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Title Page

Gemtuzumab ozogamicin plus midostaurin in conjunction with standard intensive therapy for *FLT3*-mutated acute myeloid leukemia patients – Czech Center experience.

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Author Contributions

B.W. and J.M. – contributed to study conception and design, implemented material preparation, data collection and analysis; composed and revised manuscript.

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Competing Interests

The authors declare no competing financial interests.

Running Title

Gemtuzumab Ozogamicin plus Midostaurin in Therapy of AML.

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Main Body

For more than four decades, conventional therapy for acute myeloid leukemia (AML) has been represented by cytarabine/anthracycline-containing regimens, followed by consolidation therapy, including allogeneic hematopoietic stem cell transplantation (allo-HSCT). In recent years, approach to the treatment of AML has significantly shifted toward the use of novel and effective, target-directed therapies, including anti-CD33 immunoconjugate, gemtuzumab ozogamicin (GO), and inhibitor of mutant FMS-like tyrosine kinase 3 (*FLT3*), midostaurin (MIDO).

A large meta-analysis evaluating data from five randomized controlled trials of GO addition to induction chemotherapy among cytogenetically favorable and intermediate AML patients revealed a significant relapse risk reduction and improved long-term overall survival.[1] The definitive favorable benefit/risk ratio of GO added to standard intensive chemotherapy (IC) of AML was confirmed in the final analysis of the ALFA-0701 randomized trial.[2] Similarly, the multitargeted kinase inhibitor midostaurin in addition to standard chemotherapy provided significant beneficial effect on prolonged overall and event-free survival among patients with *FLT3*-mutated AML across all *FLT3* subtypes.[3] Moreover, a midostaurin-based combination therapy toxicity profile was favorable, non-additive, and comparable to standard intensive treatment. However, certain patient subgroups with regards to the interaction of gender, European Leukemia Net (ELN) risk group, and *FLT3* subtype did not derive significant benefit from combined treatment with midostaurin.[3] Based on study results, both MIDO and GO were approved by the European Medicines Agency (EMA) in 2017 and 2018, respectively, for treatment of AML.[4,5]

In literature, robust data on a MIDO plus GO combination with standard IC in newly diagnosed *FLT3*-mutated/CD33+ AML is lacking. There have only been limited conference

abstracts of ongoing studies published.[6-8] Since both drugs were available at once for newly diagnosed AML patients in real life, and the combining of GO plus MIDO with standard IC did not represent a pharmacological contraindication, we decided to employ and retrospectively evaluate the effectiveness and safety of a GO+MIDO+standard IC in patients treated at two Czech hematological centers.

Our retrospective study included random successive newly diagnosed patients with AML, CD33 positivity plus *FLT3* mutation and of good or intermediate cytogenetics, fit for intensive therapy, treated with GO+MIDO+standard induction IC (7+3 regimen using cytarabine 200 mg/m^2 continuous infusion D1-7 plus daunorubicin 60 mg/m^2 D1-3). No other prespecified criteria was applied. Midostaurin was orally administered at 50 mg BID during D8-21, and GO was used at 3 mg/m^2 QD intravenously on D1, D4, and D7, respectively, according to Summary of product characteristics (SPC). Subsequently, patients in CR without serious adverse events to GO after induction chemotherapy received 1-2 consolidations with GO+MIDO (GO 3 mg/m^2 D1 intravenously plus MIDO 50 mg BID during D8-21 orally plus daunorubicin 60 mg/m^2 D1-2 intravenously plus cytarabine 1 g/m^2 BID on D1-4 intravenously). Patients were diagnosed from the period 13-Jul-2020 through 09-Jun-2022 at two Czech hematological centers. Data were obtained from a detailed real-world AML patient database - DATOOL-AML (Database of Acute Leukemia-Tool) on behalf of CELL group (Czech Leukemia Study Group for Life) covering epidemiology, AML characteristic, therapy, safety, and outcome.

Research was undertaken respective of relevant guidelines and regulations with project approval by the Multicentric Ethics Committee of the Brno University Hospital (Number 01-191022/EK). All involved patients signed their informed consent.

Basic statistical methods were applied to describe absolute and relative frequency for categorical variables, median, mean, minimum, and maximum for continuous variables, respectively.

A total of 11 patients with *FLT3*+/CD33+ AML (64% men; median age 44 yrs) were evaluated with a 53week median follow-up (Mean: 52, Range: 6-104) since AML diagnosis. Most patients had AML with recurrent genetic abnormalities (46% *NPM1;* 9% *RUNX1::RUNX1T1;* 9% *RUNX1*), 2 AML not otherwise specified (18%), and 2 AML therapy-related (18%), respectively. *FLT3*-ITD was present in 6 patients (55%), *FLT3*-TKD in 3 cases (27%), and both *FLT3*-ITD and *FLT3*-TKD in 2 patients (18%), respectively. The majority had normal cytogenetic findings (82%). The median baseline white blood count was $50x10^9$/L (1.4-426.0). Regarding ELN risk 2017 stratification, 7 cases were classified as favourable (64%), 1 intermediate (9%), and 3 adverse (27%), respectively. Patient characteristics are shown in Supplemental table 1.

The median number of days from diagnosis to initiation of combined intensive induction treatment was 8 days (4-12). Initially, nine (82%) patients received cytoreduction with hydroxyurea, leukapheresis was additionally undertaken in 3 (27%) of them. After GO+MIDO+IC induction, a dominant part of the cohort attained complete remission (10; 91%), of which 1 patient with *NPM1* and 2 patients with *FLT3*-ITD/*FLT3*-TKD mutations reached molecular MRD negativity (27%). In one patient with refractory disease (9%), a FLAG (fludarabine, cytarabine and filgrastim) salvage regimen resulted in hematologic CR followed by allo-HSCT. A total of 6 (55%) patients continued with 1-2 consolidations including GO+MIDO, and 3 (27%) of them subsequently underwent allo-HSCT. Regarding the GO+MIDO use in consolidation, two (18%) patients were not evaluable due to the data cut-off

exactly at the time of response assessment after induction, and two (18%) patients did not continue GO at the discretion of physicians due to toxicity. Finally, all patients achieved CR, from which all *NPM1*-mutated patients reached molecular CR (46%) (Supplemental table 2).

The median time to neutrophil recovery to $1.0x10^9$/L / platelet recovery to $50x10^9$/L was, following start of induction treatment, 38 days and 29 days, respectively, and after the 1st consolidation with GO+MIDO, 19 days and 22 days, respectively. Adverse events after induction treatment involved 1 case of infection grade 3 (9%), 1 case of sinusoidal obstruction syndrome (SOS) grade 2 (9%), two cases of bleeding (gastrointestinal grade 3, gynecological gr. 2) (18%), one case of *Clostridium difficile* infection grade 2 (9%), eight cases of bilirubin / liver transaminases elevation grade 1-2 (73%), and one case of liver transaminases elevation grade 3 (9%). Following consolidation therapy, we noted two cases of infection grade 3 (18%), three cases of liver transaminases elevation gr. 1-2 (27%), respectively. In two patients (18%), GO was not added to consolidation owing to serious infectious complication and SOS after induction, related to GO with a high probability, respectively. Subsequently, within the second consolidation, GO was not administered in 2 (19%) cases due to allo-HSCT (Supplemental table 2). Midostaurin was not in any case interrupted or discontinued due to toxicity.

At the last follow-up, a total of 10 patients (91%) were still alive; one patient with therapy-related AML in molecular CR (*NPM1*) died during aplasia after haploidentical HSCT resulting from infectious complications (9%) (Figure 1). Complete remission lasted in a total of seven patients (7/11; 64%); three patients relapsed (3/11; 27%) - two of them had molecular relapses (2/11; 18%) and one hematological relapse (1/11; 9%), respectively.

Our study emphasized the excellent effectiveness of GO plus MIDO in addition to standard IC for newly diagnosed *FLT3*-mutated/CD33+ AML patients with good tolerability and no unusual increase in toxicity, respectively.

Among literature, a number of studies separately evaluated the efficacy and safety of either GO or MIDO added to standard induction chemotherapy in newly diagnosed AML.[1-3] To the best of our knowledge, an original article analyzing GO-based intensive treatment results in combination with MIDO and standard chemotherapy has not yet been published. Over the previous two years, ongoing randomized study results have been presented in the form of conference abstracts. The first of these was a study by Röllig et al.[6] reporting a phase I trial of 11 patients with newly diagnosed *FLT3*-mutated AML combining standard induction chemotherapy with MIDO and GO. Similar to our results, the 30-day mortality among all enrolled patients was 0%, notwithstanding one case of SOS observed. Similarly, composite CR was reached in 91% of patients. Authors defined the GO standard dose on days 1+4 and the MIDO standard dose on days 8-21 of induction treatment as the maximum tolerable dose which can be safely combined with standard IC in newly diagnosed AML. Another phase I dose-finding study by Borate et al.[7] assessing the safety and preliminary efficacy of GO+MIDO+IC combination in 8 newly diagnosed *FLT3*-mutated AML yielded promising responses and good tolerability with no dose-limiting toxicity. Composite CR rate was 75%. Moreover, no treatment-related deaths in the first 30 days were documented. One patient had a serious adverse event designated by a GO-related grade 4 SOS. Finally, the third published abstract concentrated on MIDOTARG pilot trial results evaluating GO+MIDO+IC safety in 59 newly diagnosed *FLT3*+ AML and the impact on MRD kinetics.[8] Induction course treatment compliance was comparable to our results (100% vs. 100%). The difference between the MIDOTARG pilot trial and our study was the number of GO doses during induction treatment (2 vs. 3, respectively). Day 60 mortality 0% was the same as in our study. No SOS cases were

reported compared to our 1 case (0% vs. 9%, respectively). Time to neutrophil recovery to $1.0x10^9$/L was 32 days compared to 38 days in our cohort. The longer time to neutrophils recovery could be associated with the higher total dose of GO administered within induction in our cohort compared to the MIDOTARG trial. Similarly, time to platelet recovery to $100x10^9$/L was 29 days compared to 32 days in our study / 35 days in ALFA-0701.[2,8] Furthermore, CR/CRi was achieved in 88% vs. 91% in our study.[8] In our study, only one patient died due to infection in molecular CR (9%).

Our study's major strength is its unique focus on a homogenous patient cohort with *FLT3*-mutated/CD33+ AML treated by GO+MIDO+IC at two academic hematology centers. Study constraints concern only the limited number of evaluated cases.

In summary, our data highlighted a high response rate and good tolerability with no evidence of increased toxicity of GO plus MIDO added to standard IC in patients with newly diagnosed *FLT3*-mutated/CD33+ AML, with exception of slightly prolonged recovery of neutrophils count. Our results should be validated by a larger patient sample with longer follow-up.

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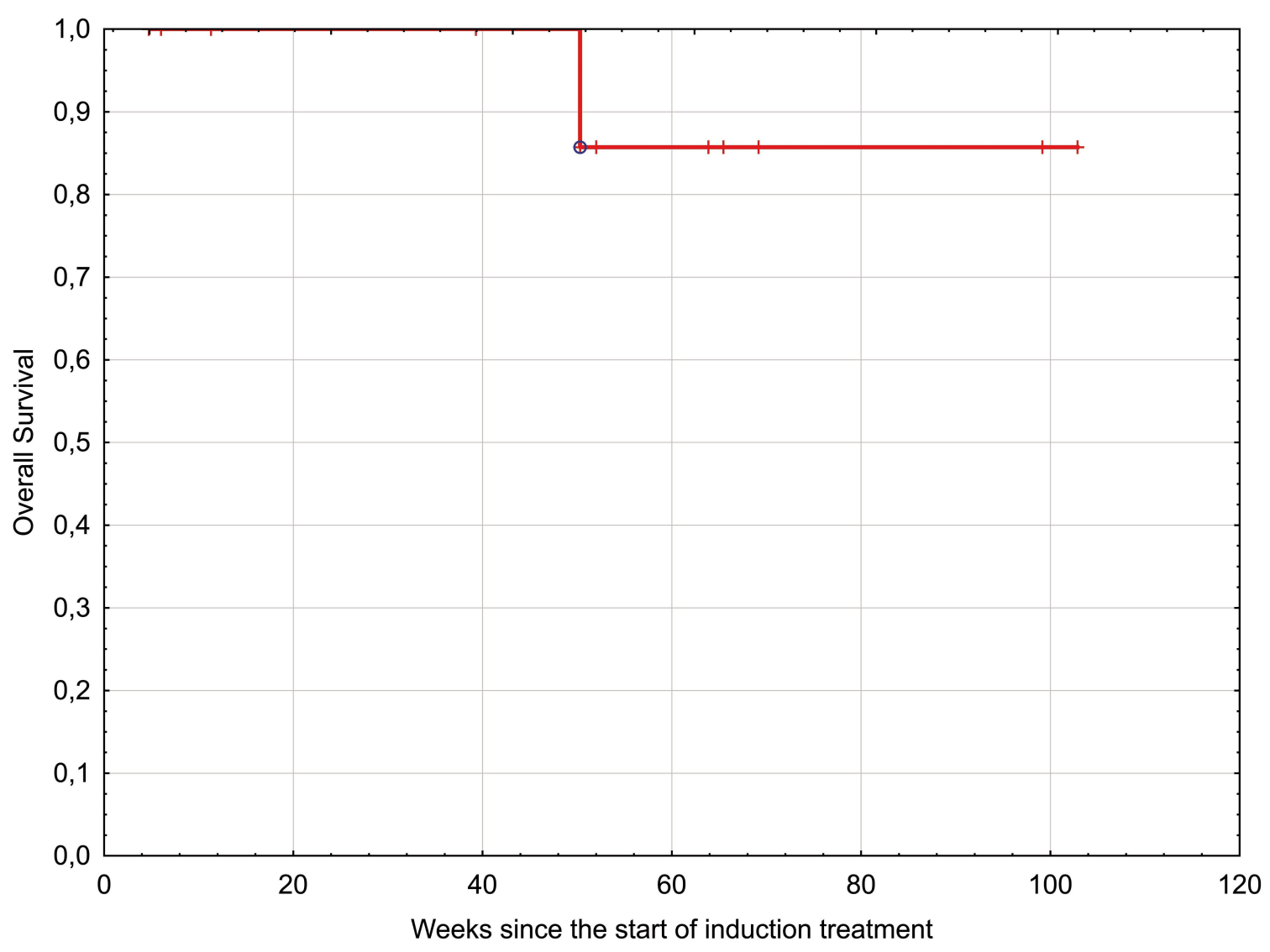
Figure 1. Overall Survival of Patients with Newly Diagnosed AML Treated with GO+MIDO+IC Regimen.

Figure 1 shows the overall survival of patients in weeks since the start of GO+MIDO+IC induction treatment.

Abbreviations: AML – Acute Myeloid Leukemia; GO+MIDO+IC – Gemtuzumab Ozogamicin+Midostaurin+Intensive Chemotherapy


1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
Overall Survival
0
20
40
60
80
100
120
Weeks since the start of induction treatment

Supplemental table 1. Enrolled Study Patient Characteristics at the Time of AML Diagnosis.

Pt. No.	Age/ Gender	ECOG	AML (WHO 2016)	Genetics	*FLT3* Subtype	*FLT3* Allelic Ratio	ELN Risk 2017
1	57/M	0	With recurrent genetic abnormalities	*NPM1*	ITD	Low (<0.5)	Favourable
2	27/F	0	With recurrent genetic abnormalities	*NPM1*	ITD	Low (<0.5)	Favourable
3	52/M	1	With recurrent genetic abnormalities	*NPM1*	TKD	-	Favourable
4	30/M	2	NOS (M2)	-	ITD	High (≥0.5)	Adverse
5	26/M	1	With recurrent genetic abnormalities	*RUNX1::RUNX1T1*	TKD	-	Favourable
6	41/M	2	With recurrent genetic abnormalities	*RUNX1*	ITD / TKD	Low (<0.5)	Adverse
7	61/M	0	Therapy-related	-	ITD	High (≥0.5)	Adverse
8	49/F	1	With recurrent genetic abnormalities	*NPM1*	ITD	Low (<0.5)	Favourable
9	32/F	1	With recurrent genetic abnormalities	*NPM1*	TKD	-	Favourable
10	54/M	1	NOS (M4)	-	ITD / TKD	Low (<0.5)	Intermediate
11	44/F	1	Therapy-related	*NPM1*	ITD	Low (<0.5)	Favourable

Abbreviations: AML – Acute Myeloid Leukemia; M – men; F – female; WHO – World Health Organization; NOS – Not Otherwise Specified; ITD – Internal Tandem Duplication; TKD – Tyrosine Kinase Domain; ELN – European Leukemia Net

Supplemental table 2. Patient Treatment Outcomes and Toxicity following GO+MIDO+IC Regimen.

1st Cycle of GO+MIDO+IC	2nd Cycle of GO+MIDO+IC		3rd Cycle of GO+MIDO+IC	Subsequent Therapy	Final Efficacy	Efficacy at last FU	Status at last FU
Reason for GO discontinuation	**Efficacy**	**Reason for GO discontinuation**	**Efficacy**				
Infection				4cy IDAC+MIDO	CR_{mol-}	$R1_{mol}$	Alive
NA	CR_{mol+}	NA	ND	1cy IDAC+MIDO	CR_{mol-}	$R1h_{em}$	Alive
NA	ND	NA	CR_{mol+}	2cy IDAC+MIDO	CR_{mol-}	CR_{mol-}	Alive
Treatment failure				1cy FLAG / 1cy HDAC / Allo-HSCT	CR¶	CR¶	Alive
NA#					CR*	CR*	Alive
NA	CR_{mol-}	Allo-HSCT		Allo-HSCT	CR_{mol-}	$R1_{mol}$	Alive
NA	CR_{mol+}	NA	CR_{mol+}	Gilteritinib / Allo-HSCT	CR_{mol-}	CR_{mol-}	Dead
NA	CR_{mol+}	NA	CR_{mol-}		CR_{mol-}	CR_{mol-}	Alive
NA	CR_{mol+}	Allo-HSCT		Allo-HSCT	CR_{mol-}	CR_{mol-}	Alive
SOS				1cy HDAC+MIDO	CR_{mol-}	CR_{mol-}	Alive
NA#					CR*	CR*	Alive

Pt. No.	1	2	3	4	5	6	7	8	9	10	11
Efficacy	CR_{mol-}	CR_{mol+}	CR_{mol+}	RD	CR*	CR_{mol-}	CR_{mol+}	CR_{mol+}	CR_{mol+}	CR_{mol-}	CR*

Abbreviations: GO+MIDO+IC – Gemtuzumab Ozogamicin+Midostaurin+Intensive Chemotherapy; cy - Cycle; CR – Complete Remission; CR_{mol-} – Molecular Complete Remission; CR_{mol+} – Complete Remission with Positive Molecular Minimal Residual Disease; RD – Refractory Disease; FU – Follow-up; NA – Not Applicable; SOS – Sinusoidal Obstruction Syndrome; ND – Not Done; $R1_{mol}$ – First Molecular Relaps; $R1_{hem}$ – First Hematological Relaps; Allo-HSCT – Allogeneic Hematopoietic Stem Cell Transplantation; IDAC – Intermediate Dose of Cytarabine; HDAC – High Dose of Cytarabine; FLAG – Fludarabine+Cytarabin+G-CSF

* - Molecular MRD data were not available at the time of analysis.

¶ - Molecular MRD cannot be measured.

- Unavailable data owing to short follow-up