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Review

Update on the role of gemtuzumab-ozogamicin in the treatment of acute myeloid leukemia

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***Abstract*:** Gemtuzumab-ozogamicin (GO) is an antibody-drug conjugate (ADC) in which a monoclonal antibody targeting CD33 is covalently linked to the toxin calicheamicin. GO was initially approved by the United States Food and Drug Administration (FDA) for the treatment of adult patients with CD33$^+$ acute myeloid leukemia (AML) in 2000. However, GO was recalled from the US market due to the lack of efficacy, and higher incidence of hepatotoxicities, including hepatic veno-occlusive disease (VOD), observed in phase 3 SWOG-0106 study. Since then, several other phase 3 studies have evaluated the efficacy of GO in the frontline treatment of adult patients with AML using different GO doses and schedules. The pivotal study that led to the reconsideration of GO was the French ALFA-0701 study, which used a lower and fractionated dose of GO in combination with standard chemotherapy (SC). Patients treated with the GO combination had a significantly longer survival outcome. The modified schedule also improved the toxicity profile. A systematic review and meta-analysis of over 3000 patients treated in five phase 3 studies showed that adding GO to SC improved relapse-free and overall survival. Most importantly, 6 mg/m^2 dose of GO was associated with higher grade $\geqslant$3 hepatoxicities and VOD than 3 mg/m^2. The survival benefit was significant in the favorable and intermediate cytogenetic risk groups. This led to the reapproval of GO in 2017 for the treatment of patients with CD33$^+$ AML. Currently, several clinical trials are exploring the role of GO with various combinations and in eliminating the measurable residual disease in patients with CD33$^+$ AML.

Keywords: AML, antibody-drug conjugate, gemtuzumab-ozogamicin

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Introduction

Acute myeloid leukemia (AML) is an aggressive clonal hematopoietic disorder of stem cells and progenitor cells. The incidence of AML has been steadily increasing over the past few years. The American Cancer Society's estimated incidence of AML in 2022 is 20,050 and approximately 11,540 deaths.[1] Historically, treatment for AML has been categorized as 'intensive' (i.e. cytarabine plus an anthracycline, most frequently using a 7 + 3 regimen) and 'low-intensity' (i.e. hypomethylating agents or low-dose cytarabine) chemotherapy. However, better understanding of the biology and molecular aspects of the disease has changed the therapeutic landscape of AML and led to the development of monoclonal antibodies, including antibody-drug conjugates (ADC) and small molecule inhibitors.

One of the challenges with monoclonal antibodies and ADC for AML therapeutics is the lack of AML-specific antigens that could be targeted. CD33 is expressed in 80–90% of all AML. However, it is also expressed on normal hematopoietic stem cells, myeloid progenitor cells, and well-differentiated cells.[2–4] The near-universal expression of CD33 in AML has made it an attractive target for treating AML. Gemtuzumab-ozogamicin (GO) is an ADC in which a monoclonal antibody targeting CD33 is covalently linked

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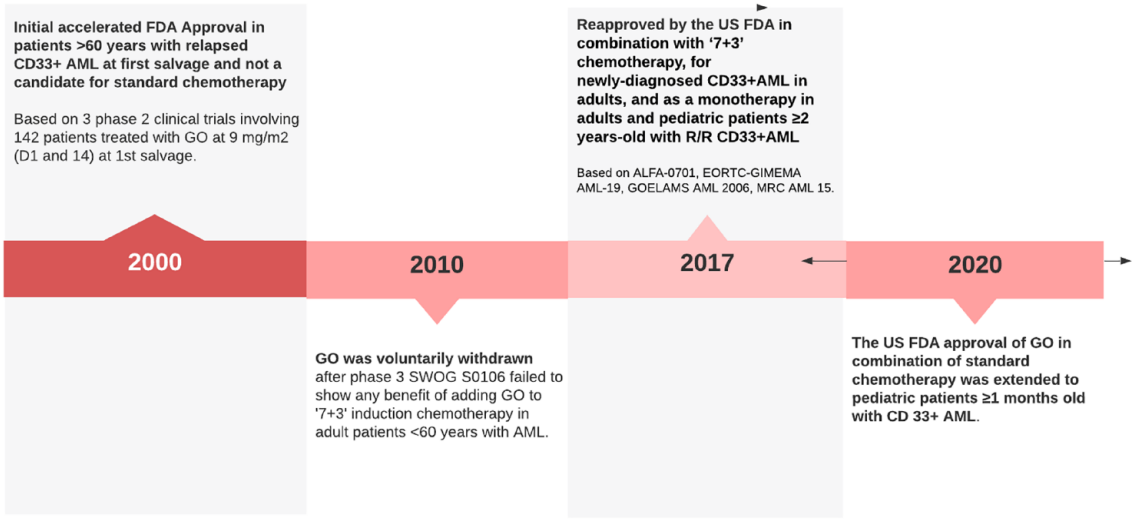

Figure 1. Timeline of gemtuzumab-ozogamicin initial and reapproval by the United States Food and Drug Administration.

to the toxin calicheamicin. GO is the first (and at the time of this writing, the only) ADC approved for the treatment of patients with AML. GO is also used to treat patients with acute promyelocytic leukemia (APL).

In this review, we will discuss the role of GO in the treatment of patients with non-APL AML.

Gemtuzumab-ozogamicin in AML

Mechanism of cytotoxicity

The binding of GO to CD33 antigen results in GO-CD33 complex, which is rapidly internalized into the AML blast cell. In the cytoplasm, the GO-CD33 complex is routed into the lysosome, where it is rapidly hydrolyzed in acid environment resulting in the release of calicheamicin. The calicheamicin derivative is then reduced to highly reactive species causing single and double strand DNA breaks. If the DNA damage is not repaired, apoptosis is triggered by the ataxia-telangiectasia mutated (ATM) and ATM-and Rad3-related (ATR) kinases through the phosphorylation BAX and BAK proteins. The latter results in the release of cytochrome-c and activate caspase 9 and 3 leading to apoptosis of AML blast cells.[5] The CD33 antigen expression on AML blast membrane is typically renewed after the GO-CD33 complex is internalized which may offer a rationale for the effectiveness of fractionated dosing of GO.

Gemtuzumab-ozogamicin initial approval

GO was initially approved by the US Food and Drug Administration (FDA) in 2000 (Figure 1) for the first-salvage treatment of adult patients ⩾60 years with $CD33^+$ AML, who were not suitable for cytotoxic chemotherapy, based on the results of three early-phase clinical trials.[6] All three trials had similar clinical trial design and GO was administered at 9 mg/m^2 on days 1 and 14 (two doses) as the first salvage in 277 patients. However, the inclusion criteria were different among those three trials. One study included adult patients who had first complete response (CR) for at least 6 months. The second study also included patients who underwent prior stem cell transplant (SCT). The third study included only adult patients ⩾60 years with a duration of CR1 of ⩾3 months. Thirteen percent of the study patients achieved a CR. In these studies, although GO was generally well tolerated and thus approved for older patients, toxicities, particularly liver toxicity, were higher in patients who received a SCT after treatment with GO. Five patients died from sinusoidal obstruction syndrome (SOS) after SCT.

Gemtuzumab-ozogamicin in frontline treatment

The efficacy of GO in the salvage setting with an acceptable safety profile in the phase 2 studies led researchers to investigate the effectiveness of GO in the frontline setting. Therefore, GO was

Table 1. Summary of phase 3 studies involving gemtuzumab-ozogamicin in the frontline treatment of adult patients with AML.

Phase 3 trials	Number of patients	Age (years)	GO induction dose and schedule	CR (%)	RFS	OS
MRC AML15	1099	18–59	3 mg/m^2 on D1	82	5-year – 39%	5-year – 43%
SWOG-0106	595	18–60	6 mg/m^2 on D4	75	5-year – 43%	5-year – 46%
GOELAMS AML 2006 IR	238	18–60	6 mg/m^2 on D1	92	3-year – 51%	3-year – 53%
ALFA-0701	278	50–70	3 mg/m^2 on D1, 4, and 7 (capped at 5 mg)	81	2-year – 50%	2-year – 53%
NCRI AML16	1115	51–84	3 mg/m^2 on D1	62	3-year – 21%	3-year – 25%
EORTC-GIMEMA AML19	237	61–75	6 mg/m^2 on D1, 3 mg/m^2 on D8, and 2 mg/m^2 monthly × 8 cycles	15	1-year – 10%	1 year – 24%

AML, acute myeloid leukemia; CR, complete remission; GO, gemtuzumab-ozogamicin; OS, overall survival; RFS, relapse-free survival.

explored in the frontline treatment of patients with CD33$^+$ AML in five prospective randomized phase 3 trials (MRC AML15, SWOG-0106, GOELAMS AML 2006 IR, ALFA-0701, NCR AML16, Table 1). However, it is essential to note that GO was withdrawn from the market before those studies resulted, except for the S0106 study. The initial approval of GO was actually contingent on the results of S0106, a prospective randomized phase 3 trial.

SWOG S0106 study was a phase 3 study that evaluated the efficacy of GO in combination with standard induction chemotherapy ('7 + 3') in adult patients <60 years with untreated AML across all cytogenetic risk groups.[7] Patients were randomized to receive '7 + 3' induction chemotherapy (daunorubicin dose of 45 mg/m^2) with or without GO 6 mg/m^2 on day 3. All patients received three cycles of cytarabine (3 g/m^2) as consolidation chemotherapy. Patients in CR were randomized to observation or GO at 5 mg/m^2 and administered once every 28 days for three courses (Figure 2).

The S0106 study was terminated early due to higher induction mortality in the GO arm (5.5% *versus* 1.4%) and lack of improvement in outcomes.[7] Therefore, GO was voluntarily withdrawn from the US market in 2010. Some of the drawbacks acknowledged by S0106 study investigators were that GO was administered on D4, unlike other randomized studies being conducted at around that same time (Table 1). In addition, the induction mortality rate of 1.4% in the standard chemotherapy arm of S0106 was generally lower than what had been reported in other studies involving anthracycline-based chemotherapy.[8]

The UK MRC AML15 phase 3 randomized controlled trial (RCT) explored the efficacy of the combination of GO and intensive chemotherapy in induction and consolidation treatment of adult patients < 60 years with AML, compared with the standard intensive chemotherapy arm.[9] The study also randomized patients to different intensive chemotherapy backbones (Figure 2) at induction and consolidation. GO was administered once on D1 of the induction and consolidation cycle at a dose of 3 mg/m^2 (irrespective of CD33 status). Allogeneic SCT was allowed in the study for patients with adverse-and intermediate-cytogenetic risk AML and available matched-sibling donors. A total of 1113 patients were treated. The CR rate was 82% with GO plus chemotherapy compared with 83% [OR = 1.04 (0.76–1.42), $p = 0.8$] with intensive chemotherapy alone. Similarly, 5-year overall survival (OS) and relapse-free survival (RFS) were 43% *versus* 41% and 39% *versus* 35%, respectively. Although the study showed no improvement in the outcomes with the addition of GO to different intensive chemotherapy regimens, the pre-planned subgroup analysis showed that patients with favorable-risk cytogenetics derived a significant benefit from GO added to chemotherapy, with 5-year OS of 79% *versus* 51%, $p = 0.0003$. The induction mortality and 30-day mortality were similar between the GO combination and

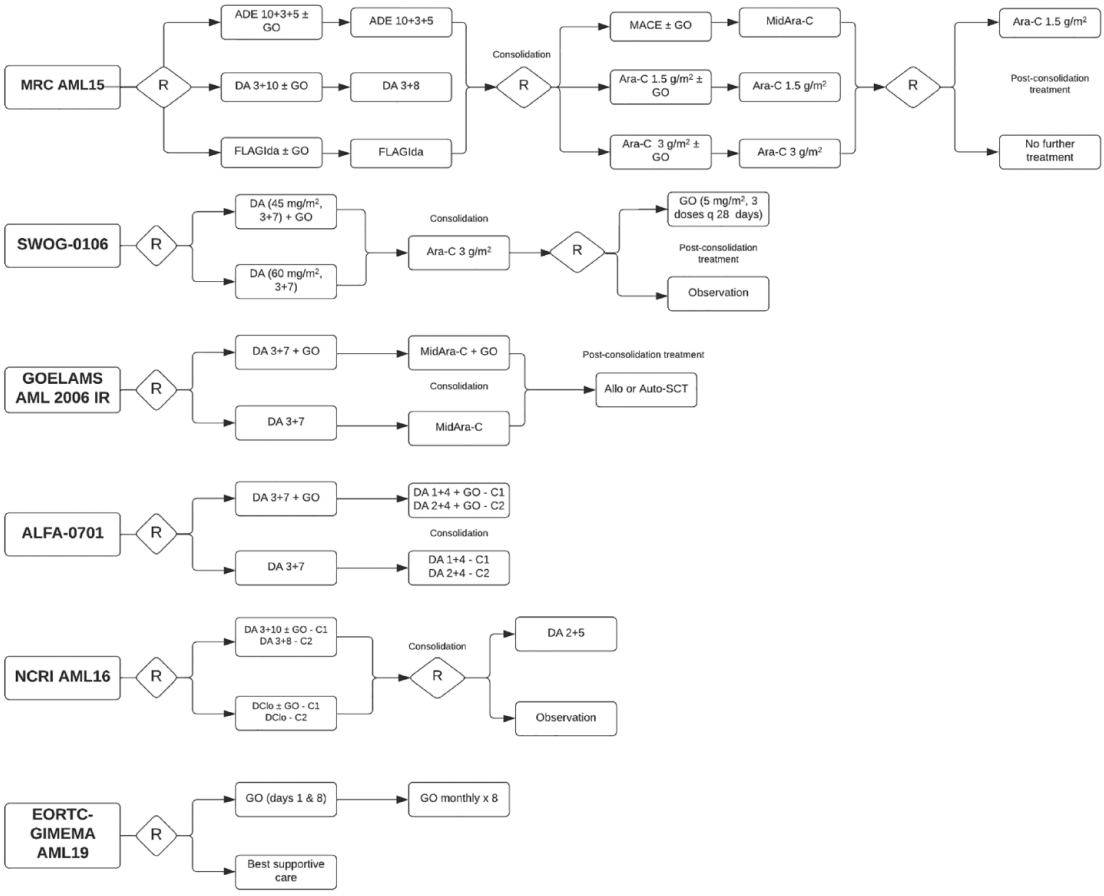

Figure 2. Study design of all phase 3 clinical studies involving GO in the frontline treatment of patients with AML.
ADE, daunorubicin, cytarabine, and etoposide; Ara-C, cytarabine; C1/2, course 1/2; DA, daunorubicin and cytarabine; DClo, daunorubicin and clofarabine; FLAG-Ida, fludarabine, cytarabine granulocyte colony-stimulating factor, and idarubicin; MACE, amsacrine, cytarabine, and etoposide; MidAC, mitoxantrone and cytarabine; R, randomization; SCT, stem cell transplant.

chemotherapy-only arms (7% *versus* 6%, $p = 0.6$ and 11% *versus* 10%, respectively). The hepatotoxicity was reportedly not worse with the GO combination, and there was no SOS in study patients. In prior studies, patients who proceeded to SCT within 120 days of the last GO treatment had higher rates of hepatoxicity.[10] However, this was not observed in patients who underwent SCT in the MRC AML15 study.

In the GOELAMS AML 2006 IR study, GO (6 mg/m^2) was added to '7 + 3' chemotherapy and the consolidation regimen (mitoxantrone and intermediate doses of cytarabine) on day 1 of both induction and of first consolidation cycle. The comparator arm was chemotherapy alone.[11] The study included patients aged 18 to 60 years with favorable or intermediate-risk AML (per European LeukemiaNet, ELN 2010 risk classification). Patients with favorable risk were treated with a second consolidation followed by autologous SCT, while patients with intermediate risk were treated with one or two cycles of consolidation followed by allogeneic SCT or autologous SCT (if no donor was available). Two hundred and thirty-eight patients were treated in this study. The CR rate was non-significantly higher in the GO group (92% *versus* 87%). Although numerically higher with GO, there was no significant difference in the 3-year event-free survival (EFS, 51% *versus* 33%) or OS (53% *versus* 46%). Among patients with intermediate-risk AML who

Table 2. Incidence of hepatoxicities and hepatic veno-occlusive disease in phase 3 studies involving gemtuzumab-ozogamicin in the frontline treatment of adult patients with AML.

Phase 3 trials	Age (years)	Number of patients	GO induction dose and schedule	Incidence of hepatic VOD/SOS (*n*)	Incidence of grade ⩾ 3 hepatotoxicities (%)
MRC AML15	15–71	1099	3 mg/m^2 on D1	0	NA
SWOG-0106	18–60	595	6 mg/m^2 on D4	0	NA
GOELAMS AML 2006 IR	18–60	238	6 mg/m^2 on D1	4	23
ALFA-0701	50–70	278	3 mg/m^2 on D1, 4, and 7 (capped at 5 mg)	2	6
NCRI AML16	51–84	1115	3 mg/m^2 on D1	0	17
EORTC-GIMEMA AML19	61–75	237	6 mg/m^2 on D1, 3 mg/m^2 on D8, and 2 mg/m^2 monthly × 8 cycles	0	7

AML, acute myeloid leukemia; GO, gemtuzumab-ozogamicin; NA, not available; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease.

did not receive an allogeneic SCT, the EFS was significantly longer when treated with GO (54% *versus* 27%, $p=0.0308$). However, this did not translate to an OS improvement. The early deaths were similar between both groups (10% *versus* 4%). The grade ⩾ 3 hepatoxicities were significantly higher in patients treated with GO (23% *versus* 13%, $p=0.031$, Table 2). Notably, 4 patients treated with GO during the induction phase suffered hepatic veno-occlusive disease (VOD). The study showed that adding GO to intensive chemotherapy might benefit patients with intermediate-risk AML who did not proceed with allogeneic SCT.

The French ALFA-0701 study compared the efficacy of GO + '7 + 3' chemotherapy with '7 + 3' chemotherapy alone in treating patients aged 50–70 years with untreated non-APL AML.[12] GO was administered at a dose of 3 mg/m^2 (maximum dose of 5 mg) on days 1, 4, and 7 during induction and day 1 of each of two consolidation cycles. A total of 278 patients were treated in the study. There was no difference in the CR rates between the two groups [81% *versus* 75%, odds ratio (OR): 1.46, 95% confidence interval (CI), 0.20–2.59, $p=0.25$]. The 2-year EFS and RFS were significantly longer in the GO group (41% *versus* 17%, $p=0.0003$, and 50% *versus* 23%, $p=0.0003$, respectively). Patients treated with GO had an improved survival expectation than the control group, with 2-year OS rates of 53% *versus* 42%, $p=0.0368$ (Table 1). The subgroup analysis showed that patients with favorable and intermediate-risk cytogenetics benefited the most from the addition of GO. The induction mortality was similar in both treatment groups (6% with GO *versus* 4%, $p=0.41$). There was no difference in the incidence of grade ⩾ 3 hepatotoxicity (13% *versus* 6%, $p=0.10$). However, two patients in the GO group died from SOS during the induction and consolidation cycle, respectively. The ALFA-0701 study was the first phase 3 study to show improvement in the OS with the addition of GO to the frontline treatment of patients with AML.

Although GO was well studied in the frontline treatment of patients with AML, the question remained whether adding GO to the induction chemotherapy was efficacious since the outcomes were variable in all the phase 3 studies discussed above. This was further explored in the systematic review and meta-analysis by Hills *et al.*,[13] which included 3325 adult patients with AML enrolled in the aforementioned studies. There was no effect of adding GO on the CR + CRi rates regardless of the dose of GO used [OR: 0.91 (0.77–1.07), $p=0.3$]. The 30-day mortality rate was higher only with a GO dose of 6 mg/m^2 [OR: 2.79 (1.33–5.87), $p=0.007$]. Similarly, 6 mg/m^2 of GO was associated with non-significantly higher 100-day post-SCT mortality. The addition of GO to induction chemotherapy led to a significantly improved RFS [HR: 0.84 (0.76–0.92), $p=0.0003$] and OS [HR: 0.90 (0.82–0.98), $p=0.01$]. The absolute OS benefit at 5 years was

4%. Most importantly, the survival benefit of adding GO to chemotherapy extended to all patients except those with adverse-risk cytogenetics. The results of this meta-analysis supported the reevaluation and eventual approval of GO in the treatment of AML by the US FDA.

As 6 mg/m^2 dose of GO was associated with more toxicities, a prospective RCT, NCRI AML17, compared the outcomes of patients treated frontline with GO at 6 mg/m^2 and 3 mg/m^2.[14] A total of 788 patients were randomized to a single dose of GO at 3 mg/m^2 or 6 mg/m^2 during the first induction cycle, combined with anthracycline-based chemotherapy. There was no difference in the overall response rates (CR + CRi). Similarly, there was no difference in the 4-year RFS or OS between the two doses of GO (RFS: 44% *versus* 38%, $p = 0.3$ and OS: 50% *versus* 47%, $p = 0.3$, respectively). However, both 30-day and 60-day mortality rates were significantly higher with 6 mg/m^2 of GO (3% *versus* 7%, $p = 0.02$ and 5% *versus* 9%, $p = 0.01$, respectively). This study established that 3 mg/m^2 dose of GO was optimal and sufficient in combination with induction chemotherapy in the frontline treatment of patients with AML.

The efficacy of GO in the frontline treatment of older patients with AML was also addressed in the two prospective randomized trials, NCRI AML16 and EORTC-GIMEMA AML19. In the UK NCRI AML16 study, 1115 patients age 51 to 84 years with AML were treated with two courses of chemotherapy (daunorubicin + cytarabine or daunorubicin + clofarabine) in combination with GO (3 mg/m^2 on day 1 of cycle 1). Responders were randomized to consolidation chemotherapy *versus* no consolidation, and if no subsequent allogeneic SCT was planned, then those patients were randomized to azacitidine maintenance *versus* no maintenance.[15] There was no significant improvement in the CR rates with the addition of GO (62% *versus* 58%, $p = 0.14$, Table 1). However, there was a significant improvement in the 3-year survival outcomes with GO treatment (OS – 25% *versus* 20%, $p = 0.05$; RFS 21% *versus* 16%, $p = 0.04$). Patients who received GO experienced a significantly lower incidence of relapse than their counterparts (3-year cumulative incidence of relapse – 68% *versus* 76%, $p = 0.007$). There was no significantly higher grade ≥ 3 hepatoxicity with GO (17% *versus* 13%, Table 2), and there were no reported instances of VOD/SOS. In another study involving older patients (>60 years) with AML, EORTC-GIMEMA AML19, 237 patients were randomized to receive single-agent GO or best supportive care (BSC). GO was administered at a dose of 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8 of the induction cycle. Patients with no disease progression after induction were allowed to receive up to 8 monthly infusions of GO at 2 mg/m^2.[16] The median age of the population in this study was 77 years (range, 62–88 years) and two-thirds of the patients were older than 75 years. Ninety-four percent of the patients completed the induction course in the GO group, and over half of those patients received at least one post-induction GO infusion. Only 8% of patients completed 10 GO infusions. The CR rate was 15%, and the CR + CRi rate was 27%. There was a trend to a significantly longer median OS in patients treated with GO compared with BSC (4.9 *versus* 3.6 months, $p = 0.005$), and the estimated 1-year OS rate was 46% *versus* 29% (Table 1). The OS benefit was strikingly higher in patients with favorable and intermediate-risk cytogenetics (HR: 0.52, 95% CI, 0.34–0.77). The all-cause 30-day mortality rate was 11% in GO and 13.5% in the BSC group. The incidence of grade ≥ 3 hepatoxicity was 7% in the GO-treated group (Table 2), and there was no VOD/SOS observed in the study patients.

Gemtuzumab-ozogamicin in salvage-treatment

The role of GO as monotherapy in treating patients with CD33 + AML at first relapse was explored in several phase 2 studies.[17,18] In contrast to the initial studies that led to the initial approval of GO, the MyloFrance-1 study used a fractionated lower-dose regimen of GO similar to the scheduled used in the ALFA-0701 study. It was a single-arm, open-label study in which 57 patients with CD33$^+$ AML at first relapse were treated with single-agent GO at 3 mg/m^2 on days 1, 4, and 7. Patients that achieved a CR or CR with incomplete platelet recovery (CRp) with induction received either a higher dose (3 mg/m^2) or intermediate dose (1 mg/m^2) of cytarabine for 3 days. Hematopoietic SCT was allowed after 90 days from GO treatment. In the intention to treat population of 57 patients, the ORR (CR + CRp) was 33%. Factors such as patients' age ($\geq$60 years), duration of first remission ($\leq$12 months), or cytogenetic risk groups (intermediate *versus* poor) had no impact in the ORR.

The median OS was 8.4 months and the median RFS was 11 months. Most importantly, there were no instances of grade ⩾ 3 hepatotoxicity or VOD/SOS (even in patients who underwent allogeneic SCT, $n=3$).

Based on the results of the five prospective phase 3 studies (discussed above), especially ALFA-0701, and the MyloFrance-1 study, GO was re-approved by the US FDA in September 2017, for the frontline treatment of adult patients with untreated CD33$^+$ AML, in combination with standard chemotherapy and as monotherapy in patients ⩾ 2 years of age with CD 33$^+$ R/R AML. GO is also approved as monotherapy in frontline treatment of patients unsuitable for induction chemotherapy. In 2020, the US FDA approval was extended to include GO in combination with standard chemotherapy in all pediatric patients ⩾ 1 month old. The approval was based on the results of the phase 3 Children's Oncology Group trial AAML0531, which evaluated the outcomes of GO added to standard chemotherapy in patients 0–29 years with newly diagnosed AML. GO was administered at 3 mg/m^2/dose on day 6 of induction course 1 and on day 7 of intensification course 2. There was a significant improvement in 3-year EFS in patients treated with GO (53% *versus* 47%, $p=0.04$). However, the EFS improvement did not translate to OS improvement (69% *versus* 65%, $p=0.39$). Notably, the disease-free survival and OS were significantly improved in patients who were treated with GO and that proceeded to SCT ($p=0.02$).[19]

GO was designated as an orphan medical drug on 18 October 2000 by the European Medicines Agency (EMA) and was approved for the treatment, in combination with daunorubicin and cytarabine, of patients aged 15 years and older with previously untreated CD33$^+$ AML on 22 February 2018.[20] Similarly, Pharmaceuticals and Medical Devices Agency of Japan approved GO for the treatment of same population on 25 July 2005.

Gemtuzumab-ozogamicin mechanism of resistance

The level of CD33 expression is one of the major factors affecting the response of GO in non-core binding factor AML.[21,22] Similarly, single nucleotide polymorphisms in the splice enhancer gene of the CD33 gene (exon 2; rs12459419; C>T; Ala14Val) was shown to affect the response to GO.[23,24] Recently, five other CD33 SNPs (rs2455069, rs35112940, rs61736475, rs1803254, and rs201074739) were found to negatively impact the response to GO.[25] Multi-drug resistance (MDR) mediated by ATP-dependent drug transporters such as P-glycoprotein is a well-known cellular mechanism of chemotherapy resistance. As GO has covalently linked cytotoxin calicheamicin, MDR expression has been implicated as one of the mechanisms of resistance to GO.[26]

Ongoing studies

The question remains if there is any difference between the fixed *versus* fractionated GO dosing in combination with chemotherapy. AML-18 (ISRCTN31682779) is a phase 3 trial comparing the efficacy of '7 + 3' induction chemotherapy with one or two doses of GO in patients age > 60 years with AML or high-risk MDS. In a recent update of the trial, there was no difference in the outcomes of patients treated with fixed *versus* fractionated dose of GO. The CR/CRi rates after course 1 and 2 were 77.4% and 78.4%, respectively ($p=0.72$), although there was a trend for a higher CR + CRi rate after only one cycle with fractionated dosing (68.2% *versus* 74%, $p=0.06$). The corresponding CR/CRi measurable residual disease (MRD) negative rates were 54% and 57%, respectively ($p=0.44$). Furthermore, the 3-year OS was approximately 36%, and the cumulative incidence of relapse was 50% in both groups.[27] AML-19 (ISRCTN78449203), is another phase 3 trial evaluating the outcomes of adult patients < 60 years with AML treated with one or two doses of GO in combination with either 7+3 or fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin (FLAG-Ida). This study resumed enrollment after a temporary suspension of enrollment in 2019. Results of this study are not available at the time of this writing. Both these studies are attempting to answer this clinically relevant question.

Several therapeutic combinations of GO with novel compounds were tested preclinically. Particularly, targeting PI3K/AKT signaling has been of interest to overcome the cellular resistance of GO.[28] MK-2206, a novel compound inhibiting AKT activation was found to sensitize leukemic cells to GO. Similarly, numerous prospective trials are exploring the efficacy of the combination of GO with several chemotherapy agents or novel compounds. Some of the

Table 3. Ongoing studies involving gemtuzumab-ozogamicin in adult patients with AML.

Title	ClinicalTrials.gov identifier	Status
Pracinostat + GO in R/R AML	NCT03848754	Completed
Azacitidine + GO in R/R AML	NCT00766116	Completed
DNR + AraC and Fractionated GO at First Salvage	NCT02182596	Completed
CPX-351 + GO in R/R AML	NCT03904251	Recruiting
Venetoclax + GO in R/R CD33 + AML	NCT04070768	Recruiting
Fractionated GO in Treating MRD in AML	NCT03737955	Recruiting
Midostaurin + GO with DNR + AraC in First-line AML	NCT04385290	Active
GO in AML after SCT	NCT00044733	Completed
Fractionated GO + cladribine + AraC + G-CSF in R/R AML	NCT04050280	Recruiting
GO + fludarabine + AraC + filgrastim-sndz + idarubicin in AML and HR-MDS	NCT00801489	Recruiting

AraC, cytarabine; AML, acute myeloid leukemia; DNR, daunorubicin; G-CSF, granulocyte colony-stimulating factor; GO, gemtuzumab-ozogamicin; HR-MDS, high-risk myelodysplastic syndrome; MRD, minimal residual disease; R/R, relapsed/refractory; SCT, stem cell transplant.

interesting clinical trials are listed in Table 3. In addition, since MRD has become an established predictive marker for remission duration and OS in patients with AML, several drugs are actively being studied to eliminate MRD. Intriguingly, GO is also being evaluated in MRD clearance in patients with $CD33^+$ AML.

Conclusion

GO is the first ADC that was approved by the US FDA for the treatment of patients with AML. Despite its earlier withdrawal from the market due to the higher rate of toxicities and lack of efficacy observed in S0106, there was the fortunate continuation of research and dose optimization. Several phase 3 studies that used GO at lower/fractionated doses than S0106 showed that GO is an effective ADC in treating patients with AML both in the frontline and first salvage setting. This sequence of events highlights the need for proper study of the dose and schedule of potentially effective drugs in AML to minimize the risk of discarding potentially clinically beneficial drugs. In addition, there are ongoing studies to evaluate the efficacy of GO with chemotherapy or non-chemotherapy agents as well as in clearing MRD that may further expand the role of GO in AML.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Mahesh Swaminathan: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Jorge E. Cortes: Conceptualization; Methodology; Supervision; Writing – review & editing.

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Competing interests

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Availability of data and materials
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