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COMMENTS AND CONTROVERSIES

Gemtuzumab Ozogamicin: Time to Resurrect?

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On May 17, 2000, the US Food and Drug Administration (FDA) granted accelerated approval for the use of gemtuzumab ozogamicin (GO) in older patients (age $\geq$ 60 years) with acute myeloid leukemia (AML) in first relapse who were not considered candidates for standard cytotoxic chemotherapy.[1] Approval for this novel anti-CD33 immunoconjugate was based on a phase II trial demonstrating a 30% response rate (including complete response [CR] and CR with incomplete platelet recovery)[2] and was conditional on future demonstration of benefit in treatment of AML. Over the past 10 years, several phase II and III trials have addressed this issue.

A review of the phase II studies in 277 patients (median age, 61 years) with relapsed AML noted a response rate of 26%, essentially identical to that in the studies that led to the FDA approval.[3] GO has less GI toxicity than anthracyclines or cytarabine (Ara-C), but distinctively, it has been associated with hepatic sinusoidal obstructive syndrome (SOS).[4] However, the incidence of SOS was only 0.9% in patients who did not undergo prior or subsequent allogeneic hematopoietic cell transplantation (HCT).[3] Although SOS was more frequent after HCT, it was uncommon if more than 3.5 months had elapsed between the last GO dose and the HCT.[5]

Used alone, GO is most effective in acute promyelocytic leukemia (APL), likely because of a high surface expression of CD33, the target of GO. The combination of all-*trans*-retinoic acid (ATRA) and GO can be a substitute for ATRA plus anthracyclines in curing newly diagnosed APL, producing a response rate of 84%,[6] plausibly with less acute toxicity, less early and delayed cardiotoxicity, and a lower risk of therapy-related myelodysplastic syndrome–AML. Hence, as demonstrated by Breccia et al,[7] GO is an attractive option for the treatment of older patients with APL, with all treated patients responding with durable molecular remissions. Furthermore, GO has been successfully combined with ATRA and arsenic trioxide in newly diagnosed patients, particularly those with high-risk disease, where the high presenting WBC count puts patients at increased risk of early death and relapse. In a study conducted at the MD Anderson Cancer Center, the CR rate was 81% in high-risk patients who received GO.[8] The combination of ATRA and arsenic trioxide plus GO is now being evaluated in a North American Intergroup APL trial (SWOG [Southwest Oncology Group] 0535) for high-risk APL. Italian investigators noted that early treatment of molecular relapse of APL with single-agent GO resulted in longer survival than was seen when treatment began at hematologic relapse.[9] The relative rarity of APL, particularly of molecular relapse, makes a randomized study to confirm these findings infeasible. Other areas in which GO has significant value include the relapsed AML and pediatric settings.

Although the beneficial results in APL alone would make the availability of GO desirable, patients with APL constitute only 10% to 12% of those with AML. However, several phase II trials of GO with cytarabine plus anthracycline in relapsed AML have demonstrated that the combination is safe and well tolerated,[10,11] setting the stage for its evaluation in newly diagnosed patients. Burnett et al[12] reported a randomized trial (MRC [Medical Research Council] AML15) showing that addition of 3 mg/m^2 GO to cytarabine and daunorubicin induction in younger patients (typically age $<$ 60 years) with AML significantly improved survival in those with cytogenetically favorable risk and in 70% of patients with intermediate-risk disease. They developed a model that reproducibly allowed identification of patients who would live longer after treatment with the GO, anthracycline, and cytarabine combination. GO also improved outcomes when added to a regimen using higher doses of cytarabine (FLAG-Ida [fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin]), suggesting that it was not merely a substitute for high-dose cytarabine.[12] However, the randomized SWOG 106 study, which added 6 mg/m^2 to 3 + 7 (3-day anthracycline plus 7-day cytarabine) in untreated patients age $<$ 60 years, found an increase in 30-day mortality uncompensated by improvements in CR, event-free survival (EFS), disease-free survival, or overall survival (OS).[13] These results apparently prompted Pfizer to voluntarily withdraw GO from the market at the request of the FDA in June 2010, before the results of other randomized trials were available.

Because of the pivotal role played by the SWOG results, comment on this study seems appropriate. First, as in the MRC study, there was a survival advantage for patients with favorable cytogenetics who received GO. However, unlike in the MRC study, the doses of daunorubicin were not the same in the two randomized arms. In particular, to arrive at equitoxic doses, the daily daunorubicin doses were designated, somewhat arbitrarily, as 45 mg/m^2 in the GO arm and 60 mg/m^2 in the non-GO arm. The similar efficacy in both arms of the trial thus might be taken as evidence that GO contributed to this

efficacy. Of course, the lower dose of daunorubicin could be implicated when arguing that GO substantially added to induction mortality. However, the definition of induction mortality is less precise, given the variable time at risk, compared with overall survival, which was the same in both arms. Indeed, the induction mortality was unusually low (< 1%) in the non-GO arm of the study.

Results of three other randomized trials comparing induction chemotherapy with or without GO in newly diagnosed AML were presented at the 53rd Annual Meeting of the American Society of Hematology in 2011 and are also noteworthy (Table 1). The Acute Leukemia French Association (ALFA) compared cytarabine (200 mg/m^2 daily for 7 days) plus daunorubicin (60 mg/m^2 daily for 3 days) with or without GO 3 mg/m^2 on days 1, 4, and 7 in patients age 50 to 70 years and found improved EFS ($P = .002$) and OS ($P = .04$) in the GO arm.[14] As in the AML15 study, benefit was limited to the patients with cytogenetically favorable and intermediate-risk disease. The GOELAM (Groupe Ouest-Est Leucémies Aiguës Myéloblastiques) found that the addition of GO 6 mg/m^2 to a 3 + 7 regimen improved EFS in adults age < 60 years who did not undergo subsequent HCT.[15] Finally, Burnett et al[16] reported the results of the AML16 trial, which randomly assigned older patients (median age, 67 years; range, 51 to 84 years) to receive daunorubicin and either clofarabine or cytarabine, with or without GO 3 mg/m^2. They demonstrated a statically significant survival advantage for the patients who received GO; again, the benefit was confined to those subsets with favorable and intermediate-risk cytogenetics. Importantly, in none of these three trials was the addition of GO associated with a significant increase in induction mortality (Table 1).

Therefore, overall, five of five randomized trials have found a benefit for GO in newly diagnosed patients with favorable-risk AML, and four of five (three in primarily younger, and one in primarily older, patients) have found the same benefit in patients with intermediate-risk AML as defined by cytogenetics. Thus, a reproducible method is available to select patients likely to benefit; these constitute the majority of those age < 60 years. It might be argued that the need for GO could be dispensed with, if daunorubicin at 90 mg/m^2 replaced the typical 60-mg/m^2 dose used in most of these trials. This contention rests on the observation that to date, the benefit of GO seems most obvious in younger patients with better-risk disease, similar to those who benefitted from the escalation of the daunorubicin

Table 1. Reported Randomized Trials of Chemotherapy With or Without GO

Trial	No. of Patients: Total	No. of Patients: No GO *v* GO	Age Group (years)	Induction Chemotherapy	CR Rate (no GO *v* GO)	Induction Mortality (no GO *v* GO)	Grades 3 and 4 Liver Toxicity (no GO *v* GO)	Outcomes (no GO *v* GO)
Burnett et al[12]	1,113	557 *v* 556	< 60	DA *v* ADE *v* FLAG-Ida ± GO 3 mg/m^2 on day 1	83% *v* 82%	6% *v* 7%	Lower AST after course 1	OS for favorable risk, 51% *v* 79% (HR, 0.32; 95% CI, 0.18 to 0.59); internally validated model found 670 patients (75% of total) had predicted survival benefit (HR, 0.69; 95% CI, 0.55 to 0.87)
P						.6	.005	
Petersdorf et al[13]	627		18-60	DNR 45 mg/m^2 per day on days 1-3 + ara-C 100 mg/m^2 per day on days 1-7 + GO 6 mg/m^2 on day 4 *v* DNR 60 mg/m^2 per day on days 1-3 + ara-C 100 mg/m^2 per day on days 1-7	69% *v* 66%	0.8% *v* 5.8%	NA	RFS overall population (HR, 1.0; 95% CI, 0.69 to 1.44)
P						.002		
Castaigne et al[14]	278	139 *v* 139	50-70	DNR 60 mg/m^2 per day on days 1-3 + ara-C 200 mg/m^2 per day on days 1-7 ± GO 3 mg/m^2 per day on days 1, 4, 7	75% *v* 81%	4% *v* 6.5%	8% *v* 13%	OS overall population, 44% *v* 53% (HR, 0.7; 95% CI, 0.5 to 0.99)
P						.6	.24	.046
Delaunay et al[15]	238	119 *v* 119	18-60	DNR 60 mg/m^2 per day on days 1-3 + ara-C 200 mg/m^2 per day on days 1-7 ± GO 6 mg/m^2 on day 4	87% *v* 92%	2.5% *v* 4.2%	11.5% *v* 22%	OS ELN favorable
P						NS	.04	.0008
Burnett et al[16]	1,115	556 *v* 559	51-84	DNR 50 mg/m^2 per day on days 1, 3, 5 and CLO 20 mg/m^2 per day on days 1-5 or ara-C 100 mg/m^2 every 12 hours on days 1-10 ± GO 3 mg/m^2 on day 1	58% *v* 62%	11% *v* 12%	ALT, 4% *v* 4%	29% *v* 35% (HR, 0.81; 95% CI, 0.67 to 0.97)
P						.4	.3	

Abbreviations: ADE, cytarabine, daunorubicin, and etoposide; ara-C, cytarabine; CLO, clofarabine; CR, complete response; DA, daunorubicin plus cytarabine; DNR, daunorubicin; EFS, event-free survival; ELN, European LeukemiaNet; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; GO, gemtuzumab ozogamicin; HR, hazard ratio; NA, not available; NS, not significant; OS, overall survival; RFS, relapse-free survival.

dose from 45 to 90 mg/m^2 in two recently reported randomized trials.[17,18] However, this inadequate-dose argument flies in the face of the superior outcome seen with GO in the AML15 trial, even when the non-GO arm was intensive. In particular, given the low toxicity profile of GO, certainly at 3 mg/m^2, patients and physicians might prefer to have the drug available today rather than await the results of potential future trials randomly assigning patients between cytarabine plus daunorubicin 90 mg/m^2 and cytarabine plus daunorubicin 60 mg/m^2 plus GO. Regarding the choice and the dose of anthracycline that might be combined with GO, it seems that a relatively small dose of GO (3 mg/m^2 in the MRC and ALFA studies and 6 mg/m^2 in the GOELAM study) can be safely added to daunorubicin 60 mg/m^2 daily for 3 days, or to idarubicin 10 mg/m^2 daily for 3 days in the context of the FLAG-Ida regimen in the MRC study (Table 1).

Perhaps the most compelling reason to reverse the decision to withdraw GO is that AML is not a homogeneous disease but rather a group of diseases, some of which are particularly sensitive to the drug. Thus, although perhaps the average patient did not benefit from GO, as seen in the SWOG 106 trial, specific subsets of patients did benefit. Decades of research have emphatically demonstrated that AML differs widely both clinically (most notably in response to standard treatments) and in molecular, genetic, and epigenetic characteristics. The extreme heterogeneity in the latter is uniformly acknowledged to indicate that optimal management of AML will eventually encompass many specific regimens, with APL being an obvious example. It can be argued that if an appropriate study of the addition of GO to chemotherapy had been conducted exclusively in the cytogenetically favorable subsets of AML, we would have observed an advantage for GO much earlier and more clearly (similar to the studies demonstrating the remarkable benefit of ATRA in APL). It can also be argued that despite the flaws associated with subset analyses of randomized trials, such data should be acceptable when the same benefit is demonstrated repeatedly in several large studies. The data for the benefit of adding GO to chemotherapy for patients with better-risk AML were not available at the time of the decision to withdraw the agent from the market. However, the compelling data available from the more recently reported trials clearly suggest that the reversal of the decision is the correct way forward. On the basis of the available studies, we suggest that the most appropriate indication for reapproval of GO would be in patients with the more favorable–risk AML in addition to cytarabine- and anthracycline-based chemotherapy.

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REFERENCES

1. Bross PF, Beitz J, Chen G, et al: Approval summary: Gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clin Cancer Res 7:1490-1496, 2001
2. Sievers EL, Larson RA, Stadtmauer EA, et al: Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. J Clin Oncol 19:3244-3254, 2001
3. Larson RA, Sievers EL, Stadtmauer EA, et al: Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. Cancer 104:1442-1452, 2005
4. Rajvanshi P, Shulman HM, Sievers EL, et al: Hepatic sinusoidal obstruction after gemtuzumab ozogamicin (Mylotarg) therapy. Blood 99:2310-2314, 2002
5. Wadleigh M, Richardson PG, Zahrieh D, et al: Prior gemtuzumab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell transplantation. Blood 102:1578-1582, 2003
6. Estey EH, Giles FJ, Beran M, et al: Experience with gemtuzumab ozogamycin ("Mylotarg") and all-trans retinoic acid in untreated acute promyelocytic leukemia. Blood 99:4222-4224, 2002
7. Breccia M, Cimino G, Diverio D, et al: Sustained molecular remission after low dose gemtuzumab-ozogamicin in elderly patients with advanced acute promyelocytic leukemia. Haematologica 92:1273-1274, 2007
8. Ravandi F, Estey E, Jones D, et al: Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. J Clin Oncol 27:504-510, 2009
9. Lo-Coco F, Cimino G, Breccia M, et al: Gemtuzumab ozogamicin (Mylotarg) as a single agent for molecularly relapsed acute promyelocytic leukemia. Blood 104:1995-1999, 2004
10. Kell WJ, Burnett AK, Chopra R, et al: A feasibility study of simultaneous administration of gemtuzumab ozogamicin with intensive chemotherapy in induction and consolidation in younger patients with acute myeloid leukemia. Blood 102:4277-4283, 2003
11. Litzow MR, Othus M, Cripe LD, et al: Failure of three novel regimens to improve outcome for patients with relapsed or refractory acute myeloid leukaemia: A report from the Eastern Cooperative Oncology Group. Br J Haematol 148:217-225, 2010
12. Burnett AK, Hills RK, Milligan D, et al: Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: Results of the MRC AML15 trial. J Clin Oncol 29:369-377, 2011
13. Petersdorf S, Kopecky K, Stuart RK, et al: Preliminary results of Southwest Oncology Group Study S0106: An international intergroup phase 3 randomized trial comparing the addition of gemtuzumab ozogamicin to standard induction therapy versus standard induction therapy followed by a second randomization to post-consolidation gemtuzumab ozogamicin versus no additional therapy for previously untreated acute myeloid leukemia. Blood 114, 2009 (abstr 790)
14. Castaigne S, Pautas C, Terré C, et al: Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): A randomised, open-label, phase 3 study. Lancet 379:1508-1516, 2012
15. Delaunay J, Recher C, Pigneux A, et al: Addition of gemtuzumab ozogamycin to chemotherapy improves event-free survival but not overall survival of AML patients with intermediate cytogenetics not eligible for allogeneic transplantation: Results of the GOELAMS AML 2006 IR study. Blood 118, 2011 (abstr 79)
16. Burnett AK, Russell NH, Hills RK, et al: Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. J Clin Oncol 30:3924-3931, 2012
17. Fernandez HF, Sun Z, Yao X, et al: Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med 361:1249-1259, 2009
18. Löwenberg B, Ossenkoppele GJ, van Putten W, et al: High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 361:1235-1248, 2009

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