Gemtuzumab ozogamicin in acute myeloid leukemia: a remarkable saga about an active drug

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Despite living in an era of unprecedented progress in the understanding of the genetic and molecular biology of acute myeloid leukemia (AML), this has not translated into significant advances in therapy. Never before have so many potential targets been studied. Yet most have not advanced beyond the phase 1 and, occasionally, phase 2 studies. The few ongoing phase 3 studies seem unlikely to have more than a marginal benefit, if at all. Thus, it is not surprising that in past few decades almost no new drugs for AML have received regulatory approval. In 2000, gemtuzumab ozogamicin (GO) was granted accelerated approval by the US Food and Drug Administration based on promising phase 2 data in relapsed older adults with AML. GO held promise as a new agent that also could be efficacious in newly diagnosed AML with acceptable toxicity. Several phase 3 studies were designed to test GO in this setting. The results of a randomized study by the Southwest Oncology Group led in 2010 to the voluntary withdrawal of this agent when improved efficacy could not be demonstrated and toxicity appeared excessive. Since then, 4 randomized studies have been completed that, in aggregate, strongly support the efficacy of this agent in newly diagnosed AML with acceptable toxicity. There is a very plausible explanation for this discrepancy, making a compelling case for reapproval of GO in AML. (*Blood*. 2013;121(24):4838-4841)

Introduction

Gemtuzumab ozogamicin (GO) consists of a humanized anti-CD33 monoclonal antibody conjugated with calicheamicin, a potent antitumor anthracycline antibiotic. The story of the clinical development of this therapeutic agent has been remarkable. GO is an active therapeutic agent but is not available on the market in the United States or Europe. In May 2000, GO received accelerated approval by the US Food and Drug Administration for treatment as a single agent of patients older than 60 years with acute myeloid leukemia (AML) in first relapse who were not candidates for aggressive chemotherapy. The initial approval was based on the results of a phase 2 study of 142 patients with AML in first relapse. The complete response (CR) rate for all patients was 16%, and when a subset of patients who had incomplete platelet recovery (CRp) was added, the overall response rate was 30%. For patients older than 60 years, the overall response rate was 26%.[1] As part of the marketing approval, the US Food and Drug Administration mandated, first, completion of the ongoing studies of GO in relapsed AML and, second, the initiation of randomized clinical trials comparing GO in combination with conventional induction chemotherapy to conventional chemotherapy alone.[2] Final results of 3 phase 2 studies of GO as a single agent in relapsed AML confirmed the data from the earlier single phase 2 study[1] and yielded a response rate of 13% CR and 13% CRp, for an overall response of 26%.[3]

The SWOG study in the current issue of *Blood*

In this issue of *Blood*,[4] the Southwest Oncology Group (SWOG) describe the results of a phase 3 study, S0106, which was designed to compare in a prospective randomized trial the effects of adding GO to standard induction therapy with daunorubicin and cytarabine. In this trial, 637 adult patients younger than 60 years were randomly assigned to receive daunorubicin (45 mg/m^2 on days 1, 2, 3) and cytarabine (100 mg/m^2 per day by continuous infusion on days 1-7) and GO (6 mg/m^2 on day 4) vs standard induction therapy with daunorubicin (60 mg/m^2 on days 1-3) and cytarabine alone by continuous infusion on days 1 through 7 (DA). After induction, patients were to receive 3 courses of consolidation therapy with cytarabine (3 g/m^2 on days 1, 3, and 5). After completion of therapy, there was an additional randomization to test the role of GO as maintenance therapy vs observation. The CR rate was 69% for DA+GO and 70% for DA. Similarly, the overall efficacy, as measured by the relapse-free survival and the overall survival (OS), was similar in both groups. The effect of treatment on OS did not vary significantly among cytogenetic risk categories ($P = .45$), although among patients with favorable cytogenetics, OS was not significantly better in the DA+GO group ($P = .12$). There was no suggestion of benefit in the other cytogenetic risk groups. There was, however, increased induction mortality in the DA+GO group, at 5% vs 1% in the DA group. On the basis of the results of these data, demonstrating a lack of clinical benefit and an increased mortality in the group of patients who received GO, approval for this drug was voluntarily withdrawn in June 2010.

In this study are 2 factors to consider. First, the dose of daunorubicin in the study group, DA+GO, was only 45 mg/m^2 compared with 60 mg/m^2 in the standard group. Intensifying anthracycline doses in induction has been shown to have a survival advantage, particularly in younger patients with AML.[5,6] Thus, the 2 groups may not be strictly comparable, and the fact that the

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Table 1. Randomized studies of GO in newly diagnosed patients with AML

Study	n	Age, years	Characteristics	Dose of each administration of GO	Improved CR with GO	Improved RFS, EFS, DFS or OS with GO	Increased induction mortality	Increased hepatic toxicity
SWOG 0106[4]	637	18-60	DA+GO vs DA in induction and in maintenance	6 mg	No	No	Yes	No
MRC AML15[7]	1113	<60	Induction, consolidation, and maintenance, all with or without GO	3 mg	No	Yes: 1. Favorable cytogenetics 2. 70% of intermediate cytogenetics	No	No
ALFA 0701[9,10]	280	50-70	DA+GO vs DA in induction and in consolidation	3 mg	No	Yes: In favorable/ intermediate group	No	No
Groupe Ouest Est d'Etude des Leucémies Aiguës et Autres Maladies du Sang AML 2006 IR[10]	254	18-60	Induction with or without GO	6 mg	No	Yes: Improved EFS	No	Yes
National Cancer Research Institute AML16[8]	1115	51-84	Daunorubicin/ clofarabine induction, with or without GO	3 mg	No	Yes: In favorable/ intermediate group	No	No
Leukemia Research Fund AML14 and National Cancer Research Institute AML 16[11]	495	Older adults, for conventional chemotherapy	Low-dose cytarabine, with or without GO	3 mg	Yes	No	No	No

CR, complete remission; DA, daunorubicin/cytarabine; DFS, disease-free survival; EFS, event-free survival; FS, relapse-free survival.

efficacy was similar could suggest that the comparable response in the DA+GO group may actually be related to the dose intensification through to the addition of GO. Second, although this was a randomized trial that should inherently account for differing populations, it is noteworthy that the mortality of 5% in the DA+GO group is consistent with a typical induction mortality, as reported in the overwhelming majority of major studies in AML. In contrast, the very low induction mortality of 1% in the control group is unprecedented.

Other studies of GO in newly diagnosed AML

In addition to the SWOG study, there have been 4 major randomized studies of the use of GO in newly diagnosed patients with AML with results that are sharply in contrast to those reported by the SWOG (Table 1). In 2011, the Medical Research Council in Britain (MRC) published the results of the AML 15 trial,[7] in which 1113 patients who were predominantly younger than 60 years were randomly assigned to receive a single dose of GO (3 mg/m^2) on day 1 of the first of 2 induction courses with 1 of 3 induction randomized regimens. This randomization, with or without the addition of GO, was continued throughout consolidation and maintenance. A predefined subgroup analysis revealed an improved OS at 5 years for patients with favorable cytogenetics (79% vs 71%) but no benefit for patients with unfavorable cytogenetics. There was also an OS benefit for some patients with intermediate-risk disease, as indicated by an internally validated index using cytogenetics, age, and performance status, which predicted that approximately 70% of all intermediate-risk patients would have a 10% improvement in 5-year OS if given GO during induction. The 30% of intermediate-risk patients not likely to derive a benefit from GO were those who were older or had higher white cell counts, a worse performance status, or secondary disease. It should be noted that this advantage of GO appeared in the context of remission induction chemotherapy based on daunorubicin at a dose level of 50 mg/m^2 (3 days), which today we would probably consider suboptimal. Furthermore, of note, in the intermediate-risk group, those 30% of patients predicted to not benefit were older and had higher white blood cells counts at presentation and a worse performance status or secondary disease.[7]

The National Cancer Research Institute in Britain reported the results of their large AML 16 study in 2012,[8] in which 1115 patients with AML aged 51 to 84 years (median age, 67 years) were randomly assigned to receive daunorubicin/clofarabine with or without GO, 3 mg/m^2, on the first course of therapy. Once again, there was no difference in the initial response rate, and the treatment-related mortality was similar, without any increase in toxicity with GO. However, at a median follow-up of 30 months, the relapse rate was significantly lower with GO (68% vs 76%; $P = .007$), and the 3-year OS was significantly better (25% vs 20%; $P = .05$). This is perhaps remarkable because the study evaluated a single dose of GO at 3 mg/m^2, although, again, GO was used in combination with daunorubicin at 50 mg/m^2 for 3 days.[8]

The Acute Leukemia French Association (ALFA) presented the results of their 0701 trial at the plenary session of the American Society of Hematology annual meeting in 2011, and the final results were published in 2012.[9] In this trial, conducted in patients with newly diagnosed AML, aged 50 to 70 years, patients were randomly assigned in induction to daunorubicin/cytarabine with or without GO (3 mg/m^2, on days 1, 4, and 7). Patients in remission received 2 additional courses of daunorubicin/cytarabine as consolidation, with or without GO, at the same dose of 3 mg/m^2, on day 1 of each cycle. Thus, in this particular study, GO was administered in combination with daunorubicin at 60 mg/m^2 for 3 days and was given in a more intense regimen on 3 separate days in more than 1 cycle. Similar to the MRC study, there was no significant difference in the CR rate between the 2 groups or in the treatment-related mortality. However, the event-free survival was superior in the GO group, at 40.8% vs 17% in the control group ($P = .0003$). The OS was similarly better in the GO group, at 53.2% vs 41.9% in the control group ($P = .037$). Once again, subgroup analysis indicated that the major benefit occurred in patients in the favorable/intermediate group, but not among those with an unfavorable karyotype.[9] Thus, this study reported a survival

advantage for treatment with GO not only after a subgroup analysis but also in the entire study population.

The French Groupe Ouest Est d'Etude des Leucémies Aiguës et Autres Maladies du Sang presented results of their AML 2006 IR study at the annual meeting with the American Society of Hematology in 2011.[10] In this trial, 238 adults aged 18 to 60 years with de novo AML were randomly assigned to receive standard daunorubicin/cytarabine induction with or without GO at a dose of 6 mg/m^2 on day 4. GO was also added to consolidation therapy with mitoxantrone/cytarabine on the basis of the initial randomization. Similar to the previous 2 European studies, there was no difference in the remission rate or drug treatment-related mortality between the 2 groups. Although there was no statistical differences in the OS at 3 years among patients who did not undergo an allogeneic transplant, event-free survival was significantly higher in the GO group (53.7 vs 27%; $P = .03$).[10] At the present time, this study must be very cautiously interpreted, as the data were submitted as an abstract about 2 years ago and have not been followed-up by a peer-reviewed publication. Details regarding treatments and results are not available.

Finally, successive trials in the United Kingdom, the Leukemia Research Fund AML 14 trial and the National Cancer Research Institute AML16 trial, also evaluated the role of GO among older patients considered unsuitable for conventional intensive therapy. Four hundred ninety-five patients were randomly assigned to receive low-dose cytarabine, with or without GO, at 3 mg/m^2. In this study, the addition of GO significantly improved the remission rate (30% vs 17%, $P = .006$) but not the 1-year OS (25% vs 27%). The lack of a positive effect on any of the survival estimates appears consistent with a minor effect of GO in the category of high-risk patients with AML who are of older age.[11] This notion is also in keeping with a negative randomized study in 232 patients with newly diagnosed AML who are older than 60 years, randomly assigned to 3 cycles of GO maintenance GO therapy at 6 mg/m^2 vs no further treatment.[12]

Several things are clear from these studies. The initial concerns for the safety for GO were based on the 3 phase 2 trials that used 2 doses of GO at a dose of 9 mg/m^2 on days 1 and 14. An increased incidence of venoocclusive disease was observed and raised concerns for the use of this agent, especially among patients who may go on to receive an allogeneic stem cell transplantation. Subsequent studies that used lower doses of GO, either as a single lower dose of 3 to 6 mg/m^2 or in fractionated doses, as in the ALFA trial, generally reported less significant hepatic toxicity. Similarly, other studies of maintenance therapy with GO that also used lower doses of GO did not show a significant increase in hepatic toxicity with GO.[12,13]

A unifying interpretation of the clinical data?

Is it perhaps possible to reconcile the apparent discrepancies between different phase 3 trials regarding the effectiveness of GO? The data consistently indicate that GO is an active anti-AML with an acceptable toxicity profile when used at a dose range of 3 to 6 mg/m^2. It has become clear that remission induction treatment with daunorubicin-based schedules of 90 mg/m^2 for 3 days is more effective than similar schedules with daunorubicin at 45 mg/m^2.[5,6] The 2 studies from the United Kingdom,[7,11] which used only a single dose of GO and compared it with a suboptimal daunorubicin regimen of 50 mg/m^2, noted an effect in the more favorable subsets of patients. Thus, it seems that even a single dose of GO can somewhat compensate for a lack of dose intensity of remission induction treatment, at least in the more favorable subgroups. In the SWOG study,[4] the single bolus of GO, in combination with daunorubicin at 45 mg/m^2, which was used as the study group, represents an unfair comparison in terms of dose intensity. This could easily explain why this group appeared to lack an effect when compared with the control group that used daunorubicin at 60 mg/m^2.

The most prominent effect of GO was seen in the ALFA study,[9] in which much more GO (3 days at 3 mg/m^2 for 2 cycles) was added to a daunorubicin regimen of 60 mg/m^2 in both comparator groups. The latter study reported a benefit in favor of GO that was apparent in the entire group, as well as in subgroups. These data could indicate that the added value of GO is a result of the fact that it fills a gap in dose intensity when, for instance, the anthracycline is used at suboptimal dose levels. Nevertheless, at this point, one cannot exclude the possibility that GO also adds unique activity to the induction regimen.

That patients with adverse cytogenetics do not benefit from GO should not at all be surprising if CD33-antigen targeted dose intensification is regarded as the basis of the drug's therapeutic effectiveness. Every manipulation designed to improve the results of cytotoxic induction therapy for AML has not been beneficial for patients with adverse cytogenetics. This includes intensifying postremission therapy with high-dose cytarabine,[14] intensifying induction therapy with high-dose anthracyclines,[13] or the effect of low-dose cytarabine (compared with hydroxyurea) for patients who are not fit for conventional chemotherapy.[15] Thus, observing a response for GO, particularly in the chemosensitive subset of patients with a better prognosis, is a consistent finding in every attempt to improve the overall results in AML. The validity of subset analysis should not be negated if these are sufficiently powered and the same pattern is observed across studies, particularly if they have been predefined, as was reported in the MRC AML 15 study. Furthermore, in the AML 16 trial, the significant OS benefit justifies the evaluation of the subsets.

Concerns have also been raised by the fact that none of the trials of GO have demonstrated an improvement in the remission rate. This, however, ignores the ongoing concept of improving the quality of remissions as a means for a better long-term outcome. Current studies in acute lymphoblastic leukemia, in which the initial complete remission rate is high, are focused on a greater reduction in the leukemia burden, identified by a lower level of minimal residual disease, as a means of prolonging the survival without affecting the complete remission rate. Although minimal residual disease data in AML lag behind those of ALL, the concept is well established, and such data should not be surprising.

GO and acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) is typically characterized by their relatively high cellular surface expression levels of CD33, which makes this disease an interesting candidate for GO therapy. Indeed, in addition to the demonstrated activity in AML, GO appears to be highly active in APL. This is emphasized by the fact that GO, given as monotherapy, results in durable molecular remissions in patients with molecularly relapsed APL.[16] In fact, GO has been shown to effectively replace anthracyclines in the management of APL.[17,18]

What next?

The aggregate of the data in GO support its efficacy in APL and in newly diagnosed AML, particularly in patients with more favorable cytogenetics. These data were not available when GO was withdrawn from the market. With all the current available information about GO, we now believe that the entirety of the data should be compelling enough to allow physicians to use this important agent in AML,

especially in an era in which no new drug has been approved for AML in the past 2 decades. It would be wrong to delay approval until another large randomized study is completed.

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