Blood Spotlight

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Gemtuzumab ozogamicin for acute myeloid leukemia

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On 1 September 2017, the US Food and Drug Administration (FDA) approved gemtuzumab ozogamicin (GO) for the treatment of adults with newly diagnosed CD33$^+$ acute myeloid leukemia and for patients aged ≥2 years with CD33$^+$ acute myeloid leukemia who have experienced a relapse or who have not responded to initial treatment. This signals a new chapter in the long and unusual story of GO, which was the first antibody–drug conjugate approved for human use by the FDA. (*Blood*. 2017;130(22):2373-2376)

Background

CD33 (or Siglec 3) is a transmembrane receptor expressed by cells of myeloid origin, but not by normal hematopoietic stem cells.[1,2] The idea of using a CD33-targeted drug conjugate in the treatment of acute myeloid leukemia (AML) was initially suggested by the widespread expression of CD33 by AML blasts and the finding that in some cases, AML precursors are mainly or entirely CD33$^+$.[2] The latter was first demonstrated using X-linked glucose-6-phosphate dehydrogenase isoenzymes as markers for clonality, showing that in vitro treatment of clonal AML samples from glucose-6-phosphate dehydrogenase heterozygous women with anti-CD33 antibody plus complement could result in outgrowth of nonclonal, presumably normal hematopoiesis.[3] Further, we found that following IV infusion, radiolabeled anti-CD33 antibodies selectively bound to AML cells in the peripheral blood and marrow and were rapidly internalized, suggesting their use as a carrier for a potent drug or toxin.[4-6] In collaboration with industry, we selected as the toxin *N*-acetyl γ-calicheamicin dimethyl hydrazide, a derivative of a natural enediyne DNA-damaging antitumor antibiotic.[7] The anti-CD33 antibody was humanized and conjugated to the calicheamicin derivative using an acid-labile linker that was stable in circulation but, once internalized, quickly released the toxin under the acidic conditions of the lysosome, leading to DNA binding and cell death.[8] Following confirmation of the activity of the drug conjugate in a xenograft model, we conducted a phase 1 dose-escalation study in 40 patients with relapsed/refractory AML.[9] Elimination of morphologically detectable AML occurred in 20% of patients, with 12.5% achieving a complete remission (CR) or CR with incomplete platelet recovery (CRp). Dose escalation was stopped at 9 mg/m^2, because this dose saturated AML CD33-binding sites, even in patients with substantial numbers of circulating blasts. Because no dose-limiting nonhematological toxicities were identified, this dose (given on days 1 and 14) was chosen for 3 open-label multicenter single arm studies for patients with CD33$^+$ AML in first relapse. An interim analysis of 142 patients (median age, 61 years) found that 16.2% achieved a CR and another 13.4% achieved a CRp, for an overall CR + CRp rate of 29.6%.[10,11] Based on these results, in May 2000, gemtuzumab ozogamicin (GO) was given accelerated approval for treatment of patients age >60 years with CD33$^+$ AML who were not candidates for aggressive chemotherapy. As part of their postapproval commitment, the drug sponsor worked with the Southwest Oncology Group to develop study S0106, which randomized 637 adults up to age 60 years with de novo AML to receive up to 2 cycles of standard daunorubicin/cytarabine induction with or without a single dose of GO (6 mg/m^2) on day 4.[12] In an effort to balance toxicities on the 2 arms, the daunorubicin dose was reduced from 60 mg/m^2 in the control arm to 45 mg/m^2 in the GO arm. The results of the study showed no overall improvement in survival and increased treatment-related mortality in the experimental arm, leading to GO's withdrawal from the commercial market in October 2010. The recent reapplication and US Food and Drug Administration (FDA) approval are based on increased understanding of GO dosing, specific results of the pivotal study Acute Leukemia French Association study 701 (ALFA 701), and extensive additional clinical experience with the drug.

GO dose regimens

In the study leading to the original accelerated approval of GO, the observed toxicities of single-agent GO at 9 mg/m^2 included infusion-related toxicities (chills, fever, and mild hypotension), the significant myelosuppression expected when targeting an early myeloid differentiation antigen, and mild, transient bilirubin elevations (seen in 23% of patients).[10] Only 1 out of 142 patients had a bilirubin elevation >10× normal, and as a result, GO dosing of 6 to 9 mg/m^2 was often chosen for subsequent studies. As the drug began being used in more heavily pretreated patients or in combination with other agents, an increased incidence of toxicities, particularly veno-occlusive disease (VOD) of the liver, began to be observed.[13-15] In the briefing document prepared by the FDA for the recent GO review, the sponsors reported, and the FDA confirmed, that a substantially lower maximum serum concentration (C_{max}) would be expected with a 3 mg/m^2 dose of GO given on days 1, 4, and 7 compared with 9 mg/m^2 given on days 1 and 14 (382 vs 1730 ng/mL).[16] They further found in an analysis of 358 patients receiving single-agent GO that the incidence of VOD was highly associated with C_{max} after the first dose of GO. In a review of studies of GO monotherapy, they observed that the CR rate was equivalent using GO 3 mg/m^2 on days 1, 4, and 7 compared with doses of 6 or 9 mg/m^2 given on days 1 and 14.[16] In addition to the use of lower individual doses resulting in a lower C_{max}, ALFA-701 also introduced fractionated dosing in an effort to not only overcome the effects of the initial high

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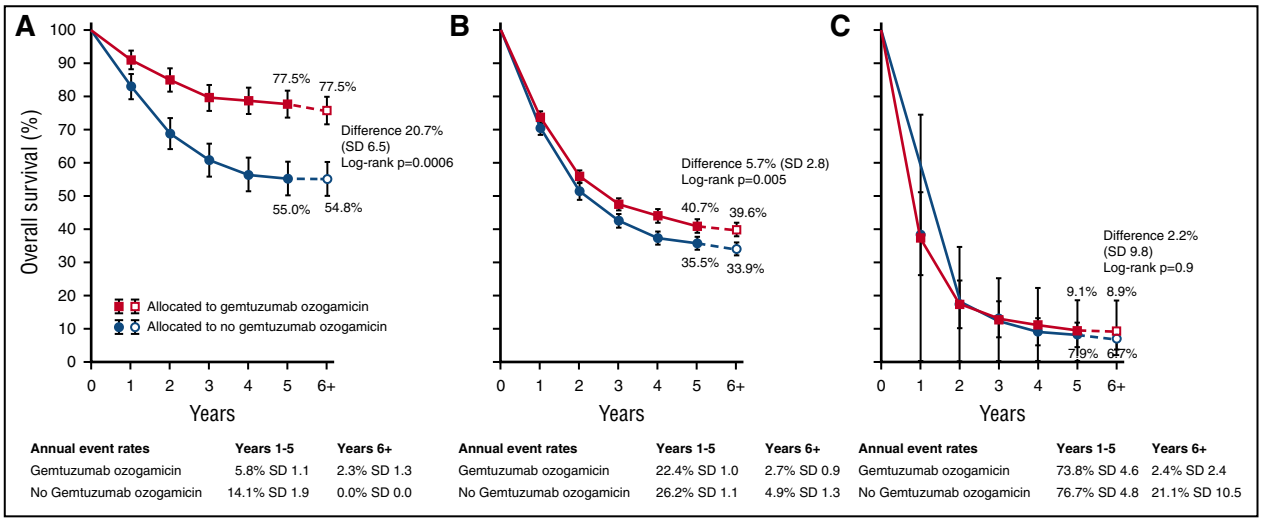

Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No Gemtuzumab ozogamicin	14.1% SD 1.9	0.0% SD 0.0

Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	22.4% SD 1.0	2.7% SD 0.9
No Gemtuzumab ozogamicin	26.2% SD 1.1	4.9% SD 1.3

Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	73.8% SD 4.6	2.4% SD 2.4
No Gemtuzumab ozogamicin	76.7% SD 4.8	21.1% SD 10.5

Figure 1. Overall survival according to cytogenetic risk category. The 3 sets of curves illustrate the overall survival of patients randomized to combination chemotherapy with or without GO. (A) Overall survival of 246 patients with favorable-risk AML. (B) Overall survival of 1827 patients with intermediate-risk AML. (C) Overall survival of 583 with adverse-risk disease.[24] SD, standard deviation.

levels of peripheral blasts present on day 1 that can act as a sink preventing the drug from binding marrow blasts but also take advantage of rapid reexpression of CD33 molecules on the cell surface of AML blasts after a first exposure to antibody.[17-19]

ALFA-701 and subsequent meta-analyses

The pivotal trial presented by the sponsor to the FDA was ALFA-0701, a French multicenter, open-label, 1:1 randomized trial of GO (3 mg/m^2 on days 1, 4, and 7) plus daunorubicin (60 mg/m^2 on days 1 to 3) and cytarabine (200 mg/m^2 as continuous infusion on days 1 to 7) (DA) versus DA alone for induction and consolidation involving 271 patients age 50 to 70 years with untreated de novo AML.[20] The CR rates in the 2 arms were similar (70.4% vs 69.9% for GO + DA vs DA), but the 3-year event-free survival (the primary end point of the study) was significantly higher in the GO + DA arm (39.8% vs 13.6%, $P < .001$). Along with S0106 and ALFA-0701, 3 other randomized trials testing the addition of GO in induction therapy have been conducted and reported.[21-23] These studies differed somewhat in patient-related variables, induction regimens, and the dose and schedule of GO.[24] A meta-analysis that included the 3325 patients entered onto these 5 studies concluded that, although not increasing the proportion of patients achieving a complete remission (odds ratio [OR], 0.91; $P = .3$), the addition of GO significantly reduced the risk of relapse (OR, 0.81; $P = .0001$) and improved relapse-free (OR, 0.87; $P = .005$) and overall survival at 5 years (OR, 0.90; $P = .01$).[24] The survival benefit was most apparent in patients with favorable risk cytogenetics (OR, 0.47; $P = .0006$) and was also seen in those with intermediate-risk disease (OR, 0.84; $P = .005$), but not in those with adverse-risk AML (OR, 0.99; $P = .9$) (Figure 1). GO doses of 3 mg/m^2 were as effective as higher doses and had improved safety. The equivalent effectiveness and improved safety of 3 mg/m^2 vs 6 mg/m^2 was confirmed in a subsequent prospective randomized trial comparing the 2 dose regimens (NCRI AML-17).[25] No studies have directly compared the fractionated dosing regimen used in the French ALFA-0701 with any of the single-dose regimens used in other trials, nor are the relative contributions of GO during induction vs consolidation understood.

GO has also been studied in pediatric AML, first in a pilot study of 350 patients demonstrating the safety of adding GO at 3 mg/m^2 to induction and consolidation and then in a prospective study (AAML0531) that randomized 1022 patients age 0 to 29 years to induction and consolidation chemotherapy with or without GO.[26,27] Remission rates were not improved with GO, but relapse risk was significantly reduced, resulting in improved event-free survival (53.1% vs 46.9% at 3 years; $P = .04$).

Factors affecting the response to GO

GO cytotoxicity requires antibody-conjugate binding to the AML cell surface, followed by internalization, hydrolysis of the linker (allowing calicheamicin activation and release from the lysosome), and calicheamicin binding to DNA (inducing single- and double-strand breaks), followed by activation of downstream pathways leading to apoptotic cell death. Factors affecting each step have been identified and shown to influence GO effectiveness in vitro.[28] Critical factors identified in clinical studies include variation in CD33 expression and multidrug-resistance mechanisms.

Clinical studies demonstrate as much as a 2 log-fold variation in CD33 expression by AML blasts with lower levels of CD33 seen in AML cases with adverse karyotype and in patients with core-binding factor (CBF) AML, whereas high expression is seen in AMLs with *FLT3*-ITD, *MLL*, and *NPM1* mutations.[29-33] CD33 expression itself does not appear to have a marked effect on AML treatment outcome using chemotherapy alone, but the addition of GO (at least at 3 mg/m^2) appears to preferentially benefit those with higher expression levels.[25,31,33] An exception may be patients with CBF AML, who appear to benefit from GO despite relatively low CD33 levels, a finding that might be explained by the inherent sensitivity of CBF blasts to cytotoxic insult. An alternative explanation is that in CBF leukemias overt disease arises from a CD33$^+$ precursor.[2] Consistent with this notion is the high activity of GO in the treatment of acute promyelocytic leukemia, which is also thought to arise from a more mature precursor.[34,35] In fact, it may be that sensitivity to GO helps define the level of differentiation of the leukemic stem cell.

Although some of the variability in CD33 expression by AML blasts relates to cytogenetic and mutational subtypes, much was unexplained until the recent demonstration that a germline CD33 single-nucleotide polymorphism, rs12459419, is associated with the expression of an alternatively spliced variant of CD33 lacking the GO-binding site (immunoglobulin V domain).[36,37] Essentially all available diagnostic antibodies target the same CD33 immunoglobulin V domain, so this single-nucleotide polymorphism defines whether AML blasts will appear to be $CD33^+$ or $CD33^-$. In the recently published pediatric AAML0531 study, the rs12459419 genotype was CC (and therefore able to bind GO) in 51% of patients, CT in 39%, and TT in 10%.[38] The addition of GO significantly lowered the relapse rate in patients with the CC genotype (26% vs 49%, $P \leq .001$) but had no effect on patients with CT or TT genotypes, resulting in a disease-free survival benefit with GO that was restricted to patients with the CC genotype.

In addition to the nature and number of CD33-binding sites, the intracellular accumulation of the toxic moiety is affected by rates of antibody-conjugate internalization and the level of adenosine triphosphate–binding cassette transporter activity such as P-glycoprotein, which exports calicheamicin from the cell.[29] Theoretically, because GO is delivered with relative specificity to leukemic marrow, adenosine triphosphate–binding cassette transport inhibition should improve the efficacy of the drug in high P-glycoprotein–expressing AMLs. To exert its cytotoxic effect, calicheamicin binds to the minor groove of DNA in a sequence-specific manner, inducing DNA single- and double-strand breaks that in turn initiate downstream pro- and antisurvival signaling events. Less is known about how these responses are modulated, but it is sobering to realize that there are many-fold differences in the sensitivity of AML clinical samples exposed to free calicheamicin using a traditional 4-day 3-(4,5-dimethylthiazol-2-yl)-2,5-dimethyltetrazolium bromide assay.[29]

GO toxicity

The acute infusion-related toxicities seen with GO are transient and usually respond to standard interventions. As expected with an agent that eliminates early myeloid precursors, bone marrow suppression is seen when GO is used as a single agent. When added to combination chemotherapy in the ALFA-701 trial, myeloid recovery following induction was not delayed, whereas platelet recovery was prolonged by 4 days. The toxicity of greatest concern is the development of VOD. The risk of VOD appears to be relatively low when individual doses of no greater than 3 mg/m^2 are used in combination with conventional therapy as part of initial therapy of AML, but the risks increase with higher doses or use of the drug in more heavily pretreated patients.[39] The recent observation that VOD is also seen with inotuzumab ozogamicin, an anti-CD22 calicheamicin conjugate, suggests that a component of GO-associated VOD is CD33 independent,[40] whereas the appearance of liver toxicity associated with SGN-CD33A, which uses a pyrrolobenzodiazepine dimer instead of calicheamicin, argues that targeting CD33 may also contribute.[41]

Going forward

The results of ALFA-701 and the meta-analysis of randomized trials support the safety and efficacy of the addition of GO to induction therapy for patients with newly diagnosed $CD33^+$ AML, establishing this as a new standard of care. The outstanding results reported from several albeit nonrandomized trials with the use of GO in recurrent APL and the combination of GO, all-*trans*-retinoic acid, and arsenic trioxide in the treatment of patients with newly diagnosed high-risk APL make these attractive treatment approaches as well.[34,42,43] Going forward, the most fruitful studies of GO itself may be those investigating the implications of CD33 splice variation and those that attempt to improve our understanding of the cellular basis for susceptibility to GO, focusing on GO uptake and trafficking, sensitivity to DNA damage, and expression of CD33 by the AML stem cell. The recent approval of midostaurin for *FLT3*-mutated AML and CPX-351 for therapy-related AML or AML with myelodysplasia-related changes presents the additional challenge of defining the relative benefits of these 3 drugs in specific subsets of AML and whether (and how) they can be effectively and safely combined.

Authorship

Contribution: F.R.A. and I.D.B. wrote the paper.

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