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## Sequential administration of gemtuzumab ozogamicin and conventional chemotherapy as first line therapy in elderly patients with acute myeloid leukemia: a phase II study (AML-15) of the EORTC and GIMEMA leukemia groups

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### A B S T R A C T

**Background and Objectives.** Acute myeloid leukemia (AML) in the elderly is associated with low rates of response to conventional chemotherapy and long-term survival, highlighting the need for innovative treatment strategies. Gemtuzumab ozogamicin (GO) is an immunoconjugate that has shown activity in relapsed AML with a favorable safety profile. The aim of this collaborative trial was to assess the feasibility, safety, and antileukemic activity of administering GO followed by conventional chemotherapy as first line therapy in patients aged 61–75 years with AML.

**Design and Methods.** Eligible patients received frontline treatment with GO 9 mg/m<sup>2</sup> infused intravenously on days 1 and 15. Following response assessment to GO, patients were started on conventional chemotherapy consisting of the MICE regimen (mitoxantrone, cytarabine, etoposide). No further treatment was planned for complete responders.

**Results.** Among the 57 evaluable patients, 38 (67%) completed the entire sequential treatment as planned. The overall response rate to the entire induction sequence was 54.4% (31/57), with complete remission (CR) in 35.1% and complete remission with incomplete platelet recovery (CRp) in 19.3%. Rates of failure due to treatment-related mortality or resistant disease were 14.1% (3 toxic deaths during the GO segment, 5 during MICE) and 29.9%, respectively. An initial response to GO was documented in 20 patients (35.1%), with CR in 22.8% and CRp in 12.3%; 6 additional patients entered a partial remission. Reversible myelosuppression and liver toxicity were the main adverse events during both segments of induction. Frontline GO was associated with modest mucosal and gastrointestinal toxicity, but grade 3–4 pancytopenia was universal and prolonged. Hepatic veno-occlusive disease developed in 3 patients after GO and 2 after MICE, resulting in 4 deaths from liver failure. One-year survival at follow-up was 34%. Twelve patients continue in CR/CRp after a median of 226 days.

**Interpretation and Conclusions.** The sequential combination of GO and conventional chemotherapy is a feasible and active treatment strategy for older patients with untreated AML. This novel regimen is now being compared in a phase III trial (AML-17).

**Key words:** gemtuzumab ozogamicin, chemotherapy, AML, older patients.

**T**reatment outcomes for patients with acute myeloid leukemia (AML) have improved substantially over the last decade, especially for patients who are less than 60 years of age and who are better able to tolerate treatment regimens that include intensive induction/consolidation chemotherapy and hematopoietic stem cell transplantation (HSCT).<sup>1</sup> In these patients, complete remission (CR) rates of 70%–80% have been reported. In addition, approximately 40% of patients younger than 60 years of age have prolonged disease-free survival of 5 years.<sup>2,3</sup> In contrast, older patients with AML have CR rates of 40%–60% with conventional chemotherapy and disease-free survival of less than 20% at 3 years.<sup>4–6</sup> Since more than 50% of AML cases occur in patients over 60 years old, treatment of older patients with AML remains a therapeutic challenge.<sup>7</sup> Most patients in this age group

are less able to tolerate the intensive chemotherapy regimens associated with higher remission rates, have pre-existing hematologic disorders, and are more likely to have a higher incidence of poor-risk cytogenetic abnormalities or expression of the multidrug resistance phenotype.<sup>7–9</sup>

Gemtuzumab ozogamicin (GO) is an immunoconjugate that has shown promising activity in relapsed AML.<sup>10–12</sup> It is composed of a humanized anti-CD33 antibody linked to the potent antitumor antibiotic calicheamicin and provides a novel method of drug delivery by using the monoclonal antibody to target CD33<sup>+</sup> leukemic cells.<sup>13–17</sup> CD33 is an antigen expressed during myeloid cell differentiation and is found on the surface of leukemic blasts in >90% of AML cases, but is not present on normal hematopoietic stem cells or, with few exceptions, on normal tissues.<sup>18</sup> By targeting cells that only

express this antigen, GO is able to eliminate the leukemic blasts from the marrow and blood without many of the systemic toxicities associated with traditional chemotherapeutic agents.<sup>12,19-20</sup> In combined phase II studies of 142 patients with AML in first relapse, GO monotherapy (two doses of 9 mg/m<sup>2</sup> given 14 days apart) was associated with a 30% overall complete remission rate, including a 26% response rate in patients over 60 years of age.<sup>11,21</sup> Although myelosuppression and reversible increases in levels of serum bilirubin and transaminases were commonly observed, severe mucositis and grade 3-4 infections were not. These results led to the recent US Food and Drug Administration approval of GO for the treatment of patients over 60 years of age with relapsed AML.<sup>22</sup> As a consequence of these encouraging early results, interest in extending the use of GO to frontline treatment of AML in combination with conventional chemotherapy, in particular as a means of improving the quality of induced remissions, has increased.<sup>23</sup> When applied to younger patients with previously untreated AML, this combination strategy appears reasonably well tolerated and associated with promising rates of initial response.<sup>24-25</sup>

To get more insights into the feasibility of such a combined approach, the EORTC Leukemia Group (EORTC-LG), in collaboration with the Italian Cooperative Group GIMEMA, conducted a phase II study of GO and conventional chemotherapy with mitoxantrone, cytarabine, and etoposide (the MICE regimen) for induction of remission in previously untreated AML patients aged 61 to 75 years old. A sequential scheduling design was selected for this combination trial for the following two reasons: (i) to assess the toxicity and antileukemic activity of single agent GO when given frontline in previously untreated AML; (ii) to minimize the risk of additive acute toxicity potentially resulting from the two regimens given concurrently.

## Design and Methods

### Patients

Patients 61-75 years of age with previously untreated AML and who had a World Health Organization (WHO) performance status (PS) of grade 0 to 1 were allowed to participate in the study. Patients were required to have previously untreated primary or secondary AML (including AML after myelodysplastic syndrome) with a diagnostic bone marrow containing at least 20% leukemic blasts according to the recently developed WHO criteria.<sup>25</sup> Patients were excluded from the study if they had previously received treatment for their AML with other cytotoxic agents (except hydroxyurea for no more than 7 days and/or corticosteroids) or if they had acute promyelocytic leukemia (FAB M3), blast

crisis of chronic myeloid leukemia, or leukemia supervening after other myeloproliferative diseases. In addition, patients with active central nervous system (CNS) leukemia, concomitant progressive malignant disease, active uncontrolled infection, or inadequate renal or liver function (i.e. creatinine or bilirubin > 3 times the upper limit of normal) were not allowed to participate in the study.

Although not a requirement for entry into the trial, CD33 expression was evaluated locally by immunophenotyping leukemic blasts at diagnosis in all patients with adequate samples of bone marrow aspirates. If 20% or more of marrow blasts expressed the CD33 antigen, the patient was considered to have CD33<sup>+</sup> AML. Cytogenetic studies on pretreatment bone marrow were performed locally according to standard protocols. Centrally reviewed karyotypes were interpreted using the International System for Cytogenetic Nomenclature (ISCN) criteria.<sup>26</sup> Risk groups were defined as follows: the *favorable*-risk group included patients with t(8;21) or chromosome 16 abnormalities; the *unfavorable*-risk group included patients with abnormalities of chromosome 5 and 7 (-5/5q-, -7/7q-) or complex karyotypes (>3 abnormalities); the *intermediate*-risk group included patients with normal cytogenetics or -Y alone; and all other abnormalities were lumped together in the *other*-risk group. The patients with unknown, not done, or unsuccessful cytogenetics were included in the *unknown*-risk group.

This study was approved by the European Organization for the Research and Treatment of Cancer (EORTC) Protocol Review Committee and by the Ethical Committee of each participating institution. Written, informed consent according to ICH/EU GCP, and national/local regulations was obtained from each patient before participation.

### Treatment

Patients received frontline GO at the FDA-approved dose/schedule of 9 mg/m<sup>2</sup> as a single 2-hour IV infusion on days 1 and 15. The second dose was given, irrespective of the peripheral blood status, if patients had recovered from non-hematologic toxicities resulting from the previous injection and had no evidence of uncontrolled infection or disease progression, but no more than 28 days were allowed between doses. Patients were routinely premedicated with acetaminophen and antihistamines to prevent or reduce infusion reactions. Bone marrow aspirates were obtained on day 14 for assessment of cellularity and 28 days following the last GO dose for assessment of response. Within 7-10 days of response assessment and regardless of the type of response achieved after GO, patients began conventional chemotherapy consisting of the MICE regimen: mitoxantrone 7 mg/m<sup>2</sup>/day as a 30-min IV infusion on days 1,

3, and 5 (3 doses), etoposide 100 mg/m<sup>2</sup>/day as a 1-hr IV infusion on days 1–3 (3 doses), and cytarabine 100 mg/m<sup>2</sup>/day as a continuous IV infusion on days 1–7. No postremission therapy was planned for patients achieving complete remission unless decided otherwise by the treating physicians.

### Response criteria

The primary efficacy end point in this study was the rate of complete remission induced by the sequential administration of GO and MICE chemotherapy; secondary end points included the rate of response to frontline GO, disease-free survival (DFS) and overall survival (OS). Complete remission (CR) was defined by the bone marrow being shown to contain fewer than 5% blast cells, a cellularity of at least 20% with maturation of all cell lines, an absence of Auer rods and of extramedullary leukemia, and a blood smear free of leukemic blasts. The absolute neutrophil count had to be at least  $1.5 \times 10^9/L$ , and the platelet count greater than  $100 \times 10^9/L$ . On the basis of the phase I/II clinical results indicating that in some responders to GO a delay in platelet recovery may occur, the additional category of CRp was introduced.<sup>10–11</sup> Patients with CRp met all CR parameters with the exception of full platelet recovery, while remaining platelet transfusion independent. Partial remission (PR) was defined as 5%–10% blasts or < 5% blasts in the presence of Auer rods in a bone marrow of adequate cellularity, with a blood smear without leukemic blasts. Treatment failure was defined by failure to achieve CR, CRp, or PR. Relapse following CR/CRp was defined as reappearance of blasts in the blood or the finding of more than 5% blast cells in the bone marrow that were not attributable to another cause such as marrow regeneration.

### Toxicity criteria

All toxicities reported during therapy were evaluated according to the National Cancer Institute Common Toxicity Criteria (CTC–NCI, version 2.0).

### Statistical methods

All patients were registered prospectively at the EORTC Data Center in Brussels. The duration of survival was calculated from the date of start of treatment until the date of death from whatever cause. For patients achieving CR/CRp after induction, DFS was calculated from the date of remission until the date of relapse or death in CR/CRp. Actuarial curves were computed using the Kaplan–Meier technique, and the standard errors of the estimates were obtained from Greenwood's formula. An intent-to-treat analysis was used; all eligible patients who started frontline GO were included for the evaluation of remission rate and OS. The CR/CRp rate and the 95% confidence interval were computed. The associa-

**Table 1. Baseline characteristics of the study group (n = 57).**

Median age (yrs)	68 (range 61–73)
Male/female	40/17
Performance status 0/1	21/36
Primary/secondary AML	43/14
FAB subtype	
M0/M1/M2	4/8/28
M4/M5/M6/unknown	3/5/4/5
Cytogenetic risk group	
Intermediate	20
Other	11
Unfavorable	9
Unknown	17

tion of baseline characteristics with response outcome was examined using Kendall's  $\tau$  test. The cut-off date for the statistical analyses was November 30, 2002. SAS 8.1 statistical software was used.

## Results

### Patients' characteristics

From 09/2000 to 10/2001, 64 consecutive patients fulfilling the eligibility criteria from 15 institutions were enrolled into this study. Four patients were found to be not eligible either because of a WHO performance status > 1 (2 patients) or the presence of severe comorbid conditions (2 patients). Among the remaining 60 patients, 3 withdrew consent before starting treatment thus leaving a total of 57 patients evaluable for response and toxicity.

Demographics and baseline characteristics of the 57 evaluable patients are shown in Table 1. The median age was 68 years (range, 61–73 years), 40 patients were male, and 43 had primary AML. CD33 positivity on bone marrow blasts was documented in 84.6% of the 52 patients for whom immunophenotyping data were available. Cytogenetic data were evaluable in 40/57 patients (70%): 20 (35%) and 9 (16%) were classified in the intermediate and the unfavorable-risk group categories, respectively; 11 (19%) patients had other chromosomal abnormalities and none had a favorable karyotype.

### Treatment outcome

Of the 57 patients who were started on GO, 47 (82%) received the scheduled second injection. The primary reasons 10 patients did not receive the second dose were disease progression (4 patients: 2 died rapidly of leukemia-related complications, and 2 were switched

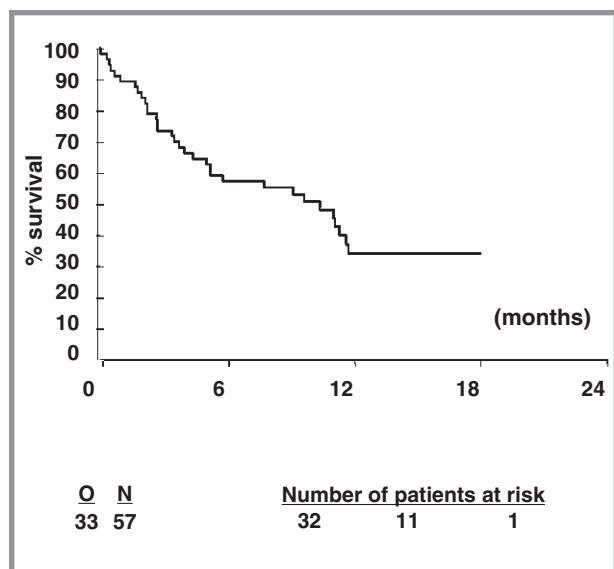


Figure 1. Overall survival from start of therapy.

Table 2. Response to therapy.

	After GO n (%)	Overall n (%)
CR	13 (22.8)	20 (35.1)
CRp	7 (12.3)	11 (19.3)
CR+CRp	20 (35.1)	31 (54.4)
PR	6 (10.5)	1 (1.8)
Failure	28 (49.1)	17 (29.9)
Toxic death	3 (5.3)	8 (14.1)

to immediate MICE), early death (2 patients), toxicity (2 patients: 1 infection, 1 liver dysfunction), and protocol violations (2 patients). The rate of initial response to GO was 35.1% (95% CI, 22.9%–48.9%) with 13 CR and 7 CRp, as listed in Table 2; 6 additional patients achieved PR (10.5%). Of the remaining 31 patients, 3 (5.3%) died of toxicity, and 28 were resistant. Altogether, 51 patients survived GO therapy and 38 of them (75%) were given one course of the MICE regimen after a median interval of 49.5 days (range 12–77 days) from the first GO injection. Reasons for not starting MICE included excessive toxicity (11 patients: 8 infection, 3 liver dysfunction), refusal (1 patient), and protocol violation (1 patient).

Response to the induction sequence is shown in Table 2. The overall complete remission rate (ORR) was 54.4% (31/57; 95% CI, 40.7%–67.6%). The CR and CRp rates were 35.1% and 19.3%, respectively. One patient (1.8%)

achieved PR, and 17 (29.9%) had resistant disease. Five patients died of complications during the MICE segment, for an overall treatment-related mortality of 14.1% (8/57). MICE chemotherapy substantially improved overall response. Among the 19 evaluable patients whose disease failed to respond initially to GO, the addition of MICE was effective in achieving remission in 10 (53%), inducing a CR in 7 and a CRp in 3. Of the 57 patients enrolled in this trial, 33 have died. With a median follow-up of 12 months, the estimated probability of survival at 1 year was 34% (SE = 7.2%) (Figure 1). Leukemia recurred between 39 and 372 days in 18 of the 31 patients who had CR/CRp, and 1 additional patient died in CRp on day 18. The median DFS was 190 days, and was similar for both CR and CRp patients.

### Safety and tolerability

As expected, severe myelosuppression was universally seen during both segments of the sequential induction program. In particular, grade 3–4 neutropenia and thrombocytopenia were quite prolonged after GO with complete responders requiring a median of 37 and 32 days from the first infusion to recover neutrophil and platelet counts > 500/ $\mu$ L and > 50,000/ $\mu$ L, respectively. Hematopoietic recovery post-MICE was not compromised by previous exposure to GO as indicated by the fact that the number of days to recover neutrophil and platelet counts was fully comparable with those of an historical group of patients treated with MICE alone (median of 24 days for both). Additional grade 3–4 toxicities that occurred during therapy are shown in Table 3. The most common non-hematologic adverse events reported during GO therapy included infusion-related allergic reaction (1.8%), hypertension (3.6%), hypotension (3.6%), hemorrhage (3.6%), renal dysfunction (5.3%), elevated SGPT (5.3%) and bilirubin (8.8%), infection (28%), and febrile neutropenia (40.4%). Of note, mucositis-related side effects (stomatitis, diarrhea) were unusual: only 1.8% of patients experienced severe gastrointestinal toxicity during this segment. As expected, severe mucositis occurred more frequently during MICE (5.3%) and was associated with the usual cohort of grade 3–4 adverse events typically seen during conventional chemotherapy, such as hemorrhage (13.1%), hyperbilirubinemia (13.1%), infection (31.6%), and febrile neutropenia (36.8%). Signs and symptoms suggestive of hepatic veno-occlusive disease (VOD) were observed in a total of 5 patients, of whom 4 died of liver failure. Three cases of VOD occurred during therapy with GO: 1 patient died 9 days after the first infusion, 1 patient died 20 days after the second dose right after a CRp status had been documented, 1 patient developed VOD 20 days after the second dose and recovered. Two episodes of VOD occurred following MICE (after 10 and 21 days), and both were fatal: neither of the two patients



had evidence of grade 3–4 liver dysfunction during the preceding GO segment. Overall, the mortality rate for the entire induction program was 14.1% (8/57). A total of 3 patients died during GO therapy, one each of acute respiratory distress syndrome, infection, and VOD. The causes of the 5 toxic deaths which occurred during MICE were infection (n=1), heart failure (n=1), multi-organ failure (n=1), and VOD (n=2).

### Prognosis by pre-treatment characteristics

Baseline characteristics including age, type of AML, WBC count, and marrow blastosis were not predictive of treatment outcome in this study. Furthermore, the CR/CRp rate after GO was apparently not influenced by CD33 positivity (15/44 with CD33<sup>+</sup> AML, 34%; 3/8 with CD33<sup>-</sup> AML, 37.5%; Kendall's  $\tau = -0.13$ ,  $p = 0.39$ ), although patients with a high degree of CD33 expression (> 80% positive blasts) tended to respond more favorably to the immunoconjugate (7/14, 50%) compared to those expressing the antigen in 20–80% of blasts (8/30, 26.7%). The impact of cytogenetics on initial response to GO was of borderline significance (Kendall's  $\tau = 0.29$ ,  $p = 0.057$ ): 9 of 20 patients with an intermediate-risk karyotype achieved CR/CRp versus 3 of 11 and 1 of 9 in the other-risk and the unfavorable-risk group, respectively; the rate of response in the unknown-risk group was 7 of 17. Cytogenetics, however, became highly influential (Kendall's  $\tau = 0.49$ ,  $p = 0.004$ ) when response to the entire induction sequence was considered: CR/CRp was achieved by 15 of 20 with intermediate-risk, 4 of 11 in the other-risk cytogenetic group, 2 of 9 in the unfavorable-risk group and 10 of 17 in the unknown-risk group.

## Discussion

Treatment of AML in the elderly continues to be a controversial issue and there is little doubt that conventional chemotherapy with curative intent is generally applied only to a minority of medically fit patients selected on the basis of age and performance status. However, the outcome of these patients following intensive treatment strategies has remained disappointing with CR rates around 50%, induction death rates of 15% to 30%, a relapse risk in complete responders in excess of 80% and a 3-year survival rate of less than 20%.<sup>2,7-8</sup> In the recently completed EORTC-LG/GIMEMA AML-13 trial, out of a total of 722 registered patients (median age 68 years; range, 60–80 years) with previously untreated AML, 697 were assessable for response to conventional induction chemotherapy. After 1 or 2 courses of MICE, CR was achieved in 382 (54.8%) and the toxic mortality rate during induction was 14.2%. With a median follow-up of 3.9 years, 3-year estimates

**Table 3. Most common grade 3 to 4 non-hematologic toxicities.**

	After GO (n = 57)	After MICE (n = 38)
Allergy	1.8	0
Hypertension	3.6	2.6
Hypotension	3.6	0
Nausea	5.3	5.2
Diarrhea	1.8	2.6
Stomatitis	0	5.3
Hemorrhage	3.6	13.1
Febrile neutropenia	40.4	36.8
Infection	28.1	31.6
Elevated creatinine	5.3	2.6
Elevated total bilirubin	8.8	13.1
Elevated transaminases	5.3	2.6
Hepatic VOD	5.3	5.3

Values expressed as % of evaluable patients.

of DFS and OS were 18.8% and 17%, respectively. Thus, there is a need to identify innovative treatment strategies and/or new antileukemic agents that are more effective and less toxic in older patients with AML. Given its tolerability and encouraging activity in relapsed AML, trials of GO combined with conventional chemotherapy in older patients with untreated AML appear reasonable. Arguably, the use of a drug that targets AML blasts more specifically could result in a better antileukemic control when combined with conventional regimens, without adding excessive extramedullary toxicity.

The results of this study indicate that the sequential administration of GO and conventional chemotherapy is a feasible strategy for first line therapy in elderly patients with AML, resulting in complete response (CR+CRp, 54.4%) and survival rates (34% at 1 year) comparable to those currently achievable with conventional regimens.<sup>5,8,27</sup> Furthermore, remission duration in this study appears promising compared with that obtained in the previous AML-13 trial, in which two additional courses of myelosuppressive chemotherapy were routinely administered as consolidation in complete responders. This latter finding is suggestive of a synergistic interaction between GO and conventional chemotherapy in increasing the depth of leukemia cyto-reduction, thus raising hopes that this novel regimen may improve the outcome of patients with this disease by enhancing the quality of the remissions induced. Thirty-eight of the 57 evaluable patients who received the first infusion of GO were able to complete the MICE segment of induction for an overall feasibility rate of 67%. Completion of the entire induction sequence was of clinical relevance as shown by the fact that out of the 19 evaluable patients whose leukemia was refractory to GO, 10 achieved com-

plete remission (7 CR, 3 CRp) following MICE, suggesting a lack of cross-resistance to the two regimens.

Taking advantage of the sequential design of this combination trial, we were able to get information on the safety and antileukemic activity of GO as frontline monotherapy in elderly patients with untreated AML. By inducing CR/CRp in 35.1% of patients, the targeted drug proved to be one of the most effective single agents currently available in this setting. Furthermore, the antileukemic activity of the drug was apparently not influenced by presenting features such as age, type of disease, WBC count, and degree of marrow blastosis. However, due to the limited number of patients included in this study, no conclusion can be drawn in this respect.

Although a positive correlation between initial response to GO and degree of CD33 expression was apparent, the relationship was not absolute as indicated by the fact that 3 of the 8 patients (37.5%) with so-called CD33<sup>-</sup> AML did enter complete remission following GO. Apart from the obvious consideration that the low predictive value of CD33 expression may just be an artifact reflecting a certain degree of heterogeneity in the level of sensitivity of the standard flow cytometric technique in use at the participating institutions, the possibility that additional CD33-independent cytotoxicity might be induced by GO must be considered, especially in light of recent observations made by Jedema and colleagues indicating that the drug is in fact able to exert a cell killing effect against several CD33<sup>-</sup> lymphoid cell lines via a non-specific phagocytosis of the immunoconjugate.<sup>28</sup>

As expected, adverse cytogenetics was associated with a significantly lower overall response rate to the entire induction program. Such an inferior treatment outcome was already apparent following GO, although the trend was of marginal significance, thus supporting the concept that the high prevalence of a chemoresistant phenotype and unfavorable cytogenetics, typically associated with advanced age, may likely contribute to a poorer clinical response to the targeted drug.<sup>9,29</sup> In this regard, a recent study of relapsed AML patients undergoing monotherapy with GO showed that expression of the P-glycoprotein (P-gp) by the leukemic blasts was associated with a worse clinical outcome.<sup>29</sup> Furthermore, *in vitro* resistance to the immunoconjugate in P-gp expressing cell lines and primary AML blasts can be overcome by P-gp inhibitors such as cyclosporine, suggesting that combined treatment with reversal agents might improve response to GO.<sup>30</sup> The toxicity observed with this sequential treatment strategy was generally manageable, supporting early clinical data indicating that the safety profile of GO is in fact somewhat different from that

observed with conventional chemotherapy.<sup>12</sup> Hematologic and hepatic toxicity were the main adverse events observed throughout the whole induction period. Myelosuppression was universal and profound after each segment of the induction program, but interestingly grade 3–4 neutropenia and thrombocytopenia were more prolonged after GO than following MICE chemotherapy, suggesting that prior exposure to the targeted drug does not compromise the ultimate regenerative potential of the bone marrow in these patients. Total duration of cytopenias was on average in excess of 50 days for patients completing both segments of the induction sequence, but this rather prolonged period of myelosuppression was not associated with an increased risk of dying from toxicity as indicated by an overall induction mortality rate of 14.1%, similar to that observed in the previous AML-13 trial in which only MICE chemotherapy was employed for remission induction. Thus, the extended myelotoxicity associated with the administration of GO followed by MICE chemotherapy may likely result in a more profound antileukemic effect without increasing the therapeutic risk in older patients with AML. Based on pharmacokinetic data indicating a satisfactory degree of saturation of CD33 binding sites when a dose of 6 mg/m<sup>2</sup> was infused,<sup>10</sup> we speculate that lower doses of GO may prove as effective and less myelotoxic in these conditions, thus allowing a higher proportion of patients to reach the MICE segment of the induction sequence. Such dose-reduction should also result in a lower incidence of severe clinical hepatotoxicity, a recognized and potentially fatal side-effect associated with the administration of GO at full doses.

This issue is now being investigated in the current AML-17 phase III trial, which was designed to prospectively address the comparative benefits of lower doses of GO combined with sequential chemotherapy versus chemotherapy alone in patients 61–75 years old with untreated AML.

*SA was the principal investigator; SA, RW, FM and TDW conceived and designed the study; FB, OA and MV were responsible for collection and management of the data; AH was responsible for central review of cytogenetic data; SS was responsible for the statistical analysis. SA, RW, FM, DS, RS, AH, CD, GL, PF, and PM were responsible for the clinical care of patients at the participating centers. The final manuscript was written by SA and critically revised and approved by all the remaining authors. The authors reported no potential conflicts of interest.*

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