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

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

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

In literature, robust data on a midostaurin plus GO combination with standard IC in newly diagnosed *FLT3*-mutated/CD33$^+$ AML are lacking. Only limited conference abstracts of ongoing studies have been published.[6-8] Since both drugs were available at once for newly diagnosed AML patients in real life, and there was no apparent pharmacological contraindication to combining GO plus midostaurin with standard IC, we decided to employ and retrospectively evaluate the effectiveness and safety of GO + midostaurin + standard IC in patients treated at two Czech hematology centers.

Our retrospective study included random successive, newly diagnosed patients with AML, CD33 positivity plus *FLT3* mutation and good- or intermediate-risk cytogenetics, fit for intensive therapy, treated with GO + midostaurin + standard induction IC (7+3 regimen using cytarabine 200 mg/m^2 continuous infusion days 1-7 plus daunorubicin 60 mg/m^2 days 1-3). No other prespecified criteria were applied. Midostaurin was given orally at a dose of 50 mg BID during days 8-21, and GO was administered at a dose of 3 mg/m^2 QD intravenously on days 1, 4, and 7, according to the Summary of Product Characteristics. Subsequently, patients in complete response without serious adverse events in reaction to GO after induction chemotherapy received one or two courses of consolidation with GO + midostaurin (GO 3 mg/m^2 on day 1 intravenously plus midostaurin 50 mg BID from day 8 to day 21 orally plus daunorubicin 60 mg/m^2 days 1 and 2 intravenously plus cytarabine 1 g/m^2 BID on days 1 to 4 intravenously).

Patients were diagnosed in the period from July 13, 2020 through June 9, 2022 at two Czech hematology centers. Data were obtained from a detailed database of real-world AML patients - DATOOL-AML (Database of Acute Leukemia-Tool) on behalf of the CELL group (Czech Leukemia Study Group for Life) covering epidemiology, AML characteristics, therapy, safety, and outcome.

This research was undertaken in respect of relevant guidelines and regulations with project approval by the Multicenter Ethics Committee of Brno University Hospital (Number 01-191022/EK). All patients involved signed informed consent.

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

A total of 11 patients with *FLT3*$^+$/CD33$^+$ AML (64% men; median age 44 years) were evaluated with a median 53-week follow-up (mean, 52 weeks; range, 6-104) since the diagnosis of AML. Most patients had AML with recurrent genetic abnormalities (46% *NPM1*; 9% *RUNX1::RUNX1T1*; 9% *RUNX1*), two had AML not otherwise specified (18%), and two had therapy-related AML (18%). A *FLT3*-internal tandem duplication (ITD) was present in six patients (55%), *FLT3*-tyrosine kinase domain (TKD) mutations in three cases (27%), and both *FLT3*-ITD and *FLT3*-TKD mutations in two patients (18%). The majority had normal cytogenetic find-

ings (82%). The median baseline white blood count was 50x10^9/L (range, 1.4-426.0). Regarding ELN 2017 risk stratification, seven cases were classified as favorable risk (64%), one as intermediate risk (9%), and three as adverse risk (27%). The patients' characteristics are shown in *Online Supplementary Table S1*.

The median number of days from diagnosis to initiation of combined intensive induction treatment was 8 days (range, 4-12). Initially, nine (82%) patients received cytoreduction with hydroxyurea and leukapheresis was additionally undertaken in three (27%) of them. After GO + midostaurin + IC induction, most of the cohort attained complete remission (n=10; 91%), among whom one patient with *NPM*-mutated AML and two patients with *FLT3*-ITD/*FLT3*-TKD mutations reached molecular minimal residual disease negativity (27%). In one patient with refractory disease (9%), a FLAG (fludarabine, cytarabine and filgrastim) salvage regimen resulted in hematologic complete remission which was followed by allogeneic HSCT. A total of six (55%) patients continued with one or two courses of consolidation including GO + midostaurin, and three (27%) of them subsequently underwent allogeneic HSCT. Regarding the use of GO + midostaurin in consolidation, two (18%) patients were not evaluable because the data cutoff was exactly at the time of response assessment after induction, and two (18%) patients did not continue GO at the discretion of their treating physicians, because of toxicity. Finally, all patients achieved complete remission, with all *NPM1*-mutated patients reaching a molecular complete remission (46%) (*Online Supplementary Table S2*).

The median time to recovery of the neutrophil count to 1.0x10^9/L and the platelet count to 50x10^9/L following the start of induction treatment was 38 days and 29 days, respectively, whereas after the first consolidation with GO + midostaurin, it was 19 days and 22 days, respectively. Adverse events after induction treatment comprised one case of infection grade 3 (9%), one case of sinusoidal obstruction syndrome grade 2 (9%), two cases of bleeding (gastrointestinal grade 3, gynecological grade 2) (18%), one case of *Clostridium difficile* infection grade 2 (9%), eight cases of elevated bilirubin/liver transaminases grade 1-2 (73%), and one case of elevated liver transaminases grade 3 (9%). Following consolidation therapy, we noted two cases of infection grade 3 (18%), and three cases of elevated liver transaminases grade 1-2 (27%). In two patients (18%), GO was not added to consolidation because of serious infectious complications and sinusoidal obstruction syndrome after induction, with a high probability of these being related to GO. Subsequently, within the second consolidation, GO was not administered in two (19%) cases because of allogeneic HSCT (*Online Supplementary Table S2)*. Midostaurin was not interrupted or discontinued due to toxicity in any case.

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

Our study highlights the excellent effectiveness of GO plus midostaurin in addition to standard IC for newly diagnosed *FLT3*-mutated/CD33$^+$ AML patients: the tolerability of the combination was good and there was not an unusual increase in toxicity.

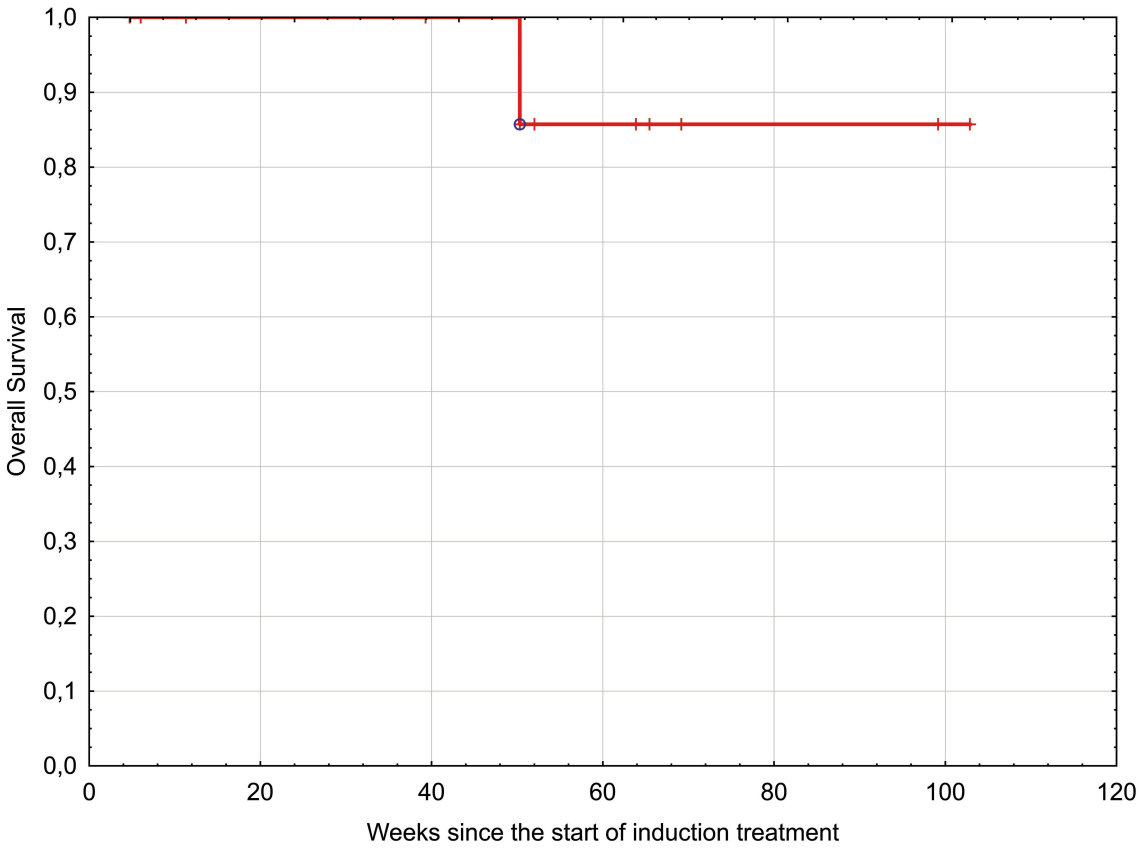

Figure 1. Overall survival of patients with newly diagnosed acute myeloid leukemia treated with the combination regimen. Overall survival of patients in weeks since the start of treatment with the combination of gemtuzumab ozogamicin + midostaurin + intensive chemotherapy induction.

A number of studies published in the literature have separately evaluated the efficacy and safety of either GO or midostaurin added to standard induction chemotherapy in newly diagnosed AML.[1-3] However, to the best of our knowledge, an original article analyzing GO-based intensive treatment in combination with midostaurin and standard chemotherapy has not yet been published. In the last 2 years, results of ongoing randomized studies have been presented in the form of conference abstracts. One such study was that by Röllig *et al.*,[6] who reported a phase I trial of 11 patients with newly diagnosed *FLT3*-mutated AML combining standard induction chemotherapy with midostaurin and GO. Similar to our results, the 30-day mortality among all enrolled patients was 0%, notwithstanding one case of sinusoidal obstruction syndrome. Similarly, a composite complete remission was reached by 91% of the patients. The authors defined the standard GO dose on days 1+4 and the standard midostaurin dose on days 8-21 of induction treatment as the maximum tolerable dose which could 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 + midostaurin + IC in eight patients with newly diagnosed *FLT3*-mutated AML yielded promising responses and the tolerability of the combination was good, with no dose-limiting toxicity. The composite complete remission rate was 75%. Moreover, no treatment-related deaths were documented in the first 30 days. One patient had a serious adverse event designated as GO-related grade 4 sinusoidal obstruction syndrome. Finally, the third published abstract concentrated on the results of the MIDOTARG pilot trial evaluating the safety of GO + midostaurin + IC in 59 patients with newly diagnosed *FLT3*$^+$ AML and the impact on minimal residual disease kinetics.[8] Compliance with the induction treatment was comparable to that in our study (100% and 100%, respectively). 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 cases of sinusoidal obstruction syndrome were reported in the MIDOTARG trial, compared to one case in our study (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 neutrophil recovery may be associated with the higher total dose of GO administered within induction in our cohort compared to that given to patients in the MIDOTARG trial. Similarly, time to platelet recovery to $100x10^9$/L was 29 days, compared to 32 days in our study and 35 days in ALFA-0701.[2,8] Complete remission with or without recovery of blood counts was achieved in 88% compared to 91% in our study.[8] In our study, only one patient died due to infection in molecular complete remission (9%).

Our study's major strength is its unique focus on a homogeneous cohort of patients with *FLT3*-mutated/CD33$^+$ AML treated with GO + midostaurin + IC at two academic hematology centers. The study limitations concern only the small number of evaluated cases.

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

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Disclosures

No conflicts of interest to disclose.

Contributions

BW and JM contributed to study conception and design, implemented preparation of the material, data collection and analysis and wrote and revised the manuscript. MČ, TK, LS, NP, TS, and IJ contributed to the data collection, commented on previous versions of the manuscript and reviewed and approved the final version.

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Data-sharing statement

Complete data can be shared upon request.

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