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Reinduction Chemotherapy with Gemtuzumab Ozogamicin and Intermediate/High-Dose Cytarabine: A Single-Center Experience

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Abstract

We performed a retrospective analysis of 9 patients with acute myeloid leukemia (AML) treated with gemtuzumab ozogamicin (GO) plus cytarabine as a salvage regimen (GO reinduction) for patients who did not achieve complete remission (CR) after the first cycle of induction chemotherapy or at first relapse. Cases of AML secondary to myelodysplastic syndrome or myeloproliferative disorder were included. CR was achieved in 6 of 9 patients, and 2 of 6 responders became long-term survivors. No non-responders survived longer than 6 months. Toxicity was mild, and the median duration of myelosuppression was less than 30 days. Stomatitis, nausea and sepsis occurred as non-hematological adverse events. Although our sample size was too small to permit definitive conclusions, GO reinduction should be considered for patients who relapse or do not achieve CR after the first cycle of induction chemotherapy. Some AML subtypes may respond more robustly than others, and further investigation is warranted.

Keywords

Gemtuzumab Ozogamicin; AML; Reinduction; Salvage

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1. Introduction

The mainstay of induction chemotherapy for acute myeloid leukemia (AML), cytarabine (AraC) and anthracycline, achieves remission in 70% - 80% of untreated patients younger than 60 years of age [1] [2]. Most patients, however, eventually relapse, and the 5-year overall survival rate for this group is as low as 40% - 45% [3] [4]. In elderly patients (≥60 years old), the remission rate is less than 50% and the long-term leukemia-free survival rate is less than 10% [4].

In general, patients who do not achieve complete remission (CR) after the first cycle of induction chemotherapy are retreated with their original regimen or with AraC and another anthracycline. Although long-term outcomes are similar for patients who require 1 versus 2 cycles of induction therapy to achieve CR [5], whether or not the patient achieves CR is critical.

Therapeutic strategies for patients with relapsed AML are limited, but a small percentage of these patients do achieve remission by salvage or reinduction chemotherapy.

Gemtuzumab ozogamicin (GO) is a humanized anti-CD33 monoclonal antibody conjugated to a highly potent antitumor antibiotic, calicheamicin, which induces double-stranded DNA breaks, cell cycle arrest, and apoptosis. GO was originally approved in the United States for the treatment of elderly patients with AML after relapse [6] [7].

In 2008, Chevallier *et al*. reported long-term disease-free survival after GO, intermediate-dose AraC and mitoxantrone in patients with CD33-positive primary resistant or relapsed AML [8]. The role of combination chemotherapy regimens consisting of GO, AraC and anthracycline for the second cycle of induction therapy or for relapsed AML should be further investigated because the efficacy of conventional chemotherapies for these patients is limited.

We treated patients with GO plus AraC with or without anthracycline at Ibaraki Prefectural Central Hospital, Japan from 2009 to 2011. Here, we report the treatment outcomes of these patients and discuss the safety and efficacy of GO with reference to recent data.

2. Patients and Methods

We performed a retrospective analysis of adult patients who were treated with GO as salvage induction chemotherapy from March 2009 to August 2011 at Ibaraki Prefectural Central Hospital, Ibaraki, Japan. AML was diagnosed at initial presentation based on the World Health Organization (Fourth Edition) and French-American-British classification systems. This study included both *de novo* AML as well as AML secondary to myelodysplastic syndrome (MDS) or myeloproliferative disorder. Cytogenetic risk groups were defined according to the Bordeaux Grenoble Marseille Toulouse (BGMT) group criteria [9]. Initial induction chemotherapy in the majority of patients consisted of the "3 + 7 regimen," *i.e.*, idarubicin (12 mg/m^2 days 1 - 3) and AraC (100 mg/m^2/day days 1 - 7). When complete remission was achieved, 3 courses of consolidation therapy consisting mainly of high-dose AraC plus anthracycline were planned.

Salvage induction chemotherapy including GO (hereafter referred to as "GO reinduction") was initiated for patients who did not achieve CR after the first cycle of induction chemotherapy or for patients at first relapse. Relapse was defined as loss of CR.

2.1. GO Reinduction

Nine patients were treated with GO reinduction (**Table 1**), which consisted of mainly high-dose AraC and GO with or without anthracyclines. Six received a remission induction regimen consisting of AraC 1000 mg/m^2 twice a day via 3-hour intravenous infusion (iv) from days 1 - 5, mitoxantrone 12 mg/m^2/day via 30-minute iv from days 1 - 3, and GO 6 mg/m^2 via 2-hour iv on day 4 or 7. One patient received idarubicin 6 mg/m^2 on days 1 - 3 instead of mitoxantrone, and 2 received a regimen without anthracyclines. These modifications were determined by the doctors in charge for each patient. All patients met certain criteria, including 1) confirmation of CD33-positive AML by immunophenotyping, 2) serum creatinine and bilirubin levels < 2 mg/dL, and 3) adequate cardiac function (ejection fraction > 50%).

All patients received standard supportive care, including prophylactic and therapeutic antibiotics, as well as transfusion of blood products to maintain platelet counts above 20 × 10^9/L. A serotonin receptor antagonist and prednisolone 40 mg/day were administered daily from days 1 - 5 for antiemesis and prophylaxis of adverse reac-

Table 1. Patient characteristics.

Patient no.	Age[a]/Sex	FAB[b,c]	Disease status[d]	Cytogenetics[e]	Cytogenetics risk group at relapse	Remission duration (months)[f]	Previous treatments		GO reinduction		
							Remission induction[g,h,i]	Consolidation[j,k]			
1	65/M	M6	Non-CR	complex karyotype	Unfavorable	*	IDA + AraC	-	AraC 2000 mg/m^2 on days 1 - 5	+MIT 12 mg/m^2 on days 1 - 3	+GO 6 mg/m^2 on day 4
2	19/F	M1	Non-CR	46, XX	Intermediate	*	IDA + AraC	-	AraC 2000 mg/m^2 on days 1 - 5	+MIT 12 mg/m^2 on days 1 - 3	+GO 6 mg/m^2 on day 4
3	81/M	MDS (RA) ⇒ M2	Non-CR	46, XY	Intermediate	*	IDA + BHAC	-	AraC 2000 mg/m^2 on days 1 - 5	+MIT 12 mg/m^2 on days 1 - 3	+GO 6 mg/m^2 on day 4
4	56/F	M1	Non-CR	Not Available	Not Available	*	IDA + AraC	-	AraC 2000 mg/m^2 on days 1 - 5	+MIT 12 mg/m^2 on days 1 - 3	+GO 6 mg/m^2 on day 7
5	73/M	M2	First relapse	46, XY	Intermediate	5	CAG	IDA + AraC, BHAC-DM	AraC 100 mg/m^2 on days 1 - 5		+GO 6 mg/m^2 on day 6
6	71/M	MDS (RA) ⇒ M2	First relapse	complex karyotype	Unfavorable	10	IDA + AraC	HDAraC + MIT, ×3	AraC 2000 mg/m^2 on days 1-5		+GO 6 mg/m^2 on day 6
7	42/M	M0	First relapse	46, XY	Intermediate	19	IDA + AraC	HDAraC + MIT, ×2	AraC 2000 mg/m^2 on days 1 - 5	+MIT 12 mg/m^2 on days 1 - 3	+GO 6 mg/m^2 on day 7
8	67/M	M0	First relapse	46, XY	Intermediate	4	IDA + AraC	HDAraC + MIT, ×3	AraC 2000 mg/m^2 on days 1 - 5	+IDA 6 mg/m^2 on days 1 - 3	+GO 6 mg/m^2 on day 7
9	62/M	Essential thrombocythemia ⇒ M2	First relapse	46, XY	Intermediate	2	IDA + AraC	HDAraC + MIT, ×1	AraC 2000 mg/m^2 on days 1 - 5	+MIT 12 mg/m^2 on days 1 - 3	+GO 6 mg/m^2 on day 4

AraC, cytarabine; IDA, idarubicin; GO, gemtuzumab ozogamicin; MIT, mitoxantrone. [a]Age at the initiation of GO therapy. [b]FAB (French-American-British) subtype at first presentation (not at the initiation of GO therapy). [c]"MDS (RA) ⇒ M2" indicates AML M2 secondary to MDS refractory anemia according to the FAB classification. [d]"Non-CR" indicates a patient who did not achieve complete remission after the first cycle of induction chemotherapy. [e]Cytogenetics at the first presentation in "Non-CR" patients, or at the first relapse. [f]"*" indicates that complete remission was not achieved before GO therapy. [g]IDA + AraC: IDA 12 mg/m^2 on days 1 - 3 and AraC 100 mg/m^2 on days 1 - 7. [h]IDA + BHAC: IDA 12 mg/m^2 on days 1 - 3 and enocitabine 200 mg/m^2 on days 1 - 7. [i]CAG: AraC 10 mg/m^2 on days 1 - 14, aclarubicin hydrochloride 14 mg/m^2 on days 1 - 4, and filgrastim 200 μg/m^2 on days 1 - 14. [j]BHAC-DM: enocitabine 170 mg/m^2 on days 1 - 5, daunomycin 30 mg/m^2 on days 1 and 4, and mercaptopurine hydrate 70 mg/m^2 on days 1 - 7.

tions to AraC. Two medications were administered prior to GO: hydroxyzine pamoate 25 mg and hydrocortisone sodium succinate 100 mg. Continuous intravenous heparin was used for prophylaxis of veno-occlusive disease (VOD) for 2 patients (Nos. 8 and 9). Ursodeoxycholic acid or monoammonium glycyrrhizinate were only used if clinically indicated. During therapy, patients were monitored by routine blood tests, including complete blood cell count, coagulation test, blood chemistry, and weekly assessment of serum 1, 3-beta-D-glucan levels.

2.2. Response Definitions

CR was defined using conventional criteria: morphologic leukemia-free state, defined by <5% blasts in a bone

marrow aspirate sample; absence of blasts with Auer rods; absence of extramedullary leukemia; absolute neutrophil count ≥ 1.0×10^9/L; platelet count ≥ 100×10^9/L; and red blood cell transfusion independence. Remission duration was measured from the date of CR to the date of relapse or death from any cause. Patients without events were censored at the date of the last follow-up. Overall survival was measured from the initiation of GO reinduction to the date of death from any cause. Survival curve was calculated by Kaplan-Meier survival analysis using Microsoft Excel.

2.3. Toxicity

Toxicities during GO reinduction were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE), version 4 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

3. Results

3.1. Treatment Outcomes

Patient characteristics are summarized in **Table 1**. Four patients did not achieve CR after the first cycle of induction chemotherapy; 5 were in the first relapse after achieving CR. Two patients (Nos. 3 and 6) had AML secondary to MDS, and 1 (No. 9) had AML transformed from essential thrombocythemia. In the relapsed patients, the median duration of remission before GO reinduction was 5 months (range, 2 - 19 months).

Response to GO reinduction and outcomes are shown in **Table 2**. CR was achieved in 6 of 9 patients, with a median time to CR of 31 days (range, 27 - 36 days). Six responders received further therapy; of these, 2 patients remained in CR (Nos. 2, 7), 3 experienced relapse (Nos. 4, 6, 8), and 1 died suddenly of non-treatment-related aspiration during CR (No. 9). Of the 3 non-responders, 1 received further treatment but died of disease progression, 1 died of sepsis, and 1 did not receive further treatment because of poor performance status. Five of the 6 patients who achieved CR, but none of the non-responders, survived for more than 6 months. Median overall survival of 9 patients was 284 days (range, 15 - 724) (**Figure 1**).

3.2. Toxicities

Toxicities are summarized in **Table 3**. Overall, the GO reinduction was well tolerated. Mild (CTCAE grades 0 - 2) nausea, headache and fever, but no coagulopathy, were observed during administration of GO and other drugs. The median durations of neutropenia (defined as neutrophil count < 0.5×10^9/L) and thrombocytopenia (platelet count < 50×10^9/L and platelet transfusion dependence) were 25 and 27 days, respectively.

One individual (patient No. 3, an 81 year-old male) died of sepsis during myelosuppression. None of the patients in this study developed severe (CTCAE grade 3 or more) hepatic toxicity or VOD.

4. Discussion

Chevallier *et al*. reported the outcomes of a single-arm study for primary resistant or relapsed AML treated by GO 9 mg/m^2 on day 4, AraC 1 g/m^2 every 12 hours on days 1 - 5, and mitoxantrone 12 mg/m^2 on days 1 - 3 [8]. Of 62 patients, 18 were refractory and 44 relapsed; rates of CR and CR with delayed platelet recovery were 50% and 13%, respectively. The overall, event-free and disease-free survival rates were 41%, 33% and 53% at 2 years, respectively. Previous attempts to combine the approved dose of GO (9 mg/m^2) with chemotherapy, however, resulted in excess toxicities, particularly liver toxicity [10]. Thus, we chose a GO dose of 6 mg/m^2 in our reinduction regimen.

In 2011, Prebet *et al*. reported treatment outcome with GO and AraC for AML in the first relapse [11]. In this retrospective analysis, 34 patients were treated with intermediate- to high-dose AraC and GO (average dose 6 mg/m^2/day, range 3 - 9) +/− other cytotoxic drugs; 21 patients (58%) were with AraC 2000 mg/m^2/day on days 1 - 5, GO, and mitoxantrone 12 mg/m^2/day on days 1 - 3. Overall response rate was 68%. Overall and event-free survival were 35 and 24 months, respectively. Comparing other 56 AML patients treated with intermediate- to high-dose AraC containing regimen without GO, improved outcome was shown in low- and intermediate-risk cytogenetics groups, although patients treated with GO were more frequently transplanted with allogeneic hematopoietic stem cell.

Recently, GO was voluntarily withdrawn from the United States market after the randomized SWOG 0106

Table 2. Treatment outcome.

Patient no.	Age[a]/Sex	Disease status[b]	Days to CR[c]	Successive treatments after GO reinduction[d,e,f,g,h,I,j,k]	Remission duration after GO reinduction (days)	Overall survival (days)	Outcome
1	65/M	Non-CR	*	FLAG-IDA, HDAraC + DNR	*	99	Died of disease progression
2	19/F	Non-CR	30	HDAraC + MIT	≥694	≥724	Alive in CR
3	81/M	Non-CR	*	-	*	15	Died of sepsis
4	56/F	Non-CR	27	HDAraC + MIT, HDAraC + DNR, FLAG-IDA, HDAraC + GO	257	284	Died of sepsis
5	73/M	First relapse	*	-	*	116	Died of disease progression
6	71/M	First relapse	33	CAG, AZA	139	344	Died of disease progression
7	42/M	First relapse	36	HDAraC + MIT, ×2	≥173	≥209	Alive in CR
8	67/M	First relapse	27	FLAG + MIT, ×3	219	312	Died of disease progression
9	62/M	First relapse	32	GO + iAraC + MIT	59	91	Died of aspiration

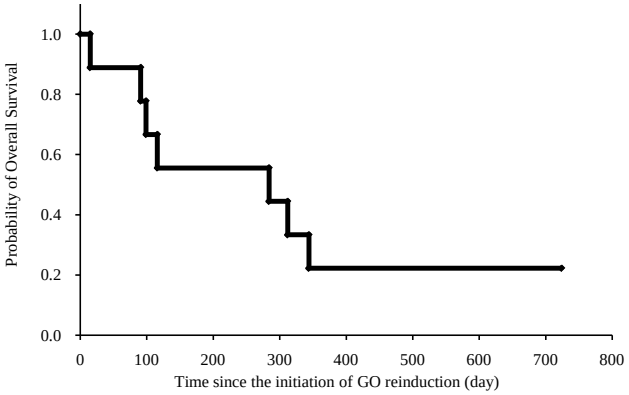
AraC, cytarabine; CR, complete remission; DNR, daunomycin; GO, gemtuzumab ozogamicin; HDAraC, high dose cytarabine; iAraC, intermediate dose cytarabine; IDA, idarubicin; MIT, mitoxantrone. [a]Age at the initiation of GO therapy. [b]"Non-CR" indicates a patient who did not achieve complete remission after the first cycle of induction chemotherapy. [c]"*" indicates that complete remission was not achieved. [d]FLAG-IDA: AraC 2000 mg/m^2 on days 1 - 5, fludarabine 30 mg/m^2 on days 1 - 5, and IDA 8 mg/m^2 on days 1 - 3. [e]HDAraC + DNR: AraC 4500 mg/m^2 on days 1 - 3 and DNR 45 mg/m^2 on days 1 - 3. [f]HDAraC + MIT: AraC 4000 mg/m^2 on days 1 - 4 and MIT 5 mg/m^2 on days 1 - 2 or on days 1 - 3. [g]HDAraC + GO: AraC 4000 mg/m^2 on days 1 - 5 and GO 6 mg/m^2 on day 8. [h]CAG: AraC 10 mg/m^2 on days 1 - 14, aclarubicin hydrochloride 14 mg/m^2 on days 1 - 4, and filgrastim 200 μg/m^2 on days 1 - 14. [i]AZA: azacitidine 80 mg/m^2 on days 1 - 7. [j]FLAG + MIT: AraC 2000 mg/m^2 on days 1 - 5, fludarabine 30 mg/m^2 on days 1 - 5, and MIT 7 mg/m^2 on days 1, 3, and 5. [k]GO + iAraC + MIT: AraC 2000 mg/m^2 on days 1 - 5, MIT 12 mg/m^2 on days 1 - 3, and GO 6 mg/m^2 on day 4.

Table 3. Adverse events.

Patient no.	Days to CR	Duration of neutropenia (days)	Duration of thrombocytopenia (days)	Non-hematological adverse event		
				Grade 1 - 2	Grade 3 - 4	Grade 5
1	*	*	*	fever, diarrhea, skin disorder, stomatitis, hepatic disorder	febrile neutropenia	
2	30	30	26	hepatic disorder	febrile neutropenia	
3	*	*	*			sepsis
4	27	25	20	fever, skin disorder	febrile neutropenia, stomatitis, nausea	
5	*	22	*		febrile neutropenia, stomatitis	
6	33	29	46	fever, stomatitis, nausea	febrile neutropenia	
7	36	38	41	diarrhea, epistaxis, anorexia, headache	febrile neutropenia	
8	27	18	28	fever, diarrhea, stomatitis	febrile neutropenia	
9	32	21	24	vomiting	febrile neutropenia, nausea	

CR, complete remission; DNR, daunomycin; GO, gemtuzumab ozogamicin; HDAraC, high dose cytarabine; iAraC, intermediate dose cytarabine; MIT, mitoxantrone. *indicates that complete remission or blood cell recovery was not achieved.

study, which added 6 mg/m^2 of GO to 3 + 7 regimen, found an increase in 30-day mortality uncompensated by improvements in CR or survival [12]. Other recent randomized trials comparing induction chemotherapy with or without GO at lower doses (<9 mg/m^2), however, found a benefit for GO in newly diagnosed AML, especially patients with more favorable cytogenetics [13] [14]. We summarize these in **Table 4** [12] [15]-[18]. Significant differences in CR rates were not found among any of the reports, however, two of five trials showed significant



The Kaplan-Meier curve shows overall survival after the initiation of salvage induction chemotherapy including GO (GO reinduction).

Figure 1. Overall survival.

Table 4. Reported randomized trials with or without GO.

Trial	No. of Patients		Age Group (years)	Induction Chemotherapy	Outcomes		Induction Mortality	Trend of a benefit for GO in favorable-risk AML
Author, year Study name	Total	No GO *v* GO			CR Rate No GO *v* GO	Survival No GO v GO	No GO *v* GO	
Petersdorf *et al*., 2009 SWOG 0106	627	229 *v* 277	18 - 60	DNR 45 mg/m^2 per day on days 1 - 3 + Ara-C 100 mg/m^2 per day on days 1 - 7 + GO 6 mg/m^2 on day 4 *v* DNR 60 mg/m^2 per day on days 1 - 3 + Ara-C 100 mg/m^2 per day on days 1 - 7	69% *v* 66%*	RFS* (data not available) EFS, NA median OS, 35 M *v* 31 M*	0.8% *v* 5.8% (p = 0.002)	NA
Burnett *et al*., 2011 MRC AML15	1113	557 *v* 556	<60	DA *v* ADE *v* FLAG-IDA ± GO 3 mg/m^2 on day 1	83% *v* 82%*	5-year RFS, 35% *v* 39%* EFS, NA 5-year OS, 41% *v* 43%*	6% *v* 7%*	Yes
Castaigne *et al*., 2012 ALFA-0701	278	139 *v* 139	50 - 70	DNR 60 mg/m^2 per day on days 1 - 3 + Ara-C 200 mg/m^2 per days 1 - 7 ± GO 3 mg/m^2 per day on days 1, 4, 7	75% *v* 81%*	2-year RFS, 23% *v* 50% (p = 0.0003) 2-year EFS, 17% *v* 41% (p = 0.0003) 2-year OS, 42% *v* 53% (p = 0.037)	4% *v* 6.5%*	Yes
Burnett *et al*., 2012 AML16	1115	556 *v* 559	51 - 84	DNR 50 mg/m^2 per day on days 1, 3, 5 and CLO 20 mg/m^2 per day on days 1 - 5 or Ara-C 100 mg/m^2 every 12 hours on days 1 - 10 ± GO 3 mg/m^2 on day 1	58% *v* 62%*	3-year RFS, 16% *v* 21% (p = 0.04) EFS, NA 3-year OS, 20% *v* 25% (p = 0.05)	11% *v* 12%*	Yes
Brunnberg *et al*., 2012	119	58 *v* 57	60 - 83	Ara-C 100 mg/m^2 per day on days 1-7 + DNR 60 mg/m^2 per day on days 1-3 *v* Ara-C 100 mg/m^2 per day on days 1-7 + GO 6 mg/m^2 on day 1 and 4 mg/m^2 on day 8	55% *v* 54%*	median RFS, 8 M *v* 14 M* EFS, NA OS, 9 M *v* 10 M*	5% *v* 19% (p = 0.021)	NA

ADE, cytarabine, daunorubicin, and etoposide; Ara-C, cytarabine; CLO, clofarabine; CR, complete remission; DA, daunorubicin plus cytarabine; DNR, daunorubicin; EFS, event-free survival; FLAG-IDA, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; GO, gemtuzumab ozogamicin; M, months; NA, not available; OS, overall survival; RFS, relapse-free survival. *no significant difference.

increases in overall survival and relapse free survival [16] [17].

Two studies reported higher mortality following a single dose of GO 6 mg/m^2 as part of induction therapy [12] [18]. This dosing is identical to our own, and we did in fact experience 1 induction mortality in our sample of 9 patients. Although it is too early to draw definitive conclusions, administration of a single dose of GO 6 mg/m^2 might result in greater toxicity during induction therapy. A lower dose of GO such as 3 mg/m^2 [15] [17], even if it were repeated [16], might be safe, with reduced risk of relapse and improved overall survival [16] [17].

AML is not a homogeneous disease but rather a group of diseases, some of which might be particularly sensitive to GO. Three of 5 trials in **Table 4** showed a similar trend of a benefit for GO in favorable-risk AML [15]-[17]. This may indicate that AML varies both genetically and clinically, and GO should be administrated to specific patients.

In conclusion, GO reinduction should be considered for patients who do not achieve CR after the first cycle of induction chemotherapy or who relapse. On the basis of available reports, GO might not improve outcomes in patients at high risk, such as the patients in this study. Further investigations are warranted.

Declaration of Interest

The authors declare that they have no conflicts of interest.

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