RESEARCH COMMUNICATION

Reduced Tumor Lysis Syndrome with Low Dose Chemotherapy for Hyperleukocytic Acute Leukemia prior to Induction Therapy

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Abstract

Patients with hyperleukocytic acute leukemia (HAL) can succumb to leukostasis. In an attempt to reduce its incidence, 45 patients with newly diagnosed HAL and hyperleukocytosis were administered half the conventional dose of etoposide and cytosine arabinoside (EA: 50mg/m2 daily each) until WBC counts were significantly reduced and standard induction therapy was initiated. We retrospectively reviewed their outcomes and analyzed potential factors with a logistic regression model. The incidence of early mortality (<30days) was 4.4% (2/45). Patients who achieved complete remission with induction chemotherapy had significantly lower median WBC counts ($26x10^9$ L-1) after low dose EA treatment than the no response patients (median WBC: $65x10^9$ L-1 ($P<0.05$). Low dose EA treatment of HAL patients reduced WBC for both lymphoid and myeloid leukemic cells and can be considered for preemptive administration to HAL patients prior to the differential diagnosis of the acute leukemia. This approach warrants further studies as a cytoreduction therapy for HAL.

Keywords: Hyperleukocytic acute leukemia - etoposide/cytrarabine, adjuvant chemotherapy

Asian Pacific J Cancer Prev, **12**, 1807-1811

Introduction

Hyperleukocytic acute leukemia (HAL) is conventionally defined as leukemia with an initial white blood cell (WBC) count greater than 100×109/L. HAL occur in 5-10% of leukemia patients. This well-recognized medical emergency has a high early mortality caused by leukostasis which often involves cerebral hemorrhage and pulmonary failure (Marbello et al., 2008). Early mortality rate is approximately 20%~30% (Wang et al., 1997; Inaba et al., 2008; Marbello et al., 2008). Prompt leukocytoreduction is necessary to prevent the high incidence of HAL-related complications and early deaths. Leukocytoreduction can improve the efficacy of subsequent induction recovery therapy. Standard chemotherapeutic treatment can induce a rapid destruction of a large tumor cell mass but may lead to tumor lysis syndrome, coagulation disorders, and higher mortality. Supportive treatments have not improved the early mortality rate (Ruggiero et al., 2008). The initial high leukocyte count of 375 adult AML patients predicted the risk for death from induction therapy as a continuous variable better than that as a specific threshold (e.g. 100 x 109 cells L-1) (Greenwood et al., 2006). In contrast, acute myeloid leukemia (AML) patients with WBC counts >50 x109 L-1 had significantly lower overall survival and higher rate of early deaths than those with WBC counts <50 x109 L-1 (Oliveira et al., 2010).

Several methods are currently being used to rapidly reduce the number of white blood cells. Leukapheresis reduces WBC, but its impact on reducing early mortality and improving outcome in hyperleukocytic leukaemia is controversial (Chang et al., 2007; Haase et al., 2009). Leukapheresis often disturbs the functions of blood platelets and blood coagulation which can lead to fatal intracerebral hemorrhages. Its cost is very high and many hospitals do not have a facility (Haase et al., 2009). Thus, leukapheresis is not the ideal method.

Current chemotherapeutic methods for leukocytoreductive therapy differ in their efficacy for acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML). Hydroxyurea at the dose 3 g/m2 or 6 g/m2 can rapidly reduce the AML leukocyte counts, but not those of ALL patients (Greenwood et al., 2006; Marbello et al., 2008). Fifteen children with ALL and hyperleukocysis were treated with low dose prednisone on an escalating five day schedule and had no early mortality (Ozdemir et al., 2009). However, leukocytoreductive therapy for ALL patients appears more effective with VP (dexamethasone, vincristine) or COP (dexamethasone,

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vincristine or cyclophosphamide) (Apostolidou et al., 2007; Nau and Lewis, 2008). Thus, the choice of the most effective cytoreduction agent depends on the type of HAL and diagnosis of the type requires time-consuming flow cytometry and cytochemical staining analyses. Furthermore, these analyses require specialized equipment which is present only in a minority of hospitals in some countries. This delay in diagnosis makes an immediate choice of chemotherapeutic agent difficult. A delay also may lead to failure of leukocytoreductive treatment and decrease effectiveness of induction therapy (Ozdemir et al., 2009). Thus, elucidation of methods that reduce leukocyte counts without triggering leukostasis in either AML or ALL patients are warranted. Methods that gradually reduce high leukocyte counts may improve early survival rate. A conventional dose of etoposide or cytosine-arabinoside (100 mg/m2, 100-150 mg/m2 respectively) is commonly administered to treat acute leukemia as induction therapy (Creutzig et al., 2008; Griffin et al., 2009). Since reduction of high WBC counts is essential for HAL, oncologists at our hospital have administered approx. half the conventional dose of etoposide and cytosine arabinoside (low dose EA) as a pretreatment on the possibility that its cytoreductive capacity would be sufficient to reduce WBC counts without induction of tumor lysis syndrome associated with standard chemotherapeutic treatment. To determine whether this initial treatment with low dose etoposide and cytosine arabinoside (low dose EA) significantly reduced tumor lysis syndrome and early mortality in ALL and AML, we performed a retrospective analysis of 45 patients with HAL who presented to our department and underwent low dose EA treatment.

Materials and Methods

Patients

Leukemia patients with hyperleukocytosis and admitted from July 2007 were administered half the conventional dose of etoposide and cytosine arabinoside due to their health status and perceived tolerability, and the potential reduced cytoreductive capacity of low dose EA. Retrospective review of our institution's records from Jul 2007 to Jan 2010 identified 45 patients admitted with newly diagnosed HAL and hyperleukocytosis. Because one patient had died within 24 hours of admittance, the retrospective analysis was performed on the 44 patients (27 males and 17 females). The symptoms of leukostasis were defined as dizziness, headache, blurred vision, tinnitus, retinal hemorrhage, change in level of consciousness, and respiratory distress. Signs and symptoms of lung leukostasis were defined as hypoxemia, dyspnea with tachypnea, and interstitial infiltrates on chest radiography. Diagnosis of leukemia was based on the French–American–British (FAB) classification and confirmed by bone marrow aspiration and biopsy, flow-cytometry, and cytogenetic studies. According to the FAB classification, the patients included 30 AML and 15 Acute lymphocytic leukemia (ALL) which included 3 Philadelphia chromosome positive B-ALL, 7 Philadelphia chromosome negative B-ALL, and 5 T-ALL (Table 1). An additional 398 cases who suffered from acute leukemia without high white blood cell counts at this hospital were used as the control group. The study was approved by the Institutional Review Board of the Xi-jing Hospital.

Treatment Methods

All patients also received supportive measures like aggressive intravenous hydration with sodium bicarbonate and oral allopurinol so as to prevent or minimize tumour lysis syndrome. Before the acute leukemia subtypes were confirmed, 39 patients were treated immediately with a reduced quantity of EA (etoposide 50mg/m2 daily, cytosine-arabinoside 50mg/m2 daily□until a significant reduction or downward trend were observed in the WBC counts and sufficient improvement was detected in the patient's clinical status. The interval between low dose EA treatment and induction chemotherapy varied among patients and was generally 3 to 7 days. When WBC counts were below 40×10 9 L-1, the patients were treated by standard induction chemotherapy including MA (Mitoxantrone,cytosine-arabinoside), HA (Homoharringtonine, cytosine-arabinoside), DA (Daunorubicin, cytosine-arabinoside), VDCLP (Vincristine, Daunorubicin, Cyclophosphamide, L-Asparaginase, Prednisone) or idarubicine. Because the effect of Hydroxycarbamide (HU) was not sufficient, six patients were treated subsequently with low dose EA. Patients with Philadelphia chromosome-positive ALL also received imatinib in combination with chemotherapy.

Complete remission (CR) exhibited clinical evidence of untransfused hemoglobin (Hb)>100g/liter, neutrophils >1.5×109/liter, platelets >100×109/liter, and a BM morphology that showed normocellularity with <5% leukemic cells. A partial response (PR) showed similar biochemical values for CR but a persistence of 6% to 25% marrow blasts. Others were no response (NR) patients. All PR and NR patients were grouped as non-CR patients.

Statistical Analysis

The primary endpoint was early death which was defined as death before induction chemotherapy. Deaths were also noted within the first 30 days of induction therapy. Comparability of clinical characteristics between the 2 groups was tested using Fisher's exact test for categorical variables and independent two sample t test for continuous variables. Continuous data are displayed as mean ± standard deviation (SD) and categorical data are represented by number (n) and percentage (%). Moreover, Mann-Whitney-U test was applied for skewed variable and data was represented as median (inter-quartile range). Logistic regression analysis was performed to analyze the odds ratio of significant factors associated with patients who had complete remission (CR). All statistical assessments were two sided and evaluated at the 0.05 level of significance. SPSS version 15 (SPSS Inc., Chicago, IL) was used for all statistical analysis.

Results

Patient Demographics

The treatments and outcomes of 44 patients (27 males

Table 1. Patients' Demographics and Clinical Characteristics (n=44)

	Total (n=44)	CR(25)	Non-CR(19)	P-value
Age (years)[1]	36.0±14.0	34.9±14.8	37.4±13.1	0.570
Gender, n(%)[2]				0.680
Male	27 (61.4)	16 (64.0)	11 (57.9)	
Female	17 (38.6)	9 (36.0)	8 (42.1)	
Type, n (%)[2]				<0.001*
AML	29 (65.9)	10 (40.0)	19 (100.0)	
ALL	15 (34.1)	15 (60.0)	0 (0.0)	
WBC ($\times 10^9$ L^{-1})[3]				0.001*
	135 (109-91)	113 (108-45)	182 (117-229)	
Hb (g/L)[3]	74 (62-80)	78 (68-81)	62 (56-77)	0.003*
Platelet count[4]	43 (30-66)	65 (41-74)	34 (18-39)	<0.001*
Neurological manifestations, n (%)[2]	14 (31.8)	6 (24.0)	8 (42.1)	0.327
Blurred, n (%)[2]	4 (9.1)	0 (0.0)	4 (21.1)	0.029*
Therapy, n (%)[2]				
DA	20 (45.4)	7 (28.0)	13 (68.4)	0.008*
MA	8 (18.2)	3 (12.0)	5 (26.3)	0.223
HA	3 (6.8)	2 (8.0)	1 (5.3)	1.000
VDCLP	15 (34.1)	15 (60.0)	0 (0.0)	<0.001*

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; DA, Daunorubicin, cytosine-arabinoside; MA, Mitoxantrone, cytosine-arabinoside; HA, Homoharringtonine, cytosine-arabinoside; VDCLP, Vincristine, Daunorubicin, Cyclophosphamide, L-Asparaginase, Prednisone; CR, complete remission; PR, partial response; NR, non-response P-values were based on [1]independent two sample t test; [2]Fisher's exact test or [3]Mann-Whitney U test. Data are represented as [1]mean ±standard deviation; [2]number (percentage) or [3]median (inter-quartile range); [4]($\times 10^9$ L^{-1})[3]

and 17 females) who had been newly diagnosed with HAL and hyperleukocytosis and were admitted to our institution from July 2007 to January 2010 were retrospectively reviewed. The incidence of HAL in our leukemic patient population was 11.3%. The 29 AML (65.9%) and 15 ALL (34.1%; 3 Philadelphia chromosome positive B-ALL, 7 Philadelphia chromosome negative B-ALL, 5 T-ALL) (Table 1) had an average age of 36.02 ± 14.01 years (range from 11 to 68 years). Fourteen patients had neurological manifestations (31.8%) and 4 patients exhibited blurred vision (9.1%).

Reduction of Hyperleukocytosis

These 45 HAL patients received low dose EA therapy immediately upon admission and the therapy and monitoring continued until their WBC of <40 x 10^9/L remained stable. The mean reduction in white blood cell count achieved by low dose EA in the 44 HAL patients was 30% on first day, 50% on second day and 76% on third day. The following clinical symptoms of hyperleukocytosis markedly improved after cytoreduction: evidence of bleeding, hepatosplenomegaly, infection, features of cardiovascular (heart failure and myocardial infarction), meningeal leukemia, and other extramedullary leukemic infiltration (leukemia cutis, chloromas, or gingival hypertrophy). Fifteen patients (9 AML and 6 ALL) with neurological manifestations and 4 patients (2 M5 and 2 M4) with blurred vision and eyeground hemorrhage detected by the fundus examination demonstrated significant symptomatic improvements as the WBC count was reduced. Severe pulmonary infections initially complicated HAL in 4 AML patients, but they didn't exacerbate during treatment with low dose EA. Three patients showed marked progress when the WBC count was reduced. One patient whose WBC count was above 400×10^9/L died in the hospital within 24 hours because of cerebral hemorrhage: the death was not considered to be related with the treatment of low dose EA. The 44 remaining patients showed no evidence of tumor lysis syndrome and no procedure-related adverse events. The treatment was well tolerated.

Induction Chemotherapy

The percent of AML and ALL patients who died during the first 30 days of induction chemotherapy were 3.4% (1/29) and 0% (0/15), respectively. Patients who achieved CR with low dose EA followed by induction chemotherapy had significantly different levels of WBC, Hb and platelet levels at baseline than the non-CR had (P<0.05). The non-CR patients (which included 13 patients (29.5%) with a partial response) had significantly higher incidence of blurred vision (Table 1). Twenty-five patients (56.8%) achieved CR after standard induction chemotherapy, such as DA (45.4%), MA (18.2%), HA (6.8%) and VDCLP (34.1%). One patient achieved CR after treatment with low dose EA. Thirteen PR patients (29.5%) obtained CR after the second cycle of induction therapy. Five patients achieved CR by second line chemotherapy (FLAG). CR was achieved on day 54 ± 6d in AML patients and on 48 ± 4 days in ALL patients. Six patients had NR (13.6%) after two standard chemotherapeutic cycles. Because HU treatment failed to reduce WBC sufficiently, six patients were treated subsequently with low dose EA. They received the same cytoreductive effect.

Potentially Predictive Factors

The change in WBC, Hb and platelet count before and after the EA treatment between patients who achieved CR and those without CR are represented in Figure 1. CR patients began low dose EA treatment with a median WBC of 113×10^9 L–1 ($10^9\times10^9$ L^{-1}, 145×10^9 L^{-1})) and finished with a median WBC of 26×10^9 L^{-1} (25×109 L^{-1}, 33×10^9 L^{-1}). In comparison, the non-CR patients had higher median WBC counts than CR patients both before (182×109 L^{-1}) (Table 1) and after the EA treatment (43×10^9 L^{-1}). NR patients had median WBC of 247×10^9 L^{-1} before and 65×10^9 L^{-1} after low dose EA. The percent reduction in median WBC of CR patients (76.96%) was only modestly higher than that in non-CR patients

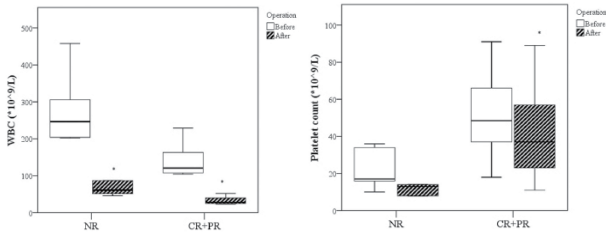

Figure 1. Change in (a) WBC, and (B) Platelet Counts Before and After Treatment *P<0.05

Table 1. Logistic Regression Model for Remission

		Univariate OR (95% C. I.)	P-value
Age (No = 44)		0.99 (0.95, 1.03)	0.561
Gender	Male	1.29 (0.38, 4.39)	0.681
	Female	1.00	
WBC change[1]		0.79 (0.61, 1.01)	0.052
Hb change[1]		1.01 (0.94, 1.08)	0.823
Platelet count change[1]		1.02 (0.99, 1.05)	0.204
Neurological manifestations			
	No	2.30 (0.63, 8.39)	0.206
	Yes	1.00	
Blurred	No	1.00	
	Yes	—	—
Type	AML	1.00	
	ALL	—	—
DA therapy	No	5.57 (1.51, 20.51)	0.010*
	Yes	1.00	
MA therapy	No	2.62 (0.54, 12.72)	0.232
	Yes	1.00	
HA therapy	No	0.69 (0.05, 7.62)	0.723
	Yes	1.00	
VDLCP therapy	No	1.00	
	Yes	—	—

[1]change between before and after the treatment

(75.46%). EA treatment reduced Hb and platelet (Figure 1b) count in patients with CR but these reductions were not significantly associated with remission (Table 2).

Risk Factors and Outcomes

During the retrospective review, the rate of responses to the low dose EA appeared to be influenced by age. Low dose EA had significantly reduced the WBC count (below 1×10^9/L) and myelosuppression in all four 60~68 years old men with AML. However, low dose EA had slowly reduced WBC count in two 10~12 year old children. These data indicated that low dose EA reduced the white blood cell more effectively in older HAL patients (>60 years old) than in younger HAL patients (<60 years old; P<0.01). However, age was not significantly associated with CR (Table 2). Table 2 shows the result of logistic regression model for patients with remission (CR). The univariate logistic regression model indicated that only one factor was significantly associated with patients who had complete remission. Patients without DA therapy were 5.57 times as likely to have had complete remission as those with DA therapy (95%C.I. =1.51 to 20.51; P=0.010)

Discussion

Efficient and tolerable methods for leukocytoreduction of hyperleukocytic leukemia can potentially reduce the early mortality rate of 20-30% (Wang et al., 1997; Inaba et al., 2008; Marbello et al., 2008). Despite the proven leukocytoreductive capability of HU, leukapheresis, and conventional dosages of chemotherapy, a high early mortality rate in HAL remains prevalent (Inaba et al., 2008; Marbello et al., 2008). In this study, we retrospectively examined the ability of low dose EA to decrease WBC counts without inducing intravascular leukostasis, cerebral hemorrhages, and pulmonary leukostasis in HAL patients. Forty four patients who had HAL were treated with low dose EA and this EA regimen reduced the WBC count by 30% on first day, 50% on second day, and 76% (median 28 x 109 L-1) on third day. This treatment was equally effective in AML and ALL patients. Only 2 of 45 patients (4%) with HAL succumbed to deaths within 30 days. These data indicated that HAL patients treated with low dose EA before induction therapy had a similar low incidence of tumor lysis syndrome as leukemia patients without HAL at our hospital. These results suggest that low dose EA treatment is the first treatment to increase the prognosis of the HAL patients to that of non-HAL leukemic patients (Wald et al., 1982; Wang et al., 1997).

Traditional leukocytoreductive measures for HAL patients include leukapheresis (Chang et al., 2007), hydroxyurea (3 g/m^2 or 6 g/m^2 and dexamethasone, vincristine or cyclophosphamide. The efficacy of these methods depend on the type of leukemia: the preferred method for treatment of AML appears to be HU (Greenwood et al., 2006; Marbello et al., 2008) whereas VP or COP (prednisolone (Ozdemir et al., 2009), dexamethasone, Vincristine or cyclophosphamide) appear to be more effective in ALL patients (Nau and Lewis, 2008). However, diagnosis of the type of HAL leukemia requires time-consuming tests which can delay treatment during a critical time; however, choosing a therapy before diagnosis risks failure of leukocytoreductive treatment and loss of opportunity for induction therapy (Ozdemir et al., 2009). The conventional dose of etoposide (100 mg/m2) or cytosine-arabinoside (100-150 mg/m^2) is used to treat acute leukemia as induction therapy and may induce a rapid destruction of a large tumor cell mass and lead to tumor lysis syndrome (Creutzig et al., 2008; Griffin et al., 2009). However, this study used one half the conventional EA dose to lower the WBC count in a slower manner. Although previous methods did not appear to reduce the incidence of leukostasis (Greenwood et al., 2006; Marbello et al., 2008), most patients tolerated the low dose EA well and did not exhibit intravascular leukostasis, cerebral hemorrhages, and pulmonary leukostasis. Their symptoms due to hyperleukocytosis markedly improved after cytoreduction by low dose EA. Forty three of forty five patients (96%) with HAL did not succumb to early mortality and received induction chemotherapy.

As a potential predictor of response to induction therapy, the WBC count at time of initiating induction chemotherapy affects its efficacy at least in one study (Oliveira et al., 2010). Improved overall survival and few early deaths were observed in AML patients with WBC counts of <50 x 10^9 L^{-1} (Oliveira et al., 2010). In agreement, this low dose EA treatment reduced the WBC to a median of 26 x 10^9/L in the patients who became CR. In contrast, the low dose EA treatment reduced the WBC counts of patients who were NR to a median of 65 x 10^9 L^{-1} which correlated with poorer overall survival and higher frequency of early deaths in AML patients with WBC of >50 x 10^9 L^{-1} (Oliveira et al., 2010). Historically, mortality in HAL from early death ranges from 20-30% with previously described treatments (Greenwood et al., 2006; Marbello et al., 2008) and is higher than the 4% observed with the low dose EA described in this study. The 2 patients who succumbed to early mortality were very

old and frail, had very fulminant HAL, and were unable to tolerate even low dose EA. The major advantage of this low dose EA treatment is its effectiveness regardless of the leukemic type. Thus, it can be initiated before the diagnosis of the type of HAL.

Remarkably, age appeared to influence the treatment of lower quantity of EA. Blood WBC counts of patients older than 60 years dropped rapidly, and continued to decline to less than 1×10^9 L^{-1} after withdrawal of chemotherapy. Hence, daily monitoring of WBC counts of low dose-EA-treated HAL patients who are > 60 yrs is necessary, and adjustment of each individual's chemotherapeutic dosage may be required. However, the WBC counts of children dropped slowly. There was not a clear continuous reaction. From our experience, the subsequent induction chemotherapy should be started when WBC count was below 40×10^9 L^{-1}: otherwise, the WBC counts increased. These data suggested that age affected the rate of WBC decline, although age was not significantly different between the responders and the nonresponders to the full therapy. One possible implication is that the EA-sensitive subset is higher in the elderly population than in the younger population.

Limitations of this study were the retrospective nature of the analysis and the small sample size. Because the WBC levels of older patients undergoing this treatment appeared to drop more rapidly than younger patients, we recommend daily monitoring of the WBC levels in all patients. In an analogous manner, reduced prednisolone has been used as a pretreatment for HAL in children with success (Ozdemir et al., 2009). Despite these limitations, the finding that HAL in both ALL and AML patients was reduced by low dose EA to WBC levels amenable to induction therapy without the often observed leukastasis suggests that this low dose EA protocol should be considered for early cytoreduction therapy of HAL.

In summary, this retrospective analysis at our hospital revealed that low dose EA treatment before induction therapy mediated effective leukocytoreduction in both lymphoid and myeloid leukemic cells. These data suggest that low dose EA could be preemptively administered to HAL patients prior to the diagnosis of the type of acute leukemia since immediate reduction in WBC count is very critical for HAL patients. Leukocytoreduction is an important initial step in the management of leukostasis and avoiding early death is essential to maintain the conditions for subsequent induction chemotherapy. This treatment is also suitable for a hospital without the equipment or training needed for leukapheresis, flow cytometry, and cytochemical staining. In this retrospective analysis of the usage of low dose EA for initial cytoreduction therapy of HAL, low dose EA appeared safe, cost-effective, and well-tolerated (no obvious side-effects). Further studies on low dose EA as an early leukocytoreduction agent in elderly, middle-age and young HAL patients are warranted

Acknowledgements

The authors declare that there is no conflict of interest with this work.

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