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Open-Label Phase II Prospective, Randomized, Controlled Study of Romyelocel-L Myeloid Progenitor Cells to Reduce Infection During Induction Chemotherapy for Acute Myeloid Leukemia

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abstract

PURPOSE Standard cytotoxic induction chemotherapy for acute myeloid leukemia (AML) results in prolonged neutropenia and risk of infection. Romyelocel-L is a universal, allogeneic myeloid progenitor cell product being studied to reduce infection during induction chemotherapy.

PATIENTS AND METHODS One hundred sixty-three patients with de novo AML (age ≥ 55 years) receiving induction chemotherapy were randomly assigned on day 0 (d0), of whom 120 were evaluable. Subjects received either romyelocel-L infusion on d9 with granulocyte colony-stimulating factor (G-CSF) starting daily d14 (treatment group) or G-CSF daily alone on d14 (control) until absolute neutrophil count recovery to 500/μL. End points included days in febrile episode, microbiologically defined infections, clinically diagnosed infection, and days in hospital.

RESULTS Mean days in febrile episode was shorter in the treatment arm from d15 through d28 (2.36 *v* 3.90; $P = .02$). Similarly, a trend toward decreased microbiologically defined infections and clinically diagnosed infection in the treatment arm was observed from d9 to d28 (35.6% *v* 47.5%; $P = .09$), reaching a statistically significant difference from d15 to d28 (6.8% *v* 27.9%; $P = .002$). Because of this, antibacterial or antifungal use for treatment of an infection was significantly less in the treatment group (d9-d28: 44.1% *v* 63.9%; $P = .01$). Significantly fewer patients in the treatment arm received empiric antifungals from d9 tod28 (42.4% *v* 63.9%; $P = .02$) and d15-d28 (42.4% *v* 62.3%; $P = .02$). Patients in the treatment arm also had 3.2 fewer hospital days compared with control (25.5 *v* 28.7; $P = .001$). Remission rates and days to absolute neutrophil count recovery were similar in the two groups. No patients in the romyelocel-L plus G-CSF group died because of infection compared with two patients in the control arm. No graft-versus-host disease was observed.

CONCLUSION Subjects receiving romyelocel-L showed a decreased incidence of infections, antimicrobial use, and hospitalization, suggesting that romyelocel-L may provide a new option to reduce infections in patients with AML undergoing induction therapy.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Approximately 20,000 new cases of acute myeloid leukemia (AML) are diagnosed each year in the United States.[1,2] The current standard of care (cytarabine- and anthracycline-based induction regimens) for younger and fit older patients[3,4] results in serious infections[5,6] and a early mortality rate of 7%-11%[7-9] despite administration of antimicrobials.[10-12] Clinical trials of intensive induction chemotherapy have reported neutropenic fever in more than 80% of patients[7,13-15] and clinically diagnosed infections (CDIs) in 50%-60%.[9,16] Myeloid growth factors are approved for use during induction chemotherapy for AML based on reduction in the median duration of neutropenia, although meta-analyses have failed to show their benefit in incidence of infections, antibiotic use, or overall survival.[15]

Myeloid progenitor cells (MPCs) are hematopoietic cells that generate granulocytes but are not capable of long-

CONTEXT

Key Objective

Patients undergoing intensive induction chemotherapy for acute myeloid leukemia (AML) have a high risk of infection-related morbidity and it is the leading cause of early mortality during AML induction. Romyelocel-L is a universal off-the-shelf myeloid progenitor cell product developed with the aim to reduce infections during induction chemotherapy–induced neutropenia.

Knowledge Generated

The results of this trial demonstrated that romyelocel-L plus granulocyte colony-stimulating factor (G-CSF) use led to statistically significant decrease in the incidence of infections after induction chemotherapy compared with G-CSF alone, particularly from days 15 to 28. This led to a lower use of empiric and treatment-directed antibiotics and a shorter length of stay in the hospital.

Relevance

Romyelocel-L plus G-CSF use during intensive induction chemotherapy for AML has the potential for reducing morbidity of infections and length of stay in the hospital during induction leading to improved outcomes and can have great impact on long-term antibiotic resistance patterns in patients with AML.

term reconstitution. Romyelocel-L (CLT-008) is a cryopreserved, universal, human allogeneic MPC product manufactured by ex vivo expansion of $CD34^+$ hematopoietic stem cells. Following infusion, MPCs produce neutrophils and may thereby mitigate the risk of bacterial and fungal infections after chemotherapy-induced neutropenia.

Given the limited supply and short shelf-life of granulocyte collections, romyelocel-L offers a more durable source of neutrophils than granulocyte transfusions.[17] These donor cells are expected to be transient, given the lack of HLA matching; and since they are differentiated, they are incapable of long-term engraftment. Consistent with the time needed for terminal neutrophil differentiation during in vitro assays and animal models, a phase I clinical trial showed that romyelocel-L can generate functional neutrophils around 6 days after administration with migration to mucous membranes, thus expecting to be increased in areas of tissue damage and ongoing infection. Therefore, the predicted onset of romyelocel-L activity is approximately 6 days postinfusion.[18] Consistent with the minimal T-cell content in romyelocel-L ($< 0.1\%$), there was no evidence of graft-versus-host disease in preclinical animal models or phase I trials.

We conducted a multicenter, randomized, open-label, phase II study of romyelocel-L plus granulocyte colony-stimulating factor (G-CSF) versus G-CSF monotherapy in patients receiving induction chemotherapy (7 plus 3− or high-dose cytarabine [HiDAC]-based regimens) for de novo AML with the aim of reducing infections during chemotherapy induced neutropenia. The primary end point was mean duration of febrile episodes. Secondary end points included the incidence of infection, antimicrobial use, and days of hospitalization.

PATIENTS AND METHODS

Study Design

Subjects provided written informed consent approved by their local institutional review board in accordance with the Declaration of Helsinki. This trial was registered at ClinicalTrials.gov identifier: NCT02282215. Eligible patients $\geq$ 55 years of age with de novo AML, who were scheduled to receive induction chemotherapy (7 plus 3− or HiDAC-based combination defined as cytarabine 4 g/m^2 or more alone or in combination with other agents such as purine analogues, anthracyclines, or etoposide), were stratified by chemotherapy regimen, age ($\leq$ 65 v $>$ 65 years of age), and WBC count at screening ($\geq 20 \times 10^9$/L or $< 20 \times 10^9$/L), and then randomly assigned in a 1:1 ratio to receive a single infusion of romyelocel-L in addition to G-CSF or G-CSF monotherapy (Fig 1).

The first day of induction chemotherapy was designated as day 0 (d0). A single dose of romyelocel-L (7.5×10^6 cells/kg) was administered in the experimental group within a 3-day window from d9 to d11. G-CSF was administered once daily starting on d14 in both groups and was continued until neutrophil recovery defined as at least one absolute neutrophil count (ANC) value of $> 500/\mu$L (Fig 2). G-CSF use before d14 was allowed if it was part of the chemotherapy regimen (eg, some HiDAC regimens). For simplicity, the period referred to as d9-d28 is the day of romyelocel-L infusion to 19 days postinfusion in the treatment arm or 9-28 days following initiation of chemotherapy in the control arm.

The onset of biologic activity of romyelocel-L is anticipated 6 days postinfusion, which, in this study, corresponds to 15 days postchemotherapy; therefore, events in both study groups during d15-d28 days following chemotherapy were analyzed as a post hoc end point (Fig 2). Additional chemotherapy was allowed at the discretion of the investigators.

Patients

Eligibility criteria (Protocol, online only) included patients with Eastern Cooperative Oncology Group performance status of 0-2 and adequate pulmonary, liver, and renal function. Patients with acute promyelocytic leukemia, secondary AML, and CNS leukemia were excluded from the study. Cytogenetic risk grouping was in accordance with

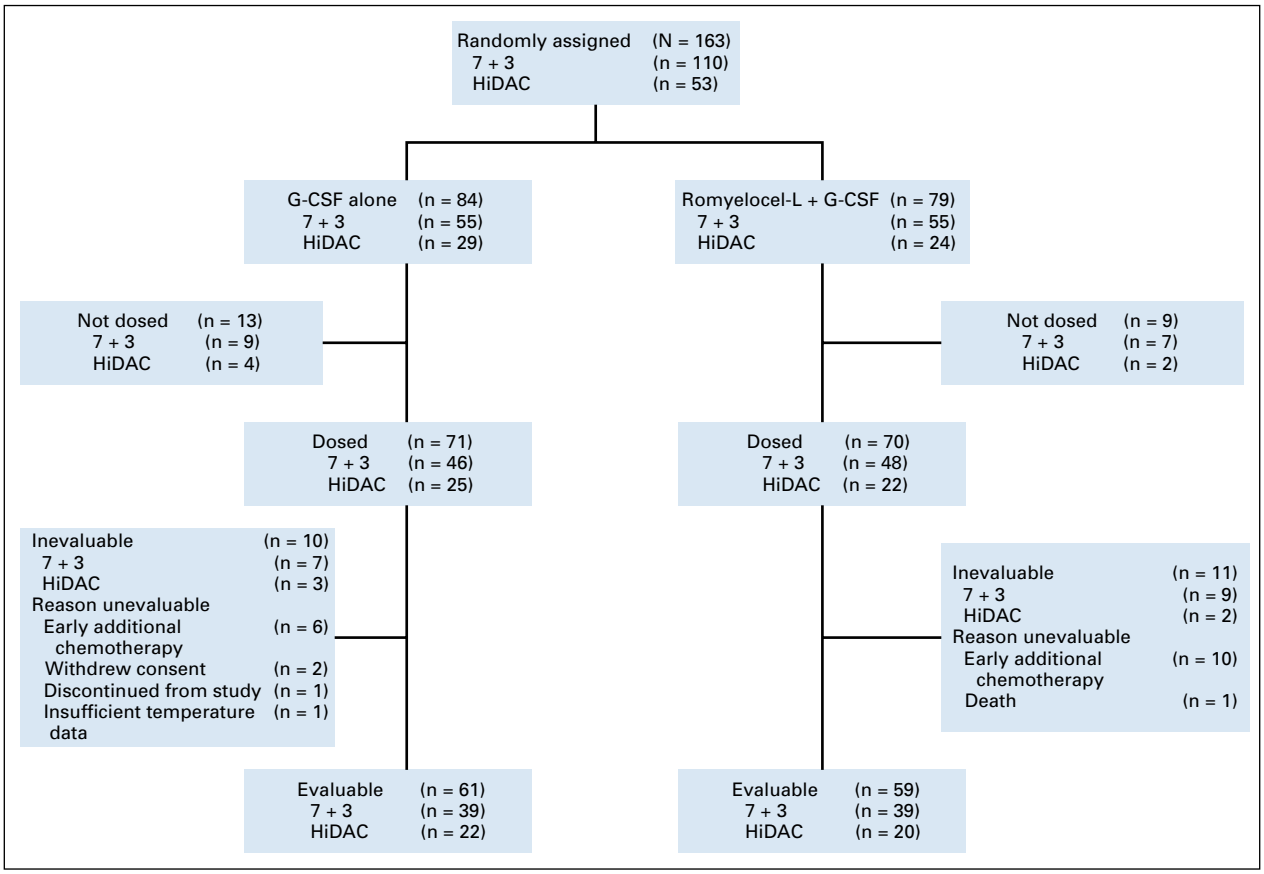

FIG 1. CONSORT diagram. G-CSF, granulocyte colony-stimulating factor; HiDAC, high-dose cytarabine.

European LeukemiaNet criteria.[19] Prophylactic antimicrobials were administered as per institutional protocols. Patients were followed for safety from d0 through d42.

End Points

The primary objective was to assess the mean duration of a febrile episode from d9 to d28. A febrile episode began on the first day of a maximum daily temperature of at least 38.0°C and ended when maximum daily temperature was < 37.5°C for at least three daily consecutive measurements.

Key secondary end points included incidence of microbiologically documented infections (MDIs) at an anatomically defined site or bacteremia with an identified pathogen; incidence of clinically documented infections (CDIs)

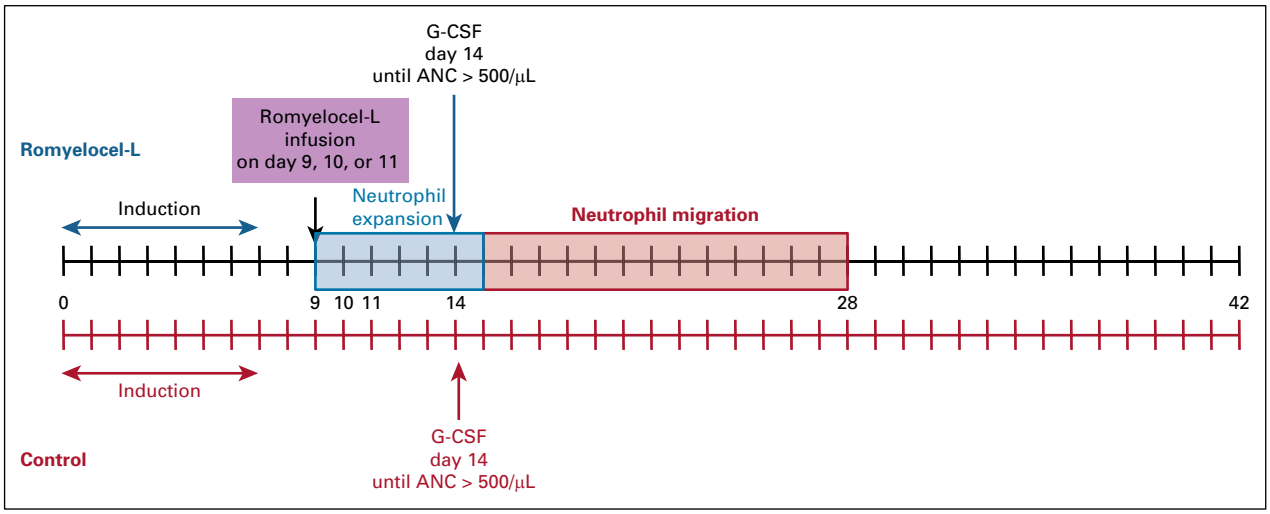

FIG 2. Schematic figure of romyelocel-L administration. ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor.

defined as findings compatible with infection at a specific anatomic site but without confirmatory microbiologic data; neutrophil recovery to 500/μL; days of hospitalization from d0; antimicrobial use; and platelet reactive antibodies (PRA) measurements.

The choice of antibiotics was decided by study sites who were encouraged to follow the Infectious Diseases Society of America's Guidelines for neutropenic fever. Antimicrobials were classified as follows: (1) Prophylactic treatment if given before any clinical infection; (2) empiric if started in response to suspected infection, including neutropenic fever, without MDI or CDI; (3) directed treatment if antibiotics were started and/or broadened based on an actual MDI or CDI. Intensification of empiric therapy was defined as change to broader-spectrum coverage based on clinical judgment, most commonly in the setting of persistent fevers without evidence of CDI or MDI.

A blinded, independent, adjudication committee composed of experts in infectious complications of hematologic malignancies evaluated all episodes of fever and infection. Antimicrobials were categorized according to Infectious Diseases Society of America (IDSA) guidelines by a fully blinded independent infectious disease expert and were categorized as prophylactic, empiric, intensification of empiric therapy, and/or directed treatment. The independent, adjudication committee characterized certain infections as minor including localized bacterial or candidal skin and soft tissues without cellulitis, localized herpes simplex or candidal infections without mucositis, and respiratory virus infections without evidence of lower respiratory tract disease.

PRA analysis was performed at d0, d14, d21, and d42 to examine the generation of alloreactive antibodies against romyelocel-L.

Statistical Analysis

Statistical testing was one-sided for all analyses and performed at the $P < .05$ significance level with the objective to demonstrate superiority over the control group. Continuous variables were summarized with means, standard deviations, medians, minimums, maximums, and number of valid cases. Treatment groups were compared using analysis of covariance or analysis of variance methods. Treatment groups were compared using an analysis of covariance model that included terms for the stratification covariates assuming normality was not violated. Nonparametric methods were used if normality assumptions were violated (as it was the case with infections). Diagnostic plots were used to assess departures from normality. Categorical variables were summarized by counts and by the percentage of subjects in the corresponding categories such as chemotherapy regimen and age and compared using Cochran-Mantel-Haenszel methods. Where appropriate, 95% CIs were constructed for key efficacy variables. One-sided P values obtained from a Cochran-Mantel-Haenszel test for Row Mean Score Difference were stratified by the variables used in the stratified random assignment. Kaplan-Meier methods were used for the analysis of time-to-event variables. All analyses and tabulations were performed using SAS Version 9.4.

RESULTS

The study defined the evaluable population a priori as patients who were randomly assigned, received any amount of romyelocel-L plus G-CSF or G-CSF alone, and remained in the study through d28 for the G-CSF alone group or for ≥ 19 days following romyelocel-L infusion in the treatment group. Because cytotoxic therapy would also target romyelocel-L and progeny, patients receiving any reinduction chemotherapy before d28 were not included in the evaluable population.

The safety population included all patients in the romyelocel-L plus G-CSF treatment group who received any fraction of the romyelocel-L infusion and all patients in the G-CSF alone treatment group who received any dose of G-CSF.

Baseline Characteristics

From 2015 through 2017, 163 patients were enrolled from 21 US centers in the United States and 120 of them were evaluable (Table 1 and Data Supplement, online only). Overall, 59 and 61 patients were evaluable in the treatment and control arms, respectively. Of the evaluable HiDAC population, 13/22 (59.1%) control and 10/20 (50.0%) treatment patients had G-CSF use starting d0-d1 as part of the chemotherapy regimen. European LeukemiaNet cytogenetic risk classification was comparable between the groups (Table 1 and Data Supplement). The primary reason patients were not evaluable was the administration of additional chemotherapy before d28 (Table 1).

Days in Febrile Episode (evaluable population)

From d9 to d28, mean days in febrile episodes was not significantly decreased in the treatment group (6.46 *v* 6.86; $P = .35$; Table 2). No significant difference was seen in the number of patients who had febrile neutropenia between the treatment arms. Although there was no significant difference in the number of febrile episodes per subject in the 7 plus 3 arm, unexpectedly, 9/22 (40.9%) control subjects had no febrile episodes from d9 to d28 (Appendix Table A1, online only) in the HiDAC arm. It is important to note that HiDAC patients generally received more steroids than 7 plus 3 patients. Among the various centers, use of steroids varied in terms of intensity and duration with no difference observed between the two arms of the study (36% in the GCSF only and 33.8% in the GCSF plus romyelocel group).

Significantly fewer days of febrile episodes (2.36 *v* 3.90 days; $P = .02$) were observed in the treatment arm from d15 to d28, which is consistent with the biologically effective period of romyelocel-L.

TABLE 1. Baseline Characteristics of Evaluable Population

	G-CSF Alone			Romyelocel-L + G-CSF			
Baseline Characteristic	**7 + 3 (n = 39)**	**HiDAC (n = 22)**	**Total (n = 61)**	**7 + 3 (n = 39)**	**HiDAC (n = 20)**	**Total (n = 59)**	**Overall Total (N = 120)**
Age group, years, No. (%)							
≤ 65	23 (59.0)	15 (68.2)	38 (62.3)	21 (53.8)	14 (70.0)	35 (59.3)	73 (60.8)
> 65	16 (41.0)	7 (31.8)	23 (37.7)	18 (46.2)	6 (30.0)	24 (40.7)	47 (39.2)
Sex, No. (%)							
Male	20 (51.3)	13 (59.1)	33 (54.1)	22 (56.4)	12 (60.0)	34 (57.6)	67 (55.8)
Female	19 (48.7)	9 (40.9)	28 (45.9)	17 (43.6)	8 (40.0)	25 (42.4)	53 (44.2)
Ethnicity, No. (%)[a]							
Hispanic or Latino	1 (2.6)	0	1 (1.7)	4 (10.3)	1 (5.0)	5 (8.5)	6 (5.0)
Not Hispanic or Latino	37 (97.4)	22 (100.0)	59 (98.3)	35 (89.7)	19 (95.0)	54 (91.5)	113 (95.0)
Unknown	1	0	1	0	0	0	1
Race, No. (%)[a]							
American Indian or Alaska Native	0	0	0	0	0	0	0
Asian	1 (2.6)	1 (4.5)	2 (3.3)	1 (2.6)	0	1 (1.7)	3 (2.5)
Black or African American	5 (12.8)	2 (9.1)	7 (11.5)	1 (2.6)	1 (5.0)	2 (3.4)	9 (7.5)
White	33 (84.6)	19 (86.4)	52 (85.2)	37 (94.9)	19 (95.0)	56 (94.9)	108 (90.0)
Unknown	0	0	0	0	0	0	0
BMI, kg/m^2							
Mean (SD)	31.38 (7.754)	30.70 (6.986)	31.14 (7.434)	30.11 (5.721)	30.04 (4.602)	30.09 (5.327)	30.62 (6.479)
Median	29.00	28.60	29.00	30.00	30.35	30.20	29.35
Min, max	18.0, 61.9	19.4, 47.6	18.0, 61.9	19.8, 40.8	23.1, 37.2	19.8, 40.8	18.0, 61.9
ECOG PS, No. (%)							
0	4 (10.3)	5 (22.7)	9 (14.8)	7 (17.9)	4 (20.0)	11 (18.6)	20 (16.7)
1	23 (59.0)	12 (54.5)	35 (57.4)	23 (59.0)	10 (50.0)	33 (55.9)	68 (56.7)
2	12 (30.8)	5 (22.7)	17 (27.9)	9 (23.1)	6 (30.0)	15 (25.4)	32 (26.7)
WBC count at random assignment (10^9/L)							
< 20 × 10^9/L, No. (%)	30 (76.9)	17 (77.3)	47 (77.0)	29 (74.4)	17 (85.0)	46 (78.0)	93 (77.5)
≥ 20 × 10^9/L, No. (%)	9 (23.1)	5 (22.7)	14 (23.0)	10 (25.6)	3 (15.0)	13 (22.0)	27 (22.5)
Primary reason unevaluable[b]							
Additional chemotherapy	6 (13.0)	0	6 (8.5)	8 (16.7)	2 (9.1)	10 (14.3)	16 (11.3)
Insufficient temperature, No. (%)							
Data	0	1 (4.0)	1 (1.4)	0	0	0	1 (0.7)
Discontinuation from study	1 (2.2)	2 (8.0)	3 (4.2)	0	0	0	3 (2.1)
Death	0	0	0	1 (2.1)	0	1 (1.4)	1 (0.7)
Other	0	0	0	0	0	0	0
Genetic group of current diagnosis, No. (%)[a]							
Favorable	16 (41.0)	6 (28.6)	22 (36.7)	13 (33.3)	2 (10.0)	15 (25.4)	37 (31.1)
Intermediate I	12 (30.8)	9 (42.9)	21 (35.0)	7 (17.9)	8 (40.0)	15 (25.4)	36 (30.3)
Intermediate II	1 (2.6)	3 (14.3)	4 (6.7)	6 (15.4)	6 (30.0)	12 (20.3)	16 (13.4)
Adverse	10 (25.6)	3 (14.3)	13 (21.7)	13 (33.3)	4 (20.0)	17 (28.8)	30 (25.2)
Unknown	0	1	1	0	0	0	1

(continued on following page)

TABLE 1. Baseline Characteristics of Evaluable Population (continued)

Baseline Characteristic	G-CSF Alone			Romyelocel-L + G-CSF			Overall Total (N = 120)
	7 + 3 (n = 39)	HiDAC (n = 22)	Total (n = 61)	7 + 3 (n = 39)	HiDAC (n = 20)	Total (n = 59)	
Prophylactic antimicrobials, No. (%)							
Antibacterials	11 (28.2)	12 (54.5)	23 (37.7)	9 (23.1)	6 (30.0)	15 (25.4)	38 (31.6)
Antifungal	19 (48.7)	9 (40.9)	28 (45.9)	16 (41.0)	8 (40.0)	24 (40.6)	52 (43.3)
Mold-active antifungals	14 (35.9)	6 (27.3)	20 (32.7)	11 (28.2)	6 (27.3)	17 (28.8)	37 (30.8)
Antivirals	13 (33.3)	5 (22.7)	18 (29.5)	13 (33.3)	2 (10.0)	15 (25.4)	33 (27.5)

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, granulocyte colony-stimulating factor; HiDAC, high-dose cytarabine; SD, standard deviation.

[a]Percentages based on subjects in the evaluable population minus subjects with missing or unknown values for that parameter.

[b]Percentages based on number of subjects in safety population.

Incidence and Timing of Nonminor MDIs and CDIs (evaluable population)

From d0 to d42, 50.8% of treatment patients and 59.0% of control patients had a CDI or MDI (Appendix Fig A1, online only). Between d21 and d42 (after ANC recovery), only one patient in the romyelocel-L plus G-CSF group and 12 patients in the G-CSF group developed a nonminor bacterial or fungal infection. All infections in the evaluable population were assessed before any additional chemotherapy.

The incidence and timing of MDIs and CDIs relative to the administration of study treatment were both notable and consistent with treatment effects of biologic agents (Fig 3). From d9 to d28, there was a 25% reduction in MDIs or CDIs in patients treated with romyelocel-L (35.6% *v* 47.5%; $P = .09$; Table 3). The 7 plus 3 group mostly drove this, and no reduction was seen in the HiDAC group.

From d15 to d28, the romyelocel-L plus G-CSF group had a 76% reduction in patients with nonminor infections (6.8% *v* 27.9%; $P = .0013$). When considered separately, a reduction in both MDIs (3.4% *v*. 11.5%; $P = .05$) and CDIs (3.4% *v* 16.4%; $P = .01$) was also observed in that period. From d15 to d28, romyelocel-L patients in the 7 plus 3 cohort had a lower incidence of nonminor infections (7.7% *v* 28.2%; $P = .01$) and CDIs (2.6% *v* 17.9%; $P = .02$), whereas romyelocel-L patients in the HiDAC cohort had significantly lower incidence of nonminor infections (5.0% *v* 27.3%; $P = .03$) and MDIs (0% *v* 13.6%; $P = .05$).

MDIs and CDIs were more common before d15 in the romyelocel-L plus G-CSF group with fewer events reported after d15 (Data Supplement) when the clinical activity of romyelocel-L is expected to take effect (Fig 3). By contrast, CDIs in the G-CSF alone group occurred at similar incidence before and after day 15, with relatively more infections occurring after day 15 in the G-CSF group.

Antimicrobial Use (evaluable population)

The use of antimicrobial agents (including antibacterial, antifungal, and antiviral) before romyelocel-L administration or d0-d8 for G-CSF alone was not significantly different

TABLE 2. Days of Febrile Episode in Evaluable Population

Study Time Period	7 + 3			HiDAC			Pooled		
	G-CSF (n = 39)	Romyelocel-L + G-CSF (n = 39)	*P*	G-CSF (n = 22)	Romyelocel-L + G-CSF (n = 20)	*P*	G-CSF (n = 61)	Romyelocel-L + G-CSF (n = 59)	*P*
Days 9-28									
LS mean (SE)	9.11 (1.034)	7.37 (1.014)	.0984	4.04 (1.223)	6.00 (1.352)	.8995	6.86 (0.827)	6.46 (0.842)	.3492
Median (range)	8.0 (0-20)	7.0 (0-17)		2.0 (0-19)	7.0 (1-11)		6.0 (0-20)	7.0 (0-17)	
Days 15-28									
LS mean (SE)	4.77 (0.739)	3.24 (0.725)	.0570	2.98 (0.935)	1.37 (1.034)	.0849	3.90 (0.589)	2.36 (0.600)	.0192
Median (range)	3.0 (0-14)	2.0 (0-11)		1.0 (0-14)	0.5 (0-8)		3.0 (0-14)	2.0 (0-11)	

Abbreviations: G-CSF, granulocyte colony-stimulating factor; HiDAC, high-dose cytarabine; LS, least square.

TABLE 3. Number of Subjects With a Nonminor MDI or CDI of Bacterial or Fungal Cause in Evaluable Population

	7 + 3				HiDAC				Pooled			
Study Time Period	**G-CSF (n = 39), No. (%)**	**Romyelocel-L + G-CSF (n = 39), No. (%)**	**% Reduction**	***P***	**G-CSF (n = 22), No. (%)**	**Romyelocel-L + G-CSF (n = 20), No. (%)**	**% Reduction**	***P***	**G-CSF (n = 61), No. (%)**	**Romyelocel-L + G-CSF (n = 59), No. (%)**	**% Reduction**	***P***
Days 9-28												
MDI or CDI	20 (51.3)	13 (33.3)	35	.0571	9 (40.9)	8 (40.0)	2	.4473	29 (47.5)	21 (35.6)	25	.0881
MDI	12 (30.8)	7 (17.9)	42	.0902	6 (27.3)	5 (25.0)	8	.4037	18 (29.5)	12 (20.3)	31	.1127
CDI	10 (25.6)	8 (20.5)	20	.3042	4 (18.2)	3 (15.0)	18	.3859	14 (23.0)	11 (18.6)	19	.2783
Days 15-28												
MDI or CDI	11 (28.2)	3 (7.7)	73	.0098	6 (27.3)	1 (5.0)	82	.0275	17 (27.9)	4 (6.8)	76	.0013
MDI	4 (10.3)	2 (5.1)	50	.1996	3 (13.6)	0	100	.0489	7 (11.5)	2 (3.4)	70	.0492
CDI	7 (17.9)	1 (2.6)	86	.0137	3 (13.6)	1 (5.0)	63	.1810	10 (16.4)	2 (3.4)	79	.0098

Abbreviations: CDI, clinically diagnosed infection; G-CSF, granulocyte colony-stimulating factor; HiDAC, high-dose cytarabine; MDI, microbiologically defined infection.

TABLE 4. Days of Hospitalization for Evaluable Population

Reduction in Hospitalization	7 + 3			HiDAC			Pooled		
	G-CSF (n = 39)	Romyelocel-L + G-CSF (n = 39)	*P*	G-CSF (n = 22)	Romyelocel-L + G-CSF (n = 20)	*P*	G-CSF (n = 61)	Romyelocel-L + G-CSF (n = 59)	*P*
Time in hospital, days									
LS mean (SE)	31.0 (1.03)	27.6 (1.01)	.0059	25.7 (1.26)	22.6 (1.40)	.0278	28.7 (0.82)	25.5 (0.83)	.0011
Median	27.0	26.0		26.0	23.5		27.0	25.0	
Range	21-43	21-37		15-41	18-34		15-43	18-43	

NOTE. LS mean and SE shown.

Abbreviations: G-CSF, granulocyte colony-stimulating factor; HiDAC, high-dose cytarabine; LS, least square.

(Data Supplement) both overall and by chemotherapy regimen. However, significantly more 7 plus 3 patients in the G-CSF alone arm received mold-active antifungals from d0 to d8 compared with the romyelocel-L group.

IDSA group 1 antibacterial use for empiric therapy of neutropenic fever for both periods was similar for the two treatment groups. From d15 to d28, significantly fewer patients in the romyelocel-L plus G-CSF treatment group had their treatment intensified with the use of IDSA group 2 antibacterials (30.5% *v* 45.9%; $P = .04$; Data Supplement). For 7 plus 3 patients, intensification of empiric therapy was significantly lower in the romyelocel-L plus G-CSF group (30.8% *v* 53.8%; $P = .03$). Antimicrobial use for treatment of infection (MDI or CDI) was significantly lower for patients in the romyelocel-L plus G-CSF arm for both periods evaluated (Data Supplement).

Days of Hospitalization (evaluable population)

The total number of days hospitalized was significantly shorter for the romyelocel-L plus G-CSF group (25.5 *v* 28.7 days; $P = .002$; Table 4). Patients on the 7 plus 3 chemotherapy cohort treated with romyelocel-L plus G-CSF had 3.4 fewer hospitalization days ($P = .006$). Similarly, patients on the HiDAC cohort receiving romyelocel-L had 3.1 fewer hospitalization days ($P = .03$).

Days to ANC Recovery (safety population)

The proportion of patients with confirmed ANC recovery from d0 to d42 was similar between groups (80.0% *v* 84.5% in treatment and control, respectively). The median time to ANC recovery was 21.0 days in both groups ($P = .48$), with the median number of days with ANC $< 500/\mu L$ being 17.0 days in both groups.

PRA Testing (safety population)

On d0, 41 treatment and 38 control patients were tested for PRA. Among these patients, 19 (46.3%) treatment and 16 (42.1%) control patients were positive for anti-HLA antibodies at d0. From d0 to d42, 41 treatment and 39 control subjects were tested for PRA. Of these, 26 (63.4%) treatment and 17 (43.6%) control patients developed a new antibody ($P = .9374$). It is noteworthy that five patients had cognate antibodies to romyelocel-L before infusion.

Adverse Events (safety population)

Treatment-emergent significant adverse events (SAEs) were less frequent in the romyelocel-L plus G-CSF group (12.9% *v* 18.3%; Data Supplement). Six patients had a romyelocel-L infusion reaction (all grade 1) that included rigors or chills, facial flushing, and fever. All SAEs, except a possibly related grade 3 pulmonary embolism, were considered not related to romyelocel-L. No patients were discontinued from the study because of an AE or SAE. No patients had graft-versus-host disease or new-onset platelet refractoriness after romyelocel-L administration.

There were three deaths reported from study entry to d42 with one in the romyelocel-L plus G-CSF arm and two in the G-CSF arm. Death was reported in one patient in the romyelocel-L plus G-CSF group because of progression of disease. Two in the G-CSF group died because of infectious complications. There was no impact of romyelocel-L on complete remission rate, disease-free survival, or overall survival.

DISCUSSION

Infectious complications associated with neutropenia remains the leading cause of morbidity and mortality after AML induction chemotherapy despite an expanded antimicrobial armamentarium.[20-23] Romyelocel-L was designed to reduce the morbidity and mortality from infections during neutropenia after myeloablative chemotherapy in AML.

Romyelocel-L was well tolerated and the safety profile of romyelocel-L plus G-CSF was comparable to G-CSF monotherapy, although there were more infectious SAEs in the G-CSF group. The primary end point was not met, since the decrease in duration of febrile episodes from d9 to d28 was not statistically significant. However, fevers occurring early after induction chemotherapy may not be specific to infection, and administration of numerous medications and antipyretics further obscures the measurement of fever. We

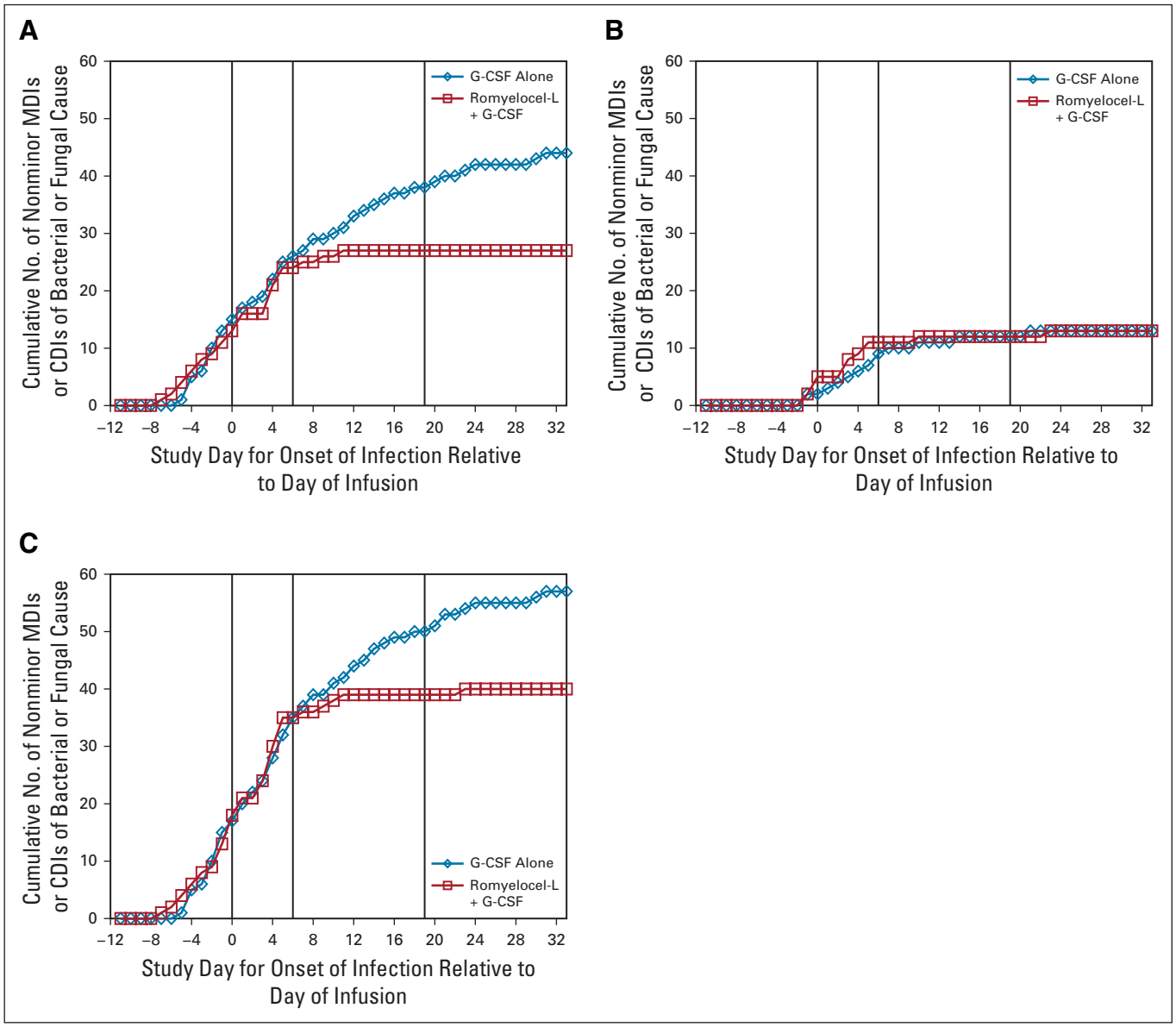

FIG 3. Incidence of infection relative to day of infusion or day 9 for control subjects during induction. The figure shows the number of nonminor MDIs or CDIs of a bacterial or fungal cause onset relative to the day of infusion (day 9 for G-CSF alone subjects) for each type of chemotherapy: (A) 7 + 3, (B) HiDAC, and (C) pooled. The vertical lines indicate the infusion day, 6 days after infusion, and 19 days after infusion. CDI, clinically diagnosed infection; G-CSF, granulocyte colony-stimulating factor; HiDAC, high-dose cytarabine; MDI, microbiologically defined infection.

therefore examined exploratory secondary end points that are more clinically relevant, including incidence of infection, use of antimicrobial agents, and length of stay in the hospital. All of these favored the romyelocel plus G-CSF group.

Of potentially greater clinical significance is the observed decrease in infections in the romyelocel-L plus G-CSF group. Both animal models of infectious challenge after induced neutropenia and in vitro studies of development of functional neutrophils from myeloid progenitors demonstrate that a period of 4-6 days is necessary before biologic activity. These data would, therefore, predict that the maximal effect of romyelocel-L should occur at d13-d15 under the conditions of this study. The divergence of infection incidence between the two groups after d15 is concordant with the predicted effect. The reduction in late infections in the romyelocel-L arm could be attributed to clearance of subclinical infections that may become apparent after ANC recovery in the control group. The decrease in infections was also accompanied by significant decreases in intravenous antibiotic utilization and days of hospitalization in the treatment group. Although this study was not designed to evaluate the emerging problem of antimicrobial resistance in immunocompromised patients, the use of romyelocel-L could reduce the use, duration, and escalation of antibiotics. This could have far-reaching

impact on long-term morbidity including after stem-cell transplantation. Similarly, shortening hospital stays decreases cost and improves patient quality of life.[24]

The use of mold-active antifungals as prophylaxis was permitted at the discretion of the institution. There were a disproportionate higher number of patients in the control group receiving mold-active antifungals. In spite of this, fungal infection rates were lower in the romyelocel-L cohort, further strengthening the evidence of its biologic effect. Our study was not powered to examine differences in survival or less common events such as intensive care support. With the availability of multiple regimens in AML and the increasing applicability of transplant in older patients, survival end points are increasingly difficult to define for supportive care interventions.

Previous trials of granulocyte infusions have shown conflicting efficacy results with many trials being retrospective in nature, generally conducted in patients with active infection and few focused on prevention of infection or antibiotic utilization.[25-28] Moreover, granulocyte infusions are associated with serious complications with 5%-10% of patients needing intensive care unit admission[29] and also with increased mortality in patients with pulmonary infections because of increased rates of transfusion-related acute lung injury.[30,31] In addition, the required granulocyte doses were not obtained by many studies because of the difficulty in obtaining enough granulocytes from G-CSF or steroid stimulated donors.[17,32] Romyelocel-L overcomes these limitations because of its safety profile and ease of administration with a single dose. Consistent with previous studies using G-CSF,[33-35] the control arm did not have reduced infections, whereas a reduction of infection was seen in the romyelocel-L plus G-CSF arm.

The study met the more clinically meaningful secondary end points showing that the incidence of infection, antibiotic use, and days of hospitalization were significantly lower in the romyelocel-L plus G-CSF arm but no reduction in the mean duration of febrile episodes was observed. As infection remains the most common cause of morbidity and mortality in patients with AML, strategies to reduce the risk of infection are an unmet need. These results provide the foundation for a phase III trial with the primary end point of reduction in infections during intensive induction chemotherapy for adults with AML. Romyelocel-L has great potential not only in reducing infections during induction chemotherapy in AML but also reducing antibiotic resistance, which remains one of the biggest concerns in infection control in immunocompromised patients.

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DISCLAIMER

R.M., A.W., R.V.S., L.K., S.P., and R.M. are current or former employees of Cellerant Therapeutics.

EQUAL CONTRIBUTION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Open-Label Phase II Prospective, Randomized, Controlled Study of Romyelocel-L Myeloid Progenitor Cells to Reduce Infection During Induction Chemotherapy for Acute Myeloid Leukemia

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APPENDIX

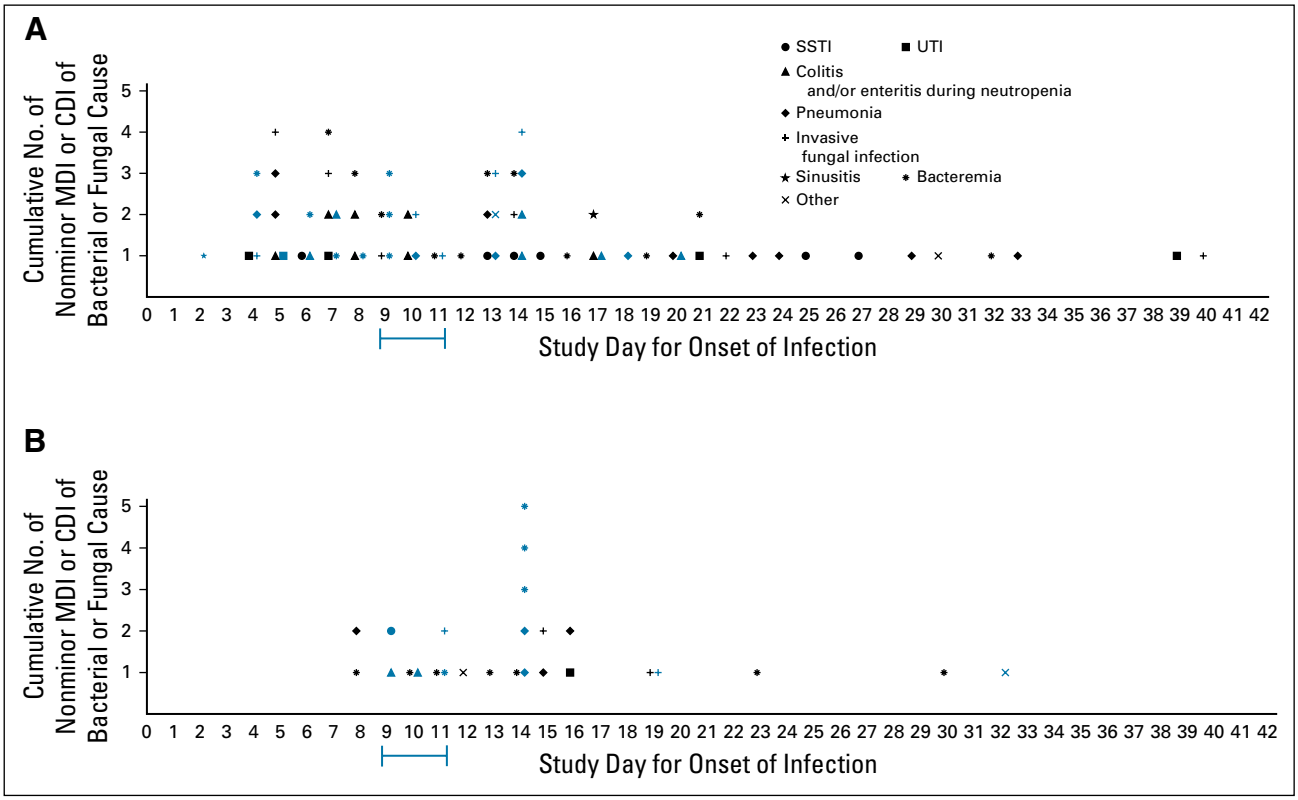

FIG A1. Classification of incidence of infections in the evaluable population: (A) 7 + 3 arm and (B) HiDAC arm. Each nonminor MDI or CDI in the evaluable population was classified. Infections in the control arm are shown in black, whereas the treatment arm is shown in blue. The onset date of the infection was diagnosed by the IAC and the brackets indicate the time frame of romyelocel-L infusion. A complete listing of all infections is described in the Data Supplement. CDI, clinically diagnosed infection; HiDAC, high-dose cytarabine; IAC, independent, adjudication committee; MDI, microbiologically defined infection; SSTI, skin and soft tissue; UTI, urinary tract infection.

TABLE A1. No. of Febrile Episodes per Subject From Day 9-28

	7 + 3, P = .32		HiDAC, P = .001		Pooled, P = .02	
Subjects With Febrile Episodes	**G-CSF (n = 39)**	**Romyelocel-L + G-CSF (n = 39)**	**G-CSF (n = 22)**	**Romyelocel-L + G-CSF (n = 20)**	**G-CSF (n = 61)**	**Romyelocel-L + G-CSF (n = 59)**
Subjects with 0 febrile episodes, No. (%)	6 (15.4)	5 (12.8)	9 (40.9)	0	15 (24.6)	5 (8.5)
Subjects with 1 febrile episode, No. (%)	28 (71.8)	28 (71.8)	13 (59.1)	19 (95.0)	41 (67.2)	47 (79.7)
Subjects with 2 febrile episodes, No. (%)	5 (12.8)	6 (15.4)	0	1 (5.0)	5 (8.2)	7 (11.9)
Subjects with 3 febrile episodes, No. (%)	0	0	0	0	0	0
Subjects with > 3 febrile episodes, No. (%)	0	0	0	0	0	0

NOTE. One-sided P value obtained from a CMH test for Row Mean Score Difference stratified by chemotherapy regimen, age group, and WBC level at random assignment ($\geq 20 \times 10^9$/L or $< 20 \times 10^9$/L).

Abbreviations: CMH, Cochran-Mantel-Haenszel; G-CSF, granulocyte colony-stimulating factor; HiDAC, high-dose cytarabine.