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Mitoxantrone as a Substitute for Daunorubicin During Induction in Newly Diagnosed Lymphoblastic Leukemia and Lymphoma

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Abstract

Background—Daunorubicin, a component of the four-drug induction chemotherapy regimen for *de novo* pediatric high-risk acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LLy), was unavailable in 2011 due to a national drug shortage. During this time, our institution substituted mitoxantrone 6.25 mg/m^2 for daunorubicin 25 mg/m^2 on induction Days 1, 8, 15, and 22. While mitoxantrone has been shown to be effective for relapsed ALL, it has not been studied in *de novo* pediatric ALL/LLy.

Procedure—We conducted a retrospective cohort study of newly diagnosed patients with ALL or LLy at our institution 1/2009–4/2013 to compare induction toxicity and response of patients treated with mitoxantrone versus daunorubicin.

Results—Eleven patients received mitoxantrone, 121 patients received daunorubicin. Induction toxicities including deaths, intensive care unit admissions, fever, bacteremia, and invasive fungal disease were similar for the two groups. Mean number of days hospitalized during induction was also similar (mitoxantrone 9.7 days vs. daunorubicin 11.2 days, P =0.60). Minimal residual disease prevalence at the end of induction was not significantly different (mitoxantrone 33.3% vs. daunorubicin 23.0%, P =0.44). The only significant difference between the groups was that a higher proportion of patients who received mitoxantrone had consolidation delayed due to myelosuppression (mitoxantrone 30.0% vs. daunorubicin 6.0%, P =0.03).

Conclusion—Induction toxicity and response for new ALL/ LLy patients treated with mitoxantrone in place of daunorubicin were similar to the toxicity and response seen with conventional daunorubicin. Mitoxantrone is a reasonable replacement for dauno-rubicin in times of drug shortage.

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Additional Supporting Information may be found in the online version of this article.

Keywords

ALL; chemotherapy; drug shortage; induction; mitoxantrone; pediatric oncology

INTRODUCTION

Current induction chemotherapy regimens for pediatric high risk (HR) acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LLy) use the anthracycline daunorubicin. In 2011, daunorubicin was not available across the United States due to a national drug shortage. During this time, a memo from the Children's Oncology Group (COG) advised replacing daunorubicin with doxorubicin, idarubicin, or mitoxantrone. Data on the proper dosing as well as the toxicity and efficacy of these alternate agents for *de novo* pediatric ALL/LLy induction were limited.

Of the potential alternatives to daunorubicin, doxorubicin is most often used for *de novo* pediatric ALL/LLy, and is currently given during delayed intensification in COG protocols. *In vitro* and *in vivo* work directly comparing the anti-leukemic activity of doxorubicin and daunorubicin has yielded mixed results. Some studies suggested an advantage of doxorubicin [1,2], but other studies supported daunorubicin [3,4] or found no difference in the anti-leukemic activity of the two drugs [5,6].

CoALL 07-03 investigated the efficacy of doxorubicin versus daunorubicin in newly diagnosed children with ALL [7]. In this study, 743 patients were randomized to upfront receive one single dose of doxorubicin 30 mg/m^2, daunorubicin 30 mg/m^2, or daunorubicin 40 mg/m^2 as a prephase to a three drug induction therapy involving prednisolone, vincristine, and three doses of daunorubicin 36 mg/m^2. Treatment response as evaluated by peripheral blast percentage decline from Days 0 to 7, minimal residual disease (MRD) at Days 15 and 29, and clear nonresponse (M3 marrow) was similar in all three treatment arms. Infectious complications during induction were also not statistically different between these groups, although the data trended toward more complications in the doxorubicin-treated group. While this study does provide clinical evidence supporting doxorubicin as a reasonable substitute for daunorubicin, repeated administration of doxorubicin throughout induction may yield different results than the single prephase dose evaluated in CoALL 07-03.

Idarubicin and the anthracenedione mitoxantrone have not been routinely used in newly diagnosed patients with ALL/LLy. Instead, these agents have been more thoroughly studied in patients with relapsed ALL [8–12]. The recent ALL R3 trial randomized 216 pediatric patients in first ALL relapse to receive either mitoxantrone or idarubicin at the start of induction [13]. This randomization was stopped prematurely because mitoxantrone-treated patients had significantly better progression-free (3-year 64.6% vs. 36.9%) and overall survival (3-year 69.0% vs. 45.2%). Grade 3 or higher toxicities during induction were significantly more common in the idarubicin-treated patients, however, the survival benefit of mitoxantrone was attributed to a reduced risk of disease-related events rather than toxicity. Given these results that support the use of mitoxantrone for relapsed pediatric ALL, it is reasonable to evaluate the use of mitoxantrone in the setting of *de novo* ALL.

In vitro and *in vivo* studies comparing mitoxantrone and daunorubicin suggest that mitoxantrone may be equally or more effective for *de novo* ALL. Kaspers et al. [5] investigated the cytotoxicity of various drugs in untreated pediatric ALL samples and found similar anti-leukemic activity for mitoxantrone and daunorubicin with the exception of T-ALL in which mitoxantrone was superior. Fujimoto and Ogawa [14], using a murine leukemia model, found that mitoxantrone-treated mice had significantly improved survival compared to those treated with daunorubicin.

During the local daunorubicin shortage in 2011, Children's Healthcare of Atlanta (CHOA) substituted mitoxantrone for daunorubicin with a 1:4 dose substitution for all newly diagnosed patients with HR-ALL/LLy. Here we describe the induction toxicity and response of these *de novo* ALL/LLy patients during the shortage treated with mitoxantrone compared with similar patients who received the standard daunorubicin for induction.

PATIENTS AND METHODS

All patients with newly diagnosed HR-ALL and LLy treated at our institution between January 2009 and April 2013 were identified. Patients included for analysis were treated with four-drug induction chemotherapy regimens involving a corticosteroid (dexamethasone 10 mg/m^2 Days 1–14 or prednisone 60 mg/m^2 Days 1–28), vincristine (1.5 mg/m^2 on Days 1, 8, 15, 22), pegaspargase (2,500 IU/m^2 Day 4), and either daunorubicin 25 mg/m^2 or mitoxantrone 6.25 mg/m^2 on Days 1, 8, 15, and 22. Patients who did not receive all of their induction therapy at our institution were excluded.

Patient baseline clinical information, toxicities, and treatment response were obtained via retrospective chart review. All toxicities that occurred from the start of induction (Day 1) until the start of consolidation (Day 36 or later if consolidation was delayed) were recorded. Length of hospitalization during induction was defined as the cumulative total days in the hospital from the start of induction until the start of consolidation. Day 29 MRD treatment response was determined from bone marrow samples by flow cytometry and classified as positive if >0.01% for B-ALL/LLy patients and >0.1% for T-ALL/LLy patients. End-induction myelosuppression was evaluated by Day 36 absolute neutrophil count (ANC) and platelet count (Plt); however, only patients who had a complete blood count (CBC) obtained on Days 34–38 were included in this analysis.

Statistical analysis was performed using GraphPad Prism version 6.02 for Windows, GraphPad Software (La Jolla, CA), www.graphpad.com. Statistical differences between study groups were assessed by a Fisher's exact test for categorical variables and a two-tailed *t*-test for continuous variables. CHOA institutional review board approved the review of patients' medical records.

RESULTS

A total of 133 patients with newly diagnosed HR-ALL or LLy treated with a four-drug chemotherapy induction regimen were identified. Eleven patients who began induction between August 2, 2011 and October 21, 2011 received mitoxantrone throughout induction due to the daunorubicin shortage. A single patient who was diagnosed just before our drug

shortage received both daunorubicin and mitoxantrone during induction; this patient was excluded from analysis. The remaining 121 patients received daunorubicin throughout induction, 84 patients before the start of the drug shortage, and 37 patients after.

The 121 patients treated with daunorubicin were first analyzed separately to determine if any statistical differences existed between patients treated with daunorubicin before and after the local shortage (August 2, 2011). Baseline clinical demographics and induction outcomes were similar for the daunorubicin patients treated pre- and post-drug shortage (Supplemental Tables SI–SII) so these two groups were combined as a single daunorubicin group for comparison with the mitoxantrone group. While not statistically significant, more patients in the more recent cohort were MRD positive at the end of induction (pre-shortage 17.9% vs. post-shortage 34.3%, P =0.09).

Patient sex, disease immunophenotype, initial white blood cell count (WBC), and induction steroid usage were similar for the daunorubicin and mitoxantrone groups (Table I). Patients in the mitoxantrone group were older; however, this difference was not statistically significant. The percentage of patients initially admitted to the intensive care unit (ICU), a marker of initial patient clinical severity independent of induction therapy, was similar for the two groups.

Induction toxicities including death, ICU admission, fever, bacteremia, and the use of an intravenous antifungal therapy for suspected invasive fungal disease were similar for both groups (Table II). The mean number of days hospitalized during induction was also not statistically different, 9.7 days for the mitoxantrone-treated patients and 11.2 days for the daunorubicin-treated patients (P =0.60).

The only significant difference between the groups was that a higher proportion of mitoxantrone-treated patients had a delay in beginning consolidation chemotherapy due to myelosuppression compared to daunorubicin-treated patients (30.0% vs. 6.0%, P =0.03). Mean ANC on Day 36 was lower for the mitoxantrone group compared to the daunorubicin group (1,390/μl vs. 2,176/μl); however, this difference was not statistically significant (P =0.19). The total percentage of patients who had consolidation delayed for any medical reason (including myelosuppression) was not statistically different between the groups. When just considering these patients who had consolidation delayed, the mean number of days delayed was not statistically different for each treatment group (mitoxantrone 6.3 days vs. daunorubicin 7.9 days, P =0.39).

No patient in the mitoxantrone group and only one patient in the daunorubicin group was an induction failure (M3 bone marrow at Day 29). The proportion of patients in the mitoxantrone and daunorubicin groups who were MRD positive at the end of induction was not statistically different (mitoxantrone 3/9 [33.3%] vs. daunorubicin 26/113 [23.0%], P =0.44).

In an effort to obtain more homogenous patient groups and minimize confounding variables, data analysis was also performed on only the B-ALL patients treated with prednisone. This sub-analysis involved 8 mitoxantrone-treated patients and 57 daunorubicin-treated patients and yielded similar results (Supplemental Table SIII). In this sub-analysis there were no

statistically significant differences between the two groups, however, more mitoxantrone-treated patients did again have a trend toward delayed consolidation due to myelosuppression (14.3% vs. 0%, P =0.11).

Table III provides additional clinical information on each of the mitoxantrone-treated patients. With a median follow-up of 22.5 months, the current event-free survival (EFS) of this group is 72.7% (8/11) and overall survival (OS) is 81.8% (9/11). In comparison, with a median follow-up of 31.1 months, the patients treated with daunorubicin prior to the drug shortage do not have a significantly different EFS (70/82, 85.4%, P =0.38) or OS (72/82, 87.8%, P =0.63).

DISCUSSION

The 2011 daunorubicin shortage forced oncologists across the United States to use alternative agents to treat newly diagnosed patients with HR-ALL/LLy. Many providers chose to substitute daunorubicin with doxorubicin. In the last year, a few groups have reported their experience with this substitution. Seattle Children's Hospital retrospectively compared nine patients with HR-ALL who during the daunorubicin shortage received doxorubicin at a 1:1 dose substitution with 37 patients who did receive daunorubicin [15]. The doxorubicin-treated patients had significantly more induction toxicities including increased rates of mucositis, typhlitis, and fungus. While MRD response between the two groups was not statistically different, the doxorubicin-treated group was also more likely to miss chemotherapy due to toxicity which could increase relapse risk. Similarly when evaluating adult ALL patients who received doxorubicin in place of daunorubicin during the shortage, Stanford University also reported more induction toxicities in doxorubicin-treated patients [16]. Prior studies comparing doxorubicin and daunorubicin in acute myelogenous leukemia (AML) likewise have found that doxorubicin-treated patients suffer more toxicities [17,18]. When evaluating the same dose exposure, doxorubicin is also considered to cause more long-term cardiac toxicity than daunorubicin [19].

Given data demonstrating increased toxicity with doxorubicin and the efficacy of mitoxantrone in relapsed ALL, we elected to substitute daunorubicin with mitoxantrone. Our study results demonstrate that mitoxantrone is a feasible alternative to daunorubicin for *de novo* pediatric HR-ALL/LLy. Mitoxantrone-treated patients did not suffer more infectious toxicities or have longer hospitalizations than daunorubicin-treated patients (Table II). One patient in the mitoxantrone cohort did die in induction; however, most of the other mitoxantrone-treated patients tolerated induction without major toxicity (Table III). In addition, while a greater proportion of mitoxantrone-treated patients had consolidation delayed (Table II); this delay was relatively short (4–8 days) and due to myelosuppression only. Thus, our data suggest that substituting mitoxantrone for daunorubicin has an acceptable toxicity profile.

Although our study showed a higher percentage of patients with end-induction MRD in the mitoxantrone group (mitoxantrone 3/9 [33.3%] vs. daunorubicin 26/113 [23.0%]), this difference was not statistically significant (P =0.44). It is noteworthy also that the cohort of patients treated with daunorubicin after the shortage conversely had a higher prevalence of

MRD (12/35 [34.3%]) than the mitoxantrone-treated patients. This observed trend of increasing MRD prevalence over time may reflect the evolution of better MRD detection capabilities at our institution. It is also important to emphasize that the ALL R3 trial for children with relapsed ALL found that patients treated with mitoxantrone in re-induction had significantly better overall survival compared with patients treated with idarubicin despite no difference between the groups in end-induction MRD [13]. The authors postulated that mitoxantrone may have had a beneficial effect due to a delayed cytotoxic effect. Mitoxantrone has complex pharmacokinetics which differs from daunorubicin, involving deep tissue penetration and sequestration with gradual release over weeks [20]. Mitoxantrone's unique pharmacokinetic profile thus might confound the significance of end-induction MRD. The pharmacokinetics of mitoxantrone could also explain the slower marrow recovery (increased number of patients who had consolidation delayed due to myelosuppression) found in our study.

We recognize that our study has limitations. It was conducted at a single institution and only involved a small number of patients treated with mitoxantrone. Our study had over 80% power with α =0.05 to detect a 10% versus 45% difference in the daunorubicin and mitoxantrone groups respectively, but only approximately 50% power to detect a difference of 10% versus 30%. We thus were adequately powered to only detect large differences between the groups and may have failed to detect real differences in toxicity and response that are clinically significant. We also only focused on induction, so cannot address potential benefits or toxicities that may appear later in the course of therapy related to mitoxantrone use during induction. Regarding cardiotoxicity specifically, while mitoxantrone was developed in part to reduce cardiotoxicity compared to anthracyclines, the actual risk of mitoxantrone-induced cardiotoxicity is currently not well defined [21]. Finally, while we report that the current EFS and OS is not significantly different between the mitoxantrone and the daunorubicin-treated patients, our study is not adequately powered for EFS and OS analysis. Furthermore with a median follow-up time of only approximately 2 years, the reported EFS and OS should be interpreted with caution as most patients have not even completed therapy. Despite our study limitations, we provide initial data that mitoxantrone appears to be a reasonable replacement for daunorubicin during HR-ALL/LLy induction.

Chemotherapy agents are often first proven to be clinically effective in the relapsed setting before being used to treat *de novo* disease. Given the clinical success of mitoxantrone in treating relapsed ALL, it is possible that mitoxantrone used upfront in *de novo* HR-ALL/LLy induction regimens may also improve outcomes. The prognosis of childhood ALL has dramatically changed from the 1960's with a survival rate of only about 10% to our current 5-year overall survival rate that exceeds 90% [22,23]. Much of this progress has been achieved not by new drug development, but by validating more efficacious combinations of existing chemotherapy agents. While modern oncology research is focused on developing new small molecules or immunologic therapy that specifically target cancer cells [23], it is still possible that cure rates could be further improved using already existing drugs like mitoxantrone. While this small study does not provide any evidence that mitoxantrone is superior to daunorubicin for *de novo* HR-ALL/LLy, it does suggest that

induction toxicity is similar and thus it may be safe to further investigate the use of mitoxantrone for *de novo* HR-ALL/LLy in a larger, prospective study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Sandberg J, Howsden FL, DiMarco A, et al. Comparison of the antileukemic effect in mice of adramycin with daunomycin. Cancer Chemother Rep. 1970; 54:1–7. [PubMed: 5527012]
2. Schwartz HS, Grindey GB. Adriamycin and daunorubicin: A comparison of antitumor activities and tissue uptake in mice following immunosuppression. Cancer Res. 1973; 33:1837–1844. [PubMed: 4720795]
3. Buick RN, Messner HA, Till JE, et al. Cytotoxicity of adriamycin and daunorubicin for normal and leukemia progenitor cells of man. J Natl Cancer Inst. 1979; 62:249–255. [PubMed: 310906]
4. Wang JJ, Chervinsky DS, Rosen JM, et al. Comparative biochemical studies of adriamycin and daunomycin in leukemic cells. Cancer Res. 1972; 32:511–515. [PubMed: 5061305]
5. Kaspers GL, Veerman AJ, Pieters R, et al. In vitro cytotoxicity of mitoxantrone, daunorubicin and doxorubicin in untreated childhood acute leukemia. Leukemia. 1994; 8:24–29. [PubMed: 8289494]
6. Sallan SE, Camitta BM, Frei E III, et al. Clinical and cytokinetic aspects of remission induction of childhood acute lymphoblastic leukemia (ALL): Addition of an anthracycline to vincristine and prednisone. Med Pediatr Oncol. 1977; 3:281–287. [PubMed: 284168]
7. Escherich G, Zimmermann M, Janka-Schaub G, et al. Doxorubicin or daunorubicin given upfront in a therapeutic window are equally effective in children with newly diagnosed acute lymphoblastic leukemia. A randomized comparison in trial COALL 07-03. Pediatr Blood Cancer. 2013; 60:254–257. [PubMed: 22948968]
8. Graham ML, Estrada J, Ragab AH, et al. Phase II trial of mitoxantrone in acute lymphocytic leukemia of childhood. A Pediatric Oncology Group study. Invest New Drugs. 1991; 9:263–267. [PubMed: 1783526]
9. Rosen PJ, Rankin C, Head DR, et al. A phase II study of high dose ARA-C and mitoxantrone for treatment of relapsed or refractory adult acute lymphoblastic leukemia. Leuk Res. 2000; 24:183–187. [PubMed: 10738999]
10. Wells RJ, Odom LF, Gold SH, et al. Cytosine arabinoside and mitoxantrone treatment of relapsed or refractory childhood leukemia: Initial response and relationship to multidrug resistance gene 1. Med Pediatr Oncol. 1994; 22:244–249. [PubMed: 7906380]
11. Leahey AM, Bunin NJ, Belasco JB, et al. Novel multiagent chemotherapy for bone marrow relapse of pediatric acute lymphoblastic leukemia. Med Pediatr Oncol. 2000; 34:313–318. [PubMed: 10797352]
12. Thomson B, Park JR, Felgenhauer J, et al. Toxicity and efficacy of intensive chemotherapy for children with acute lymphoblastic leukemia (ALL) after first bone marrow or extramedullary relapse. Pediatr Blood Cancer. 2004; 43:571–579. [PubMed: 15382275]
13. Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): An open-label randomised trial. Lancet. 2010; 376:2009–2017. [PubMed: 21131038]
14. Fujimoto S, Ogawa M. Antitumor activty of mitoxantrone against murine experimental tumors: Comparative analysis against various antitumor antibiotics. Cancer Chemother Pharmacol. 1982; 8:157–162. [PubMed: 7105379]

15. Gardner RA, Thomson B, Hawkins DS. Substitution with doxorubicin for daunorubicin during induction for high risk pediatric acute lymphoblastic leukemia results in increased toxicity. Pediatr Blood Cancer. 2013; 60:338–339. [PubMed: 23015453]

16. Patel S, Liedtke M, Ngo D, et al. A single-center experience of the nationwide daunorubicin shortage: Substitution with doxorubicin in adult acute lymphoblastic leukemia. Leuk Lymphoma. 2013; 54:2231–2235. [PubMed: 23383599]

17. Yates J, Glidewell O, Wiernik P, et al. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: A CALGB study. Blood. 1982; 60:454–462. [PubMed: 6953986]

18. Buckley JD, Lampkin BC, Nesbit ME, et al. Remission induction in children with acute non-lymphocytic leukemia using cytosine arabinoside and doxorubicin or daunorubicin: A report from the Childrens Cancer Study Group. Med Pediatr Oncol. 1989; 17:382–390. [PubMed: 2677628]

19. Shankar SM, Marina N, Hudson MM, et al. Monitoring for cardiovascular disease in survivors of childhood cancer: Report from the cardiovascular disease task force of the Children's Oncology Group. Pediatrics. 2008; 121:e387–e396. [PubMed: 18187811]

20. Alberts D, Peng Y, Leigh S, et al. Disposition of mitoxantrone in cancer patients. Cancer Res. 1985; 45:1879–1884. [PubMed: 3978648]

21. van Dalen EC, van der Pal HJ, Bakker PJ, et al. Cumulative incidence and risk factors of mitoxantrone-induced cardiotoxicity in children: A systematic review. Eur J Cancer. 2004; 40:643–652. [PubMed: 15010064]

22. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: A report from the Children's Oncology Group. J Clin Oncol. 2012; 30:1663–1669. [PubMed: 22412151]

23. Hunger SP, Loh ML, Whitlock JA, et al. Children's Oncology Group's 2013 blueprint for research: Acute lymphoblastic leukemia. Pediatr Blood Cancer. 2013; 60:957–963. [PubMed: 23255467]

TABLE I

Baseline Demographic and Clinical Characteristics of Mitoxantrone Versus Daunorubicin-Treated Patients

	Mitoxantrone (n =11)	Daunorubicin (n =121)	*P*-Value
Sex			1.00
Male	7 (63.6%)	78 (64.5%)	
Female	4 (36.4%)	43 (35.5%)	
Age			0.20
<10 years	2 (18.2%)	49 (40.5%)	
>10 years	9 (81.8%)	72 (59.5%)	
Mean	12.3 years	10.7 years	0.35
Disease[a]			0.34
B-ALL	8 (72.7%)	77 (63.6%)	
B-LLy	1 (9.1%)	3 (2.5%)	
T-ALL	1 (9.1%)	29 (24.0%)	
T-LLy	1 (9.1%)	11 (9.1%)	
Initial WBC ($\times 10^3/\mu l$)			0.75
<50	8 (72.7%)	73 (60.3%)	
50–100	1 (9.1%)	25 (20.7%)	
>100	2 (18.2%)	23 (19.0%)	
Mean	67.9	78.2	0.82
Admission to intensive care unit at initial presentation	3 (27.3%)	27 (22.3%)	0.71
Induction steroid[b]			0.69
Dexamethasone	2 (18.2%)	19 (15.7%)	
Prednisone	9 (81.8%)	101 (83.5%)	

[a] One patient in daunorubicin group had mixed phenotype (B- and T-cell) leukemia;

[b] One patient in daunorubicin group received both dexamethasone and prednisone during induction.

TABLE II

Induction Outcomes of Mitoxantrone Versus Daunorubicin-Treated Patients

	Mitoxantrone	Daunorubicin	*P*-Value
Death	1/11 (9.1%)	3/121 (2.5%)	0.30
Intensive care unit admission	0/11 (0%)	12/121 (9.9%)	0.60
Fever	4/11 (36.4%)	44/121 (36.4%)	1.00
Bacteremia	1/11 (9.1%)	17/121 (14.0%)	1.00
Presumed invasive fungus	1/11 (9.1%)	9/121 (7.4%)	0.59
Mean total number of days hospitalized during induction[a]	9.7	11.2	0.60
Start of consolidation delayed due to low ANC or Plt[b]	3/10 (30.0%)	7/116 (6.0%)	0.03
Start of consolidation delayed for any medical reason[b]	3/10 (30.0%)	16/116 (13.8%)	0.17
MRD positive[c]	3/9 (33.3%)	26/113 (23.0%)	0.44

[a] Patients who died during induction were excluded;

[b] Patients who died during induction or received consolidation at other institutions were excluded;

[c] Patients who died during induction or lymphoma patients with no bone marrow disease at diagnosis were excluded.

TABLE III

Clinical Information of Mitoxantrone-Treated Patients

No.	Age (years)	Diagnosis	Initial WBC (×10^3/μl)	Major induction complications	No. days consolidation delayed	End of induction MRD, %	Follow-up (months)	Current status
1	12.1	B-ALL	3.0	None	0	0.02	24.6	CR1
2	18.6	B-ALL	88.3	Fever/neutropenia, *Klebsiella pneumoniae* and *Viridans streptococcus* bacteremia	0	0	24.2	CR1
3	14.6	B-ALL, hypodiploid	2.5	Rigors with negative blood cultures (treated with antibiotics ×7 days)	0	0.12	20.4	s/p BMT, relapsed, died from disease
4	10.3	B-ALL, Ph+[a]	151.7	None	7	0	23.9	CR1
5	16.5	B-ALL	1.5	Mucositis, fever/neutropenia	0	0	23.7	CR1
6	3.9	T-ALL	463.9	Tumor lysis (treated with leukapheresis and dialysis)	4	1.6	23.1	CR1
7	4.2	T-LLy	14.6	Intubated due to tumor mass at presentation, vocal cord dysfunction, fever/neutropenia, pulmonary embolism	8	0	22.5	CR1
8	16.9	B-ALL	2.3	Port site infection	0	0	22.4	CR1
9	10.1	B-ALL, hypodiploid	3.1	None	0	0	22.2	s/p BMT, CR1
10	14.2	B-LLy	15.3	None	0	n/a	20.9	Relapsed, active disease
11	13.4	B-ALL	0.3	Hyperglycemia, fever/ neutropenia, upper extremity deep vein thrombosis, periorbital cellulitis, sinusitis, fungal lung infection, sudden death due to pulmonary hemorrhage	n/a	n/a	0.8	Died from toxicity on induction Day 26

[a]Philadelphia chromosome positive, started imatinib treatment induction Day 30.