CLINICAL TRIALS AND OBSERVATIONS

A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia

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Key Points

- The addition of gemtuzumab ozogamicin to induction or maintenance therapy failed to improve the complete response rate or overall survival in patients with acute myeloid leukemia.

This randomized phase 3 clinical trial evaluated the potential benefit of the addition of gemtuzumab ozogamicin (GO) to standard induction and postconsolidation therapy in patients with acute myeloid leukemia. Patients were randomly assigned to receive daunorubicin (45 mg/m^2 per day on days 1, 2, and 3), cytarabine (100 mg/m^2 per day by continuous infusion on days 1–7), and GO (6 mg/m^2 on day 4; DA+GO) vs standard induction therapy with daunorubicin (60 mg/m^2 per day on days 1, 2, and 3) and cytarabine alone (DA). Patients who achieved complete remission (CR) received 3 courses of high-dose cytarabine. Those remaining in CR after consolidation were randomly assigned to receive either no additional therapy or 3 doses of GO (5 mg/m^2 every 28 days). From August 2004 until August 2009, 637 patients were registered for induction. The CR rate was 69% for DA+GO and 70% for DA ($P = .59$). Among those who achieved a CR, the 5-year relapse-free survival rate was 43% in the DA+GO group and 42% in the DA group ($P = .40$). The 5-year overall survival rate was 46% in the DA+GO group and 50% in the DA group ($P = .85$). One hundred seventy-four patients in CR after consolidation underwent the postconsolidation randomization. Disease-free survival was not improved with postconsolidation GO (HR, 1.48; $P = .97$). In this study, the addition of GO to induction or postconsolidation therapy failed to show improvement in CR rate, disease-free survival, or overall survival. This trial is registered with www.clinicaltrials.gov as #NCT00085709. (*Blood*. 2013;121(24):4854-4860)

Introduction

Standard induction therapy for acute myeloid leukemia (AML) is a combination of cytarabine and an anthracycline. For the last 30 years, there has been only limited improvement in complete remission (CR) rates and overall survival (OS) with chemotherapy, and the improvements that have occurred are primarily the result of dose escalation of standard agents during induction and consolidation and improvements in supportive care.[1-4] For patients younger than 60 years, a CR is typically obtained in 65% to 80% of patients, but the majority of these patients will relapse if treated with standard consolidation chemotherapy.

The majority of AML cells express the CD33 surface antigen, which is not expressed on normal hematopoietic stem cells or nonhematopoietic cells.[5,6] Initial trials of radiolabeled anti-CD33 antibodies showed that the antigen rapidly internalized after antibody binding.[7,8] These observations suggested that an antibody–chemotherapy immunoconjugate targeted to CD33 might be an effective way to treat AML. Gemtuzumab ozogamicin (GO) was developed, consisting of a humanized anti-CD33 monoclonal antibody conjugated to calicheamicin, a highly potent antitumor antibiotic.[9] Initial phase 2 data for this agent showed promise for patients treated in first relapse. Among 142 CD33-positive patients with recurrent AML treated with 2 doses of GO, 23 patients achieved CR and 19 achieved CR with incomplete platelet recovery, for an overall response rate of 30%.[10,11] These results led to the accelerated approval of the drug by the US Food and Drug Administration (FDA) for treatment of patients older than 60 years with AML in first relapse who were not candidates for aggressive chemotherapy.

The availability of GO prompted further investigation of this agent in combination with chemotherapy. Although the approved dose of GO was 9 mg/m^2 given twice 14 days apart, initial studies demonstrated consistent saturation of CD33 receptors at a dose of 6 mg/m^2.[9] A phase 1/2 trial, W-R 206, was undertaken to define the maximum tolerated dose of daunorubicin and cytarabine (DA) administered with a dose of GO known to saturate CD33 receptors (6 mg/m^2). The maximally tolerated doses were estimated to be daunorubicin 45 mg/m^2 per day on days 1 through 3 and cytarabine 100 mg/m^2 on days 1 through 7, with GO 6 mg/m^2 on day 4. A multi-institutional phase 2 trial was opened in October 2001,

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Table 1. Pretreatment characteristics of 595 adult patients with previously untreated AML, by treatment group

	DA+GO (n = 295)		DA (n = 300)		
	Median	Min–Max	Median	Min–Max	P*
Age, years	47	18-60	48	18-60	.44
White blood cells, 10^9/L	10.7	0.5-545.0	12.5	0.2-243.5	.48
Peripheral blood blasts, % (n = 555)	34	0-99	27	0-99	.16
Neutrophils, % (n = 574)	9	0-97	10	0-72	.66
Absolute neutrophil count, 10^9/L (n = 574)	1.1	0-171.6	0.9	0-40.1	.32
Hemoglobin, g/dL (n = 583)	9.1	3.5-18.0	9.1	4.4-29.1	.81
Platelets, 10^9/L (n = 593)	53	2-7900	55	7-9300	.39
Bone marrow blasts, % (n = 584)	66	7-100	65	3-100	.72
	Patients	**%**	**Patients**	**%**	
Age, years					
<35	57	19%	56	19%	.92
≥35	238	81%	244	81%	
Sex					
Female	135	46%	147	49%	.46
Male	160	54%	153	51%	
French-American British classification					
M1	67	23%	58	20%	.76
M2	76	26%	68	24%	
M4	73	25%	71	25%	
M4eos	9	3%	10	3%	
M5	38	13%	47	16%	
M6	4	1%	9	3%	
M7	3	1%	3	1%	
M0	21	7%	23	8%	
Unknown	4	—	11	—	
Performance status					
0	117	40%	118	40%	.37
1	147	50%	136	46%	
2	22	7%	31	10%	
3	8	3%	13	4%	
Unknown	1	—	2	—	

*Two-sided *P* value from Wilcoxon test (continuous variables), Fisher's exact test (age group, sex), or Pearson's χ-square test (French-American British classification, performance status).

evaluating these doses. Of 43 evaluable patients, 37 (84%) achieved CR. The incidence of elevated liver function tests including aspartate aminotransferase (2%), alanine aminotransferase (2%), and bilirubin (9%) was acceptable.[12]

Given the manageable toxicity of this combination with promising efficacy in the phase 2 trial, the Southwest Oncology Group (SWOG) initiated study S0106 to compare in a prospective randomized trial the effects of adding GO to standard induction therapy with DA alone. To ensure adequate anthracycline dose intensity in the control group, this protocol employed daunorubicin at 60 mg/m^2 on days 1 through 3 with cytarabine at 100 mg/m^2 per day by continuous infusion on days 1 through 7. In addition, the protocol included a second randomization to test whether administration of GO after consolidation therapy would improve disease-free survival (DFS). These 2 randomizations were designed to determine whether any beneficial effect from GO was achieved by administration during either induction or postconsolidation therapy, or possibly both. Study S0106 was an intergroup study with patient enrollment from several cooperative groups including SWOG, the National Cancer Institute of Canada, the Leukemia Group of Middle Sweden/the Swedish AML Group, Cancer and Acute Leukemia Group B, and the Eastern Cooperative Oncology Group.

Methods

Patient population

Patients with AML according to the World Health Organization criterion (≥20% blasts), aged 18 to 60 years, and with a Zubrod performance score of from 0 to 3 and adequate organ function (bilirubin ≤2 × institutional upper limit of normal, serum glutamic oxaloacetic transaminase and serum glutamic pyruvate transaminase ≤3 × institutional upper limit of normal, and left ventricular ejection fraction ≥ 50%) were eligible. Patients with acute promyelocytic leukemia (M3 AML), unstable cardiac arrhythmias or angina, or known hepatitis B or active hepatitis C were not eligible. Prior in situ cervical carcinoma or adequately treated prior basal or squamous cell skin cancer or stage I or II cancer in remission were permitted, as was any prior cancer from which the patient was disease-free for 5 years. Patients with AML arising from a prior hematological malignancy were ineligible. One prior dose of intrathecal chemotherapy for acute leukemia was permitted, but patients could not have received prior systemic chemotherapy for leukemia. All patients provided written informed consent in accordance with local policies, federal regulations, and the Declaration of Helsinki.

Study design and treatment groups

Patients were initially randomly assigned 1:1 between 2 induction regimens: either DA+GO, daunorubicin 45 mg/m^2 by IV push on days 1 through 3, cytarabine 100 mg/m^2 by continuous IV infusions on days 1 through 7, and gemtuzumab ozogamicin 6 mg/m^2 by 2-hour IV infusion on day 4; or DA, daunorubicin 60 mg/m^2 by IV push on days 1 through 3 and cytarabine

Table 2. Pretreatment cytogenetic characteristics of 496 adult patients with previously untreated AML, by treatment group

	DA+GO (n = 254)		DA (n = 242)		
	Patients	%	Patients	%	P*
Risk group					
Favorable	37	15	44	18	.47
Intermediate	137	54	132	55	
Unfavorable	62	24	55	23	
Indeterminate	18	7	11	5	
Normal	106	45	103	46	.85
CBF†	31	13	40	18	.20
inv(16)	17	7	23	10	.32
t(8;21)	14	6	17	8	.58
−7, 7q, −5 or −5q	29	12	22	10	.46
−7, 7q−	24	10	15	7	.19
−5, 5q−	14	6	14	6	1.00
+8	28	12	19	9	.28
11q23	11	5	13	6	.68
−17	9	4	6	3	.60
−18	6	3	5	2	1.00
t(9;11)	5	2	4	2	1.00
t(6;9)	4	2	2	1	.69
inv(3)	3	1	3	1	1.00
21q22	3	1	3	1	1.00
Marker/ring	17	7	9	4	.16
Complex‡	36	15	34	15	1.00
Other abnormality	79	34	74	33	.92

*Two-sided *P* value from Pearson's χ-square test (Risk group) or Fisher's exact test (normal or specific abnormalities, based on 234 DA+GO and 223 DA patients.

†Core binding factor.

‡Three or more clonal cytogenetic abnormalities.

Table 3. Treatment outcomes following induction chemotherapy of 595 adult patients with previously untreated AML, by treatment group

		CR		CR or Cri		Resistant disease		OS at 5 years		RFS at 5 years	
Group	Patients	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
DA+GO	295	69	63-74	76	69-79	15	12-20	46	40-52	43	36-50
DA	300	70	64-75	74	69-79	20	16-25	50	44-56	42	35-49
*P**		.59		.36		.065		.85		.40	

*One-sided *P* value for superior outcome (higher CR rate, lower RD, HR<1) in DA+GO group, based on Fisher's exact test (CR, RD) or logrank test (OS, RFS).

100 mg/m^2 by continuous IV infusion on days 1 through 7. Marrow response was assessed on day 14, and if there was aplasia with less than 5% blasts, growth factor therapy (sargramostim (rhGM-CSF), filgrastim (G-CSF) or pegfilgrastim) could begin at the treating physician's discretion. For both groups, a second course using the DA regimen was allowed for patients with marrow having more than 20% cellularity and more than 40% blasts on day 14, or with 5% or more blasts on a subsequent examination. The induction randomization was stratified by patient age (<35 years vs ⩾35 years). Patients who achieved CR and were afebrile and free of infection, with adequate organ function, performance status, and resolution of any central nervous system involvement, were eligible to receive 3 courses of consolidation therapy with cytarabine 3 g/m^2 by 3-hour continuous IV infusion every 12 hours on days 1, 3, and 5. Consolidation courses were administered monthly.

After completing consolidation therapy, patients who continued to meet the criteria for consolidation and who had not experienced sinusoidal obstructive syndrome during or after induction therapy were eligible for postconsolidation randomization (1:1) between GO (5 mg/m^2, 3 doses at least 28 days apart) vs observation. The postconsolidation randomization was stratified by prior use of GO (yes vs no) and preinduction cytogenetic risk group (favorable vs intermediate vs unfavorable vs indeterminate). Patients were required to have an absolute neutrophil count higher than 1000/mm^3 and a platelet count higher than 100 000/mm^3 to receive each cycle of postconsolidation GO.

Treatment outcomes

CR, CR with incomplete hematologic recovery (CRi), partial response (PR), and resistant disease (RD) were defined according to the International Working Group Guidelines.[13] DFS was measured from the day of postconsolidation randomization until relapse from CR or death from any cause, whichever occurred first, with observation censored at the day of last contact for patients last known to be alive without report of relapse. OS was measured for all patients from the day of initial randomization until death from any cause, with censoring at the day of last contact for patients last known to be alive. Relapse-free survival (RFS) was measured for patients who achieved CR from the day of CR until relapse or death from any cause, with the same censoring as DFS. Adverse events were graded according to version 3.0 of the Common Terminology Criteria for Adverse Events (accessible at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Statistical considerations

This study had 2 primary objectives: to test whether the CR rate was higher among patients randomly assigned to the DA+GO group and to see whether postconsolidation DFS was higher among patients randomly assigned to the GO group. A total of 342 evaluable patients were required for the second objective. This number of patients, accrued over the course of 4.5 years and with 3 years' additional follow-up, would ensure that a 1-sided test at the 2.5% critical level had 90% power if the true DFS hazard ratio (HR; GO: observation) is 0.67. This HR corresponds to increases in 1-year DFS from 50% to 63% and from 75% to 83% for patients with unfavorable and favorable/intermediate cytogenetics, respectively. It was also predicted that half of all patients entering the study would enter the postconsolidation randomization; that is, that 684 patients would be available for the first objective. This would ensure 90% power if the true CR rates were 81% with DA+GO and 70% with DA (2-sided test at the 5% critical level).

Data were collected and evaluated according to the standard practices of SWOG. Fisher's exact text and logistic regression analysis were used to analyze the effects of treatment group and other covariates on CR, CR/CRi, CR/CRi/PR, and RD. Logrank tests and proportional hazards regression were used to analyze OS, RFS, and DFS. All HR values comparing treatment groups are for DA+GO relative to DA or GO relative to observation; therefore, an HR lower than 1 indicates a superior outcome in the GO-containing group. The statistical significance of treatment effects on response, OS, DFS, and RFS is represented by 1-sided *P* values for superior outcomes in the DA+GO induction or GO maintenance groups; all other *P* values are 2-sided. Confidence intervals (CIs) are at the 95% confidence level. The following results were based on data available February 3, 2013.

Interim analyses and early closure

This study was monitored by the SWOG Data and Safety Monitoring Committee (DSMC). Interim analyses of induction results were scheduled when 228 and 456 patients were evaluated for response to induction chemotherapy. Three interim analyses of postconsolidation DFS were scheduled when 25%, 50%, and 75% of the expected number of events occurred, respectively. On August 11, 2009, the DSMC reviewed the second scheduled interim analysis of CR rates, which was based as planned on the first 456 evaluable patients. The CR rates in that analysis were 66% in 227 patients in the DA+GO group and 69% in 229 patients in the DA group, and the hypothesis that the DA+GO regimen increases the CR rate by 12% was rejected at the predefined significance level ($P < .0025$). Additional analyses showed that RFS was not significantly better on the DA+GO group. The DSMC also reviewed the first planned interim analysis of postconsolidation DFS. That analysis rejected the hypothesis that GO improves DFS, with a hazard ratio (observation: GO) of 1.5 at the prespecified significance level ($P < .001$). On the basis of these results, as well as the higher incidence of fatal toxicities in the DA+GO group, the DSMC recommended closure of both the induction and postconsolidation randomizations. This recommendation was reviewed and accepted by the study team and SWOG leadership, and the study was closed to accrual on August 20, 2009.

Results

From August 2004 through August 2009, 637 adult patients with AML were randomly assigned to induction with the DA+GO or DA regimen. Thirty-nine patients (20 DA+GO and 19 DA) were

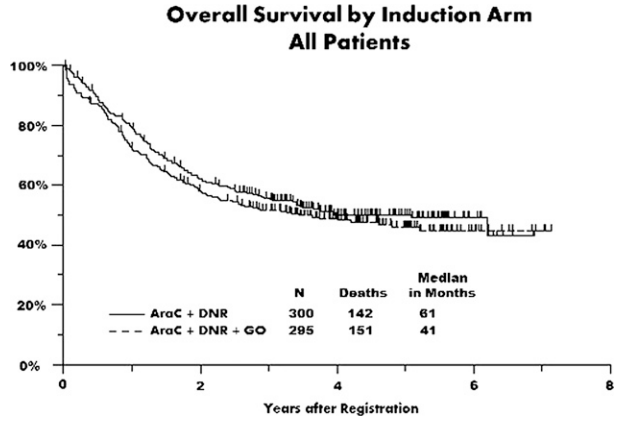

Figure 1. OS of 595 adult patients with AML by induction treatment group. Tick marks indicate censored observations.

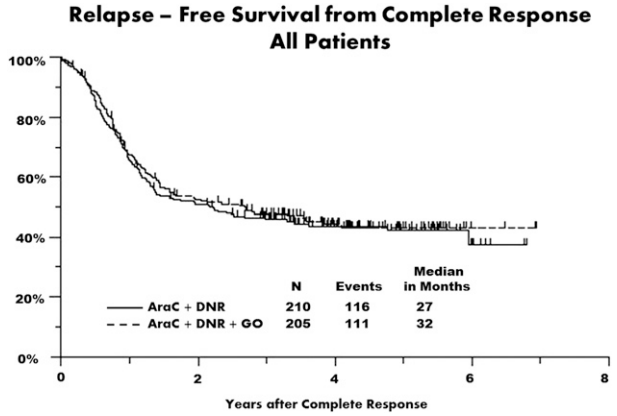

Figure 2. RFS of 415 adult patients with AML who achieved complete response, by induction treatment group. Tick marks indicate censored observations.

ineligible because of secondary AML (n = 22), diagnosis other than AML (n = 9), acute promyelocytic leukemia (M3 AML) (n = 5), or age older than 60 years, inadequate organ function, or coexisting malignancy (n = 1 each). Three additional patients (2 DA+GO and 1 DA) refused to participate after randomization. The following analyses are based on the remaining 595 patients (295 DA+GO and 300 DA). Pretreatment characteristics of these patients, including karyotype, were balanced between the induction groups (Tables 1 and 2).

Induction therapy

Five patients (3 DA+GO and 2 DA) received no protocol therapy because of refusal, physician's recommendation, lack of insurance coverage, or injuries unrelated to treatment. In addition, 3 DA+GO patients did not receive GO because of elevated liver function tests, lung hemorrhage, and the trial's closure, and 2 patients in the DA group were treated with the DA+GO regimen.

Treatment outcomes are summarized in Table 3. The CR rate was 69% in the DA+GO group and 70% in the DA group ($P = .59$). CR rates after the first induction course were also similar (61% with DA+GO and 59% with DA), as were the CR rates of patients who received a second induction course of DA (44% for 54 patients in the DA+GO group and 48% for the 66 patients in the DA group). The rates of CRi and PR in the 2 groups were 6% and 1% with DA+GO and 4% and 1% with DA. Including CRi and PR as responses did not alter the conclusion that response rates to DA+GO and DA alone were similar. The rate of RD was somewhat lower in the DA+GO group, at 15% vs 20%, but this difference was not statistically significant ($P = .065$).

A total of 293 patients have died, and the remaining 302 were last known to be alive between 14 days and 7.1 years (median, 4.1 years; only 6 patients have less than 120 days' follow-up). As shown in Figure 1, OS was not significantly better in the DA+GO group, with a median of 41 months compared with 61 months in the DA group (HR, 1.13; 95% CI, 0.90-1.42; $P = .59$). The trend toward longer OS with DA was primarily a result of a significantly higher number of early deaths in the DA+GO group: 17 DA+GO patients died within 30 days compared with only 4 DA patients.

The effect of treatment on OS did not vary significantly among cytogenetic risk categories ($P = .45$). Among patients with favorable cytogenetics, OS was somewhat, although not significantly, better in the DA+GO group (HR, 0.54; 95% CI, 0.19-1.55; $P = .12$). However, in the 3 other cytogenetic risk groups, there was no suggestion of benefit with DA+GO (Table 4). In multivariate analysis, OS decreased significantly with increasing age and absolute peripheral blast count, was significantly poorer for patients with performance status 2 to 3, and varied significantly among cytogenetic risk groups. Adjusting for these covariates, treatment group had little effect on the treatment comparison (HR, 1.19; 95% CI, 0.94-1.53; $P = .92$).

Of the 415 patients who achieved CR, 194 have relapsed and another 33 have died with no report of relapse. RFS was slightly, but not significantly, better in the DA+GO group (HR, 0.97; 95% CI, 0.75-1.26; $P = .40$; Figure 2). Similar results were seen in the 445 patients who achieved CR or CRi (207 relapsed and 41 others died; HR, 0.99; 95% CI, 0.78-1.28; $P = .48$). In multivariate analysis, RFS decreased significantly with increasing age and white blood cell count. Adjusting for these covariates had little effect on the treatment comparison (HR, 0.98; 95% CI, 0.75-1.27; $P = .43$). RFS was better in the DA+GO group among patients with favorable cytogenetics (HR, 0.49; 95% CI, 0.21-1.18; $P = .043$; Figure 3), but not in the other cytogenetic groups (Table 4).

Consolidation therapy

Of the 415 patients who achieved CR, 376 were registered for consolidation, although 2 of these were ineligible for consolidation because of inadequate liver function. Of the 39 patients not registered, 19 were removed to pursue hematopoietic cell transplantation (DA+GO = 10; DA = 9). Three of the 374 eligible patients received no protocol consolidation because of AML relapse, refusal,

Table 4. Induction treatment outcomes of 595 adult patients with AML by treatment group, within cytogenetic risk categories

		CR			Resistant disease			OS			RFS		
Cytogenetic category and group	Patients	CR	CR%	*P**	RDs	RD%	*P**	Deaths	HR†	*P**	Events	HR†	*P**
Favorable													
DA+GO	37	29	78	.99	2	5	.91	5	0.54	.12	7	0.49	.043
DA	44	41	93		1	2		11	1.00		18	1.00	
Intermediate													
DA+GO	137	103	75	.76	18	13	.26	68	1.24	.88	59	0.98	.46
DA	132	103	78		22	17		57	1.00		61	1.00	
Unfavorable													
DA+GO	62	34	55	.26	15	24	.11	41	0.96	.42	19	0.90	.38
DA	55	26	47		20	36		39	1.00		17	1.00	
Unknown													
DA+GO	59	39	66	.22	10	17	.15	37	1.25	.83	26	1.23	.76
DA	69	40	58		18	26		35	1.00		20	1.00	

*One-sided *P* value for superior outcome (higher CR rate, lower RD, HR < 1) in DA+GO group, based on Fisher's exact test (CR, RD) or Cox regression likelihood ratio 1test (OS, RFS).

†HR, hazard ratio of DA+GO relative to DA.

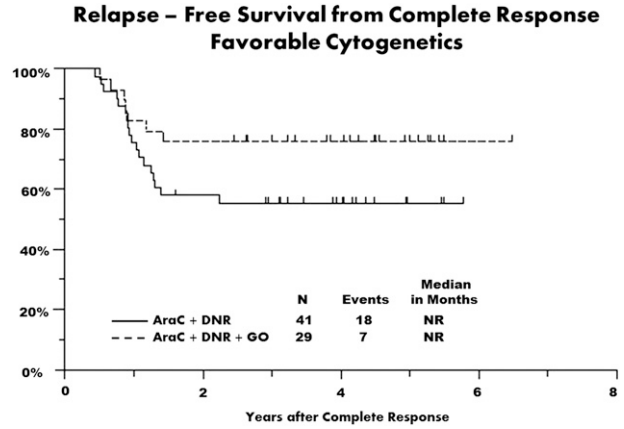

Figure 3. RFS from CR in patients with favorable risk cytogenetics, by induction treatment group. Tick marks indicate censored observations.

or late induction toxicities, and 12 others relapsed or died while on consolidation. Another 68 patients received only 1 or 2 cycles because of toxicity (n = 11), refusal (n = 9), or other reasons (n = 48), most (n = 43) because they were referred for hematopoietic cell transplantation (DA+GO = 22; DA = 21). The remaining 288 patients received some (n = 3) or all of the planned 3 cycles.

Postconsolidation therapy

A total of 174 patients who achieved CR were registered for the postconsolidation randomization. Five of these were ineligible for the randomization because of AML relapse (n = 2), absolute neutrophil count lower than 1000/mm^3 (n = 2), or inadequate liver function before consolidation (n = 1). Of the 169 eligible patients, 85 were randomly assigned to the GO maintenance group. Seven of the 85 patients did not receive GO because of refusal (n = 6) or the study's early termination (n = 1). Fifty-four patients received all planned GO cycles; that is, until AML relapse (n = 7) or 3 cycles (n = 47). Eleven patients were removed from GO maintenance early because of toxicity (primarily prolonged cytopenias), 6 others were removed because of refusal, 5 were removed because of the study's early termination, and 2 were removed for other reasons.

Fifty-three patients randomly assigned to receive GO and 40 randomly assigned to observation ultimately relapsed, and 3 others (2 GO and 1 observation) died in remission. As shown in Figure 4, DFS was not significantly better in the GO group (HR, 1.48; 95% CI, 0.99-2.22; $P = .97$) and was not superior to the observation group in any cytogenetic risk group (Table 5).

Toxicity

The 5 patients who received no protocol treatment and 4 other patients receiving DA were not evaluated for induction toxicity. Induction toxicities are summarized in Table 6. The rate of fatal induction toxicity was significantly higher in the DA+GO group ($P = .0062$); details of the fatal induction toxicities are provided in Table 6. The fatal induction toxicities in the DA+GO group were not characterized by an increased number of patients with abnormal liver function tests or sinusoidal obstructive syndrome. Six DA+GO patients expired because of hemorrhage: 4 because of central nervous system hemorrhage and 2 because of pulmonary events. Grade 4 thrombocytopenia (PLT $< 25 \times 10^9$/L) was somewhat more frequent in the DA+GO group (140/292 patients [48%]) than in the DA group (125/294 patients [43%]; $P = .21$). Overall, the rate of grade 4 or fatal nonhematologic induction toxicity was higher in the DA+GO group (21% vs 12%; $P = .0054$), although about 80% of patients in both groups had 1 or more nonhematologic toxicity of grade 3 or higher.

Three hundred seventy patients who received consolidation were evaluated for toxicity. One patient had fatal toxicity (lung infection after 2 consolidation cycles), and 55 others had grade 4 nonhematologic toxicities, most frequently infections (n = 19) and febrile neutropenia (n = 31). No consolidation patient had grade 3 or grade 4 liver toxicity.

All 78 patients who received any GO maintenance therapy were evaluated for toxicity. There were no fatal maintenance toxicities, although 4 patients had grade 4 infection and/or febrile neutropenia (with grade 4 hepatic toxicities in 1 patient), and another had grade 4 hyperglycemia. Thirty-nine patients (50%) had grade 3 to 4 thrombocytopenia, including 16 patients (21%) with grade 4.

Discussion

Efforts to improve the outcome of the treatment of patients with AML have taken a number of different directions, including dose escalation of standard agents and incorporation of hematopoietic cell transplantation as postremission therapy. There has been a paucity of new agents introduced and approved for treatment of AML. GO is the single new agent that has been approved by the FDA during the last 15 years for treatment of AML. Given the single-agent activity of GO, as well as subsequent phase 2 data combining GO with a standard 7 + 3 combination, SWOG conceived of this trial, which was developed with the drug sponsor, Wyeth, to fulfill Wyeth's postapproval commitment to the FDA. The dose of anthracycline differed in the 2 induction groups, as the 45 mg/m^2 dose of daunorubicin was roughly estimated as the maximum tolerated dose in a previous phase 2 trial when GO was administered concurrently at 6 mg/m^2. A daunorubicin dose of 60 mg/m^2 per day for 3 days was selected for the control group to provide a sufficiently dose-intense, and hopefully equitoxic, regimen for young patients receiving induction therapy for AML.

The results of this trial failed to demonstrate improvement in complete response rate, RFS, or OS survival when GO was added to either induction therapy or postconsolidation therapy. Given the failure to demonstrate prespecified overall improvement at the second planned interim analysis of induction and the first interim analysis of postconsolidation therapy, the SWOG DSMC recommended closure of both the induction and postconsolidation randomizations.

There was a significant difference in fatal induction rates between the 2 groups. The fatal induction toxicity rate in the DA+GO

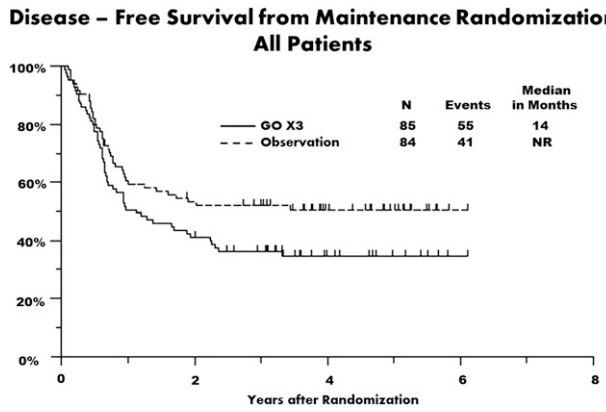

Figure 4. DFS of 169 adult patients with AML, by postconsolidation treatment group. Tick marks indicate censored observations.

Table 5. DFS of 169 adult patients with AML by postconsolidation treatment group, within cytogenetic risk categories

	DFS			
Cytogenetic category and group	**Patients**	**Events**	**HR***	***P*†**
Favorable				
GO	19	13	3.67	1.00
Observation	21	5	1.00	
Intermediate				
GO	53	33	1.03	.54
Observation	52	31	1.00	
Unfavorable				
GO	3	2	4.55	ND‡
Observation	4	1	1.00	
Unknown				
GO	10	7	1.31	.67
Observation	7	4	1.00	

*HR, hazard ratio of DA+GO relative to DA.

†One-sided *P* value for superior outcome (HR < 1) in DA+GO group, based on Cox regression likelihood ratio test.

‡*P* value not calculated because of small sample size. GO group: 2 relapses at 49 days and 15 months after postconsolidation randomization and 1 alive in CR at 42 months; observation group: 1 relapse at 19 months and 3 alive in CR at 36, 58, and 66 months.

group was 5.5% vs 1.4% in the standard group, with only a single death in the DA+GO resulting from liver toxicity. The remarkable result was the very low induction death rate of 1.4% in the control group. The induction death rate in the DA+GO group was similar to that seen in contemporaneous large phase 3 trials with a similar population. Eastern Cooperative Oncology Group 1900 had an induction death rate of between 4.5% and 5.5% in the 2 groups[2]; Medical Research Council (MRC) AML 15, which randomly assigned patients either to receive GO or not, had an induction rate of 7% (GO group) vs 6%.[12] The induction toxicity rate seen in the GO group of this study was very typical for chemotherapy trials for patients of this age; the very low death rate in the control group accounted for the difference in the fatal induction rate for this trial.

In contrast to S0106, 4 phase 3 randomized trials have shown potential benefit to the addition of GO to induction therapy in particular circumstances. The MRC AML 15 study included 1113 patients who were randomly assigned to receive 3 mg/m^2 of GO on day 1 of induction with DA, DA plus etoposide, or fludarabine, cytarabine, G-CSF, and idarubicin.[14] Those randomly assigned to GO also received the drug during consolidation. Although there was no difference in overall CR rate, RFS, or OS among all patients, the effect of GO on OS varied significantly among cytogenetic risk groups ($P = .001$). In particular, GO was associated with significantly better OS in patients with favorable risk karyotype (79% vs 51% at 5 years; $P = .0003$), no benefit in those with adverse karyotypes, and a trend for benefit in intermediate-risk patients. An internally validated prognostic index identified approximately 70% of patients with a predicted benefit of 10% in 5-year survival. In the Groupe Ouest Est d'Etude des Leucémies Aiguës et Autres Maladies du Sang AML 2006 IR trial, 238 intermediate-risk patients aged 18 to 60 years were randomly assigned to receive GO at 6 mg/m^2 on day 1 with DA induction and during mitoxantrone plus cytarabine consolidation.[15] Patients with matched siblings were allocated to allogeneic hematopoietic cell transplantation. Considering all patients, the 3-year event-free survival and OS in the GO group were 51% and 53%, respectively, whereas in the group without GO, they were 33% and 46% (P = NS). In the subset that could not receive an allogeneic transplant because they lacked a matched sibling, there was improved event-free survival associated with the administration of GO (53.7% vs 27%; $P = .0308$).

Two additional randomized trials have shown benefit in the addition of GO to chemotherapy for older adult patients. In the Acute Leukemia French Association 0701 trial, 280 patients aged 50 to 70 years were randomly assigned to receive 3 doses of GO at 3 mg/m^2 on days 1, 4, and 7 of DA induction, and again on day 1 of each of 2 courses of consolidation therapy with DA.[16] There was no significant difference in CR rate between the 2 groups. However, there was improved event-free survival (40.8% vs 17.1% at 2 years; $P = .0003$), RFS (50.3% vs 22.7%; $P = .0003$), and OS (53.2 vs 41.9%; $P = .037$) for those patients who received GO. Survival benefit was seen in patients with favorable or intermediate-risk cytogenetics, but there was no benefit in patients with poor risk karyotype. There also was no difference in mortality between the 2 groups, but greater thrombocytopenia was seen in the GO treatment group. In the MRC AML16 trial, 1115 older patients were randomly assigned to receive 3 mg/m^2 of GO on day 1 of either DA or daunorubicin plus clofarabine.[17] There was no significant difference in CR rate or toxicity between groups. With a median follow-up of 30 months, the 3-year cumulative incidence of relapse was significantly lower with GO (68% vs 76%; $P = .007$), and 3-year survival was significantly better (25% vs 20%, $P = .05$). The benefit appeared to be present across disease subgroups.

S0106 failed to find a beneficial effect for the 3-drug combination of gemtuzumab ozogamicin, daunorubicin (at 45 mg/m^2 per day for 3 days), and cytarabine compared with daunorubicin (at 60 mg/m^2 per day for 3 days) and cytarabine alone. Why S0106 failed to find a similar benefit as seen in the previously mentioned trials is unclear. All the other trials administered GO on day 1 of therapy instead of day 4, as was done in S0106. Most of the other studies (with the exception of MRC 16) also exposed patients to GO during both induction and early in consolidation. Further, none of the other trials attenuated the dose of anthracycline in the GO combination. Finally, the current trial was unusual, in that the standard induction chemotherapy had less than a 2% induction mortality rate, which is the lowest ever seen in a cooperative group study. Any or all of these factors may have contributed to the inconsistency in conclusions among trials.

The role of GO in the treatment of AML remains poorly defined, and the optimal dose and schedule have not been established.[18] Given the rapid reexpression of the antigen after antibody binding, it is interesting to speculate whether nonhematopoietic toxicities can be avoided and efficacy improved by using lower, repetitive dosing, as was done in the Acute Leukemia French Association 0701 trial. It is also uncertain how to identify patients most likely

Table 6. Summary of induction toxicities among 586 adult patients with AML

	DA+GO (n = 292)		DA (n = 294)	
	Patients	**%**	**Patients**	**%**
Any fatal toxicity	16	5	4	1
Infection and/or febrile neutropenia	5		2	
Central nervous system hemorrhage	4		1	
Acute respiratory distress syndrome, dyspnea	3		0	
Lung hemorrhage	2		0	
Transfusion related acute lung injury with infection and central nervous system hemorrhage	1		0	
Liver dysfunction	1		0	
Other	0		1	
Any grade 4+ nonhematologic	61	21	36	12
Any grade 3+ nonhematologic	236	81	244	83

to benefit from GO. Burnett et al have argued that GO is particularly beneficial for patients with favorable or intermediate cytogenetics, those who are younger, and those with good performance status.[14] Although the overall results of S0106 were negative, there was a trend toward improved RFS and OS with GO in those with favorable risk cytogenetics.

On the basis of the results of S0106, Pfizer voluntarily withdrew GO from the US market in June 2010 before the results of some of the other randomized trials were known. Whether the results of these other studies will alter the fate of GO is unknown.[19] However, other anti-CD33 antibody–drug conjugates are entering clinical trials, so further studies of this general approach will be undertaken.

In conclusion, this study failed to confirm beneficial effects from the addition of gemtuzumab ozogamicin to standard induction of cytarabine and daunorubicin at 45 mg/m^2 per day for 3 days when compared with an intensive induction regimen using a daunorubicin dose of 60 mg/m^2 per day for 3 days. This result differs from that of several other studies, and there are no easily identifiable reasons to explain the difference. Of interest, virtually all studies, including this one, at least suggest a possible role for GO in the treatment of certain patients with AML. Given the heterogeneous nature of the disease, further efforts to incorporate the addition of this or similar targeted therapies in the appropriate situation should be considered.

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Authorship

Contribution: S.H.P., K.J.K., M.S., C.W., and F.R.A. designed the research; S.H.P., K.J.K., M.S., C.W., J.B., H.P.E., P.J.S., R.K.S., M.S.T., L.S., R.B.W., and F.R.A. analyzed the data; S.H.P., K.J.K., M.S., C.W., T.N., R.A.L., R.K.S., R.B.W., and L.S. performed research; and S.H.P., K.J.K., M.S., R.A.L., H.P.E., P.J.S., M.S.T., L.S., and F.R.A. wrote the manuscript.

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