Remission Induction Therapy of Untreated Acute Myeloid Leukemia Using a Non-Cytarabine-Containing Regimen of Idarubicin, Etoposide, and Carboplatin

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BACKGROUND. The safety and efficacy of idarubicin, etoposide, and carboplatin as remission induction therapy for patients younger than 60 years with untreated acute myeloid leukemia was studied as an alternative to standard regimens based on cytarabine plus anthracycline.

METHODS. Eligible patients received idarubicin (36–40 mg/m^2), etoposide (500 mg/m^2), and carboplatin (1000–1500 mg/m^2) over 5 days. Those who achieved complete remission received a single course of cytarabine 1.5 gm/m^2 every 12 hours for a total of 12 doses. D-xylose absorption was studied as a marker for cytotoxic therapy–induced gut mucosal damage. Cytogenetic and immunophenotyping studies were performed at the time of diagnosis and examined for prognostic importance.

RESULTS. Remission was achieved in 29 (67%) of 43 patients with a single induction course. The median leukemia free and overall survival times were 15.4 months (95% CI 6.5–24.2) and 12.5 months (95% CI 5.9–19.1), respectively. Induction mortality was 14%. Karyotype (normal, simple, or complex vs. very complex) was the strongest predictor of remission (79% vs. 25%, $P = 0.01$), leukemia free survival (odds ratio [OR] 19.3, 95% CI 2.7–138.9), and overall survival (OR 5.4, 95% CI 2.1–13.9). Dose-limiting gut mucosal toxicity was greatest during Weeks 2 and 3. Bloodstream infections occurred in 49% of patients at a median of 12 days. Grade 3–4 diarrhea, nausea, stomatitis, esophagitis/dysphagia, and vomiting developed in 33%, 26%, 23%, 9%, and 2% of cases, respectively, at a median of 17, 16, 11, 15.5, and 21 days, respectively.

CONCLUSIONS. This regimen was active in adults younger than 60 years with untreated acute myeloid leukemia and normal, simple, or complex karyotypes. Remission duration was confounded by karyotype. Mucosal toxicity limited the tolerability of this regimen. These adverse effects might be overcome by increasing the intensity of postremission therapy and modifying the dosing schedule. ***Cancer* 1998;83:1344–54.** © *1998 American Cancer Society.*

KEYWORDS: acute myeloid leukemia, non-cytarabine-based induction regimens, mucosal toxicity.

The optimal strategy for managing patients with newly diagnosed, untreated acute myeloid leukemia (AML) is controversial. Over the last 2 decades, standard remission induction of adult AML has been based on a regimen containing anthracycline plus cytarabine. Approximately 60–80% of untreated adults younger than 60 years are able to achieve complete remission (CR) with this approach; however, one-quarter or more have required more than one induction course, resulting in greater infectious morbidity, greater blood product utilization, and longer periods of hospitalization.[1–8]

High dose cytarabine (HDARA-C)–based induction regimens have been associated with high remission rates in single-institution trials[9] but only average remission rates (52–71%) in larger multicenter trials.[7,10] Concerns regarding prolonged myelosuppression, intestinal epithelial damage, and invasive microbial disease have limited the acceptance of these strategies.[7,11,12] HDARA-C–based regimens have also been applied in postremission consolidation with encouraging results for overall and disease free survival.[1,7,13]

A non-cytarabine-based approach with mitoxantrone and etoposide has been shown to be safe, well tolerated, and effective for adult patients with relapsed or refractory AML,[14,15] for AML developing from myelodysplastic states,[16] and as first-line therapy for untreated AML in the elderly.[17] This experience led us to examine a similar approach to treating a younger patient population by combining etoposide with idarubicin, a newer anthracycline with proven activity in adult AML when combined with cytarabine.[3–5] Carboplatin, an agent active in relapsed or refractory AML,[18] was included in the regimen for the potential of non-cross-resistance. We now report the results of this open Phase II pilot study, which evaluated the safety and efficacy of idarubicin, etoposide, and carboplatin as remission induction therapy for untreated AML patients younger than 60 years.

PATIENTS AND METHODS

Patients

Adult patients younger than 60 years were eligible for inclusion by the following criteria: a diagnosis of untreated AML, defined according to the French–American–British (FAB) criteria;[19,20] no nonhematologic end organ failure unrelated to leukemia or uncontrolled congestive cardiac failure; a left ventricular ejection fraction within the institutional normal range, determined by gated cardiac acquisition studies or by echocardiography; a serum creatinine level of $\leq$300 μmol/L; and written informed consent. All patients received indwelling, multilumen, cuffed central venous catheters. The study was sanctioned by the University of Manitoba Committee on the Use of Human Subjects in Research and by the review board of the Health Sciences Centre.

Study Protocol

The study was an open-label, uncontrolled Phase II clinical trial. Idarubicin was administered as a 10-minute intravenous infusion at 12 mg/m^2 on Days 1, 3, and 5 for the first 8 subjects and at 8 mg/m^2 on Days 1–5, inclusive, for the subsequent 35 subjects. This dosing schedule was consistent with the mitoxantrone schedule used in our previous trial of non-cytarabine-based induction therapy.[17] Etoposide 100 mg/m^2 was administered as a 1-hour infusion daily on Days 1–5, inclusive. Carboplatin was administered as a continuous infusion daily on Days 1–5, inclusive. The initial dose of 300 mg/m^2/day was empirically reduced to 200 mg/m^2/day after administration to the first 8 subjects because of concerns regarding carboplatin-related diarrhea; however, the results for all 43 subjects were pooled when the analysis at the end of the study revealed no differences in demographics, outcome, toxicities, or intestinal epithelial damage. The antiemetic regimen included dexamethasone 8 mg administered intravenously every 12 hours plus metoclopramide 0.5–1 mg/kg and diphenhydramine 50 mg administered intravenously every 4 hours on Days 1–6, inclusive. Ondansetron 8 mg administered intravenously every 8 hours was substituted for metoclopramide if breakthrough nausea and vomiting occurred. Allopurinol was administered to all patients daily until Day 10. A bone marrow aspirate and trephine biopsy were obtained at baseline for diagnosis, on Day 14 for assessment of cellularity and impact on the leukemic cell population, and again at the time of bone marrow recovery for assessment of response. If the bone marrow was not aplastic, or if the leukemic cell population had not fallen to $<$5% of the total nucleated cell count, then a repeat study was performed on Day 21. If no further eukemic cell reduction was observed, subjects were considered nonresponsive and were offered high dose cytarabine (1.5 g/m^2 infused over 1 hour every 12 hours for 12 consecutive doses) with or without mitoxantrone (12 mg/m^2 administered daily intravenously on Days 7, 8, and 9) as salvage therapy. Those who had CR received a single course of postremission consolidation therapy with high dose cytarabine (1.5 g/m^2 infused over 1 hour every 12 hours for 12 consecutive doses) approximately 4 weeks after the documentation of CR. Prednisolone eye drops were prescribed every 4 hours until 48 hours after the last dose of cytarabine to prevent cytarabine-induced conjunctivitis. Subjects with unfavorable karyotype or an initial leukocyte count of $>25 \times 10^9$/L were considered at higher risk for early relapse and were offered bone marrow transplantation in first CR. All others were observed until relapse, at which time they were eligible for bone marrow transplantation. Subjects were followed until death or the end of follow-up (December 31, 1995).

Cytologic and Cytogenetic Studies

Immunophenotyping was performed using standardized techniques with a Profile II flow cytometer (Coulter Electronics, Hialeah, FL). Karyotype analysis

was attempted at initial presentation for all patients and analyzed according to an international system for human cytogenetic nomenclature.[21] Karyotypes were classified using the modified Chicago and complexity classification systems[22,23] and analyzed as described in previous reports.[17,24] The complexity classification was based on the detection of clonal abnormalities as follows: normal (diploid karyotype without clonal abnormalities), simple clonal abnormality (arising from a single chromosomal structural abnormality), complex clonal abnormalities (arising from two to five chromosomes), and very complex clonal abnormalities (arising from more than five chromosomes). Cytogenetic data for 42 patients (98%) were available for analysis.

Supportive Care

Patients were managed in single, high-efficiency, particulate air-filtered hospital rooms according to a standardized neutropenia protocol.[25] Patients received oral chemoprophylaxis with a fluoroquinolone and acyclovir as previously described.[12] Antifungal chemoprophylaxis was not recommended. Febrile neutropenic episodes were managed with empiric, parenteral, antibacterial and antifungal therapy according to established guidelines.[26] Platelet and packed red blood cell transfusions were administered as prophylaxis for a platelet count of $<20 \times 10^9$/L or hemoglobin of <90 g/L, respectively.

Definitions

The definitions of response were based on Cheson et al.[20] as follows: CR was defined by a bone marrow examination showing trilineage regeneration and less than 5% blast forms associated with recovery of the circulating absolute neutrophil count to 1×10^9/L and the platelet count to 100×10^9/L; partial response was defined by a bone marrow examination showing trilineage regeneration but between 5% and 25% blast forms associated with recovery of the circulating neutrophil and platelet counts as for CR, or by a bone marrow examination showing <5% blast forms and trilineage regeneration without recovery of the circulating neutrophil or platlet counts; and no response was defined by circumstances that did not fit either of these definitions. Induction death was defined by death occurring within 60 days of the first day of induction.[6]

Nonhematologic Toxicity

Diarrhea, nausea, stomatitis, esophagitis/dysphagia, and vomiting were graded according to the National Cancer Institute of Canada Modified Common Toxicity Criteria. Because these criteria provided little information about the temporal relation of toxicities, we examined the time to onset and the duration, both in days, of the worst grade of a given toxicity for each patient. The effect of the induction regimen on the functional integrity of the upper gastrointestinal epithelium was studied by serial measurements of D-xylose absorption, as described previously.[12,17]

Statistical Analysis

The data were analyzed on an intent-to-treat basis using SPSS statistical software, Version 6.1 (SPSS Inc., Chicago, IL). Categoric and continuous data were evaluated using the chi-square contingency table method and Student's t test, respectively. Time-to-event analyses were performed according to the Kaplan–Meier method.[27] Leukemia free survival (LFS) was defined from the CR date until relapse, death, or the end of follow-up. Because the times between the dates of diagnosis, trial enrollment, and first treatment were short, overall survival (OS) was defined as the period from the date of diagnosis until death or the end of follow-up. Several variables were examined for univariate correlations with the achievement of remission, LFS, and OS; these variables were pretreatment, patient-related (age, gender, and body surface area), and disease-related (FAB subtype; circulating leukocyte, leukemic cell, neutrophil and platelet counts; immunophenotype; karyotype [standard vs. poor and normal, simple, or complex vs. very complex]; serum lactate dehydrogenase; presence or absence of Auer rods; and presence or absence of myelodysplasia). Significant ($P < 0.1$) independent variables were then entered into multivariate models using stepwise logistic regression or the Cox proportional hazards regression model[28] to identify independent prognostic correlations. Analyses of variance (ANOVA) were applied to the evaluation of D-xylose absorption studies for remission induction. A P value of less than 0.05 was considered significant. All tests were two-tailed.

RESULTS

Forty-three consecutive patients were referred for treatment and considered eligible for entry into the study (Table 1). The distribution of FAB subtypes was consistent with our previous experience.[6] CD34 stem cell phenotype was documented in 63% of 40 subjects on whom data were available. Karyotypes classified by the complexity and the modified Chicago systems are shown in Tables 2 and 3, respectively. Three patients (7%) had a preceding myelodysplasia, 2 of whom had very complex karyotypes and 1 of whom had a normal diploid karyotype. Complex and very complex karyotypes were observed in 14 of 42 patients (33%).

TABLE 1
Patient and Disease Characteristics

Characteristics	No. of patients (%)
Total no. of patients	43
Age (yrs)	
Median (range)	47 (17–59)
Gender	
Male:female	23:20
FAB subtype	
M0	4 (9%)
M1	3 (7%)
M2	16 (37%)
M3	6 (14%)
M4	6 (14%)
M5	6 (14%)
M6	1 (2%)
RAEB-t	1 (2%)
Hematologic data at diagnosis, median (range)	
Leukocytes, $\times 10^9$/L	8 (0.6–226.8)
Absolute neutrophils, $\times 10^9$/L	0.6 (0–28.9)
Hemoglobin, g/L	81 (41–129)
Platelets, $\times 10^9$/L	40 (9–341)
Peripheral blasts, $\times 10^9$/L	2 (0–210.9)
Bone marrow blasts, %	74 (31.2–97.4)
CD34 Stem cell phenotype, n[a]	
Present	25
Absent	15
Duration of neutropenia, median days	
$<0.1 \times 10^9$/L	18
$0.1–0.499 \times 10^9$/L	5
$0.5–0.999 \times 10^9$/L	2
Time bone marrow recovery, median days	
Neutrophils $>0.5 \times 10^9$/L	27
Last platelet transfusion	21
Blood product utilization, median units	
Packed red blood cells	11
Random donor platelets	66
D-xylose absorption studies[b], mmol/L ± SEM	
Baseline	0.83 ± 0.04
Week 1	0.58 ± 0.04
Week 2	0.48 ± 0.04
Week 3	0.35 ± 0.03
Week 4	0.74 ± 0.03

FAB: French–American–British classification of acute myeloid leukemia; SEM: standard error of mean.
[a] Immunophenotype data were available for 40 of the 43 patients.
[b] $P < 0.0001$, analysis of variance.

Outcome

The outcomes for all 43 patients are illustrated in Figure 1. Overall, 29 (67%; 95% confidence interval [CI], 48–82%) of the 43 patients achieved CR at a median of 29 days (range, 25–49 days), all with a single course of therapy. One (2%) had a partial response, 7 (16%) had no response, and 6 (14%) died during the induction period (3 of refractory leukemia, 2 of infection, and 1 of hemorrhage). One patient who achieved a partial response received a second induction course but failed to achieve a remission, refused further therapy, and subsequently died of refractory leukemia and sepsis. Seven patients who failed to achieve CR received high dose cytarabine–based salvage therapy. Although 2 of them achieved CR, all subsequently died of refractory leukemia.

Outcomes according to karyotype classification are shown in Tables 2 and 3. Only 2 of 8 patients (25%) with very complex karyotypes achieved remission, compared with 27 of 34 (79%) with normal, simple, or complex karyotypes ($P = 0.01$). Karyotype complexity (normal, simple, or complex vs. very complex) was the strongest predictor of remission in a stepwise multiple logistic regression model (OR, 22.3; 95% CI, 2.4–216.7; $P = 0.008$). CR was achieved by 3 of 7 patients (43%) with abnormalities of chromosomes 5 or 7 and by none of 4 patients with hypodiploid or hyperdiploid karyotypes (Table 3).

OS and LFS are shown in Figure 2. The median OS for the 43 patients was 12.5 months (95% CI, 5.9–19.1). Fifty-three percent, 34%, and 15% of patients remained alive at 12, 24, and ≥36 months, respectively. Among those who achieved CR, the median LFS was 15.4 months (95%CI, 6.5–24.2), with 50% and 15% leukemia free at 12 and ≥24 months, respectively (Fig. 2). Tables 2 and 3 show the influence of karyotype classified by the complexity and modified Chicago systems, respectively, on the LFS ($P = 0.0006$, log rank test) and OS ($P = 0.001$, log rank test). The Cox proportional hazards model showed that a normal, simple, or complex karyotype at diagnosis was the strongest predictor of prolonged LFS (OR, 19.3; 95% CI, 2.7–138.9; $P = 0.003$) and OS (OR, 5.4; 95% CI, 2.1–13.9; $P = 0.0005$), respectively.

Postremission consolidation was administered to 26 (90%) of those who achieved CR (Fig. 1). Of five patients who achieved CR and underwent bone marrow transplantation in first CR after consolidation, four are relapse free and one (with a poor prognosis karyotype) relapsed and died of refractory leukemia. Of 21 patients who received the single consolidation course, 6 (29%) remain alive and well and 15 (71%) have relapsed.

Toxicities

The duration of neutropenia, time to bone marrow recovery, and blood product utilization are shown in Table 1. Table 4 details the nonhematologic toxicites, graded according to the National Cancer Institute of Canada Modified Common Toxicity Criteria. The number of patients who experienced a given toxicity as the worst grade of toxicity is given along with the duration of the toxicity and the time of onset. The cumulative incidences of the worst grades of these toxicities over the induction period are shown in Fig-

TABLE 2
Response, Leukemia Free Survival, and Overall Survival According to the Complexity Classification of Karyotype

Karyotype classification[a]	No. of subjects	Complete remission	Leukemia free survival[b] (median, mos)	Overall survival[c] (median, mos)
Normal	17	13 (76%)	15.7	12.4
46, XX [n = 10]				
46, XY [n = 7]				
Simple	11	9 (82%)	21.8	29.9
46, XX, t(15;17)(q22;q11) [n = 2]				
46, XY, t(15;17)(q22;q11) [n = 2]				
46, XY, t(15;17)(q22;q21)				
46, XX, t(4;15;17)(p16;q21;q22)				
46, XY, t(8;21)(q22;q22)				
46, XX, t(1;11)(q11;q13 or 14)				
46, XX, t(9;22)(q34;q11)				
46, XY, del(11)(p?) / 46, XY				
47, XX, +8				
Complex	6	5 (83%)	15.4	10.4
46, XY, del(1)(p3;p?) or (p13;p?), add (7)(q12), add (18)(q21), del (20)(q11)				
45, XX, dup(6)(p11;q21), −7, del (8)(q22;q24.1)				
46, XY, inv(3)(q21;q26), t(7;11)(p13;p13)				
46, XY / 46, XY, −9, + Mar / 46, XY, del (12)(p12) / 46, XY, del(9)(q22?), del (12)(p12)				
47, XY, +8, t(9;11)(p22;q23) / 46, XY				
46, XY, t(8;21)(q22;q22) / 46, idem, add (16)(p13.3) / 46, XY				
Very complex	8	2 (25%)	1.5	3.7
45–46, X, ?add (Y), −5, ?add (17), −18, −19, −20, −21, +iso (21), + 6 Mar [Cp4] / 46, XX				
43, XX, −15, −16, −17, −20, −21, +2 Mar / 43, XX, −15, −16, −17, −20, −21, −22, +3 Mar / 46, XX				
44, XY, −5, add (13)(?p13), −16, add (17)(?p11), add (18)(p11), −19, −22, +2 Mar / 44, idem, −add (13), del (13), add (13)(?p13), del (13)(q?) / 44, idem, add (12)(q24), −add (13), +13				
46, XY, t(9;22)(q34;q11) / 73, XX, t(9;22)(q34;q11), t(9;22)(q34;q11), t(9;22)(q34;q11), +1, +2, +2, +6, +6, +8, +8, +10, +10, +11, +11, +13, +13, +14, +14, +15, +15, +18, +18, +19, +19, +20, +20, +21, +21				
46, t(X;2)(q13;p21)Y, t(10;10)(p13;q11.2), −17, + Mar / 46, idem, der (8) t(8;8)(p23;q11) / 47, idem, +7, der (8) t(8;8)(p23;q11) / 47, idem, der (8) t(8;8)(p23;q11) / 46, XY				
40, X, −3, −5, −7, −8, −9, −15, −17, −18, −20, −21, −4, +6 Mar / 41, idem, +7 Mar / 42, idem, +8 Mar				
47, XY, −7, −12, −13, −17, −18, −20, −22, −del (9)(q32), t(12;20), + 7 Mar / 48, idem, +8 Mar / 49/50, idem, + multiple markers				
40–44 + multiple markers (not further characterized)				

[a] Complexity classification.[22,23]
[b] $P = 0.0006$, log rank test.
[c] $P = 0.001$, log rank test.

ure 3. Grade 3–4 toxicities for diarrhea, nausea, stomatitis, esophagitis/dysphagia, and vomiting were observed in 33%, 26%, 23%, 9%, and 2% of cases, respectively, at a median of 17, 16, 15.5, 19.5, and 21 days, respectively.

Infectious Morbidity

Infection was documented at diagnosis in 22 patients (51%). A total of 111 infections were observed in 43 patients during induction, and 36 infections were observed in 26 patients who received consolidation. During induction, bloodstream infections, microbiologically documented nonbacteremic infections, clinical infections, and unexplained fevers were observed in 21 (49%), 21 (49%), 29 (67%), and 8 patients (19%), respectively, at a median of 12, 9, 12, and 10 days, respectively. Forty-five infections (41%) were mucosa-associated. In addition, neutropenic enterocolitis and invasive fungal infection were observed 13 (30%) and 10 (23%) of 43 induction recipients, respectively. The invasive fungal infections included 7 cases of fungemia, 4 cases of hepatosplenic candidiasis, 1 case of *Aspergillus* pneumonia, and 1 case of pneumonia and enterocolitis due to *Aspergillus* species.

D-xylose Absorption Studies

Absorption of D-xylose (Table 1) was the lowest during the second and third weeks, coincident with the periods of the lowest neutrophil counts (data

TABLE 3
Response, Leukemia Free Survival and Overall Survival According to the Modified Chicago Classification of Karyotype

Karyotype classification[a]	No. of subjects	Complete remission[b]	Leukemia free survival (mos)[c]	Overall survival (mos)[d]
Normal	17	13 (76%)	15.7[e]	12.4[e]
46, XX [n = 10]				
46, XY [n = 7]				
t(8;21)	2	2 (100%)	6.03/5.67	6.93/15.87
46, XY, t(8;21)(q22;q22)				
46, XY, t(8;21)(q22;q22) / 46, idem, add (16)(p13.3) / 46, XY				
Abnormal 16	0			
t(15;17)	6	6 (100%)	21.8[e]	29.97[e]
46, XX, t(15;17)(q22;q11) [n = 2]				
46, XY, t(15;17)(q22;q11) [n = 2]				
46, XY, t(15;17)(q22;q21)				
46, XX, t(4;15;17)(p16;q21;q22)				
Abnormal 5 and/or 7	7	3 (43%)	4[e]	5.73[e]
46, XY, del(1)(p3;p?) or (p13;p?), add (7)(q12), add (18)(q21), del (20)(q11)				
45, XX, dup(6)(p11;q21), −7, del (8)(q22;q24.1)				
44, XY, −5, add (13)(?p13), −16, add (17)(?p11), add (18)(p11), −19, −22, +2 Mar / 44, idem, −add (13), del (13), add (13)(?p13), del (13)(q?) / 44, idem, add (12)(q24), −add (13), +13				
45–46, X, ?add (Y), −5, ?add (17), −18, −19, −20, −21, +iso (21), + 6 Mar [Cp4] / 46, XX				
40, X, −3, −5, −7, −8, −9, −15, −17, −17, −18, −20, −21, −4, +6 Mar / 41, idem, +7 Mar / 42, idem, +8 Mar				
47, XY, −7, −12, −13, −17, −18, −20, −22, −del (9)(q32), t(12;20), + 7 Mar / 48, idem, +8 Mar / 49/50, idem, + multiple markers				
40–44 + multiple markers (−5, −11, −13, −14, −15, −19 not further characterized)				
Abnormal 11q23	1	1 (100%)	3.93	4.87
47, XY, +8, t(9;11)(p22;q23) / 46, XY				
Pseudodiploid	5	4 (80%)	15.37[e]	17.57[e]
46, XY, inv(3)(q21;q26), t(7;11)(p13;p13)				
46, XX, t(1;11)(q11;q13 or 14)				
46, XY / 46, XY, −9, + Mar / 46, XY, del (12)(p12) / 46, XY, del(9)(q22?), del (12)(p12)				
46, XY, del(11)(p?) / 46, XY				
46, XY, del(11)(p?) / 46, XY				
46, XX, t(9;22)(q34;q11)				
Hypodiploid	1	0	—	0.97
43, XX, −15, −16, −17, −20, −21, +2 Mar / 43, XX, −15, −16, −17, −20, −21, −22, +3 Mar / 46, XX				
Hyperdiploid	3	0	—	1.57[e]
47, XX, +8 / 46, XX				
46, XY, t(9;22)(q34;q11) / 73, XX, t(9;22)(q34;q11), t(9;22)(q34;q11), +1, +2, +2, +6, +6, +8, +8, +10, +10, +11, +11, +13, +13, +14, +14, +15, +15, +18, +18, +19, +19, +20, +20, +21, +21				
46, t(X;2)(q13;p21)Y, t(10;10)(p13;q11.2), −17, + Mar / 46, idem, del (8) t(8;8)(p23;q11) / 47, idem, +7, der (8) t(8;8)(p23;q11) / 47, idem, der (8) t(8;8)(p23;q11) / 46, XY				

[a] Modified Chicago classification.[22,23]
[b] $P = 0.02$, chi-square test.
[c] $P = 0.0007$, log rank test.
[d] $P < 0.0001$, log rank test.
[e] Values are medians.

not shown), the most severe nonhematologic toxicities and the highest incidence of invasive infection. Ninety-one percent of the bloodstream infections occurred during the second and third weeks of induction. The median time from the first day of induction until abnormal D-xylose absorption tests was 14 days (95% CI, 8–20).

DISCUSSION

The purpose of this single institution pilot study was to examine the efficacy and safety of a non-cytarabine-containing combination of idarubicin, etoposide, and carboplatin for remission induction therapy of untreated acute myeloid leukemia in adults younger than 60 years. The results suggest that this regimen

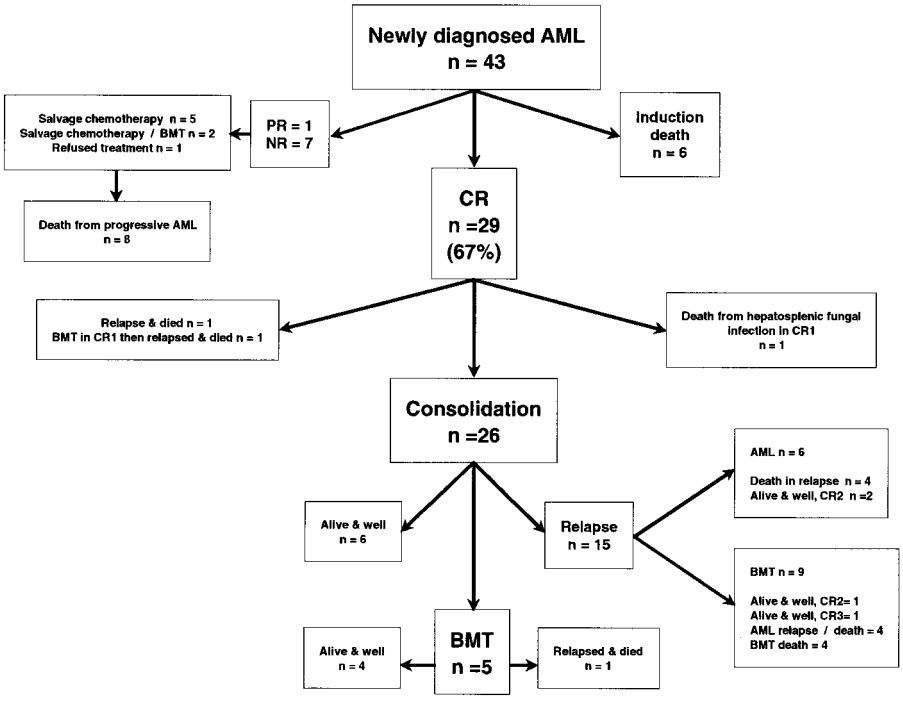

FIGURE 1. Outcomes are shown for 43 patients who underwent induction therapy with idarubicin, etoposide, and carboplatin. AML: acute myeloid leukemia; CR: complete remission; PR: partial response; NR: no response; BMT: bone marrow transplantation; CR1: first complete remission; CR2: second complete remission; CR3: third complete remission.

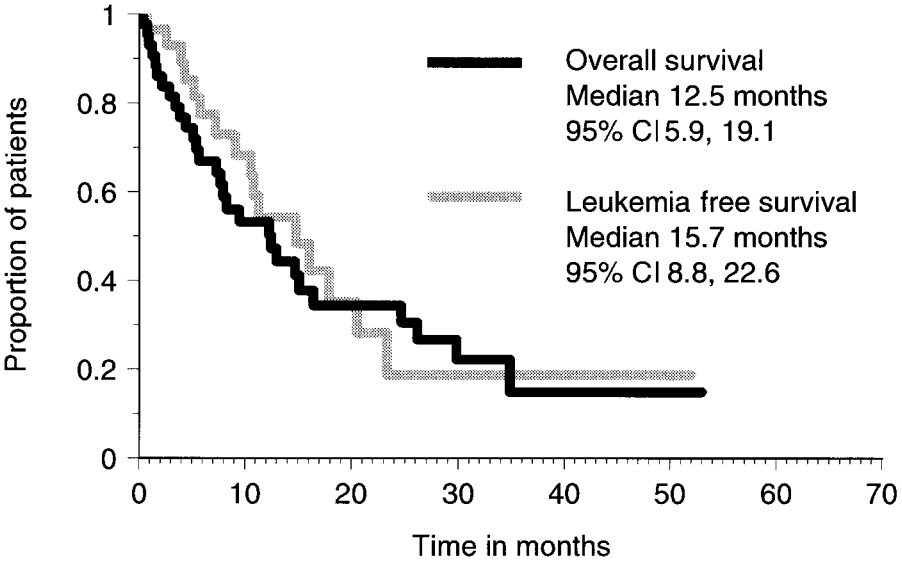

FIGURE 2. Overall survival (n = 43) and leukemia free survival (n = 29) are shown in months. CI: confidence interval.

has at least average antileukemic activity with respect to remission induction; however, intestinal mucosal damage appears to be the limiting nonhematologic toxicity. The complete remission rate, LFS, and OS observed in this study were greatly influenced by the high incidence of poor prognostic karyotypes.

The overall remission rate of 67% observed in this study seems somewhat inferior to the rates of 79–83% reported previously in clinical trials evaluating induction regimens based on idarubicin plus cytarabine administered to similar patient populations,[3–5] but it is within the ranges of 56–75% and 52–73% observed for standard "7 + 3"-type cytarabine plus daunorubicin–based[1–8] and high dose cytarabine–based[7,10,12] induction regimens, respectively. Further, a retrospective comparison of induction therapy with idarubicin, etoposide plus carboplatin, and cytarabine plus daunorubicin administered to adult AML patients younger than 60 years at this institution demonstrated similar remission rates (64% and 73%, respectively) and induction deaths (17% in both groups).[29]

Karyotype was a significant confounding bias that

TABLE 4
Nonhematologic Toxicities Observed during Remission Induction Therapy

	Grade[a]				
Toxicity	**1**	**2**	**3**	**4**	**Total**
Diarrhea					
No. of patients[b]	4	23	11	3	41 (95%)[e]
Day of onset (range)[c]	5 (2–18)	7 (1–33)	17 (9–22)	15 (14–30)	13 (1–33)
Duration, days (range)[d]	2 (2–4)	6 (1–4)	2 (1–5)	2 (1–4)	11 (1–28)
Nausea					
No. of patients[b]	19	8	11		38 (88%)[e]
Day of onset (range)[c]	7 (1–19)	14 (1–33)	16 (2–30)		9 (1–32)
Duration, days (range)[d]	3 (1–12)	5 (1–10)	5 (1–24)		6.5 (1–37)
Stomatitis					
No. of patients[b]	15	15	6	4	40 (93%)[e]
Day of onset (range)[c]	15 (1–33)	8 (2–25)	16 (3–27)	7.5 (1–22)	11 (1–35)
Duration, days (range)[d]	8 (4–21)	9 (2–18)	5 (2–14)	4 (2–12)	15 (4–46)
Esophagitis/dysphagia					
No. of patients[b]	2	10	3	1	16 (37%)[e]
Day of onset (range)[c]	10.5 (3–18)	7.5 (1–19)	22 (17–27)	6	12 (3–25)
Duration, days (range)[d]	6.5 (1–12)	8 (1–15)	1 (1–6)	17	13.5 (1–25)
Vomiting					
No. of patients[b]	11	20	1	0	32 (74%)[e]
Day of onset (range)[c]	9 (2–27)	15 (1–33)	21		11.5 (2–32)
Duration, days (range)[d]	2 (1–5)	2.5 (1–20)	2		4 (1–28)

[a] Grading is based on National Cancer Institute of Canada Modified Common Toxicity Criteria.
[b] No. of patients who experienced a given grade of toxicity as the worst grade of toxicity.
[c] Median day of onset of a given grade of toxicity, in days, relative to the first day of induction therapy.
[d] Median duration, in days, of a given grade of toxicity.
[e] Cumulative no. of patients (% of the total sample of 43 patients) who experienced any grade of a given toxicity.

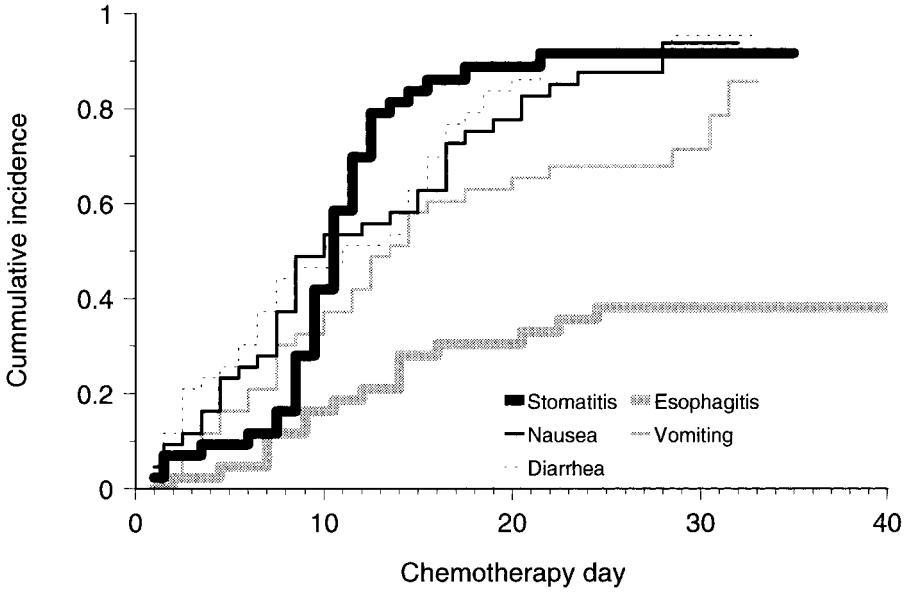

FIGURE 3. The cumulative incidence of the worst grades of diarrhea, nausea, stomatitis, esophagitis/dysphagia, and vomiting during the course of induction therapy is shown.

influenced response in our study. Complex and very complex karyotypes that have been linked to the expression of multidrug resistance[30] were observed in one-third of our study subjects, compared with a range of 6% to 21% observed in previously reported studies of patients with newly diagnosed AML.[24,31,32] This incidence is similar to that reported for elderly AML patients at our institution.[17] Only 25% of our patients with karyotypes classified as very complex achieved remission, compared with 79% of those clas-

sified as normal, simple, or complex (Table 2, $P = 0.003$). Very complex karyotype was the strongest predictor of failure to achieve remission (OR, 22.3; 95% CI, 2.3–216.7; $P = 0.008$). The studies of induction regimens based on idarubicin plus cytarabine did not report remission rates as a function of karyotype; accordingly, it was not possible to compare our results directly with the results of these studies. However, the remission rate achieved by our patients with karyotypes classified as normal, simple, or complex was comparable to that reported for subjects younger than 60 years in the studies of regimens based on idarubicin plus cytarabine. Abnormalites of chromosomes 5 or 7, which have been reported to be poor prognostic indicators, were present more often (17% of the time) in our patients compared with previous reports of 2–12%.[24,31,33,34] Three (43%) of these patients in our study achieved remission, a rate comparable to the range of 22–46% previously reported.[32,33,35]

The median LFS and OS of 15.4 months and 12.5 months, respectively, for patients who received idarubicin, etoposide, and carboplatin induction followed by high dose cytarabine consolidation in our study, were comparable to the ranges of 9.4–14.3 months and 12–19.7 months for LFS and OS, respectively, reported for induction regimens based on idarubicin or daunorubicin plus cytarabine.[2–5,8,10,13,29] However, the percentage of patients leukemia free or alive at 4 years was only 15% in our study. This was comparable to ranges of 9–21% and 11–22% for 4-year LFS and OS, respectively, among patients younger than 65 years who received standard daunorubicin plus cytarabine induction followed by daunorubicin plus cytarabine or high dose cytarabine–based consolidation in the study of Weick et al.,[7] and it was also comparable to the ranges published as long term follow-up[36] to the idarubicin versus daunorubicin plus cytarabine induction trials.[3–5] However, our results appear inferior to those in a report by Mayer et al.,[1] in which the 4-year LFS and OS for patients younger than 60 years who received standard daunorubicin plus cytarabine induction followed by graded intensities of cytarabine-based consolidation from 100 mg/m^2/day to 6 g/m^2/day were 24–44% and 35–52%, respectively. The Australian Leukemia Study Group[10] reported 5-year disease free survival (DFS) and OS of 41% and 31%, respectively, for patients younger than 60 years who received high dose cytarabine–based induction followed by daunorubicin plus cytarabine consolidation. The Southwest Oncology Group[7] reported 4-year DFS and OS of 25–34% and 24–52%, respectively, for patients younger than 65 years who received high dose cytarabine–based induction and consolidation. Finally, we reported a 43% 3-year DFS for AML patients younger than 60 years who received high dose cytarabine postremission consolidation.[6]

As in previous reports,[3,24] karyotype was a powerful influence on survival in our study. It was difficult to compare our results to the studies of the Australian Leukemia Study Group[10] and the Southwest Oncology Group[7] because the impact of karyotype on survival was not reported in those studies. However, among patients classified as having intermediate (i.e., t(15;17) or normal diploid karyotypes) and unfavorable karyotypes (i.e., karyotypes not classified as Inv(16), t(8;21), t(15;17), or normal diploid), the Cancer and Leukemia Group B (CALGB) reported median remission durations of 13–22 months and 10–14 months, respectively, for patients who received standard daunorubicin plus cytarabine induction followed by graded doses of cytarabine for consolidation.[37] The median LFS among patients in our study similarly classified and analyzed were 15.7 months (95% CI, 6.9–24.5) and 5.2 months (95% CI, 2.3–8.2), respectively. These observations suggest that the durability of the responses obtained with idarubicin, etoposide, and carboplatin was comparable to that reported by the CALGB for patients with intermediate prognosis karyotypes, but inferior to the durability of responses reported for patients with unfavorable karyotypes. The overrepresentation of poor prognostic karyotypes in our study may partly account for some of our observations; however, a suboptimal antileukemic effect of the induction regimen, the single course of high dose cytarabine for postremission consolidation, or both could also account for the inferior 4-year LFS and OS. Many investigators have given two or more courses of postremission therapy after induction.[1,2,7,10,38] The antileukemic effect of the single course of postremission therapy in our study may have been suboptimal, thus obscuring the contribution of the induction regimen to the LFS and OS. This consideration is supported by the observation that four of the five patients who underwent bone marrow transplantation as part of the postremission treatment plan in first remission remain alive and leukemia free.

Although the duration and degree of myelosuppression and blood product utilization were similar to those in previous reports,[5,6,9,17] intestinal mucosal toxicity was the major factor limiting the tolerance and applicability of this regimen. Grade 3–4 diarrhea, nausea, stomatitis, esophagitis/dysphagia, and vomiting occurred in 33%, 26%, 23%, 9%, and 2% of our patients, respectively, compared with 0–16% for diarrhea,[3,4] 3–17% for nausea and vomiting,[3,4] and 3–10% for mucositis[3,4] with other idarubicin-based regimens. However, the median duration of Grade 3–4 toxicities was 2–5 days. Furthermore, the onset of Grade 3–4

toxicites and the greatest degrees of D-xylose malabsorption occurred during Weeks 2 and 3.

Neutropenic enterocolitis and bloodstream infections as clinical consequences of mucosal barrier disruption were observed in almost one-third and one-half of our patients, respectively, at the end of the second week of induction. These observations were coincident with the neutrophil nadir; the onset of the worst grades of diarrhea, nausea, stomatitis, esophagitis/dysphagia, and vomiting; and the greatest degrees of cytotoxic therapy–induced intestinal epithelial damage as measured by D-xylose absorption studies. Correlations between mucosal damage, particularly in recipients of high dose cytarabine–based regimens, and invasive viridans streptococcal infections or invasive fungal infections in neutropenic cancer patients have been reviewed previously.[11,12] Our observations that recipients of idarubicin, etoposide, and cytarabine experienced higher mean infection rates than recipients of cytarabine plus daunorubicin (2.38 $\pm$ 0.96 vs. 2.17 $\pm$ 0.5, respectively)[29] further supports this correlation.

In summary, the combination of idarubicin, etoposide, and carboplatin demonstrated remission induction activity as high as other reported antileukemic regimens[1–8] in patients with normal, simple, or complex karyotypes. Furthermore, this regimen offered no advantage for remission induction or LFS in patients with very complex karyotypes. Although our study was not designed to address the issue of non-cross-resistance, the similarity of antileukemic activity to standard cytarabine-based regimens might suggest cross-resistance between the regimens, a conclusion that conflicts with the experience of previous trials of non-cytarbine-based regimens used to treat relapsed or refractory AML.[14,15] Finally, the toxicity profiles demonstrated that the study regimen used as reported reached the limits of mucosal toxicity and tolerance, making it unfeasible to improve response rates by dose intensification. Although further studies of modified dose schedules and more intensive postremission therapy may overcome these toxicity and outcome problems, our experience would suggest that a definitive Phase III randomized trail comparing idarubicin, etoposide, and carboplatin with standard regimens regimens based on cytarabine plus anthracycline is likely unwarranted.

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