



Use of gemtuzumab ozogamicin in relapsed refractory acute myeloid leukemia: Multi-center real life data from Turkey

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ABSTRACT

We retrospectively evaluated the use of gemtuzumab ozogamicin (GO) in relapsed refractory (R/R) acute myeloid leukemia (AML) patients. Twenty-one CD33 positive R/R AML patients who received GO as a single agent in 4 hematology centers were included in this study. The median age was 59, and the median ECOG performance score was 2. According to cytogenetic analysis, 1 patient had favorable risk, 12 patients with intermediate, and 8 patients with adverse risk. The overall response rate was 52.3%. Partial response was achieved in 3 of 8 patients with adverse risk. 33.3% of patients developed grade 3 anemia. Grade 4 neutropenia and thrombocytopenia were observed in 80% of the patients. One of the patients died due to sinusoidal obstruction syndrome / veno-occlusive disease (SOS / VOD) due to GO side effects. GO may be considered as a good option for salvage therapy in R/R AML patients.

1. Introduction

Acute myeloid leukemia (AML) is a genetically and biologically heterogeneous disease. Uncontrolled abnormal clonal proliferation of myeloid precursors causes leukemic blasts to accumulate in the bone marrow and severe deterioration in normal hematopoiesis [1]. Although complete remission is observed in 40% to 60% of the patients with induction chemotherapy, relapse of the disease observed in two-thirds of these patients. Patients with relapsed / refractory (R/R) disease have poor outcomes and the 5-year survival rate for patients is 10%. The optimal treatment in patients with R/R AML is uncertain [2,3]. Salvage chemotherapy regimens commonly used for young patients with R/R AML include FLAG - IDA (fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor) and MEC (mitoxantrone, etoposide, and cytarabine) treatments. FMS - like tyrosine kinase 3 (FLT3) inhibitor drugs such as midostaurin and quizartinib can be used alone or in combination with hypomethylating agents in patients with R/R AML [4]. Isocitrate dehydrogenase (IDH) 1 enzyme inhibitor ivosidenib and

IDH 2 enzyme inhibitor enasidenib are other options in the treatment of R/R AML [5,6]. Gemtuzumab ozogamicin (GO) is also used for relapsed / refractory cases. GO is a humanized anti-CD33 monoclonal antibody conjugated to calicheamicin, a powerful antitumor antibiotic that cleaves double-stranded DNA in specific sequences. CD33 (sialic acid-binding Ig-like lectin-3 / SIGLEC-3) is a transmembrane receptor expressed in myeloid cells, suppressing the inflammatory and immune response. CD33 also regulates cytokine production and intercellular adhesion [7]. CD33 is a surface antigen seen in blasts in more than 80% of cases in AML patients. While they are found on the surface of normal hematopoietic precursor cells, they are neither present on normal hematopoietic stem cells nor on the surface of non-hematopoietic cells or tissues [8]. GO was withdrawn from use in the treatment of AML in 2010 due to its toxic effects and causing premature death. It was put into use again in 2017 with the reorganization of the dosing regimen. Today, GO has been recommended as a first-line treatment for newly diagnosed AML patients. For CBF-AML (RUNX1-RUNX1T1- or CBFMYH11-positive AML), the authors recommend 7 days of

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cytarabine, 3 days of daunorubicin, and 1–3 days of GO in induction in ESMO 2020 guidelines (II, A) [9]. Their recommendation is based primarily on the meta-analysis of five studies with GO which is showed that adding GO to conventional induction therapy provides a survival benefit [10]. Also, in this guideline, the authors recommended GO with 7 + 3 induction therapy for favorable or intermediate risk (ELN) AML patients (II, C) [9]. In our study, we evaluated the use of GO in R/R AML patients as multi-center real-life data.

2. Methods

2.1. Patients

Twenty-one CD33 positive R/R AML patients who received GO as a single agent in 4 hematology centers were included in the study. The diagnosis was established according to the World Health Organization (WHO) myeloid neoplasms classification [11]. CD33 levels were evaluated by flow cytometry from bone marrow aspiration samples and values above 20% were considered positive. Cytogenetic investigations were performed using reverse transcriptase-polymerase chain reaction (RT-PCR) and next-generation sequencing (NGS) methods. Cytogenetic risk assessment was made according to the European Leukemia Net (ELN) classification [12].

2.2. Treatment schedule

Three different treatment schedules were used in retrospectively evaluated patients. Fourteen patients received 3 mg/m²/day on days 1, 4 and 7; 5 patients received 3 mg/m²/day on day 1, and 2 patients 6 mg/m²/day on days 1 and 14. All patients received diphenhydramine and acetaminophen as premedication.

2.3. Response criteria and safety

Treatment response was evaluated using the National Comprehensive Cancer Network (NCCN version 3.2021) guidelines [13]. The overall response was defined as a complete response (CR) and partial remission (PR). Adverse event staging was evaluated using the World Health Organization (WHO) toxicity scale [14].

2.4. Statistical analyses

Results were analyzed using Statistical Package for the Social Sciences (SPSS) 18.0 (SPSS Inc., Chicago, USA). The Kaplan Meier method was used for frequency and descriptive statistics, survival curve, and analysis of demographic data. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

In this study, a total of 21 patients were included, and their demographic and clinical characteristics are summarised in Table 1. The median age was 59 years (35–81). Nine (42%) of the included patients had an ECOG performance status of 2. Cytogenetic analysis of all patients was available, demonstrating 1 patient in the favorable risk group, 12 patients in the intermediate, and 8 in the adverse risk group. Before GO treatment, 2 patients had autologous hematopoietic stem cell transplantation (auto-HSCT) and 1 patient had allogeneic hematopoietic stem cell transplantation (allo-HSCT). The patient who was performed allo-HCT was followed up in remission after transplantation and relapse was detected 25 months later. For the two auto-HCT patients, post-HCT relapses were detected after 3 and 10 months, respectively.

Table 1
Demographic and clinical characteristics.

Characteristics	Number of patients (n = 21)
Age	
Median (range)	59 (35–81)
< 65	9
≥65	12
Gender	
Female / Male	8 / 13
AML type	
AML with RGA	2
AML with MRC	7
AML, NOS	12
Cytogenetics	
Favorable	1
Intermediate	12
Adverse	8
Extramedullary involvement	3
Performance status	
ECOG 1	5
ECOG 2–3	16
Prior treatment	
Median (range)	2 (1–4)
CD 33 level before treatment (range)	78 (28–100)

AML with MRC: AML with myelodysplasia-Related Changes, AML, NOS: AML, Not Otherwise Specified, AML with RGA: AML with recurrent genetic abnormalities.

3.2. Treatment response

The mean follow-up time of the patients was 21 ± 12,7 months and GO duration was 15.7 ± 10.1 months after diagnosis. The patients received median 2 (1–4) lines of treatment before GO. Eleven patients responded to GO. One of them had achieved a CR and 10 patients had a PR. Ten patients did not experience any response. Each patient's treatment response was evaluated after each cycle (Table 2). Regarding the response rates after the first cycle of the treatment; the morphological complete response was observed in 1 patient, partial remission in 10 patients, and nonresponse in 10 patients. Five patients died in the 2nd month of the treatment. In the 3rd month, only 4 patients received the treatment because of treatment change or death. Two of these 4 patients had a partial response. The overall response rate was 52.3%. A total of 10 patients died during the study. The overall survival was 38.5% in the sixth month and 14% in the first year. The mean overall survival was 5.2 months. The survival chart is shown in Fig.-1.

3.3. Cell surface antigen positivity and GO efficacy

The median CD33 level of the patients detected by flow cytometry before treatment was 88% (28–100%). No relation was found between baseline CD 33 levels and treatment response. CD33 alteration after treatment could not be analyzed for all patients. Because that statistically significant result not obtain, CD33 levels could not be compared before and after treatment.

3.4. Safety

Hematological adverse events are summarized in Table 3. Five patients developed neutropenic fever and died due to sepsis. In the blood

Table 2
Treatment response.

	1.month	2.month	3.month
Complete response(n)	1	1	–
Partial response(n)	10	5	2
Unresponsiveness to treatment(n)	10	4	2
Death(n)	–	5	5
Treatment change(n)	6	1	

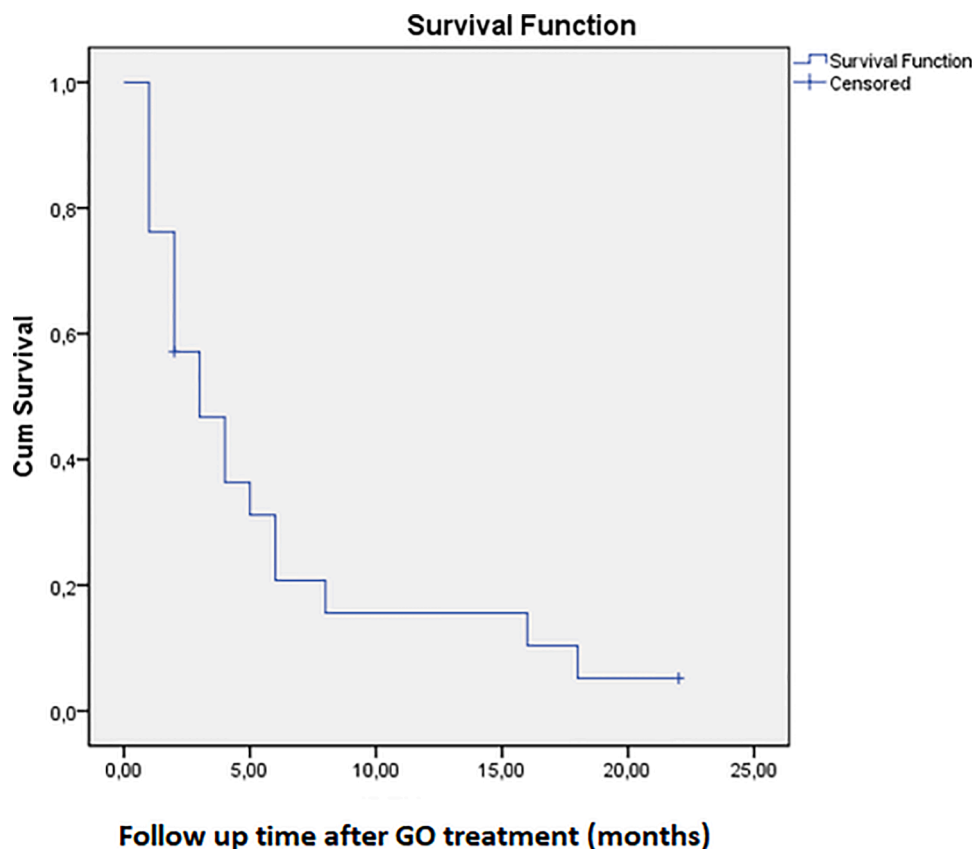


Fig. 1. Kaplan-Meier Survival Analysis.

Table 3
Hematological Side Effects.

	Anemia (n)	Thrombocytopenia (n)	Neutropenia (n)
None	5	1	1
Grade 1	4	1	1
Grade 2	3	–	1
Grade 3	7	2	1
Grade 4	2	17	17

cultures of patients who died from sepsis, Acinetobacter, ESBL-positive E. Coli, and enterococcus faecium were found in 1, 2, and 1 patient, respectively. No agent was obtained in 1 patient. One of the patients died due to sinusoidal obstruction syndrome / veno-occlusive disease (SOS / VOD) due to GO side effects.

4. Discussion

The clinical effectiveness of GO is initially evaluated in 3 open-label, single-arm, determined in Phase II first relapse AML studies. In these studies, a total of 277 patients received GO at a dose of 9 mg/m² every 2 weeks and the overall response rate was 26%. Regarding the hematological side effects, stage 3/4 neutropenia and thrombocytopenia were 98% and 99% respectively. VOD / SOS side effects were seen in 5% of patients [8]. MyloFrance-1 is a phase II single-arm open-label study that evaluates the use of a divided dosing schedule of GO at the first relapse in CD33 + AML patients (Days 1, 4, and 7 with the dose of 3 mg/m²). In this study among 57 patients, the total response rate was 33%. Concerning the side effects, stage 3/4 anemia and thrombocytopenia were observed at a rate of 10%, while no patient had VOD / SOS [15]. A meta-analysis comparing GO dose schedules was performed in patients with R/R AML. This study showed that a lower-dose "fractionated" schedule of 3 mg/m² on days 1, 4, and 7 were associated with less early

mortality, hemorrhage, and VOD; without an apparent decrease in CR rate [16].

In a recent study, Hosono et al. were evaluated 19 R/R AML patients who were treated with GO as a single agent retrospectively. Six patients responded to treatment and the overall response rate was 31.6% in this study. The most common adverse event was febrile neutropenia (84%) [17].

In real-life data from France, 94 AML patients were evaluated retrospectively. Twenty-two of them were newly diagnosed AML patients and were treated with fractionated doses of GO. This study showed that the overall response rate was 65% and disease-free survival was 8 months in the R/R group [18].

In our study, 80% of patients received GO as a lower-dose fractionated schedule. Similar to the literature, progression-free survival was 7.8 months. The overall response rate was 52.3% and that was above the literature data. In the study of Hosono et al., all patients died in the first year, whereas in our study, 3 patients were alive in the first year [17]. Similar to the literature, response rates decreased the longer the follow-up.

The randomized, phase III ALFA-0701 trial showed that the main toxicity associated with GO was prolonged thrombocytopenia. In this study, persistent grade 3/4 thrombocytopenia was observed in 16% of patients in the GO arm compared with 3% in the control arm. Inasmuch that, the study protocol (following an amendment on December 2009) recommended that GO should not be used during consolidation in patients with a platelet count < 100 × 10⁹/L by day 45 after the initiation of chemotherapy [19]. Notably, the term CRp was first used in relation to the use of GO, recognizing that approximately half of the responders did not fully recover platelet counts [20]. In our study, grade 4 neutropenia and thrombocytopenia were common consistent with the literature, but none of them persistent.

Previous studies demonstrated that while patients with favorable and intermediate cytogenetic risk benefit from GO treatment, patients

with adverse cytogenetic risk did not [21]. While the literature data does not recommend GO treatment at the first line in patients with AML diagnosed with adverse cytogenetic risk, there is not enough data in R / R cases. In our study, while the partial response was obtained in 3 of 8 patients with adverse cytogenetic risk, one patient with favorable cytogenetic risk was unresponsive to treatment. Considering the subgroup analysis, these patients with adverse and favorable cytogenetic risk had received two lines of treatment before GO. CD33 level before GO treatment was 88% in the patient with favorable cytogenetic risk, 68%, 33% and, 100% in the three patients with the adverse risk group, respectively (Table 4). These data suggest that response can be obtained from GO treatment in patients with an adverse cytogenetic risk profile diagnosed with R / R AML, regardless of the previous treatment number and independent of CD33 level.

In a study published in 2004, 24 patients with R/R AML were evaluated and five patients had myeloid sarcoma. Two of these patients were given a monthly dose of GO 9 mg/m² and a complete response was obtained. Two of the patients were given a dose of GO 6 mg/m² once a month and regression were detected in the lesions. One patient remained resistant to treatment [22]. In a case report published in February 2020, three patients with R/R AML and low-performance scores were evaluated. GO treatment was given to two of these patients while one patient developed stage 2 respiratory failure and another developed acute kidney injury. In all three cases, respiratory failure and rapid recovery in renal function, and improvement in performance scores were reported after GO treatment [23]. In our study, myeloid sarcoma was detected on the skin during the recurrence in one patient, and completely resolved lesions occurred after the first cure with GO treatment. In one patient refractory to primary therapy, myeloid sarcoma was detected in the skin during the follow-up, lesions regressed after the first cycle of GO treatment and completely resolved after the second cycle. Another patient in our study was relapsed after allo-HSCT with an isolated testicular involvement and femoral mass. He was managed successfully with GO in addition to radiotherapy [24]. He is currently alive without disease and similar to this case, there are cases in the literature showing that the use of GO is safe and effective in patients with isolated extramedullary relapse after allo HSCT [25]. These data suggest that GO can reach a therapeutic concentration not only in the blood and bone marrow but also in some tissues.

The limitations of the study consist that the study was a retrospective study, there is a limited number of patients, the GO treatment protocols were not standardized and it was a heterogeneous sample group that differed from the previous treatment lines. On the other hand, our study

is important in terms of it encourages the use of GO therapy in AML patients with extramedullary involvement. Also, the study suggests that response can be obtained from GO treatment in patients with an adverse cytogenetic risk profile diagnosed with R / R AML. More studies are needed to support this.

Ethical approval

The University Faculty of Medicine Ethical Committee granted approval for this study (date: 02.06.2020, number: 2020–90).

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CRediT authorship contribution statement

Fellowship Assistant Ayşe Hilal Eroğlu Küçükçiler: Conceptualization, Supervision, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Medical Doctor Professor İrfan Yavaşoğlu:** Conceptualization, Supervision, Data curation, Formal analysis, Writing – review & editing. **Fellowship Assistant Cem Selim:** Conceptualization, Supervision, Data curation, Writing – original draft, Writing – review & editing. **Fellowship Assistant Cansu Atmaca Mutlu:** Supervision, Data curation, Writing – review & editing. **Fellowship Assistant Abdullah Karakuş:** Supervision, Data curation, Writing – review & editing. **Fellowship Assistant Mahmut Bakır Koyuncu:** Supervision, Data curation, Writing – review & editing. **Medical Doctor Professor Oktay Bilgir:** Supervision, Data curation, Writing – review & editing. **Medical Doctor Professor Orhan Ayyıldız:** Supervision, Data curation, Writing – review & editing. **Medical Doctor Professor Eyüp Naci Tiftik:** Supervision, Data curation, Writing – review & editing. **Medical Doctor Professor Ali Zahit Bolaman:** Conceptualization, Supervision, Data curation, Writing – review & editing.

CRediT authorship contribution statement

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Table 4
Patient characteristics.

AML type	Cytogenetic risk	No of prior treatment	No of GO cycles	CD33 level before GO	Response	Survival(months) after GO
Case 1	RGA	Favorable [NPM1]	2	88	Progression	2
Case 2	NOS	Adverse [t(9,22)]	2	79	Progression	1
Case 3	NOS	Adverse [t(9,22)]	1	68	PR	6
Case 4	MRC	Adverse [TP53]	2	33	PR	3
Case 5	NOS	Intermediate [SRSF2]	1	73	CR	18
Case 6	NOS	Intermediate [KCN44]	2	95	PR	16
Case 7	MRC	Intermediate [KMT2C]	2	100	PR	1
Case 8	NOS	Intermediate [SUZ12]	3	28	PR	22
Case 9	NOS	Intermediate [ATRX]	2	unknown	PR	6
Case 10	NOS	Intermediate [TET2]	2	98	Progression	1
Case 11	MRC	Intermediate [KMT2C]	2	78	Progression	2
Case 12	NOS	Intermediate [MSH6]	2	97	Progression	4
Case 13	NOS	Intermediate [DNMT3A]	1	69	PR	5
Case 14	NOS	Intermediate [TET2]	3	36	Progression	8
Case 15	MRC	Intermediate [MSH6]	3	78	Progression	4
Case 16	RGA	Adverse [t(9,22)]	4	99	Progression	1
Case 17	MRC	Adverse [ASXL1]	2	95	Progression	3
Case 18	MRC	Adverse [TP53]	2	90	Progression	2
Case 19	NOS	Adverse [RUNX1]	1	100	PR	2
Case 20	NOS	Intermediate [SRSF2]	1	99	PR	2
Case 21	MRC	Adverse [ASXL1]	2	76	Progression	1

review & editing. **İrfan Yavaşoğlu**: Conceptualization, Supervision, Data curation, Formal analysis, Writing – review & editing. **Cem Selim**: Conceptualization, Supervision, Data curation, Writing – original draft, Writing – review & editing. **Cansu Atmaca Mutlu**: Supervision, Data curation, Writing – review & editing. **Abdullah Karakuş**: Supervision, Data curation, Writing – review & editing. **Mahmut Bakır Koyuncu**: Supervision, Data curation, Writing – review & editing. **Oktay Bilgiri**: Supervision, Data curation, Writing – review & editing. **Orhan Ayyıldız**: Supervision, Data curation, Writing – review & editing. **Eyüp Naci Tiftik**: Supervision, Data curation, Writing – review & editing. **Ali Zahit Bolaman**: Conceptualization, Supervision, Data curation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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