Gemtuzumab ozogamicin

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Gemtuzumab ozogamicin (GO) is a humanized anti-CD33 monoclonal antibody conjugated to calicheamicin, a cytotoxic antitumor antibiotic. GO is indicated for the treatment of newly-diagnosed or relapsed/refractory CD33-positive acute myeloid leukemia (AML).

Keywords: acute myeloid leukemia ; gemtuzumab ozogamicin ; biomarkers ; CD33 ; FLT3 ; therapy

1. Introduction

Gemtuzumab ozogamicin (GO, Mylotarg®) is a humanized monoclonal antibody conjugated to cytotoxic compound called calicheamicin. The two molecules are covalently linked via a butanoic acid linker which is hydrolized in the acidic environment of the lysosome. GO is directed against the cluster of differentiation 33 (CD33) which represents a hallmark of myeloid leukemic blasts, widely expressed in AML patients. Previous studies have shown that it was expressed on leukemic blasts in about 90% of AML patients[1][2]. Several clinical studies have highlighted the clinical benefit of GO on patient outcome (**Table 1**). GO stands for the first antibody drug conjugate approved by the Food and Drug Administration (FDA).

Table 1. Overview of the main clinical trials evaluating GO efficacy.

Phase	Patient Population	Median Age of Patients in Years (Range)	Evaluable Patients	GO Dosing	Treatment Plan	Outcomes	Ref.
I	Relapsed/refractory AML patients	54 (24–73)	40	Escalating doses, 0.25 to 9 mg/m^2	Single arm trial, GO administered as single agent	ORR: 8/40 patients (20%)	Sievers 1999 [3]
II	AML patients in first relapse	61 (22–84)	142	9 mg/m^2, 2 doses recommended (max. 3 doses), with at least 14 days between 2 doses	Single arm trial, GO administered as single agent	ORR: 42/142 patients (30%), CR rate: 16%, CRp rate: 13%	Sievers 2001 [4]
II	De novo AML in first relapse	64 (22–80)	57	Fractionated doses: 3 mg/m^2 on days 1, 4 and 7 of the first course	Single arm trial, GO administered as single agent in induction, followed by cytarabine-based consolidation	ORR: 19/57 (33%), CR rate: 15/57 (26%), CRp: 4/57 (7%)	Taksin 2007 [5]
I/II	De novo AML in first relapse	60 (40–70)	20	Fractionated doses: 3 mg/m^2 on days 1, 4 and 7 of the first course	Single arm trial, GO combined with DA (DA dosing finding)	ORR: 13/20 patients (65%), CR rate: 11/20 patients (55%), CRp rate: 2/20 patients (10%)	Farhat 2012 [6]

Phase	Patient Population	Median Age of Patients in Years (Range)	Evaluable Patients	GO Dosing	Treatment Plan	Outcomes	Ref.
III	De novo/secondary AML	50 (15–71)	1113	3 mg/m^2 on day 1 of course 1 +/− on day 1 of the course 3	Randomization at induction and at consolidation. Induction regimen (DA or ADE or FLAG-Ida) +/− GO. Consolidation regimen (MACE or MidAC or high-dose cytarabine) +/− GO	GO- vs. no GO-arm: CR, 82% vs. 83%, OR: 1.04, 95% CI: 0.76–1.42, *p* = 0.8; 5-year OS, 43% vs. 41%, HR: 0.92, 95% CI: 0.79–1.08, *p* = 0.3; 5-year RFS: 39% vs. 35%, HR: 0.87, 95% CI: 0.73–1.02, *p* = 0.09	Burnett 2011 [7]
III	De novo AML	47 (18–60)	595	6 mg/m^2 on day 4; additional 3 doses of GO, 5 mg/m^2 for patients in CR after consolidation	Randomized trial, GO plus modified DA (daunorubicin, 45 mg/m^2/d, day 1 to day 3; cytarabine, 100 mg/m^2/d, day 1 to day 7) vs. standard DA (daunorubicin, 60 mg/m^2/d, day 1 to day 3; cytarabine, 100 mg/m^2/d, day 1 to day 7)	DA + GO vs. DA alone: ORR: 76% vs. 74%, *p* = 0.36; CR rate: 69% vs. 70%, *p* = 0.59; 5-year RFS: 43% vs. 42%, *p* = 0.40; 5-year OS: 46% vs. 50%, *p* = 0.85	Petersdorf 2013 [8]
III	De novo/secondary AML and high-risk MDS	67 (51–84)	1115	3 mg/m^2 on day 1 of the first course	Randomized trial: DA or daunorubicin/clofarabine +/− GO	GO- vs. no GO-arm: ORR: 70% vs. 68%, OR: 0.88, 95% CI: 0.68–1.13, *p* = 0.3; 3-year OS: 25% vs. 20%; HR: 0.87, 95% CI: 0.76–1.00, *p* = 0.05; 3-year RFS: 21% vs. 16%, HR: 0.84, 95%CI: 0.71–0.99, *p* = 0.04	Burnett 2012 [9]

Phase	Patient Population	Median Age of Patients in Years (Range)	Evaluable Patients	GO Dosing	Treatment Plan	Outcomes	Ref.
III	De novo AML patients with intermediate cytogenetic risk	50 (18–60)	238	6 mg/m^2 on day 4 of the induction and on day 4 of the first consolidation course	Randomized trial: intensive induction regimen (DA) +/− GO, consolidation (MidAC) +/− GO, +/− HSCT	GO- vs. no-GO-arm: CR rate: 91.6% vs. 86.5%, *p* = NS; 3-year OS: 53% vs. 46%, *p* = NS; 3-year EFS: 51% vs. 33%, *p* = NS. In non HSCT recipients, GO vs. no GO-arm: 3-year EFS: 53.7% vs. 27%, *p* = 0.0308	Delaunay 2011 [10]
III	De novo AML	62 (50–70)	271	3 mg/m^2 on days 1, 4, and 7 of induction and on day 1 of each of the subsequent two consolidation courses	Randomized trial: DA +/− GO	GO- vs. no-GO-arm: ORR: 81.5% vs. 73.5% (*p* = 0.15) (CR: 70.4% vs. 69.9%; CRp:11.1% vs. 3.7%); median EFS: 13.6 months vs. 8.5 months, HR: 0.66, 95% CI: 0.49–0.89, *p* = 0.006; median OS: 27.5 months vs. 21.8 months, HR: 0.81, 95% CI: 0.60–1.09, *p* = 0.16	Castaigne 2012, Lambert 2019 [11] [12]
III	De novo or secondary AML and high-risk MDS	50 (0–81)	788	3 mg/m^2 vs. 6 mg/m^2 on day 1 of induction	Randomized trial: GO 3 vs. 6 mg/m^2 + combined with ADE vs. DA	GO 3 mg/m^2 vs. 6 mg/m^2: ORR: 89% vs. 86%, HR: 1.34, 95%CI:0.88–2.04, *p* = 0.17; (CR rate 82% vs. 76%, OR: 1.46, 95%CI: 1.04–2.06, *p* = 0.03); 4-year OS: 50% vs. 47%, HR: 1.10, 95% CI: 0.90–1.34, *p* = 0.3; 4-year RFS: 44% vs. 38%, HR: 1.11, 95% CI: 0.91–1.35, *p* = 0.3	Burnett 2016 [13]

Phase	Patient Population	Median Age of Patients in Years (Range)	Evaluable Patients	GO Dosing	Treatment Plan	Outcomes	Ref.
III	De novo/secondary AML	67 (60–75)	472	3 mg/m^2 for 2 doses, on days 1 and 15 of induction, 3 mg/m^2 on the first day of consolidation	Randomized trial: intensive chemotherapy (MICE induction) +/− GO	GO vs. no-GO-arm: ORR: 45% vs. 49%; OR: 0.86, 95% CI, 0.6–1.23, *p* = 0.46; OS: HR: 1.20, 95% CI: 0.99–1.45, *p* = 0.07; RFS: HR: 1.08, 95% CI: 0.81–1.44, *p* = 0.61	Amadori 2013 [14]
III	De novo/secondary AML unfit for intensive chemotherapy	77 (62–88)	237	6 mg/m^2 on day 1 and 3 mg/m^2 on day 8, +/−2 mg/m^2/month for up to 8 doses	Randomized trial: GO alone vs. BSC	GO- vs. BSC-arm: median OS: 4.9 months vs. 3.6 months, HR: 0.69, 95% CI: 0.53–0.90, *p* = 0.005	Amadori 2016 [15]
I	Relapsed/refractory AML patients	12 (1–16)	29	Escalating doses, 6 to 9 mg/m^2	Single arm trial, GO administered as single agent	ORR: 8/29 patients (28%); CR rate: 14%; CRp rate: 14%)	Arceci et al. 2005 [16]
II	Refractory de novo AML or newly diagnosed secondary AML	11.5 (0.8–19.8)	45	2 to 3 mg/m^2	Non randomized multi-arm trial, GO + cytarabine + mitoxantrone (arm A) vs. GO+ cytarabine+ L-asparaginase (arm B)	Arm A vs. arm B: ORR: 55% vs. 40%, *p* = NS; 1-year EFS: 55% vs. 21.8%, *p* = NS; 1-year OS: 64.6% vs. 45.0% *p* = NS	Aplenc 2008 [17]
II	Newly diagnosed de novo AML	9.5 (0.07–21.6)	340	3 mg/m^2 on day 6 of course 1 and day 7 of course 4	Single arm trial, GO combined with intensive chemotherapy	CR rate: 83.1%; 3-year OS: 66%; 3-year EFS: 53%	Cooper 2012 [18]
III	Newly diagnosed de novo AML	9.7 (0–29)	1022	3 mg/m^2 on day 6 of induction course 1, and on day 7 of intensification course 2	Randomized trial, GO +/− standard chemotherapy	GO- vs. no-GO arm: CR rate: 88.3% vs. 85.1, *p* = 0.15; 3-year EFS: 53.1% vs. 46.9%, HR: 0.83, 95% CI: 0.70–0.99, *p* = 0.04; 3-year OS: 69.4% vs. 65.4%; HR: 0.91, 95% CI: 0.74–1.13, *p* = 0.39	Gamis 2014 [19]

COG: Children's Oncology Group; MDS: myelodysplastic syndrome; CR: Complete Remission; CRp: all criteria for CR without the full recovery of platelets count; ORR: overall response rate (CR+CRp); DA: daunorubicin plus cytarabine; DAE: cytarabine, daunorubicin, and etoposide; FLAG-Ida: fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; MACE: amsacrine, cytarabine and etoposide; MidAC: mitoxantrone and cytarabine; MICE: mitoxantrone, cytarabine, and etoposide; BSC: best supportive care, HSCT: hematopoietic stem cell transplantation; NA: Not available; NS: not significant.

2. The Target Antigen CD33

The CD33 antigen is a 67 kD single chain transmembrane glycoprotein that belongs to the sialic-acid-binding immunoglobulin-like lectins family (Siglecs). CD33 is a differentiation antigen especially expressed among physiologic myeloid progenitors and widely expressed in myeloid leukemic blasts[20]. The *CD33* gene is composed of eight exons. Exons 1 and 2 encode for the amino-terminal V-set signal peptide, an immunoglobulin-like domain mediating the sialic-acid binding, exons 3 and 4 encode the C2-set domain, and exon 5 encodes the transmembrane domain. The intracytoplasmic domain, encoded by exons 6, 7a and 7b, comprises two tyrosine-based inhibitory signaling motifs (Y340 and Y358) which, upon phosphorylation, provide docking sites for the Src homology-2 domain-containing tyrosine phosphatases (SHP) and the suppressor of cytokine signaling 3 (SOCS3)[21][22].

3. Mechanism of Action

After binding to the CD33 antigen, the GO-CD33 complex is rapidly internalized[23]. In the cytoplasm, the complex is routed in the lysosome. Under the acidic environment of the lysosome, the butanoic acid linker is hydrolyzed, releasing the toxic moiety of the GO. The calicheamicin derivative is reduced by the glutathione into a highly reactive species which induces simple- and double-stranded DNA breaks, leading to DNA-damage and cell death[24].

4.Predictive markers of efficacy

Enhanced knowledge about the GO metabolic pathway at both cellular and molecular levels has raised and improved understanding on GO response biomarkers (**Figure 1**) [25]. Predictive markers of efficacy include leukemic cells's characteristics such as high CD33 expression [26], as expected, but also non-adverse cytogenetic alterations [11][27], specific molecular lesions such as *NPM1* mutations, *FLT3-internal* tandem duplications and mutations involving signaling pathways [28], and a low 17-gene leukemic stem cell score [29].

Other factors have been shown to directly affect GO binding or intracellular concentration leading to a poorer response to GO. They include specific *CD33* polymorphims (such as the rs12459419, resulting in *CD33* exon 2 skipping, and ultimately leading to a shorter *CD33* isoform lacking the epitope for GO)[30], high ABCA1 expression (which may pump calicheamicin out of the cell before exerting its cytotoxic activity) [31] or CD33-induced proteasomal degradation through SOCS3 binding [32].

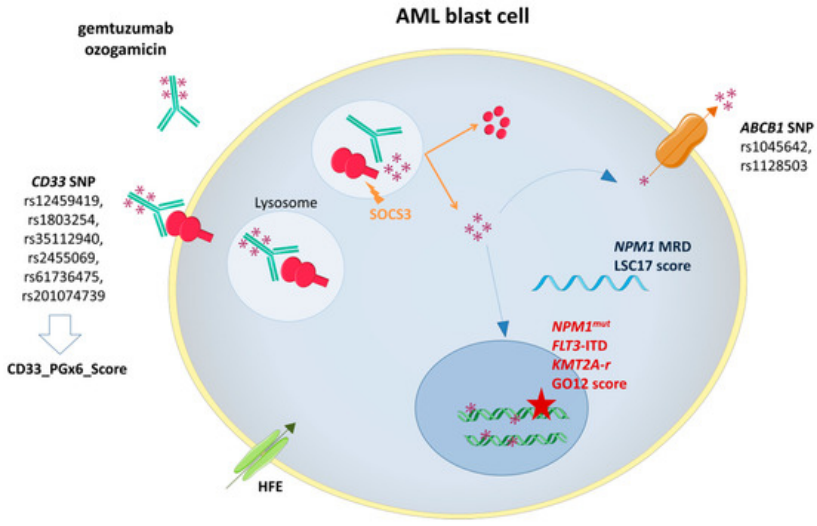

Figure 1. Gemtuzumab ozogamicin (GO) mechanism of action and biomarkers of response. SOCS3: Suppressor Of Cytokine Signaling 3; *ABCB1:* ATP-binding cassette subfamily B member 1 gene; *NPM1^{mut}:* Nucleophosmin 1 gene mutation; *FLT3*-ITD*:* FMS-Like Tyrosine Kinase 3 Internal Tandem Duplication; *KMT2A-r:* Lysine Methyltransferase 2A

rearrangement.

4.Conclusions

Given its high expression on AML blasts, CD33 antigen represents an attractive target in AML. Different clinical trials have confirmed the anti-leukemic activity of GO in CD33-positive AML cells and have shown improved outcome in AML patients. Over the past years, flow cytometry, cytogenetics, and molecular approaches, including sequencing technologies, MRD monitoring, and genotyping studies of *CD33* and *ABCB1* SNPs have offered a comprehensive analysis of promising biomarkers for GO response. Collectively, these improvements have helped to refine the subset of patients that may benefit from GO and improve patient management. Increasing knowledge of the molecular alterations in AML paves the way to new combinatory regimens that may enhance GO efficacy. Hence, ongoing trials are evaluating the feasibility and the efficacy of combining GO to FLT3-ITD inhibitors (NCT03900949, NCT04385290, NCT04293562) and Bcl-2 inhibitors (NCT04070768, NCT04070768).

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