3] Bone Marrow Transplantation Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[4] Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel

[5] The Ruth and Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel

[6] Department of Hematology, Meir Medical Center, Kfar Saba, Israel

[7] Department of Hematology, Shamir Medical Center, Zeriffin, Israel

[8] Hematological Laboratories, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

Introduction

In recent years, the somatic genetic landscape of acute myeloid leukemia (AML) has been uncovered [1, 2]. These genetic insights are not only instrumental for our understanding of the pathobiology of AML, but also significantly improve our assessment of disease prognosis and can inform clinical treatment decisions. Several of these genetic lesions are also targetable and are the focus of clinical drug development [1].

Among the most common somatic mutations in AML are mutations within the gene coding for the transmembrane receptor fms-like tyrosine kinase 3 (FLT3). Internal tandem duplication (ITD) mutations exist in one-quarter to one-third of adults with normal karyotype AML and convey inferior outcomes. Mutations within the tyrosine kinase activating loop (TKD) are less common (~ 5% of AML patients) and their

prognostic significance is less clear [1, 3]. Inhibition of FLT3 by small molecules is at the center of pre-clinical and clinical research and a number of compounds with different potency and specificity have been developed and studied in recent years [4].

In 2017, results of the phase III RATIFY study were published—a randomized placebo-controlled trial comparing the efficacy of midostaurin addition to intensive chemotherapy courses in young (18–59 years) patients diagnosed with FLT3-mutated de novo AML. Patients not treated with allogeneic stem cell transplantation received maintenance therapy for 1 year with midostaurin. The addition of midostaurin to intensive treatment improved outcomes in these patients, with a significant prolongation of overall survival (HR 0.78; $p = 0.002$) and event-free survival (HR 0.78; $p = 0.009$) [5]. Following these results, midostaurin was approved for the treatment of FLT3-mutated AML by the FDA and EMA for all age groups [6]. In contrast to the RATIFY registration trial, the approval label of midostaurin was inclusive and was not restricted by age (i.e., included patients older than 60 years of age) or by ontogeny (i.e., also included patients with secondary AML) and data regarding the safety and efficacy of midostaurin in these patient groups are lacking.

In Israel, an extended access program to midostaurin was launched on April 2016, enabling the addition of midostaurin to chemotherapy treatment in FLT3-mutated AML patients. Since the beginning of 2018, midostaurin is reimbursed by the Israeli National health insurance program.

We sought to assess the Israeli experience of adding midostaurin to intensive chemotherapy in FLT3-mutated AML patients.

Methods

Patients

This is a multi-center retrospective historical-control study that included patients from 5 hospitals nationwide. Eligible patients were those above 18 years of age, newly diagnosed AML presenting with FLT3 (ITD/TKD) mutations that were treated with intensive induction, between 2014 and 2018.

Patients with wild-type FLT3 AML or patients not treated with intensive induction were excluded. FLT3 mutational status was determined locally by the treating centers and the mutational status and allelic ratio/burden were documented and reported.

Patients with FLT3-mutated AML (ITD/TKD) were eligible to receive midostaurin through the Novartis extended access program that was launched in Israel in April 2016 (Fig. 1). Midostaurin was later approved during January 2018 for the treatment of FLT3-mutated AML through the National health insurance program. In order to control for toxicity and efficacy outcomes in the midostaurin-treated patients, a historical control cohort was created and included patients with FLT3-mutated AML treated with intensive induction in the 2 and a half years prior to the introduction of midostaurin. Data were extracted from an electronic data base. Baseline characteristics, disease- and patient- specific parameters as well as toxicity and efficacy outcomes were analyzed and compared between the midostaurin treated and untreated cohorts. The study protocol was approved by the Institutional Review Board.

Treatment

Induction therapy consisted of continuous 100 mg/m^2 cytarabine for 7 days in combination with daunorubicin on days 1–3 (‘3 + 7’) for most patients and was followed by consolidation therapy with intermediate- or high-dose cytarabine or allogeneic transplantation. In this retrospective study, daunorubicin dose for induction and cytarabine dose for consolidation were subjected to local institutional policy. The decision to transplant and the timing of allogeneic transplantation were also at the discretion of the treating physician. Midostaurin was administered according to the dosing schedule used in the RATIFY study [5]. Supportive care during therapy was given per institutional policies.

Statistical analysis

The response criteria were defined in accordance with the European LeukemiaNet Guidelines [1]. Toxicity was classified based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [7]. Patient characteristics were summarized using frequencies (number and percentages) for categorical and median and range for continuous variables. Overall survival (OS) was defined as the time from AML diagnosis to death. Disease-free survival (DFS) was defined as the time from complete remission (CR) until the first event (relapse or death) or the time of the last follow-up. To compare patients based on categorical variables, we used the χ^2 test. Medians were compared using the Mann-Whitney test. The probability of OS was estimated by the Kaplan-Meier method. The log-rank test was used to compare survival distributions in patients treated with midostaurin and controls. Significance levels were set at 0.05. Statistical analyses were performed by using the SPSS software (version 21, SPSS Inc., Chicago, IL) and Graph Pad Prism software (version 6.0, San Diego, CA).

Results

Patient and treatment characteristics

Sixty-nine patients were included in the analysis, with a mean follow-up time of 18.4 (± 15) months for surviving patients.

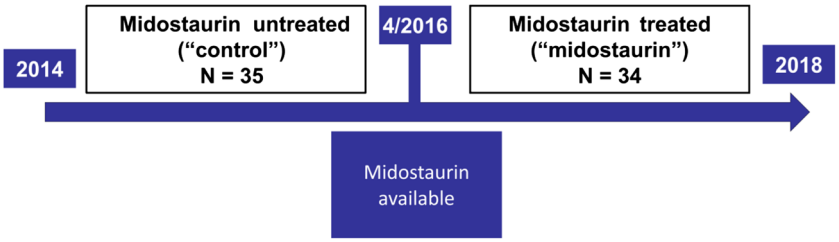

Fig. 1 Time frame of study and patient cohorts

Of those, 34 patients were treated with midostaurin and 35 patients served as a historical control group.

The median age of patients was 60 years (26–82); 32% and 20% of patients were over the ages of 65 and 70 years, respectively. Genders were equally represented. FLT3-ITD mutations were detected in 65 patients (94%) and TKD mutation was detected in 4 patients (6%). Ten patients (14%) had secondary leukemia, 87% had normal karyotype, and 64% were NPM1 mutated (Table 1).

No differences were noted between the midostaurin-treated cohort ($n = 34$) and the historical control cohort ($n = 35$) in terms of age, gender, leukemia ontogeny, cytogenetics, NPM1 status, presenting blood counts, extramedullary involvement, performance status, and comorbidity scales. Frequency of high and low FLT3 allelic burden was comparable between the two groups (Table 1).

No differences were noted between the groups in terms of daunorubicin dose for induction (45, 60, and 90 mg/m^2/day in 9%, 46%, and 36% of patients, respectively). Groups were comparable in the number of patients receiving consolidation treatment (76% vs. 65%, $p = 0.3$), the median number of consolidation cycles per patients and in cytarabine dosing.

Twenty-six of the 34 patients (76%) in the midostaurin group received the drug as planned during induction and the full 14-day midostaurin course was given in most patients during induction (69%). In 8 patients (24%), midostaurin was initiated only at the post-induction courses due to technical delays in drug supply related to access issues (Table 2).

Eleven patients (32%) in the midostaurin cohort experienced dose reductions or interruptions at different phases of therapy: during induction, six patients stopped treatment due to severe adverse events (septic shock, grade IV refractory thrombocytopenia with purpura, QT prolongation, and drug interactions), 1 did not receive midostaurin after consolidation due to suspected late toxicity post-induction (hemorrhagic necrotizing gastritis, previously reported [8]), and 4 patients had interruptions of treatment during consolidation: two patients due to adverse events (new onset atrial fibrillation, severe sepsis) and two patients due to molecular relapse.

Toxicity

Similar to the RATIFY study, in our study, most adverse events were aligned with those expected in patients post-AML intensive chemotherapy treatments. Overall toxicity was comparable between the cohorts (Table 3).

Episodes of febrile neutropenia occurred in 62 and 60% of intensive treatment cycles in patients in the midostaurin and control groups, respectively ($p = 0.8$).

Other frequent toxicities, documented in over 5% of intensive treatment cycles (Table 3), were skin rash, gastrointestinal and hepatic toxicity, thrombotic events, and HSV infections.

In the RATIFY study, rate of grade 3–5 rash was significantly higher in the midostaurin group than in the placebo group. In our study, we did not observe severe rashes; grade 1 or 2 rashes were reported in similar rates between the two groups—8% in the midostaurin group vs. 13% in the control group ($p = 0.3$).

Other common side effects were hepatic and gastrointestinal toxicities, mostly grade 1 or 2 with similar rates between groups (Table 3): Hepatic toxicity was seen in 13% of midostaurin patients versus 8% in the control group ($p = 0.4$). Gastrointestinal toxicity was observed in 21% of midostaurin patients and in 13% of control group ($p = 0.2$).

Additional adverse events more common in the midostaurin group that did not reach statistical difference were grade 1 or 2 HSV infections (9% vs. 2%, $p = 0.07$) and grade 1 or 2 thrombotic events (6% vs 2%, $p = 0.2$).

Patients in the midostaurin group had routine electrocardiogram testing to monitor QTc interval due to known effect of QTc prolongation by midostaurin. Only one patient in the midostaurin group (3% of cohort) had QTc prolongation which led to drug stoppage. Control group did not routinely have ECG testing, though no QTc prolongation was recorded.

Other uncommon but severe adverse events among midostaurin-treated group that affected sporadic patients but led to midostaurin halt were as follows: atrial fibrillation grade 2 (1 patient, 3%), severe refractory thrombocytopenia and purpura (1 patient, 3%), and grade 4 encephalopathy (1 patient, 3%) which was most probably related to sepsis.

Median time to neutrophil count recovery (> 500 per microliter) was 24 days in the midostaurin group and 25 days in the control group, parallel to the time frame demonstrated in the RATIFY study. Median time to platelet count recovery (> 50,000 per microliter) was 23 days in the midostaurin group and 21 days in the control group (non-significant).

Table 1 Demographic and disease characteristics at baseline

Characteristics	Midostaurin (34)	Control (35)	*p* value
Gender, *n* (%)			
Male	19 (56)	18 (51)	0.7
Median age, years (range)	60 (31–76)	60 (26–82)	0.9
ECOG			
0	21 (62)	16 (45.5)	0.2
1	10 (29)	17 (48.5)	
2	3 (9)	2 (6)	
Median Charlson Comorbidity Index (CCI)	4	4	0.7
Disease characteristics			
FAB classification, *n* (%)*			
M0		1 (3.5)	
M1	3 (11)	7 (25)	NA
M2	7 (27)	7 (25)	
M4	14 (54)	10 (36)	
M5	2 (8)	2 (7)	
M6		1 (3.5)	
Karyotype, *n* (%)*			
Normal karyotype	27 (87)	25 (86)	0.9
Abnormal karyotype	4 (13)	4 (14)	
FLT3, *n* (%)			
ITD	31 (91)	34 (97)	0.3
TKD	3 (9)	1 (3)	
High allelic burden (> 0.5)**	13/28 (46)	16/26 (62)	0.2
NPM1 mutated, *n* (%)	24 (71)	20 (57)	0.2
2017 ELN risk stratification by genetics, *n* (%)			
Favorable	11 (33)	5 (14)	0.1
Intermediate	18 (55)	21 (60)	
Adverse	4 (12)	9 (26)	
Leukemia, *n* (%)			
De novo	28 (82)	31 (89)	0.5
Secondary	6 (18)	4 (11)	
WHO classification			
AML, NOS	8 (23)	12 (34)	NA
Therapy-related myeloid neoplasms	6 (18)	4 (11)	
AML with mutated NPM1	19 (56)	17 (49)	
AML with CBFB-MYH11	1 (3)	0	
AML with MDS related changes		2 (6)	
Clinical and laboratory characteristics at presentation			
Median white blood count (range) (× 10^9/l)	24 (2.4–248)	45 (0.5–397)	0.1
Median hemoglobin level (range) (g/dl)	10.5 (6.6–14.4)	10.3 (3.9–14)	0.5
Median platelet count (range) (× 10^9/l)	88 (20–217)	64 (15–448)	0.06
Median creatinine level (range) (mg/dl)	0.8 (0.46–1.8)	0.8 (0.58–2.18)	0.6
Median % marrow blasts	77	70	0.5
Extramedullary involvement, *n* (%)	4 (12)	6 (17)	0.5

*Data available for part of the cohort;**Data available for 28 of 31 patients with FLT3-ITD mutation in the midostaurin group and 26 of 34 patients with FLT3-ITD mutation in the control group. *NA*, not applicable

Nine patients (29%) received midostaurin with 90 mg/m^2 daunorubicin in induction. Average time until neutrophil and platelet recovery was 24 ± 3 days and 21 ± 4 days, respectively. This was comparable with the time of count recovery in patients receiving lower doses of daunorubicin for induction in the midostaurin group.

Table 2 Treatment characteristics

Variables	Midostaurin ($n = 34$)	Control ($n = 35$)	p value
Induction			
Daunorubicin dosage, n (%)*			
45 mg/m^2	4 (12)	2 (6)	0.7
60 mg/m^2	16 (47)	15 (46)	
90 mg/m^2	12 (35)	12 (36)	
No anthracycline	2 (6)	4 (12)	
Number of patients that received consolidation chemotherapy (%)	26 (76)	19 (65)	0.3
Median number (range) of consolidation cycles	1.5 (1–4)	1 (1–5)	0.09
Type of consolidation, n (%)			
HiDAC	18 (72)	14 (74)	0.4
IDAC	7 (28)	4 (21)	
Other**		1 (5)	
HSC transplantation, n (%)	22 (65)	19 (54)	0.4
HSC transplantation in CR, n (%)	21 (95)	13 (68)	0.04
Midostaurin treatment			
During induction, n (%)	26 (76)		
Median days of treatment	14 (4–14)		
Number of patients with dose reduction, n (%)	1 (4)		
During consolidation	22/26 (85)		
Median days of treatments	14 (0–56)		
Number of patients with dose reduction	0		
Midostaurin maintenance, n (%)	1 (3)		

*In the control group: one patient received Vyxeos, one patient data is missing. **One patient's data is missing (midostaurin group), 1 patient received LDAC + venetoclax post-induction d/t clinical decline (control group)

Response characteristics

CR/CRi rates were 80% and 57% in the midostaurin and control groups, respectively ($p = 0.047$).

Overall, no difference in number of patients who underwent transplantation was seen: Twenty-two (64%) patients in the midostaurin group and 19 (54%) in the control group ($p = 0.4$) received allogeneic hematopoietic stem cell transplantation (HSCT), Table 2.

However, of those transplanted, significantly more patients in the midostaurin group were transplanted in first complete remission as opposed to latter time points (95% vs. 68% of

Table 3 Summary of frequent adverse events during induction and consolidation courses*

Variables	Midostaurin (77 intensive treatment cycles)		Control (61 intensive treatment cycles)		p value
	Any grade	Grades 3–4	Any grade	Grades 3–4	
Hematological adverse events, n (%)					
Neutropenic fever episodes, n (%)	48 (62)	48 (62)	37 (60)	37 (60)	0.8
Mean time to neutrophil recovery, days (±SD)	28 (±15)		32 (±20)		0.6
Mean time to platelet recovery, days (±SD)	26 (±14)		28 (±16)		0.9
Non-hematological adverse events, n (%)					
Rash	6 (8)	0	8 (13)	0	0.4
Gastrointestinal toxicity	16 (21)	1 (1)	8 (13)	0	0.2
Hepatic toxicity	10 (13)	2 (6)	5 (8)	1 (7)	0.4
Thrombotic events	5 (6)	0	1 (2)	0	0.2
HSV infection (HSV1 or HSV2)	7 (9)	0	1 (2)	0	0.07

*Included are adverse event episodes reported in over 5% of intensive treatment cycles. Data presented as number of events (% of intensive treatment cycles number)

transplanted patients in the midostaurin and control group, respectively, $p = 0.04$). Only one of the patients in the midostaurin group was transplanted with active disease as compared to 6 patients in the control group (32%).

Early death rate (mortality at 100 days) was higher in the control group than in the midostaurin group (7 patients vs. 1 patient, $p = 0.055$).

Median survival for the entire cohort was 14 months; it was not reached for patients who received midostaurin and was 11 months in patients who did not receive the drug ($p = 0.085$, Fig. 2). The median DFS for the entire cohort was 9 months: it was 13 (range 8–18) months in the midostaurin group vs. 6 (range 3–9) months in the control group ($p = 0.09$).

Discussion

This is the first report to our knowledge on the safety and efficacy of adding midostaurin to intensive chemotherapy in a real-life setting.

In contrast to the patients included in the RATIFY trial [5], we also included older patients (32% and 20% of patients were over the age of 65 and 70 years, respectively) and patients with secondary AML (18% of midostaurin-treated patients). Assessing the toxicity and efficacy in this setting is of great importance, especially since midostaurin is approved in North America and Europe without regards to age or leukemia ontogeny. We found that midostaurin appears to be safe in this population and can be delivered with full dosing in most older patients and in those with secondary AML. Furthermore, a third of our cohort received midostaurin with intensified daunorubicin induction (90 mg/m^2). This approach also seems safe, did not lead to attenuation in neutrophil and platelet count recovery, and may be an attractive approach since this anthracycline dosing schedule was suggested to be beneficial in patients with FLT3-mutated AML as compared with the standard 60 mg/m^2 dosing [9]. In contrast to the results reported in the RATIFY study, we observed higher rates of remission in the group of patients that received midostaurin as compared with historical controls (80% vs. 57%, $p = 0.047$). The effect of midostaurin on remission rate may be affected by the way remission is defined. In the RATIFY trial, CR rate was significantly higher in patients randomized to midostaurin compared with placebo (68% vs 61%, two-sided Fisher's exact $p = 0.04$) when an expanded CR definition was used (CRs during protocol treatment and those in the 30 days following treatment discontinuation) [5]. In our analysis, the median time from initiation of induction therapy to remission assessment was 32 days (range 22–63) in the control group and 33 days (range 14–45) in the midostaurin group. Additional factors that could potentially contribute to higher remission rates in the midostaurin group as compared with controls in our analysis are the more inclusive combined CR and CRi end-point utilized (as compared with CR only in the RATIFY) and the yet unknown effect of intensified daunorubicin doses (90 mg/m^2) in combination with midostaurin on the chance of achieving remission (although small patient numbers , we documented a 91% remission rate in the midostaurin group and 69% in the control group for patients treated with intensified daunorubicin doses; $p = 0.32$). Patient and disease characteristics known to affect remission rates were not statistically different between the midostaurin and control groups in our study although there were more favorable-risk patients in the midostaurin group that could potentially contribute to higher remission rates.

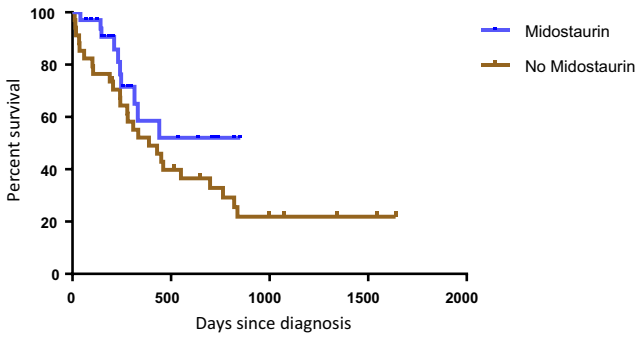

Fig. 2 Kaplan-Meier overall survival analysis between the two cohorts ($p = 0.085$)

Despite the small sample size and relatively short follow-up periods, a trend towards improved DFS (median DFS 13 vs. 6 months; $p = 0.09$) and in OS (NR vs. 11 months; $p = 0.085$) was observed in the midostaurin-treated group as compared with the historical controls, respectively. This beneficial effect may be related to the higher remission rates and increased transplantation rates in first remission. Allogeneic transplantation in first remission is widely accepted as an appropriate intervention in non-favorable risk FLT3-ITD-mutated patients [1] and sequencing transplant after midostaurin-based therapy seems to be particularly beneficial [6]. The higher rates of early death (defined as mortality at 100 days) reported for the control group as compared with the midostaurin group (7 patients vs. 1 patient, $p = 0.055$) could further contribute to the better outcomes in the midostaurin-treated group.

Further evidence for the efficacy and safety of adding midostaurin in older patients was recently presented. A large German phase II trial enrolled 284 adult patients up to the age of 70 years with FLT3-mutated AML to induction and consolidation therapies with the addition of midostaurin as per the RATIFY protocol [10]. In contrast to the RATIFY trial, all patients with a matched related or unrelated donor were planned for allogeneic transplantation in first remission and those transplanted also received midostaurin maintenance for 12 months. Of note, in this cohort, one-third of patients were between 60 and 70 years of age and 13% had secondary AML.

The complete remission (CR) rate was 76% and was comparable between younger (< 60 years) and older (> 60 years) patients. Two-year EFS and OS were 37.7% (95% CI, 32–44.3%) and 50.9% (95% CI, 44.9–57.6%), respectively. Age did not affect EFS in this analysis ($p = 0.51$) but a trend towards improved OS was observed in younger patients ($p = 0.07$). These outcomes were compared with 415 historical patients enrolled on 5 previous AMLSG trials recruiting between 1993 and 2008. A propensity score-weighted analysis revealed significant improvements in EFS for midostaurin-treated groups overall (hazard ratio (HR), 0.58; 95% CI, 0.48–0.70; $p < .001$) and in older patients (HR, 0.42; 95% CI, 0.29–0.61). In this trial, older patients had significantly more high-grade cardiac toxicities ($p = 0.04$) and a trend towards pulmonary toxicities (p = 0.07) [10].

Our study has several limitations. It is a retrospective study with limited number of heterogenous patient populations and non-uniform treatment approaches. Nonetheless, this is the first report on the use of midostaurin in combination with intensive induction in the off-trial setting including higher risk patients such as older patients and those with secondary AML. Furthermore, the use of intensified daunorubicin induction with midostaurin is reported for the first time. This report, along with other reports to come, may aid in better delineating the toxicity and efficacy of FLT3 inhibition in unselected populations in the clinic.

Compliance with ethical standards

Conflict of interest OW, YO, and PR report past membership on an advisory board for Novartis, OW received speaker honoraria from Novartis.

Midostaurin was supplied by Novartis via an extended access program from April 2016 to January 2018.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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