Vol.5, No.5A, 8-16 (2013)
http://dx.doi.org/10.4236/health.2013.55A002

Gemtuzumab ozogamicin in the treatment of adult acute myeloid leukemia*

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Received 14 March 2013; revised 15 April 2013; accepted 1 May 2013

ABSTRACT

Gemtuzumab ozogamicin (GO) is a humanized anti-CD33 monoclonal antibody conjugated to a derivative of an antitumor antibiotic, calicheamicin. GO was approved for the treatment of relapsed acute myeloid leukemia (AML) in the United States (US) in 2000. However, GO was withdrawn from the US market in June 2010, because a large-scale clinical trial failed to show additive or synergistic effects with conventional chemotherapy for newly diagnosed AML. GO is currently available only in Japan. However, several large clinical studies have demonstrated beneficial effects of GO when added to chemotherapy for AML in recent years; therefore, reconsideration of GO availability is gaining attention. Therefore, the role and efficacy of GO as monotherapy or in combination therapy for *de novo* or relapsed AML should be positively investigated.

Keywords: Gemtuzumab Ozogamicin; Acute Myeloid Leukemia; Acute Promyelocytic Leukemia; Monotherapy; Combination Chemotherapy; Sinusoidal Obstruction Syndrome; Veno-Occlusive Disease

1. INTRODUCTION

Gemtuzumab Ozogamicin On and Off

Acute myeloid leukemia (AML) is the most common subtype of acute leukemia in adults. The incidence of AML is higher in elderly people 65 years of age or older, and the median age at onset is approximately 62 to 64 years [1,2]. Conventional chemotherapy results in complete remission in more than 70% of patients younger than 65 years of age [3-5], and the proportion of long-term survivors has improved to 30% - 40% of all AML patients in past decades. Although chemotherapy regimens for AML have remained mostly unchanged over the last 30 years, supportive care, including antimicrobial agents and blood component transfusions, has been significantly improved, enabling the use of more intensive chemotherapies. Among elderly AML patients, however, therapeutic outcomes are less satisfactory; approximate 40% to 65% of elderly AML patients achieve complete remission, although 85% of them relapse within two to three years [6-8].

Gemtuzumab ozogamicin (GO) is an anti-CD33 monoclonal antibody that is conjugated to a cytotoxic agent, calicheamicin [9]. CD33 is expressed in approximately 90% of myeloblasts in patients with AML, as defined by the presence of the antigen on more than 20% of leukemic blast cells [10]. GO is rapidly internalized after binding to CD33 on the cell surface. The endocytosed anti-CD33 complex translocates to the lysosome, then the acidic environment of the component causes the release of a calicheamicin derivative resulting in double-strand breaks in DNA and ultimately cell death [11].

In May 2000, the United States (US) Food and Drug Administration (FDA) granted approval for the use of GO to treat AML patients in a first relapse who are 60 years of age or older or are not indicated for chemotherapy of standard intensity [12,13]. Following the US approval, GO was approved in Europe and Japan to treat AML patients with this same status [14]. However, a required post-approval study (SWOGS01016) that evaluated GO combined with conventional chemotherapy for newly diagnosed AML patients under 61 years of age failed to confirm any clinical benefits and instead demonstrated an increased rate of treatment-related mortality [15]. These results prompted Pfizer, Inc. to voluntarily withdraw GO from the US market in 2010, before the results of other randomized trials were made available.

*Disclosure: We have no conflicts of interest with regard to any companies or individuals.

However, in recent years, several prospective randomized trials of elderly *de novo* AML patients have demonstrated a statistically significant survival advantage for patients who receive GO [16-18]. Therefore, the efficacy of GO is currently being reevaluated.

2. GO IN THE TREATMENT OF AML AS A MONOTHERAPEUTIC AGENT

2.1. Recommended Dosage of GO

Based on the results obtained in a phase I dose escalation trial for relapsed or refractory CD33-positive AML, the recommended dosage of GO as monotherapy is 9 mg/m^2 twice with an interval of at least 14 days [19]. This dosage was determined in a phase II study based on the rationale that more than 75% of CD33 sites are consistently saturated with GO at this dose. This dosage regimen was also considered to contain a tolerable dose level in terms of hematologic toxicity in a phase I study [12, 13,19].

2.2. GO as a Monotherapeutic Agent and Its Efficacy for AML

Three open-label, multicenter phase II studies were conducted to evaluate the efficacy and safety of single-agent GO in the treatment of patients with AML at the first recurrence [13]. These studies included 277 patients with a median age of 61 years. The overall response rate was 26% of the enrolled patients, with a 13% complete remission (CR) rate and a 13% CR with incomplete platelet recovery (CRp) rate. The median recurrence-free survival was 6.4 and 4.5 months for patients who achieved a CR and CRp, respectively. These interim results led to the approval of GO by the FDA for the treatment of patients with CD33-positive AML in a first recurrence who are 60 years of age or older and are not candidates for cytotoxic chemotherapy [20]. A number of studies of relapsed, refractory and untreated AML have been performed (**Table 1**). The overall response rates range from 17% to 33% [12,21-25]. These results suggest that GO as a monotherapeutic agent exhibits limited efficacy for all types of AML, except for acute promyelocytic leukemia (APL).

2.3. Adverse Effects of GO

Regardless of the indications for GO in AML patients who are not candidates for intensive chemotherapy, myelosuppression is observed in the majority of patients treated solely with GO. Although grade 3 to 4 neutropenia (98%) and thrombocytopenia (99%) have been observed, the incidence rates of grade 3 to 4 sepsis (17%) and pneumonia (8%) are relatively low [13]. Grade 3 to 4 hyperbilirubinemia develops in 29% of patients and elevated serum transaminase levels are observed in 18% of patients, presumably due to dissociation of calicheamicin during the intrahepatic metabolism of GO [13]. GO is associated with less gastrointestinal toxicity than anthracyclines or cytarabine; however, it is distinctively associated with hepatic sinusoidal obstruction syndrome (SOS)/veno-occlusive disease (VOD) [26]. The incidence of SOS has been reported to be only 0.9% among patients who do not undergo prior or subsequent allogeneic hematopoietic cell transplantation (HSCT) [13]; however, 5% of patients who undergo allogeneic HSCT within three months after GO administration develop SOS [20]. The use of fractionated dosing with a reduced total dose of GO exhibits similar therapeutic efficacy; therefore, this protocol has the potential to reduce the incidence of SOS [21,23].

Table 1. Gemtuzumab ozogamicin as a monotherapeutic agent in acute myeloid leukemia patients.

Reference	Number of patients	Median age (range)	AML status	Dose and schedule	CR/CRp (%)	RFS	OS
Sievers *et al*. (12)	142	61 (22 - 84)	First relapse AML	9 mg/m^2 D1 and D15	16/13	6.8 mo	5.9 mo
Taksin *et al*. (21)	57	64 (22 - 80)	First relapse AML	3 mg/m^2 D1, 4, and 7	26/7	11.0 mo	8.4 mo
Piccaluga *et al*.(22)	24	63 (20 - 75)	Relapsed, refractory AML	6 or 9 mg/m^2 for 2 - 3 doses	13/8	6.0 mo	2 mo
Amadori *et al*. (23)	56	78 (62 - 86)	Untreated AML	Arm A: 3 mg/m^2 D1, 3, and 5	21/0	NR	NR
				Arm B: 6 mg/m^2 D1 and 8	18/4	NR	NR
Amadori *et al*. (24)	40	76 (61 - 89)	Untreated AML	9 mg/m^2 D1 and D15	10/7	6.1 mo	4 mo
Nabhan *et al*. (25)	12	75 (66 - 79)	Untreated AML	9 mg/m^2 D1 and D15	27/0	NR	NR

Abbreviations: AML, Acute myeloid leukemia; CR, Compete remission; CRp, Complete remission with imcomplete platelet recovery; RFS, Relapse free survival; OS, Overall survival; NR, Not reported.

3. EFFICACY OF GO AS COMBINATION THERAPY FOR ADULT AML PATIENTS

3.1. Early Clinical Trials Demonstrating Beneficial Effects of GO

Several trials have evaluated the efficacy of GO combined with chemotherapy as first-line therapy and for refractory/relapsed AML. Dose reduction of GO is required when used in combination with other cytotoxic agents due to its toxicity profile. In recent years, seven randomized phase III trials of newly diagnosed AML patients were performed (**Table 2**) [15-18,27-29]. In a United Kingdom Medical Research Council (MRC) AML15 trial, 1113 AML patients younger than 60 years of age without APL were randomly assigned to either receive or not receive GO as part of induction therapy [16]. The patients received a single dose of GO (3 mg/m^2) on day 1 of the induction course as a component of three induction regimens consisting of daunorubicin and cytarabine (DA), cytarabine, daunorubicin and etoposide (ADE) or fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin (FLAG-Ida). Subsequently, the patients not intended to undergo allogeneic HSCT were randomly assigned to receive GO combined with amsacrine, cytarabine and etoposide (MACE) or sole high-dose cytarabine. Although there were no differences in the overall response or survival rates among the two arms, there was a significant survival benefit for patients with favorable cytogenetics and a tendency toward a benefit for intermediate-risk patients. However, no benefits for patients in the poor-risk group were observed in the subgroup analyses based on cytogenetics [16].

3.2. A Large-Scale Trial That Failed to Show Any Benefits of GO

A second randomized multicenter phase III trial was conducted by the South West Oncology Group (SWOG) [15]. This study (SWOG S0106) randomly assigned 627 newly diagnosed patients younger than 60 years of age to receive induction therapy with DA with or without GO (6 mg/m^2). Patients who achieved a CR received consolidation chemotherapy with three courses of high-dose cytarabine. Following the administration of consolidation therapy, a second round of randomization was performed to assign the patients to receive either three doses of GO (5 mg/m^2 every 28 days) or no further treatment. An interim analysis demonstrated a CR rate of 74% in both arms, while no differences were observed in relapse-free survival (RFS), disease-free survival (DFS) or overall survival (OS). In addition, the incidence of fatal adverse events during induction therapy was significantly higher in the group that received GO compared with that observed in the control arm (5.8% vs 0.8%). This randomized study was stopped in early stage after the interim analysis, and GO was withdrawn from the US market in 2010.

Table 2. Gemtuzumab ozogamicin in combination with chemotherapy in relapsed and refracrory AML patients.

Study (reference)	Number of patients	Median age (range)	GO dose	Combined drug	CR	RFS/EFS/DFS	OS	Induction mortality
					GO (+) vs (−)	GO (+) vs (−)	GO (+) vs (−)	GO (+) vs (−)
Setting: induction therapy								
SWOG SO106 (15)	627	18 - 60	6 mg/m^2	DA	66% vs 69%	50% vs 49% at 2y RFS	31m vs 34 m	5.8% vs 0.8%
MRC AML15 （16）	1113	0 - 71 (49)	3 mg/m^2	DA, ADE, FLAG-Ida	82% vs 83%	39% vs 35% at 5y RFS	42% vs 40% at 5y	7% vs 6%
UK NCRI AML16 (17）	1115	51 - 84 (67)	3 mg/m^2	DA, Dclo	62% vs 58%	21% vs 16% at 3y RFS	25% vs 20% at 3y	12% vs 11%
ALFA-0701（18）	280	58 - 62 (62)	3 mg/m^2 × 5	DA	81% vs 75%	40.8% vs 17.1% at 2y EFS	53.2% vs 41.9% at 2y	6.5% vs 4%
GOELAMS AML 2006 IR (27)	254	18 - 60 (50)	6 mg/m^2	DA	92% vs 87%	51% vs 33% at 3y EFS	53% vs 46% at 3y	4.2% vs 2.5%
Setting: postremission therapy								
ECOG E1900 (28)	657	18 - 60 (47)	6 mg/m^2 + ASCT vs HD-AraC		-	33.6% vs 35.9% at 4y DFS	40.8% vs 41.9% at 4y	-
HOVON-43 (29)	232	60 - 78 (66)	6 mg/m^2 × 3	-	-	17% vs 16% at 5y DFS	28% vs 21% at 5y	-

Abbreviations: GO, Gemtuzumab ozogamicin; CR, Complete remission; RFS,Rrelapse free survival; EFS, Event free survival; DFS, Disease free survival; OS, Overall survival; DA, Daunorubicin/Cytarabine; ADE, Cytarabine/Daunorubicin/Etoposide; FLAG-Ida, Fludarabine/Cytarabine/Granulocyte colony-stimulating factor/Idarubicin; Dclo, Daunorubicin/Cllofarabine.

3.3. Clinical Trials Demonstrating Beneficial Effects of GO in Recent Years

More recently, the results of the United Kingdom National Cancer Research Institute (UK NCRI) AML16 trial were published in 2012. This study randomly assigned 1115 elderly patients (median age: 67 years) to receive daunorubicin and either clofarabine or cytarabine with or without GO (3 mg/m^2) [17]. There were no differences in the CR rate; however, the 3-year cumulative incidence of relapse was significantly lower (GO vs no GO: CIR at 3 years 68% vs 76%; p = 0.007) and the 3-year survival rate was significantly higher in the GO arm (3 year OS 25% vs 20%; p = 0.05). The addition of GO did not increase the mortality rate during the administration of induction chemotherapy. A meta-analysis of 2, 228 patients included in the MRC AML 15 and UK NCRI AML 16 trials also showed significant improvements in the relapse and OS rates in the GO arm (3 mg/m^2 GO) [17].

The Acute Leukemia French Association (ALFA) investigated whether the addition of low fractionated-dose GO to standard front-line chemotherapy improves event-free survival (EFS) as the primary end point [18]. In the phase 3 ALFA-0701 study, 280 patients between 50 to 70 years of age were randomly assigned to receive DA with or without GO (3 mg/m^2 on days 1, 4 and 7 during induction and day 1 of each of the two consolidation chemotherapies). The CR rate during induction did not differ between the arms; however, the EFS, OS and RFS were significantly improved in the GO group without an increase in the risk of death from toxicity. At the time point of two years, the EFS was estimated to be 17.1% in the control group versus 40.8% in the GO group (p = 0.0003), while the OS was 41.9% versus 53.2% (p = 0.0368) and the RFS was 22.7% versus 50.3%, respectively (p = 0.0003). The results of the cytogenetic and genotypic analyses demonstrated a survival benefit among the patients with favorable or intermediate cytogenetics compared to that observed in the patients with unfavorable cytogenetics and a survival benefit among the patients positive for the *FLT*3-internal tandem duplication (ITD) mutation compared to that observed in the patients negative for this mutation [18]. Among the patients with the *NPM*1 mutation and a *WT*-1 expression, more patients in whom the levels of the transcripts decreased below the detection limits at postinduction were found in the GO arm compared to the control arm. Furthermore, the detectable *NPM*1 and *WT*-1 transcript levels at postinduction in non-GO arm were associated with a higher relapse rate [30].

In a Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang (GOELAMS) AML 2006 IR study, 254 patients ranging from 18 to 60 years of age with de novo AML were randomly assigned to receive DA with or without GO (6 mg/m^2 for induction and first consolidation chemotherapy) [27]. In the subset of patients with intermediate cytogenetics who were unable to receive subsequent allogeneic HST, the EFS was significantly higher in the GO group (GO vs no GO: 53.7% vs 27%; p = 0.0308), while there were no differences regarding OS. These trials demonstrated that the addition of a low dose of GO to cytarabine and anthracycline-based induction and consolidation chemotherapy improves survival, but not CR rates, without increasing GO toxicity in AML patients with more favorable cytogenetics.

3.4. Beneficial Effects of GO Have Not Been Demonstrated in Postremission Therapy

The Eastern Cooperative Oncology Group (ECOG) and the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) evaluated the efficacy of GO as postremission therapy. In the ECOG trial E1900, patients with favorable and intermediate cytogenetics received postremission therapy with two courses of high-dose cytarabine followed by GO (6 mg/m^2) and autologous HST or autologous HST alone [28]. There were no differences in DFS (GO vs no GO: DFS at 4 years 33.6% vs 35.9%; p = 0.54) or OS (41.3% vs 41.9%; p = 0.52) between the arms. In the HOVON-43 study, elderly patients with AML in a first CR following intensive induction chemotherapy were randomized to receive three cycles of GO (6 mg/m^2 every four weeks) or no postremission therapy [29]. There were no significant differences between the treatment groups in OS or DFS (GO vs no GO: DFS at 5 years 17% vs 16%). Therefore, these trials demonstrated that GO does not exhibit beneficial effects in postremission therapy.

3.5. GO Combined with Chemotherapy Is Effective for Relapsed AML

A number of GO-containing combination chemotherapies for relapsed and refractory AML have been reported (**Table 3**) [31-42]. The response rates observed in these studies range from 12% to 68% and appear to increase as time progresses. The toxicity profile is variable from study to study, particularly with respect to liver toxicity. In a dose escalation trial of relapsed and refractory AML, which was conducted by the Cancer and Leukemia Group B (CALGB), a combined regimen with GO (9 mg/m^2) and high-dose cytarabine (HiDAC) was safely administered, resulting in a CR rate of 32% [40]. In an encouraging phase II study, GO combined with intermediate-dose cytarabine and mitoxantrone (MIDAM) produced a complete remission rate as high as 63% and an overall survival (OS) of 9.5 months in patients with pri-

Table 3. GO in combination chemotherapy in relapsed and/or refractory acute myelid leukemia patients.

Reference	Number of Patients	Median age (range)	GO dosage	Additional agents	CR/CR p (%)	Incidence of VOD (%)
Cortes *et al.* (31)	17	55 (20 - 70)	9 mg/m^2 D1	Ara-C, Topotecan	12	5.9
Alvarado *et al.* (32)	14	61 (34 - 74)	6 mg/m^2 D1, 15	Ara-C, Idarubicin	21/21	14.3
Tsimberidou *et al.* (33)	32	53 (18 - 78)	4.5 mg/m^2 D1	Ara-C, Fludarabine, CSA	28/6	9.4
Specchia *et al.* (34)	21	52 (36 - 68)	3 mg/m^2 D1, 14	Ara-C, Mitoxantrone	9/9	0
Chevallier *et al.* (35)	62	55.5 (16 - 71)	9 mg/m^2 D4	Ara-C, Mitoxantrone	50/13	3
Schlenk *et al.* (36)	94	48 (22 - 62)	3 mg/m^2 D1	Ara-C, Mitoxantrone, ATRA	30/20	9
Fianchi *et al.* (37)	53	69 (65 - 77)	6 mg/m^2 D9	Ara-C, G-CSF	43/2	2
Martin *et al.* (38)	48	47 (20 - 68)	9 mg/m^2 D8	Ara-C, Fludarabine, Idarubicin	29/27	15
Litzow *et al.* (39)	26	60 (27 - 75)	6 mg/m^2 D5	Ara-C	12	NR
Stone *et al.* (40)	37	64 (55 -70)	9 mg/m^2 D7	Ara-C	32	NR
Prebet *et al.* (41)	34	51 (24 - 71)	3 - 9 mg/m^2	Ara-C ± Mitoxantrone, Etoposide, Irinotecan	68	6
Farhat *et al.* (42)	20	60 (50 - 70)	3 mg/m^2 D1, 4, 7	Ara-C, Daunorubicin	55/10	0

Abbreviations: GO, Gemtuzumab ozogamicin; CR, Compete remission; CRp, Complete remission with imcomplete platelet recovery; VOD, Veno occlusive disease.

mary refractory and relapsed AML [35]. A meta-analysis revealed patients with mutated *NPM*1, but not concurrent *FLT*3-ITD, to show a favorable overall response (OR) rate of 85% and a 5-year survival rate of 80% [43]. The German Austrian AML study Group (AMLSG) 04 - 05 trial evaluated the efficacy of high-dose cytarabine, mitoxantrone and all-trans retinoic acid (ATRA) in combination with GO (GO-A-HAM) in younger adult patients with primary refractory AML [36]. The CR rate was 50% and 12% of the patients achieved a partial remission (PR). The incidence of VOD following allogeneic HSCT within three months after GO-A-HAM was 9% without differences when compared with historical controls. The patients with adverse cytogenetics and/or *FLT*3-ITD exhibited a significantly inferior OS of 38% after one year of follow-up compared to the 81% observed in the remaining patients. However, the OS of the patients who received allogeneic HSCT was similar between the groups [36]. More recently, the outcomes of combined regimens with intermediate to high-dose cytarabine (IHDAraC) and IHDAraC with GO (3 - 9 mg/m^2, average 6 mg/m^2) were retrospectively compared in patients with a first relapse of AML [41]. The OR rate (GO vs no GO: 68% vs 45%; p = 0.04), EFS (24 months vs 6 months; p = 0.002) and OS (median, 35 months vs 6 months; p = 0.001) were significantly higher in the GO group. These effects, however, were restricted to patients with low-risk and intermediate-risk cytogenetics. In the treatment of elderly patients with refractory or relapsed AML, GO combined with cytarabine and G-CSF, but not anthracycline (G-AraMy regimen), was acceptable in terms of both myeloid and non-myeloid toxicities. The OR rate was 57% and the median OS was nine months [37].

3.6. GO Fails to Exhibit Efficacy in Some Combination Regimens for Relapsed AML

In contrast to these favorable results, a retrospective study showed that the addition of GO to fludarabine, cytarabine, G-CSF and idarubicin (FLAG-Ida) failed to improve the response rate, duration of response or OS compared with FLAG-Ida alone [38]. The ECOG conducted a randomized phase II study of patients with primary refractory and relapsed AML [39]. These patients were randomly assigned to receive intermediate-dose cytarabine with GO (6 mg/m^2) (Arm A), intermediate-dose cytarabine with liposomal daunorubicin (Arm B) or intermediate-dose cytarabine with cyclophosphamide and topotecan (Arm C). The CR/CRp rate was as low as 12% in Arm A, 7% in Arm B and 4% in Arm C. The median OS for all treatment arms was 3.4 months without significant differences between the groups [39]. In a non-randomized phase II study in which two combination regimens with fludarabine, cytarabine and idarubicin with or without GO (9 mg/m^2) (FLAG-IM and FLAG-I) were compared without demonstrating any beneficial effects of

GO, the addition of GO failed to improve the OR rate (GO vs non-GO: 56% vs 52%) or overall survival time (5.0 months vs 8.8 months) in patients with relapsed or refractory AML [38]. Currently, several studies are investigating the efficacy of GO-containing combination regimens with vorinostat [44], azacitidine [45] and decitabine [46].

4. GO IS A POTENT ANTILEUKEMIC AGENT AGAINST ACUTE PROMYELOCYTIC LEUKEMIA (APL)

GO exhibits a significant and potent activity against both newly diagnosed and recurrent APL. This efficacy results from a high surface expression of CD33 and low expression levels of P-glycoprotein in APL cells [47-49]. LoCoco *et al*. reported the efficacy of GO as monotherapy (6 mg/m^2 on days 1 and 15) for molecular relapsed APL [50]. In this study, patients who achieved molecular remission subsequently received additional GO treatment. Eighty-eight percent of the patients obtained a molecular response and 44% of the responders remained in sustained molecular remission. Ravandi *et al*. investigated the outcomes of a combined regimen with ATRA and arsenic trioxide (ATO) with or without GO in newly diagnosed patients with APL [51]. GO was given to high-risk patients with a presenting leukocyte count over 10,000/L and was further added if the leukocyte count increased above 30,000/L during induction chemotherapy. The OR rate with GO was 92% after induction and the molecular remission rate was 94% three months after the completion of three rounds of consolidation with ATRA and ATO with favorable outcomes and fewer complications compared with historical controls. Aribi *et al*. showed similar results among eight patients with APL in a first recurrence who were treated with ATRA, ATO and GO [52]. All patients had previously received ATRA as a single agent or in combination with other chemotherapies. All patients achieved a molecular CR, and six of the eight patients were alive and had remained in remission after a median follow-up of 36 months. Based on the results of these studies, GO is indicated in many aspects of APL.

5. CONCLUSION

GO is a CD33-molecular targeting agent for use in the treatment of AML and is effective depending on the aspects and status of AML and the combination of some chemotherapeutic agents. The toxicity profile of GO is acceptable in all ages, and dose reduction of GO appears to reduce the incidence of liver toxicity, particularly SOS. From this point of view, the use of GO treatment is an attractive therapeutic approach. Therefore, the reappearance of GO in the treatment of AML is expected worldwide. Further investigations regarding the optimized use of GO should be conducted.

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