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ORIGINAL ARTICLE

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Treatment of acute leukemia with idarubicin, etoposide and cytarabine (IDEA). A randomized study of etoposide schedule

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Abstract *Background*: The differences in toxicity of etoposide following continuous or bolus infusion are unknown. *Methods*: We studied the schedule-dependent toxicity of high-dose etoposide when combined with high-dose cytarabine and idarubicin (IDEA) in 138 patients with acute leukemia. Four groups of patients were studied: group I, relapse; group II, secondary acute myeloid leukemia (AML); group III, de novo AML, age >60 years; and group IV, induction failure or blast crisis of myeloproliferative syndrome. Treatment for groups I–III was idarubicin 8 mg/m^2 per day days 1–3, cytarabine 2000 mg/m^2 once a day days 1–6, and etoposide 1600 mg/m^2 total dose. Group IV treatment differed by cytarabine given twice daily days 1–6. Patients were randomized to etoposide as a continuous infusion days 1–6 or as a bolus infusion over 10 h on day 7. *Results*: Continuous infusion etoposide produced significantly more oral mucositis than bolus etoposide. In groups I–III, comparing continuous and bolus etoposide, there was a median of 3 vs 0 days of grade 2 or more oral mucositis ($P < 0.0001$) and 13.5 vs 0 days of total parenteral nutrition (TPN) ($P = 0.0003$). Group IV patients had a median 7 vs 0 days of grade 2 or more oral mucositis ($P < 0.01$) and 21 vs 7 days of TPN ($P < 0.003$), respectively. There were no differences in hematologic recovery, length of hospital stay, complete remission rate or overall survival between the two etoposide schedules. Of groups I–III patients, 51% achieved complete remission, and 11% died from treatment-related complications. *Conclusion*: The toxicity profile of high-dose etoposide is schedule-dependent with prolonged exposure producing significantly more non-hematologic toxicity.

Keywords High-risk leukemia · Etoposide · Schedule dependency · Randomized

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Introduction

Etoposide is an effective agent in acute leukemia. In a large randomized study, the addition of etoposide to standard-dose cytosine arabinoside (cytarabine) and daunorubicin was found to prolong the complete remission (CR) duration and overall survival (OS) in patients under 55 years of age with de novo acute myelogenous leukemia (AML) [1]. The additional benefit of etoposide was not confirmed in another study of similar design [2]. Etoposide has been utilized as a component of conditioning regimens for allogeneic hematopoietic stem cell transplantation (HSCT) in early- and advanced-stage hematologic malignancies [3, 4, 5, 6], generally given as a short intravenous (i.v.) bolus infusion. Etoposide has also been given as a short i.v. infusion when combined with busulfan as a conditioning regimen for autologous HSCT for AML [7, 8, 9, 10].

Although etoposide is known to be useful in acute leukemia, the ideal dosing schedule is not defined. Initial studies with the murine leukemia cell line L1210 demonstrated a schedule dependency of etoposide [11]. There was an increase in cytotoxicity when the same dose of etoposide was administered over 5 days rather

than over 1 day. Randomized clinical studies in patients with lung cancer have shown inconsistent support for the hypothesis that there is increased toxicity and efficacy with prolonged etoposide exposures compared to short infusions [12, 13, 14, 15, 16]. In these studies etoposide was used at doses of 130–1500 mg/m^2. There are no reported randomized studies in which etoposide schedule dependency was evaluated in patients with hematologic malignancies. In several phase II studies, high doses of etoposide (2400 – 4200 mg/m^2) have been used given either as a bolus over 4–10 h or as a 60-h continuous infusion [3, 4, 5, 6, 7, 8, 17].

The dose limiting toxicity (DLT) of etoposide is oral mucositis. Grade 2 or greater oral mucositis occurs in 10–50% of leukemia/lymphoma patients [1, 3, 17, 18, 19, 20, 21]. This is a significant source of morbidity, often leading to the need for total parenteral nutrition (TPN) and narcotic support. It would be helpful to know if one etoposide schedule (continuous vs bolus) produces less oral mucosal toxicity. The least-toxic etoposide schedule would be preferred in protocols adding etoposide to anthracyclines and cytarabine in patients with acute leukemia if efficacy is not compromised. In this study, we combined idarubicin, etoposide and cytarabine (IDEA) as induction therapy for high-risk acute leukemia patients. We evaluated the schedule-dependency of high-dose etoposide by randomizing patients to etoposide as a continuous infusion over 6 days or as a bolus over 10 h. Our primary objective was to determine whether a difference in oral mucosal toxicity could be demonstrated between the two schedules.

Materials and methods

Eligibility

Patients aged over 16 years with a diagnosis of high-risk acute leukemia were eligible for enrollment. Enrolled patients were stratified into one of four groups. Group I comprised AML or acute lymphoblastic leukemia (ALL) in relapse, group II comprised AML with antecedent myelodysplasia (MDS) or treatment-induced AML following prior chemotherapy and/or radiotherapy, group III comprised de novo AML in patients ≥60 years of age, and group IV comprised patients with AML or ALL who had failed to achieve remission with initial induction therapy or first remission lasting less than 3 months (“primary induction failure, PIF”) or myeloproliferative disease in blast crisis (MPD-BC). The first four patients with MPD-BC were stratified into group II; subsequent patients were stratified into group IV.

Patients were required to have adequate organ function with a serum creatinine (Cr) < 2.0 mg/dl and a left ventricular ejection fraction ≥50%. All patients gave written informed consent according to guidelines of each institution’s internal review board for human research. A bone marrow aspirate and biopsy was classified by the French-American-British Cooperative group criteria [22]. Standard cytogenetic banding was carried out on the bone marrow aspirate when possible. Cytogenetics for AML were classified as unknown, favorable [t(8;21), inv(16), t(15;17), +14], unfavorable [−5 or 5q−, −7 or 7q−, inv(3), 11q23 abnormality, 17p abnormality or i(17q), 20q−, +13, t(9;22), more than abnormalities], or intermediate (normal, and all other cytogenetic abnormalities) based on the criteria of Leith et al. [23]. Cytogenetics for ALL were classified as unknown, favorable (hyperdiploidy), unfavorable [t(9;22), t(4;11), other 11q23 abnormalities, hypodiploidy, t(8;14) or other Burkitt variants], and intermediate (normal, 9p abnormality).

Treatment

Treatment for groups I–III consisted of idarubicin 8 mg/m^2 i.v. daily on days 1–3, cytarabine 2000 mg/m^2 i.v. over 2 h once daily on days 1–6 and etoposide 1600 mg/m^2 i.v. total dose. Treatment in group IV differed only in the administration of cytarabine (same dose) twice daily on days 1–6. Since group IV patients were at greater risk than group I–III patients for treatment failure, the total cytarabine dose was intensified in group IV patients. Patients were block randomized within each group to receive etoposide either by continuous i.v. infusion over 6 days (days 1–6) or as a bolus i.v. infusion over 10 h on day 7. The etoposide concentration in normal saline was 0.4 mg/ml for the continuous infusion and 0.6 mg/ml for the bolus infusion. Cytarabine doses were adjusted according to daily assessment of renal function as follows: reduced to 1000 mg/m^2 when Cr was 1.5–1.9 mg/dl and held on days when the Cr was ≥2.0 mg/dl. These adjustments were based on our observation of a higher risk of neurotoxicity when high-dose cytarabine is administered during periods of renal insufficiency [24, 25]. Cytarabine was discontinued on finding any evidence of neurotoxicity, and not resumed. The daily idarubicin dose was decreased to 4 mg/m^2 if the total bilirubin was 1.6–3.0 mg/dl and decreased to 2 mg/m^2 if the total bilirubin was > 3.0 mg/dl. The etoposide dose was not reduced for elevated bilirubin or creatinine. Patients who achieved a CR or hematologic remission and were not eligible to proceed to HSCT were eligible to receive a single course of consolidation chemotherapy identical to their induction course. Patients who relapsed after IDEA chemotherapy were permitted to enroll in the study a second time and be re-randomized.

Supportive care

Fluoromethalone ophthalmic drops were administered four times a day on days 1–8 to prevent cytarabine ocular toxicity. Intravenous vancomycin was begun when the central venous catheter was placed and discontinued when the absolute neutrophil count (ANC) reached 500/μl. Amphotericin B was given prophylactically at 0.3 mg/kg per day i.v. when the ANC was under 500/μl after the administration of cytarabine had been completed. The dose of amphotericin B was escalated for antibacterial antibiotic-refractory fever or documented or suspected fungal infection. Granulocyte colony-stimulating factor (5 μg/kg per day subcutaneously) was started on day 14 and discontinued when the ANC was > 1500/μl for 2 days. Platelet transfusions were administered prophylactically when the morning platelet count was < 20,000/μl during the first year of the study and < 15,000/μl thereafter. Packed red blood cell (PRBC) transfusions were administered to keep the hematocrit > 25%. TPN was given when the enteral caloric intake was < 25% of the patient’s estimated daily needs.

Toxicity and response

Hematologic and non-hematologic toxicities were evaluated daily by the inpatient attending physician. Non-hematologic toxicities of the mucosa, skin and liver were graded according to the University of California, San Francisco (UCSF) Bone Marrow Transplant toxicity grading scale (Table 1), which is a modification of the Bearman scale designed to assess high-dose chemotherapy toxicities [26]. CR was defined as ANC > 1000/μl, platelets > 100,000/μl, normal bone marrow morphology with < 5% blasts and normal cytogenetics with all of these parameters lasting 1 month. “Hematologic remission” was defined as attainment of the above morphologic parameters but with evidence of persistent disease only by cytogenetics. The patients with MPD-BC who achieved

Table 1 Toxicity grading scale

Toxicity	Grade			
	1	2	3	4
Oral mucosa	Erythema	Pain requiring continuous narcotics or preventing eating	Ulcerations over >25% oral surface	Airway compromise requiring intubation
Skin	Erythema	Erythema with dry desquamation	Erythema with wet desquamation or ulcers	Extensive necrosis requiring surgical debridement
Hepatic				
Total bilirubin	<3 mg/dl	3–10 mg/dl	>10 mg/dl	Encephalopathy or hepatorenal syndrome
Alkaline phosphatase	2–5 × upper limit of normal	>5–10 × upper limit of normal	>10 × upper limit of normal	

chronic phase were considered a CR. Treatment-related mortality (TRM) was any death during induction hospitalization which was not attributed to resistant acute leukemia. OS was calculated from the time of randomization until death from any cause or censored at the date of last follow-up in surviving patients [27].

Statistical evaluation

The primary endpoint of this study was to evaluate oral mucosal toxicity comparing two etoposide dosing schedules. Consolidation courses of IDEA were not considered in the evaluation of the primary endpoint. The secondary endpoint was to describe the tolerability (TRM, hematologic recovery, and other non-hematological toxicities) of this regimen. Sample size calculations were based on our previous clinical experience with a twice-daily intermediate-dose cytarabine and etoposide regimen in which patients had a median of 4 days of grade 2 or greater mucositis [28]. In this prior regimen, etoposide was administered twice daily, mimicking a continuous infusion [28]. For the purposes of this study, continuous etoposide was considered the "control" arm and bolus etoposide the "experimental" arm. We hypothesized that the duration and maximum degree of oral mucositis would be different between the two etoposide schedules, but were unsure which would produce less toxicity. The initial sample size was 17 patients per treatment arm within each stratification group to detect a minimum difference of 4 days of mucositis between the two treatment arms (either direction), with a type I error of 0.05 and a power of 0.8. Groups I–III patients were analyzed together as they all received daily cytarabine. Group IV patients were analyzed separately as they received twice-daily cytarabine. The raw data were analyzed using the Mann-Whitney *U*-test [29] and the proportions analyzed using the Chi-squared test. OS was plotted according to the method of Kaplan and Meier [30] and analyzed using the Gehan Wilcoxon test [31]. All tests were two-tailed.

Results

Patient features

From October 1993 to January 1997, 138 patients with high-risk acute leukemia were enrolled on the IDEA protocol (Table 2). Of these 138 patients, 119 were evaluable for the primary endpoint; 19 were inevaluable due to lack of adequate toxicity data. The median age of the 138 patients was 61 years (range 18–86 years). The final analysis was carried out in July 2002 with a median follow-up of survivors of 56 months (range 12–100 months). Seven patients were enrolled a second time after relapse from their initial IDEA therapy.

Table 2 Patient demographics

	Group				
	I	II	III	IV	I–IV
Number					
Continuous	17	21	16	16	70
Bolus	14	18	22	14	68
Leukemia (*n*)					
Myeloid	26	39	38	30	133
Lymphoid	5	0	0	0	5
Age (years)					
Median	47	64	68	44.5	61
Range	18–84	36–76	60–86	20–69	18–86
Cytogenetics (*n*)					
Favorable	1	0	1	0	2
Intermediate	18	6	10	8	42
Unfavorable	3	16	8	14	41
Unknown	9	17	19	8	53
Prior acute leukemia treatment (*n*)					
None	0	39	38	2	79
High-dose cytarabine	18	0	0	11	29
Autologous HSCT	5	0	0	1	6
Allogeneic HSCT	1	0	0	0	1

The majority of the 61 patients in groups I and IV had received prior acute leukemia therapy (Table 2). In relapsed patients (group I), the median duration of the previous remission was 16 months. No group II patient had received any prior acute leukemia therapy but two patients had received prior 5-azacytidine for MDS and two had secondary MDS after adjuvant chemotherapy and involved-field radiotherapy for prior solid malignancy. Cytogenetics were available in 62% of patients (85/138; Table 2). The majority had intermediate ($n=42$) or unfavorable ($n=41$) cytogenetic risk disease. Two patients had favorable cytogenetics.

Of 34 group II and III patients achieving CR ($n=29$) or hematologic remission ($n=5$) after IDEA induction, 27 (79%) received IDEA consolidation chemotherapy. The median age of the consolidated patients was 68 years (range 49–82 years). Consolidation was administered a median of 74 days (range 55–87 days) from day 1 of IDEA induction. Of the 34 group II and

III patients, 12 did not receive IDEA consolidation because of early relapse (8), toxicity from IDEA therapy (3) and refusal (1). Nineteen patients underwent HSCT after IDEA induction.

Non-hematologic toxicity

There was significantly more oral mucositis in patients randomized to continuous etoposide compared to bolus etoposide as measured by days of grade 2 or more mucositis and by maximum grade of mucositis (Table 3). In groups I–III combined, grade 2 or more mucositis occurred in 61% of patients (28/47) receiving continuous etoposide compared with 6% (3/48) receiving bolus etoposide ($P < 0.0001$). In group IV, grade 2 or more mucositis occurred in 85% of patients (11/13) receiving continuous etoposide compared to 27% (3/11) receiving bolus etoposide ($P = 0.004$). The days of TPN use and parenteral narcotic use were greater in continuous etoposide patients than in bolus etoposide patients ($P < 0.01$). Skin (data not shown) and hepatic (Table 3) toxicities were not different between the randomized etoposide schedules either in groups I–III or in group IV. There was no difference in the modification of cytarabine doses based on renal function comparing continuous etoposide patients (12/70, 17%) to bolus etoposide patients (7/68, 10%; $P = 0.3$). Cytarabine neurotoxicity occurred in one patient in each randomized treatment group. The overall TRM was 11% (12/108) in groups I–III and 13% (4/30) in group IV. The causes of TRM were infection (7), intracranial hemorrhage (2), multiorgan failure (1), respiratory failure (2), and multifactorial (4).

Hematologic recovery

Hematologic recovery was the same in all patient groups irrespective of etoposide schedule (Table 4). Group IV bolus etoposide patients took 1 week longer to achieve platelets ≥100,000/μl than groups I–III bolus etoposide patients ($P = 0.04$). There was no difference in the days of hospitalization for induction chemotherapy between patients randomized to continuous etoposide and those receiving bolus etoposide (Table 4). However, group IV

Table 4 Hematologic recovery. The values are medians (range)

Parameter	Etoposide schedule		*P* value
	Continuous	Bolus	
Neutrophils ≥1000/μl (days)			
Groups I–III	25 (16–105)	24 (20–34)	0.15
Group IV	26.5 (19–50)	26 (23–51)	0.91
Platelets ≥100,000/μl (days)			
Groups I–III	31.5 (24–74)	29 (24–104)	0.35
Group IV	38 (23–72)	38 (31–61)*	1.0
Platelet transfusions (*n*)			
Groups I–III	12.5 (4–34)	11 (3–33)	0.08
Group IV	16 (6–50)	13 (3–25)	0.21
RBC transfusions (units)			
Groups I–III	10 (2–25)	9 (3–21)	0.17
Group IV	15 (8–24)	13 (3–25)	0.59
Hospital days			
Groups I–III	31 (11–108)	29 (22–54)	0.21
Group IV	33 (26–61)	38 (27–59)**	0.62

*$P = 0.04$,**$P < 0.03$, bolus etoposide group IV vs bolus etoposide groups I–III

Table 3 Non-hematologic toxicity. The values are medians (range)

Parameter	Etoposide schedule		*P* value
	Continuous ($n = 60$)	Bolus ($n = 59$)	
Grade ≥2 mucositis (days)			
Groups I–III	3 (0–40)	0 (0–9)	< 0.0001
Group IV	7 (0–32)	0 (0–20)	0.01
Groups I–IV	4 (0–40)	0 (0–20)	< 0.0001
Maximum mucositis (grade)			
Groups I–III	2 (0–3)	0 (0–2)	< 0.0001
Group IV	2 (0–3)	1 (0–2)	0.01
Total parenteral nutrition (days)			
Groups I–III	13.5 (0–75)	0 (0–39)	0.0003
Group IV	21 (11–44)*	7 (0–23)	< 0.003
Parenteral narcotics (days)			
Groups I–III	9 (0–32)	0 (0–10)	< 0.0001
Group IV	13 (0–46)	0 (0–16)	< 0.01
Maximum total bilirubin (mg/dl)			
Groups I–III	2.0 (0.8–26.5)	1.4 (0.6–24.5)	0.30
Group IV	1.7 (1.1–19.7)	1.5 (1.1–19.7)	0.36
Maximum alkaline phosphatase (U/l)			
Groups I–III	220 (59–687)	176 (58–2550)	0.93
Group IV	341 (135–7000)	319 (99–3063)	0.61

*$P = 0.04$, continuous etoposide group IV vs continuous etoposide groups I–III
$n = 93$ for groups I–III; $n = 26$ for group IV

Table 5 Complete remission rates

Group	All patients	Cytogenetic risk category		
		Favorable and intermediate	Unfavorable	Unknown
I	16/31 (52%)	12/19 (63%)	1/3 (33%)	3/9 (33%)
II	15/39 (38%)	4/6 (67%)	6/16 (38%)	5/17 (29%)
III	24/38 (63%)	5/11 (45%)	7/8 (88%)	12/19 (63%)
I–III	55/108 (51%)	21/36 (58%)	14/27 (52%)	20/45 (32%)
IV	12/30 (40%)*	2/8 (25%)	7/14 (50%)	3/8 (38%)
All	67/138 (49%)	23/44 (52%)	21/41 (51%)	23/53 (43%)

*$P = 0.001$, group IV vs groups I–III

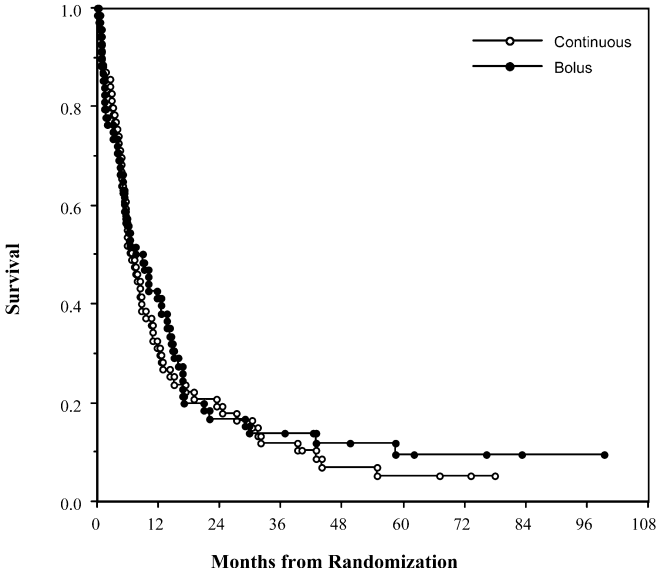

Fig. 1 Overall survival of high-risk acute leukemia patients by randomized etoposide schedule ($P = 0.9$)

bolus etoposide patients were hospitalized 1 week longer than groups I–III bolus etoposide patients ($P < 0.003$).

Treatment outcome

The overall CR rate was 49% (67/138): 51% (55/108) in groups I–III and 40% (12/30) in group IV ($P = 0.3$; Table 5). The CR rate was 50% (35/70) in patients randomized to continuous etoposide and 47% (32/68) in patients randomized to bolus etoposide ($P = 0.7$). The median OS for all patients was 7.4 months (range 0.1–100 months) with a 2-year OS of $18 \pm 3\%$. OS was not different between the two etoposide schedules ($P = 0.9$; Fig. 1).

Discussion

We demonstrated in this study that the oral mucosal toxicity of high-dose etoposide is schedule-dependent. There was significantly more oral mucositis in patients receiving the same etoposide dose as a continuous infusion than in those receiving a bolus infusion, but without any obvious difference in anti-leukemia activity. Continuous infusion etoposide resulted in more days of grade 2 or greater oral mucositis, a higher median grade of oral mucositis, more days of TPN use, and more days of parenteral narcotic use than bolus etoposide. The reduction in oral mucosal toxicity by the bolus administration of etoposide did not occur at the expense of efficacy, at least as measured by CR rate and OS. Further, there was no difference in hematologic recovery between the two etoposide schedules and no difference in other non-hematologic toxicities, such as liver and skin. These results suggest that bolus rather than continuous should be the preferred schedule of etoposide administration in patients with acute leukemia.

Our results in humans are consistent with those in the L1210 murine cell line where prolonged etoposide exposure caused greater cytotoxicity [11]. Etoposide induces single- and double-stranded DNA breaks as well as DNA-protein cross-links by inhibiting the DNA repair enzyme topoisomerase II. The DNA damage plateaus shortly after drug administration and is rapidly repaired after drug removal [32]. Prolonged etoposide exposure delays DNA repair and causes greater toxicity to normal tissues. We recommend that high-dose etoposide be given to patients with hematologic malignancy as a bolus infusion rather than as a prolonged continuous infusion in order to minimize oral mucosal toxicity.

The bolus arm of the IDEA regimen was relatively easily administered and well tolerated despite the high doses of cytarabine and etoposide. The large volume of i.v. fluids given during the 10-h bolus infusion generally required patients to receive furosemide-induced diuresis; pulmonary edema was therefore rare. Grade 2 or greater oral mucositis was 6% in groups I–III receiving once-daily high-dose cytarabine and the TRM was only 11%. In group IV patients receiving twice-daily high-dose cytarabine, grade 2 or more oral mucositis was greater (27%) than in groups I–III patients receiving once-daily high-dose cytarabine, but TRM was not different (13%). It is possible that the use of myeloid growth factors [33, 34, 35, 36, 37] and prophylactic amphotericin-B contributed to the low TRM, but the relative contributions of the etoposide schedule and the supportive care cannot be dissected.

In designing the IDEA regimen, we wished to maximize the anti-leukemia effect by delivering a high dose of etoposide while at the same time avoiding unacceptable non-hematologic toxicity. We therefore decreased the idarubicin dose by one-third of that considered a standard dose. This decision was supported by the findings of a previous study in elderly AML patients in which 8 mg/m^2 per dose of idarubicin was delivered in conjunction with cytarabine and etoposide [38]. The CR rate in that trial was 69%. Our overall CR of 49% is consistent with other regimens in the setting of high-risk acute leukemia patients (elderly, relapsed, secondary etiology, and unfavorable chromosomal abnormalities) in which the CR rate ranges from 34% to 69% [23, 36,

37, 38, 39, 40, 41, 42, 43, 44, 45]. We are continuing to explore the use of the IDEA regimen in this same patient population with an increase in the current daily idarubicin dose from 8 mg/m^2 to 12 mg/m^2 to determine if the anthracycline dose can be escalated with acceptable non-hematologic toxicity.

In summary, we provide strong evidence that the toxicity profile of high-dose etoposide is schedule-dependent. A prolonged etoposide infusion produced significantly more oral mucosal toxicity than a shorter bolus infusion of the same dose. Etoposide schedule should be taken into consideration when designing future regimens which incorporate etoposide. We also demonstrated that the IDEA chemotherapy regimen with the bolus administration of etoposide permits the combined delivery of high-dose cytarabine and idarubicin with a very acceptable toxicity profile, even in the elderly. With vigorous supportive care, including the use of myeloid growth factors and fungal prophylaxis, treatment-related morbidity and mortality are no greater than that seen with standard-dose cytarabine and/or etoposide regimens.

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