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ORIGINAL REPORT

Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial

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ABSTRACT

Purpose
To compare single-agent gemtuzumab ozogamicin (GO) with best supportive care (BSC) including hydroxyurea as first-line therapy in older patients with acute myeloid leukemia unsuitable for intensive chemotherapy.

Patients and Methods
In this trial, patients at least 61 years old were centrally randomized (1:1) to receive either a single induction course of GO (6 mg/m^2 on day 1 and 3 mg/m^2 on day 8) or BSC. Patients who did not progress after GO induction could receive up to eight monthly infusions of the immunoconjugate at 2 mg/m^2. Randomization was stratified by age, WHO performance score, CD33 expression status, and center. The primary end point was overall survival (OS) by intention-to-treat analysis.

Results
A total of 237 patients were randomly assigned (118 to GO and 119 to BSC). The median OS was 4.9 months (95% CI, 4.2 to 6.8 months) in the GO group and 3.6 months (95% CI, 2.6 to 4.2 months) in the BSC group (hazard ratio, 0.69; 95% CI, 0.53 to 0.90; $P = .005$); the 1-year OS rate was 24.3% with GO and 9.7% with BSC. The OS benefit with GO was consistent across most subgroups, and was especially apparent in patients with high CD33 expression status, in those with favorable/intermediate cytogenetic risk profile, and in women. Overall, complete remission (CR [complete remission] + CRi [CR with incomplete recovery of peripheral blood counts]) occurred in 30 of 111 (27%) GO recipients. The rates of serious adverse events (AEs) were similar in the two groups, and no excess mortality from AEs was observed with GO.

Conclusion
First-line monotherapy with low-dose GO, as compared with BSC, significantly improved OS in older patients with acute myeloid leukemia who were ineligible for intensive chemotherapy. No unexpected AEs were identified and toxicity was manageable.

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INTRODUCTION

Treatment of acute myeloid leukemia (AML) in older patients remains challenging. In this age group, the benefit associated with intensive chemotherapy is marginal and the chance for cure continues to be less than 10%.[1,2] Several host- and disease-related factors contribute to poor outcome in elderly patients with AML, including medical comorbidities, physical frailty, and increased incidence of poor-risk biologic features (eg, adverse cytogenetics, expression of multidrug resistance proteins, or prior myelodysplasia).[3] As a result, most elderly patients, in particular those over the age of 75 years and those with significant comorbidities, are not considered suitable for an intensive treatment approach. These patients are treated with best supportive care (BSC) including hydroxyurea or low-dose cytarabine, but outcomes remain dismal.[4] There is therefore an unmet medical need in this patient population for safer and more effective therapies.

Gemtuzumab ozogamicin (GO; Mylotarg, Pfizer, New York, NY) targets myeloid cells via the CD33 epitope, which is typically expressed on AML blasts. GO combines a humanized anti-CD33 monoclonal antibody with the DNA intercalator calicheamicin. In 2000, GO gained approval in the United States for the treatment of relapsed AML in older patients ineligible for intensive chemotherapy. This approval was based on an encouraging response rate of approximately 30% observed in phase II trials.[5,6] However, results in older patients with newly diagnosed AML have generally been disappointing.[7,8] In particular, we have previously reported a response rate of 17% when the licensed dose/schedule of GO (9 mg/m^2 given on days 1 and 15) was used as first-line monotherapy in older patients unfit for intensive chemotherapy.[9] Prolonged myelosuppression and excess liver toxicity resulted in an induction mortality rate of 32% in patients over the age of 75 years, suggesting the need for dose reductions and schedule adjustments to improve tolerability and efficacy in this patient population.

Based on these findings, in 2004, the European Organisation for Research and Treatment of Cancer (EORTC) and Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) consortium embarked on a randomized study (AML-19). This study was designed as a sequential phase II/III trial comparing fractionated lower doses of GO monotherapy with BSC, including hydroxyurea, in patients at least 61 years of age with newly diagnosed AML unsuitable for intensive chemotherapy. Of the two induction schedules of GO (total dose 9 mg/m^2 delivered in two or three fractions over 1 week) under comparison in the phase II part of the study, the two-fraction regimen was reported to have the best efficacy profile to warrant phase III comparison with BSC.[10] We herein report the final results of the phase III part of the study.

PATIENTS AND METHODS

Patients

Patients were eligible for the study if they had previously untreated AML (de novo or secondary to myelodysplasia) according to WHO criteria, and were deemed by the treating physician to be ineligible for intensive chemotherapy. This included all patients over the age of 75 years, as well as patients 61 to 75 years of age with a WHO performance score greater than 2 or who were unwilling to receive standard chemotherapy. Patients had to have serum creatinine and liver function test results (bilirubin and transaminases) within 1.5 times the local upper limit of normal, and their white blood cell (WBC) count had to be less than 30 $\times$ 10^9/L at the time of registration (pretreatment with hydroxyurea was permitted). Major exclusion criteria can be found in the Data Supplement. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee at each participating center. All patients provided written informed consent before enrollment.

Study Design and Treatment

In this open-label, phase III trial, eligible patients were randomly assigned (1:1) to receive either GO or BSC. Random assignment was performed centrally at the EORTC headquarters using a minimization technique, and was stratified by age (61-75 *v* 76-80 *v* $\geq$ 81 years), WHO performance score (0-1 *v* 2 *v* $>$ 2), CD33 status ($<$ 20% *v* 20%-80% *v* $>$ 80% positive blasts *v* unknown), WBC count at diagnosis ($<$ 30 $\times$ 10^9/L *v* $\geq$ 30 $\times$ 10^9/L), and center. GO treatment consisted of a single induction course, including two intravenous infusions of the immunoconjugate administered at 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8. Thereafter, patients considered to be benefiting (ie, those with complete remission [CR], partial remission, or stable disease) could receive up to eight monthly infusions of GO at 2 mg/m^2. BSC was given to all patients and included blood product transfusions, antimicrobials, and other symptomatic therapies, according to institutional policies. Hydroxyurea at doses sufficient to keep the WBC count below 20 $\times$ 10^9/L was permitted in the BSC arm only.

End Points and Definitions

The primary study end point was overall survival (OS), and the secondary end point was safety. Additional end points assessed for the GO arm only included best response, defined as CR plus CR with incomplete recovery of peripheral blood counts (CRi), disease-free survival (DFS), and progression-free survival. All efficacy end points were defined according to the revised International Working Group criteria.[11] Safety was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical Methods

A total of 234 patients was required to provide the 210 events necessary to detect a 10% improvement in 1-year OS rate, from 5% for BSC to 15% for GO, corresponding to a hazard ratio (HR) of 0.63 (power, 90%; two-sided α, 5%). The Kaplan-Meier method was used to estimate time-to-event outcomes, standard errors were computed with the Greenwood formula, and medians were presented with 95% CIs based on the Brookmeyer and Crowley method. OS was compared using the two-sided log-rank test, and the Cox proportional hazards model was used to estimate the HR and its 95% CI. Exploratory analyses of the heterogeneity of treatment effect among subgroups were performed using the Cox model, and presented graphically using forest plots. For time-to-event outcomes, the intent-to-treat principle was followed. Safety analyses were

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	GO, n = 118	BSC, n = 119	Overall, N = 237
Age, years			
61-75	41 (34.7)	44 (37)	85 (35.9)
76-80	49 (41.6)	52 (43.7)	101 (42.6)
$\geq$ 81	28 (23.7)	23 (19.3)	51 (21.5)
Median, range	77, 62-88	77, 66-88	77, 62-88
Sex			
Male	57 (48.3)	73 (61.3)	130 (54.9)
Female	61 (51.7)	46 (38.7)	107 (45.1)
WHO PS			
0-1	76 (64.4)	77 (64.7)	153 (64.6)
2	34 (28.8)	33 (27.7)	67 (28.3)
$>$ 2	8 (6.8)	9 (7.6)	17 (7.1)
Type of disease			
De novo	79 (66.9)	85 (71.4)	164 (69.2)
Secondary	39 (33.1)	34 (28.6)	73 (30.8)
WBC count $\times$ 10^9/L			
$<$ 30	85 (72)	89 (74.8)	174 (73.4)
$\geq$ 30	33 (28)	30 (25.2)	63 (26.6)
Cytogenetic risk			
Favorable/intermediate	59 (50)	45 (37.8)	104 (43.9)
Adverse	33 (28)	32 (26.9)	65 (27.4)
Unknown	26 (22)	42 (35.3)	68 (28.7)
CD33 status, %			
$<$ 20	10 (8.5)	14 (11.8)	24 (10.1)
20-80	58 (49.1)	58 (48.7)	116 (48.9)
$>$ 80	48 (40.7)	47 (39.5)	95 (40.1)
Unknown	2 (1.7)	0 (0)	2 (0.9)

NOTE: Data are reported as n (%).
Abbreviations: BSC, best supportive care; GO, gemtuzumab ozogamicin; WBC, white blood cell count at diagnosis; WHO PS, WHO performance score.

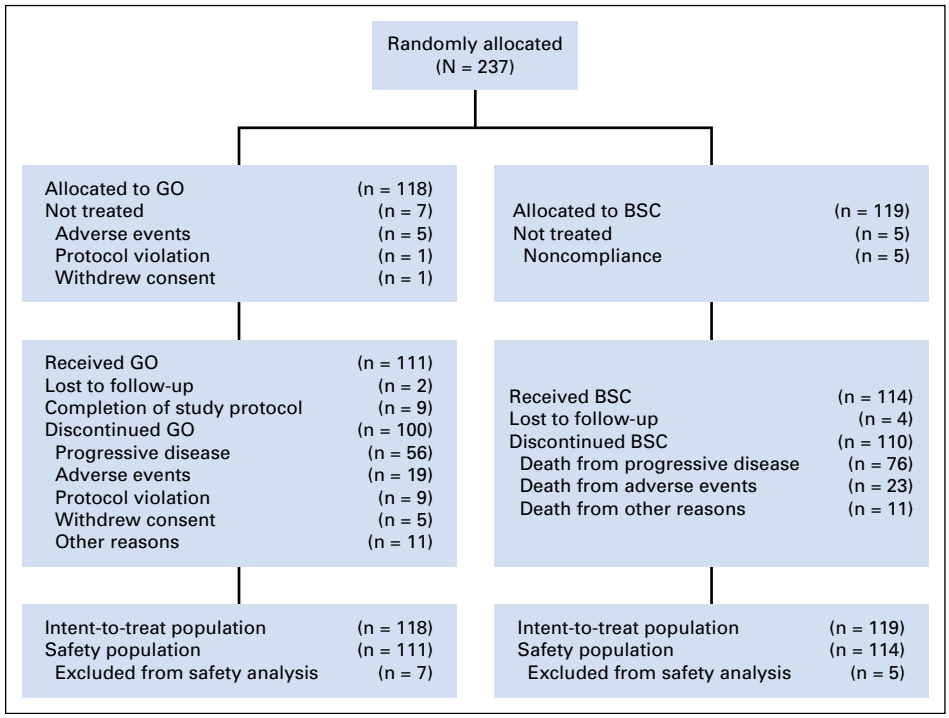

Fig 1. CONSORT diagram of patient disposition. Of the accrued patients, 55 were randomly allocated in the preceding phase II part of the trial, between November 2004 and December 2006, to receive either BSC or the two-fraction GO regimen selected for phase III comparison. Between September 2007 and May 2013, an additional 182 patients were randomized in the phase III part of the study, giving a total of 237 patients in the GO versus BSC comparison. BSC, best supportive care; GO, gemtuzumab ozogamicin.

performed on all patients who had started their assigned treatment, and who had undergone at least one postbaseline assessment. The SAS software (version 9.3; SAS Institute, Cary, NC) was used for all statistical analyses.

RESULTS

Patient Characteristics

Between November 2004 and May 2013, 237 patients from 35 sites in three European countries were randomized to GO (n = 118) or BSC (n = 119). The baseline patient demographics and clinical characteristics are listed in Table 1. Overall, the median age was 77 years (range, 62 to 88 years) and almost two-thirds of the patients were 76 years or older. Thirty-five percent of patients had a WHO performance score ≥ 2, 30.8% had secondary AML, and 27.4% had adverse cytogenetics. Patients in both arms were well balanced with respect to baseline characteristics except for a somewhat higher prevalence of men in the BSC arm, and larger favorable/intermediate cytogenetic risk group in the GO arm.

Treatment Compliance

Overall, 12 patients (GO, n = 7; BSC, n = 5) did not begin the assigned treatment due to intercurrent medical problems (GO, n = 5), noncompliance with postbaseline assessments (BSC, n = 5), protocol violation (GO, n = 1), or patient decision (GO, n = 1). These 12 patients were included in the analysis of OS, but excluded from the safety analysis (Fig 1). In the GO group, treatment was started in 111 (94%) of 118 patients, of whom 104 (94%) received the full induction course (two infusions), 59 (53%) went on to receive at least one postinduction infusion, and 9 (8%) completed the entire treatment program (ten infusions); the median number of GO infusions administered was three (range, 1-10 infusions). In total, 100 (90%) of 111 patients and 110 (96.5%) of 114 patients discontinued treatment in the GO and BSC groups, respectively, mostly due to disease progression (56 *v* 76 patients) or adverse events (AEs; 19 *v* 23 patients).

OS

At data cutoff (July 31, 2014), 228 patients had died: 113 patients (95.8%) in the GO group and 115 (96.6%) in the BSC group. Patients assigned to the GO group had a significantly longer OS than patients in the BSC group (HR, 0.69; 95% CI, 0.53 to 0.90;

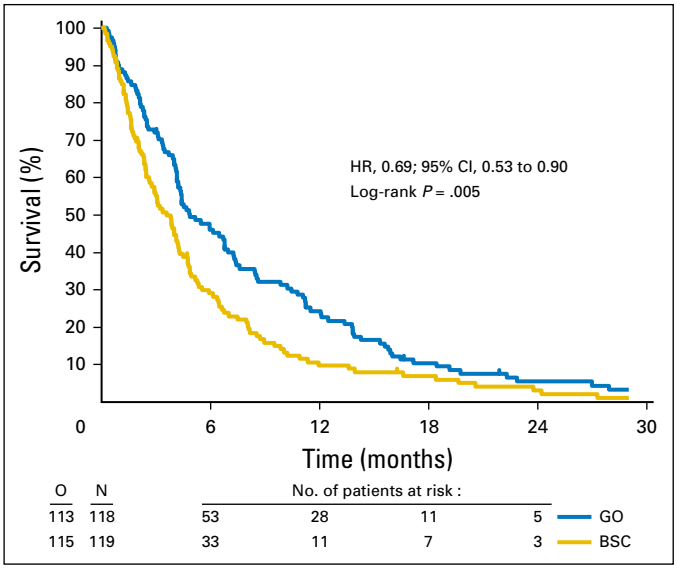

Fig 2. Kaplan-Meier plot of overall survival for gemtuzumab ozogamicin (GO) versus best supportive care (BSC) in the intention-to-treat population. HR, hazard ratio; N, number of patients; O, observed number of events.

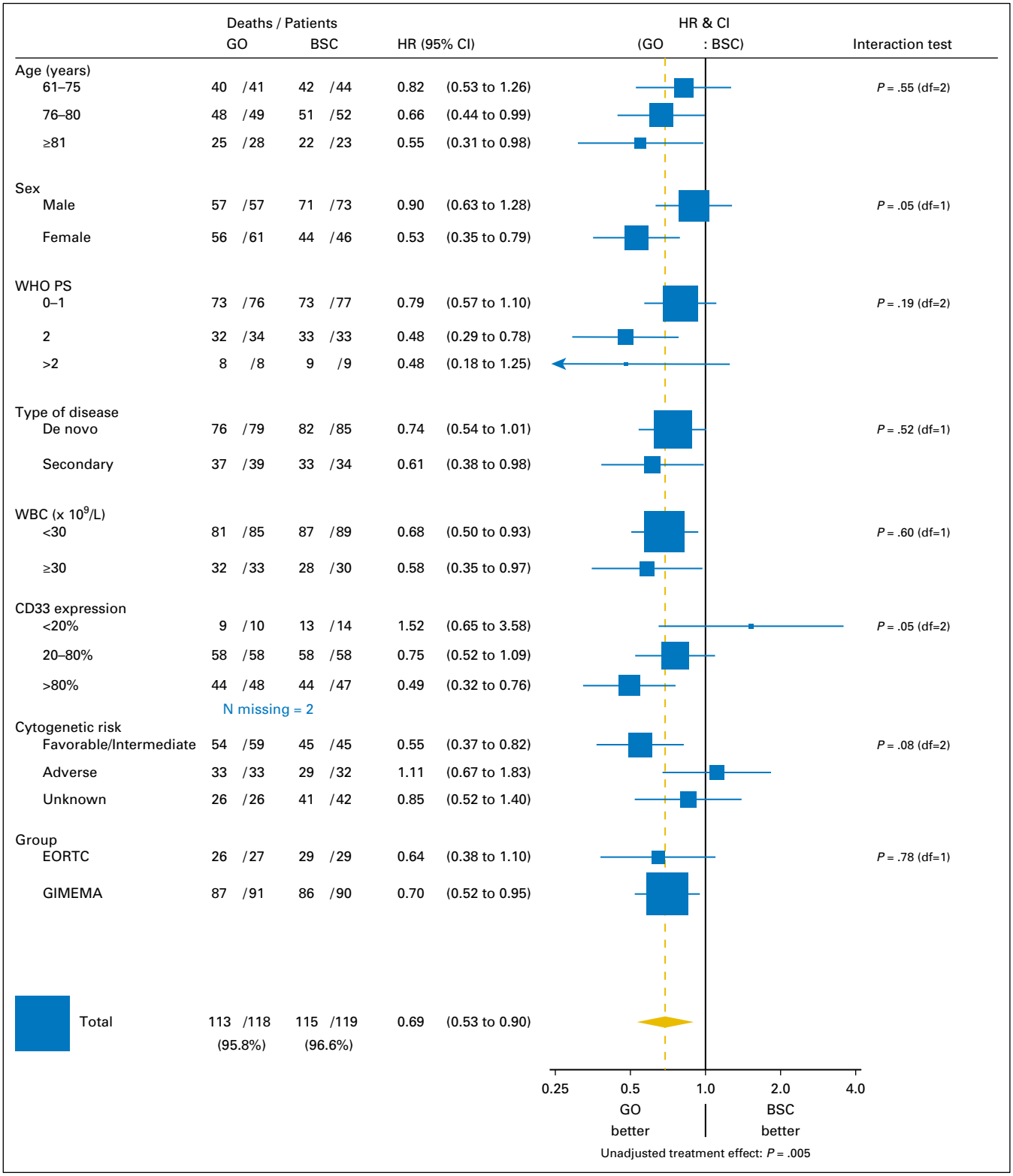

Fig 3. Forest plot analysis of overall survival by patient subgroup. Hazard ratios and interaction tests were computed using a bivariate Cox model (treatment group, covariate, treatment-covariate interaction). BSC, best supportive care; df = degrees of freedom; EORTC, European Organisation for Research and Treatment of Cancer; GIMEMA, Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto; GO, gemtuzumab ozogamicin; HR, hazard ratio; WBC, white blood cell count at diagnosis; WHO PS, WHO performance score.

P = .005; Fig 2). Median OS was 4.9 months (95% CI, 4.2 to 6.8 months) and 3.6 months (95% CI, 2.6 to 4.2 months), respectively. Estimated OS rates in the GO and BSC groups were 45.9% (95% CI, 36.7 to 54.7) and 29% (95% CI, 21 to 37.4), respectively, at 6 months, and 24.3% (95% CI, 16.9 to 32.4) and 9.7% (95% CI, 5.1 to 15.9), respectively, at 1 year. The all-cause 30-day mortality rate was similar between the groups (GO, 11% *v* BSC, 13.5%), whereas the 60-day mortality rate was lower in the GO group (GO, 17.8% *v* BSC, 30.4%).

In uni- and multivariate Cox analyses, WHO performance score, WBC count at diagnosis, and cytogenetic risk were all significant prognostic factors for OS, whereas age, CD33 expression, and sex were not (Data Supplement). After adjustment for the significant factors and CD33 status, the difference in OS between the two groups remained significant (HR, 0.68; 95% CI, 0.52 to 0.89; P = .006). Exploratory analyses were performed to establish whether the size of treatment effect on OS varied according to randomization stratification factors and selected baseline variables (ie, sex, type of disease, and cytogenetics). Significant treatment-by-covariate interactions were identified for CD33 status and sex (P = .05 for both), whereas the interaction between treatment and cytogenetic profile was of borderline significance (P = .08; Fig 3).

In patients with more than 80% CD33-positive blasts, GO significantly improved OS compared with BSC (HR, 0.49; 95% CI, 0.32 to 0.76); in contrast, the benefit of GO compared with BSC was less pronounced in patients with lower CD33 expression

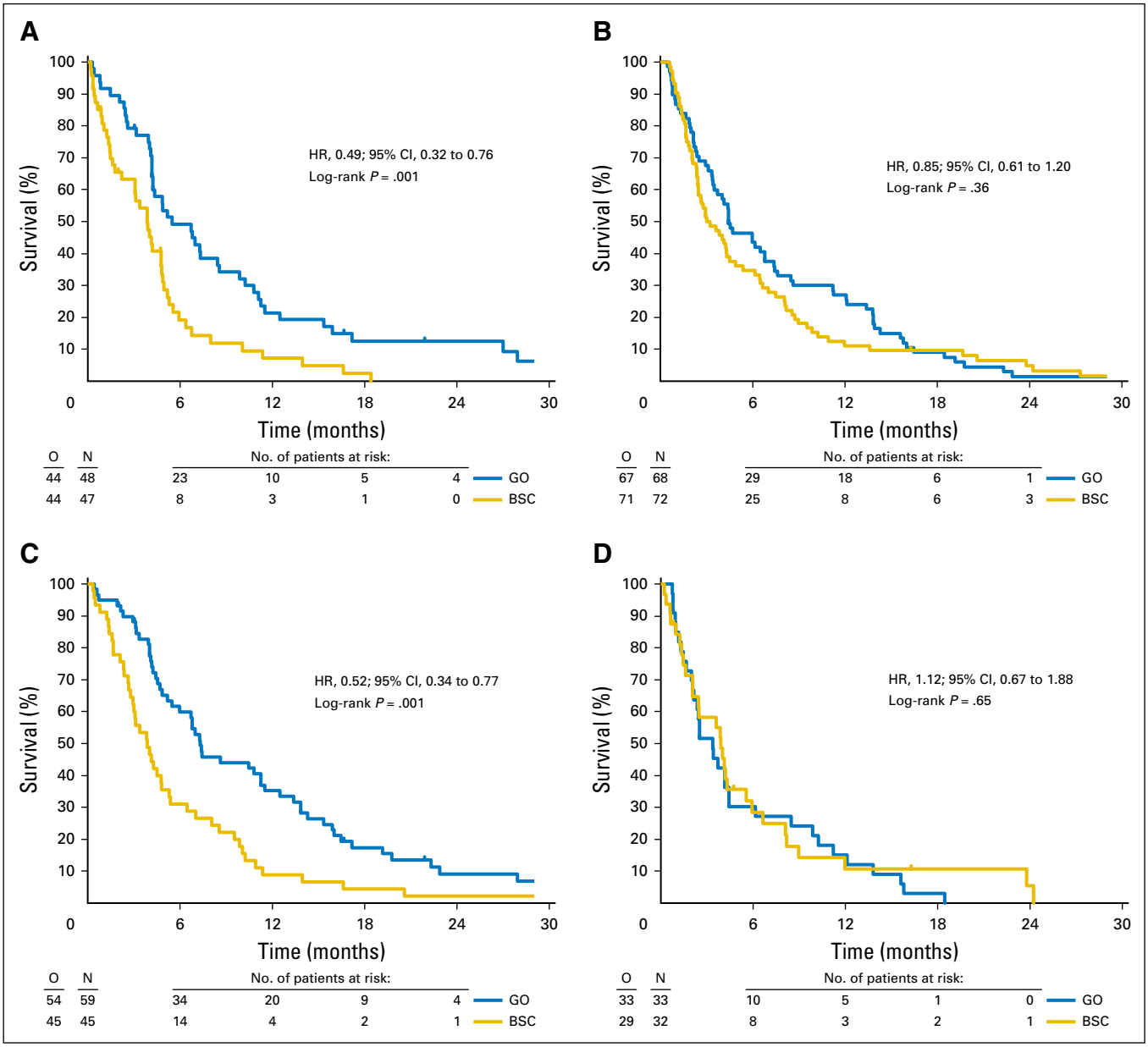

Fig 4. Overall survival in (A) patients with CD33-positive blasts > 80%, (B) patients with CD33-positive blasts ≤ 80%, (C) patients with favorable/intermediate cytogenetics, and (D) patients with adverse cytogenetics. BSC, best supportive care; GO, gemtuzumab ozogamicin; HR, hazard ratio; N, number of patients; O, observed number of events.

(Figs 4A and 4B). In patients with favorable/intermediate cytogenetic risk profiles, a significant benefit of GO compared with BSC was observed (HR, 0.52; 95% CI, 0.34 to 0.77), whereas no treatment difference was noted in the subgroup with adverse-risk disease (Figs 4C and 4D). In women, the HR for OS was nearly halved with GO (HR, 0.53; 95% CI, 0.35 to 0.79), whereas in men the estimated HR was close to 1.0 (Data Supplement). Although there was no evidence of interaction by type of disease, the benefit of GO compared with BSC seemed more apparent in the small subgroup of patients with secondary AML (Data Supplement).

Other Efficacy End Points (GO Arm)

Of the 111 patients in the GO group assessable for induction response, nine (8.1%) achieved CR and 18 (16.2%) achieved CRi, for an overall CR + CRi rate of 24.3% (Table 2). In addition, seven (6.3%) patients had a partial remission (PR) and 44 (39.6%) had stable disease (SD). Reasons for induction failure included progressive disease in 16 (14.4%) patients and toxic mortality in eight (7.2%) patients (infection, n=5; hemorrhage, n = 1; renal failure, n = 1; cardiac failure, n = 1). Nine patients subsequently improved their initial responses (five patients converted from CRi to CR, two from PR to CR, one from SD to CR, and one from SD to PR), providing an overall CR + CRi rate of 27% (30 of 111 patients), and an overall clinical benefit rate (CR + CRi + PR + SD lasting for > 30 days) of 56.7% (63 of 111 patients). The median time to a best response of CR or CRi was 36.5 days (range, 14 to 139 days). Although the CR + CRi rate did not vary according to performance status, type of disease, or WBC count at diagnosis, responses occurred less frequently in patients 61 to 75 years of age, in men, in those with adverse cytogenetics, and in those with lower CD33 expression (Data Supplement). Among the 30 patients who achieved CR/CRi, 28 relapsed or died during remission (infection, n = 2; physical deterioration, n = 1; unknown cause, n = 2). The median DFS was 5.3 months (95% CI, 3.1 to 8.0 months), with 2 patients remaining in CRi after 16 and 20 months, respectively (Data Supplement). The median OS from best response was 8.2 months (95% CI, 5.4 to 12.8 months) for complete responders (CR/CRi), and 5.8 months (95% CI, 2.9 to 9.9 months) for patients achieving PR or SD lasting for longer than 30 days (Data Supplement). The median PFS for the whole cohort of 118 patients who were randomly allocated to GO treatment was 2.8 months (95% CI, 2.4 to 3.8 months; Data Supplement).

Table 2. Response Outcomes for 111 Patients in the GO Arm

Outcome	Induction Response	Best Response
CR + CRi	27 (24.3)	30 (27)
CR	9 (8.1)	17 (15.3)
CRi	18 (16.2)	13 (11.7)
PR	7 (6.3)	6 (5.4)
SD	44 (39.6)	43 (38.7)
Progressive disease	16 (14.4)	16 (14.4)
Induction death*	8 (7.2)	8 (7.2)
Not evaluable	9 (8.1)	8 (7.2)

NOTE: Data are reported as n (%).
Abbreviations: CR, complete remission; CRi, complete remission with incomplete blood count recovery; GO, gemtuzumab ozogamicin; PR, partial remission; SD, stable disease.
*Deaths attributed to induction-associated adverse events.

Safety

Although pancytopenia was universally seen during GO induction, the incidence of nonhematologic AEs overall, grade ≥ 3, and AEs with an outcome of death were similar between the groups (Table 3). Grade ≥ 3 infections were the most frequent AEs in both groups, occurring in 35.1% of GO-treated patients but also documented in 34.2% of BSC recipients. GO was not associated with increased rates of febrile neutropenia, bleeding, or organ damage. In particular, the frequency of grade ≥ 3 liver AEs was slightly increased in the GO group (7.2% *v* 6.1%), but no episodes of GO-related veno-occlusive disease were reported.

DISCUSSION

In this trial, OS for older patients with newly diagnosed AML unsuitable for intensive chemotherapy was significantly improved with low-dose GO monotherapy compared with BSC, meeting the primary objective of the study. In these patients, most of whom were older than 75 years and had coexisting comorbidities, the median OS was 4.9 months in the GO group compared with 3.6 months in the BSC group (P = .005), resulting in a survival advantage of 14.6 percentage points (24.3% *v* 9.7%) at 1 year.

Exploratory subgroup analyses revealed no interaction between baseline patient characteristics and treatment effect for OS, with the exception of CD33 expression status, sex, and cytogenetic profile. Although the reasons for the smaller GO effect seen in men remain unclear, the shorter OS observed in patients with low or minimal CD33 expression is consistent with the results reported by our group in a study of single-agent GO for elderly patients with untreated AML unfit for intensive chemotherapy.[9] This confirms the preclinical prediction that GO would be most effective for a leukemia that expresses CD33 at high levels.[12]

However, this issue remains controversial because other trials, particularly those in which GO was used in combination with chemotherapy, failed to identify a correlation between CD33 expression and clinical outcome.[13,14] Moreover, when OS was analyzed according to cytogenetic profile, the effect of GO appeared greater in patients with favorable/intermediate-risk

Table 3. Nonhematologic AEs Reported in > 5% of Patients (Safety Population)

AE	GO (n = 111)		BSC (n = 114)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Overall incidence	97 (87.3)	68 (61.2)	103 (90.4)	77 (67.5)
Infection	49 (44.1)	39 (35.1)	48 (42.1)	39 (34.2)
Febrile neutropenia	20 (18)	20 (18)	27 (23.7)	27 (23.7)
Bleeding	28 (25.2)	14 (12.6)	34 (29.8)	14 (12.3)
Fatigue	51 (45.9)	13 (11.7)	69 (60.5)	24 (21)
Liver	57 (51.3)	8 (7.2)	52 (45.6)	7 (6.1)
Cardiac	31 (27.9)	7 (6.3)	37 (32.5)	16 (14)
Metabolic	18 (16.2)	4 (3.6)	17 (14.9)	7 (6.1)
Renal	7 (6.3)	4 (3.6)	9 (7.9)	5 (4.4)
Death due to any AE	19 (17.1)		23 (20.2)	

NOTE: Data are reported as n (%).
Abbreviations: AE, adverse event; BSC, best supportive care; GO, gemtuzumab ozogamicin.

AML, but not in those with adverse-risk disease. This finding is consistent with the results from a recent metaanalysis of five large randomized trials, in which small doses of GO were combined with first-line chemotherapy in both younger and older patients with AML. The results showed that the survival benefit associated with GO treatment was observed mainly in patients with favorable/intermediate-risk but not adverse-risk cytogenetics.[15]

As used in this trial, GO produced an overall CR rate of 27% (CR, 15.3%; CRi, 11.7%), with an additional 29.7% of patients achieving PR (5.4%) or SD lasting for more than 30 days (24.3%), resulting in an overall clinical benefit rate of 56.7%. This encouraging clinical activity translated into a median OS and DFS of 8.2 and 5.3 months, respectively, for complete responders, and a median OS of 5.8 months for patients achieving lesser responses. In addition, this low-intensity GO regimen was generally well tolerated, with all-grade and grade ≥ 3 AEs occurring at comparable frequency between arms. Although associated with significant myelosuppression, induction treatment with GO did not result in increased incidence and severity of infections, bleeding complications, or other nonhematologic toxicities, with no differences noted between arms in all-cause early mortality or overall death rates due to AEs. Of importance, liver toxicity, a hallmark of GO safety profile, was not increased in GO recipients. Furthermore, it appeared to be less frequent and severe than previously reported by our group in a first-line trial, in which a more intensive GO regimen was used in elderly patients with AML unfit for intensive chemotherapy.[9]

At the time this trial was designed, treatment options for elderly patients with AML unfit for intensive chemotherapy were extremely limited. In addition, there was no standard of care beyond palliative hydroxyurea combined with BSC. As the study progressed, a number of low-intensity regimens were investigated for these patients. Low-dose cytarabine (LDAC) is the prototype for a nonintensive approach, producing higher rates of CR (18% *v* 1%) and OS when randomized to BSC and hydroxyurea.[16] However, median OS was only 5 months for the LDAC recipients, and no benefit was seen in patients with adverse cytogenetics.

Attempts to improve upon these results by using a variety of novel agents (including GO), given either alone or in combination with LDAC, have generally been unsuccessful.[17-21] However, the polo-like kinase inhibitor volasertib has been reported to significantly extend both event-free survival and OS when combined with LDAC in a phase II comparison with LDAC alone,[22] but results from a recently completed phase III trial are still awaited. Studies of epigenetic therapy with azacitidine or decitabine have reported CR rates in the range of 15% to 30% with encouraging median survival times, particularly in patients presenting with less proliferative AML.[23-25]

However, when compared with physician's choice of BSC or LDAC in a phase III trial, decitabine treatment failed to significantly extend survival in treatment-naïve elderly patients with poor-risk AML, despite producing a better CR rate.[26] Likewise, results from a phase III trial comparing first-line azacitidine with conventional care regimens (ie, standard chemotherapy, LDAC, or BSC only) in elderly AML patients yielded comparable response rates and a nonsignificant OS benefit with azacitidine.[27] Of note, phase II data for azacitidine combined with GO have shown encouraging remission and survival rates in elderly patients with newly diagnosed AML, suggesting possible synergy between hypomethylating agents and GO.[28,29]

In summary, the findings from our study indicate that single-agent GO, at the chosen dose and schedule, is tolerable and leads to improved OS, as compared with BSC, in older patients with AML unsuitable for curative treatment. These findings suggest that single-agent GO could represent a new option for this patient group. These results, which add to the mounting evidence that withdrawal of GO from the market in 2010 (due to lack of benefit and increased toxicity in a phase III trial[30]) was premature,[31] support further investigations of GO in combination with other novel agents in this patient population of high unmet need.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Final approval of manuscript: All authors

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