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Chemotherapy for Initial Induction Failures in Childhood Acute Lymphoblastic Leukemia: a Children's Oncology Group Study (POG 8764)

Michael Joyce, MD¹, Brad H. Pollock, PhD², Meenakshi Devidas, PhD³, George Buchanan, MD⁴, and Bruce Camitta, MD⁵

¹Nemours Children's Clinic, Jacksonville FL

²Department of Epidemiology and Biostatistics, and the Cancer Therapy and Research Center, University of Texas Health Sciences Center, San Antonio TX

³Department of Biostatistics, College of Public Health and Health Professions, University of Florida and the Children's Oncology Group, Gainesville FL

⁴University of Texas Southwestern Medical Center, Dallas TX

⁵MACC Fund Center for Cancer and Blood Disorders, Medical College of Wisconsin and Children's Hospital of Wisconsin, Milwaukee WI

Abstract

Children with acute lymphocytic leukemia (ALL) who fail to enter remission have a poor prognosis. In a previous study, 9 of 14 children with induction failure entered remission after teniposide (VM26) plus cytosine arabinoside (Ara-C). We attempted to confirm these results. Twenty children received teniposide (200 mg/m²/day IV) for 3 days and cytosine arabinoside (100 mg/m²/day continuous IV infusion) for 7 days. There were 3 complete and 3 partial responses. Two additional patients achieved a complete response after a second, shorter course of the same agents. Although VM26 plus Ara-C is an active combination for treatment of ALL induction failure, it does not appear as effective as in the initial report. Better treatments for this problem are needed.

Introduction

Acute lymphocytic leukemia (ALL) is the most common cancer in children. In 1960 < 5 % of children with ALL entered long term remission. Today 75 to 80 per cent of children with ALL are cured ¹. In the Children's Oncology Group (COG), risk group assignment for induction therapy for childhood ALL is based on age and white blood cell count (WBC) at diagnosis. Children ages 1.0-9.99 years with an initial WBC < 50,000 are standard risk and receive three drug induction (vincristine, prednisone and asparaginase). Children 10 or who have a WBC ≥ 50,000 are at higher risk and receive four drug induction (vincristine, prednisone, daunorubicin and asparaginase). Complete remission rates for standard and higher risk groups are 98-99%. Children who fail to enter a complete remission after induction therapy have a poor long term prognosis.^{2, 3, 5}

Address correspondence to: Bruce Camitta, MD, MACC Fund Center for Cancer and Blood Disorders, 8701 Watertown Plank Road, Milwaukee, WI 53226.

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Many agents have been utilized in the treatment of induction failure. In a pilot study, teniposide (VM26) plus cytosine arabinoside induced remission in nine of 14 patients with induction failure.² Two of those nine patients had a sustained complete remission with standard maintenance therapy (6-mercaptopurine daily and methotrexate weekly) for three years. The present study was initiated to confirm this response rate and to determine if subsequent intensive multi-agent chemotherapy regimen would result in improve long term survival.

Methods

This study enrolled 20 patients between October 8, 1991 and May 1993. Patients less than 21 years of age were eligible if their ALL had not entered remission after four weeks of initial treatment (induction failure). Informed consent was obtained according to institutional and federal requirements before initiating treatment.

Treatment is outlined in Table 1. Induction therapy consisted of three doses of teniposide (200 mg/M2/day) and seven days of cytosine arabinoside (100 mg/M2/day) by continuous infusion. Age adjusted triple intrathecal therapy⁴ (methotrexate, cytosine arabinoside and hydrocortisone) was given on day 1. Responses were based on marrow morphology (assessed locally without central review). Bone marrow aspirates were performed on day 10 to assess response. If marrow was aplastic or severely hypocellular, repeat bone marrow aspirates were performed every 7-14 days until recovery of bone marrow and definitive assessment of complete remission could be made. Marrows were assessed as M1 if less than 5% lymphoblasts, M2 if >5% and < 25% lymphoblasts, and M3 if >25% lymphoblasts. If bone marrow aspirate was M2 or M3 on day ten, patients proceeded immediately to extended induction/consolidation therapy. All patients were to receive a second course. (extended induction/consolidation) consisting of two days of teniposide and five days of cytosine arabinoside by continuous infusion.

Patients who were in complete remission at the end of extended induction/consolidation were eligible for continuation therapy. Rotating combinations of chemotherapy that included methotrexate, daunomycin, teniposide, 6-mercaptopurine and triple intrathecal therapy were administered during weeks 1-31. Weeks 31-127 maintenance therapy with daily 6-mercaptopurine and weekly methotrexate. Triple intrathecal therapy was given every twelve weeks. Antimicrobial therapy, blood products, and general supportive care were provided as was required for good patient care. Toxicities were grade by standard NCI criteria.

Results

Patient characteristics are summarized in Table 2. All patients had B-precursor ALL. The median age was 10 years (range 0.5-18 years). Median WBC at initial diagnosis of ALL was 57,000/ul (range 2,000 to 370,000/ul). Three patients were Philadelphia chromosome positive. Other chromosomal abnormalities included 11q- and t(9:15).

Response: Induction

Responses are summarized in Table 3. Three patients (#1, # 4, #15) entered complete remission and three patients (# 6, #14, #16) had a partial response to one course of teniposide plus cytarabine. Thirteen patients had a persistent M3 marrow after the initial induction treatment. The overall response (CR + PR) was 30%. One patient (10) died of septic shock and was not evaluable for response.

Response: extended induction

Fifteen of nineteen patients who were eligible received the second course of teniposide and cytarabine. One patient (#2) was too ill to continue on therapy. Two patients (#9 and #17) were removed from the study by their physicians due to lack of response to the first course of induction therapy. One patient (#15) entered complete remission following induction therapy, but was removed from the study to undergo an allogeneic bone marrow transplant. Four patients (#4, #8, #16, #20) were in complete remission following extended induction/consolidation therapy (26%). Only patient #4 had achieved complete remission following the first course of teniposide and cytarabine. Patients #8 and #20 had no response to induction but went into complete remission following a second course of teniposide and cytarabine. Patient #16 had a partial response to induction therapy and entered complete remission after the second cycle. Patients #3 and #6 had partial responses to the second course of teniposide and cytarabine: patient #3 had no response to induction therapy while patient #6 had a partial response to induction. The overall response rate of extended induction/consolidation was 40% (6/15). Seven patients had no response to the second cycle of teniposide and cytarabine and thus were not eligible to continue on the study: all of these patients had also failed to respond to the first cycle of chemotherapy. Patients #1 and #14 developed progressive disease following extended induction/consolidation therapy. Patient #1 had been in complete remission following induction and patient #1 had had a partial response.

Post-induction treatment

Four patients received continuation/maintenance chemotherapy. Patients #4, #16, and #20 relapsed at 9, 14 and 3 months respectively and died of progressive disease. Patient #8, taken off study in remission at seven months to undergo an allogeneic bone marrow transplant, died of graft vs. host disease nine months after entering the study.

Three patients (#1, #5, and #8) who were taken off study due to progressive or persistent disease underwent bone marrow transplantation (2 autologous, 1 allogeneic) after unspecified further treatment. All four were surviving at their last known follow up. One patient (#15) had an allogeneic transplant in complete remission after one course of study-specified induction. He was in complete remission more than 6 years later.

Toxicity

Toxicities (graded according to standard National Cancer Institute Common Toxicity Criteria) are summarized in Table 4. The most common toxicity was severe myelosuppression. Fever and neutropenia occurred in sixty per cent of the patients. Bacteremia occurred in 4 patients. Three patients developed fungal infections including one who died. Gastrointestinal complications were mild. Two patients developed stomatitis and two developed diarrhea. Only one patient had neurotoxicity (a short duration seizure).

Discussion

Long term disease free survival for childhood ALL has continued to improve. Despite these improvements, treatment of induction failure remains a clinical challenge. Disease-free survival for this very high risk group of patients is approximately 5-25% when treated with chemotherapy alone. Teniposide and cytarabine were used in a pilot study of 14 children with induction failure ALL.² Their regimen consisted of teniposide (165mg/M2) and cytarabine (300 mg/M2) administered twice a week for 4 weeks. Nine patients achieved complete remission (64%). The nine patients who achieved CR were given continuation therapy with oral 6-mercaptopurine and methotrexate. Four of the nine patients relapsed between 2 to 21 months of treatment. Two patients completed 30 months of treatment.

The response rate in our study was less than in Ochs' study. Although the rates are not substantially significantly different (possibly due to the small numbers of patients in both studies) other possibilities should be considered. The biologic features of the patients in both studies were similar. In Ochs et al, nine of fourteen patients had higher risk ALL and six of fourteen had a WBC >100,000/ul. In our study, fourteen of twenty patients had higher risk ALL and eight of twenty had a white blood cell count > 100,000/ul. The higher response rate in Ochs' study might be related to dose intensity. In that study, the total doses of teniposide and cytarabine were 1320 mg/M² and 2400 mg/M², respectively. In our study the total doses of teniposide and cytarabine were 600 mg/M² and 700 mg/M² respectively.

The majority of patients in our study and the Ochs study died of disease. Only two of the 14 patients in Ochs' study were long term survivors with chemotherapy alone. No patients in the current study who were treated with chemotherapy alone were long term survivors.

Four non-responders in our study remained in complete remission following further therapy that included stem cell transplantation. The use of stem cell transplantation in the treatment of ALL after induction failure has been reported by others.⁵ In that study, disease free survival was 26.5% in 52 patients treated with chemotherapy versus 56% for 25 patients treated with a matched sibling stem cell transplant.

The data in this study do not confirm the initial optimistic report of a cytosine arabinoside-etoposide regimen for treatment of induction failure in ALL. Many other chemotherapy regimens have been used to treat children and adults with induction failure/refractory ALL. These include: idarubicin and cytarabine^{6,7}; fludarabine, cytarabine and G-CSF (FLAG)⁸; mitoxantrone and cytarabine⁹; and clofarabine¹⁰ in addition to Phase I/II studies of single agents. In all of these studies, remission rates were lower than in previously untreated patients. In addition, for patients entering remission, remission duration was short. Alternative approaches for this very high risk population are needed.

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Table 1**Chemotherapy**

<u>Induction</u>		
Days 1 to 3	VM-26 200 mg/M2/ dose IV	TIT
Days 1 to 7	Ara-C 100 mg/M2/ day CI IV	
<u>Extended Induction</u>		
Days 1 to 2	VM-26 200 mg/M2/ dose IV	
Days 1 to 5	Ara-C 100 mg/M2/ day CI IV	
<u>Continuation</u>		
Weeks 1, 6, 11, 16, 21, 26	Methotrexate 200 mg/M2 IVP	TIT
	Methotrexate 800 mg/M2 IV over 24 hours	
Weeks 2, 7, 12, 17, 22, 27	Methotrexate 20 mg/M2 IM day 1	TIT
	6-Mercaptopurine 50mg/M2 P.O. daily for 7 days	
Weeks 3, 13, 23	Daunomycin 30 mg/M2 IV day 1 and day 4	TIT
	Ara-C 150 mg/M2 IV over 24 hours for three days	
Weeks 8, 18, 28	VM-26 165 mg/ M2 IV over one hour day 1 and 4	
	Ara-C 150 mg/M2 IV over 24 hours for three days	
Week s 31-127	Methotrexate 20 mg/M2 IM day 1	TIT every 12 weeks
	6-Mercaptopurine 50 mg/M2 PO daily for 7 days	

Ara-C = cytosine arabinoside

CI = continuous infusion

IV = intravenous

IVP = intravenous push

PO = oral

TIT = age adjusted triple intrathecal therapy (methotrexate, hydrocortisone, cytarabine)

VM26 = teniposide

Table 2

Patient characteristics

<u>Patient #</u>	<u>Age(yr)</u>	<u>Gender</u>	<u>WBC</u>	<u>Cytogenetics</u>
1	6/12	F	22	
2	17	M	176	t(9:15)
3	18	M	112	t(9:22)
4	5	F	29	
5	5	M	115	
6	5	M	13	
7	13	F	58	t(9:22)
8	14	M	45	
9	1	M	255	
10	2	M	16	
11	12	F	9	
12	12	M	16	t(9:22)
13	11	M	2	
14	13	M	122	
15	5	M	96	
16	15	F	45	
17	15	F	56	
18	9/12	F	100	11 q-
19	9	F	370	
20	9	M	366	

F = female, M = male; WBC/ 10^3 /ul; Bp = B-precursor

Table 3**Outcomes**

Patient Number	Post Induction status	Post extended induction status	Consolidation	Outcome
1	CR	PD	AUTO BMT	ALIVE 3+ YRS
2	NR	TOO ILL TO CONTINUE		DECEASED 7 MONTHS
3	NR	PR	PD 1 MONTH	DECEASED 13 MONTHS
4	CR	CR	RELAPSED 9 MONTHS	DECEASED 13 MONTHS
5	NR	NR	HD MTX (CR) AUTOBMT	ALIVE 3+ YEARS
6	PR	PR	MUD BMT	ALIVE 6+ YRS
7	NR	NR		DECEASED 5 WEEKS
8	NR	CR	ALLO BMT	DECEASED 9 MONTHS POST BMT GVHD
9	NR	DID NOT COMPLETE		DECEASED 8 WEEKS
10	DIED-SHOCK FUNGUS			DECEASED 1 MONTH
11	NR	NR		DECEASED 2 MONTHS
12	NR	NR		DECEASED 4 MONTHS
13	NR	NR		DECEASED 1 MONTH
14	PR	PD		DECEASED 2 YEARS
15	CR		ALLO BMT	ALIVE 1+ YRS LOST TO F/ U
16	PR	CR	RELAPSED 14 MONTHS	DECEASED 16 MONTHS
17	NR	TAKEN OFF STUDY		DECEASED 8 MONTHS
18	NR	NR		DECEASED 4 MONTHS
19	NR	NR	CYCLO DOXO, VCR ALLOBMT	DECEASED GVHD 1 YEAR
20	NR	CR	RELAPSE 3 MONTHS	DECEASED 6 MONTHS

Auto BMT = autologous bone marrow transplant; Allo BMT = allogeneic bone marrow transplant; CR = complete remission; Cyclo = cyclophosphamide; Doxo = doxorubicin; GVHD = graft vs. host disease; HDMTX = high dose methotrexate; MUD = matched unrelated donor bone marrow transplant; NR = no response; PD = progressive disease; PR = partial remission; Vcr = vincristine

Table 4

Toxicities

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ANC	4	0	0	1	15
APC	16	0	0	0	4
Platelets	3	0	0	0	16
Anemia	6	0	6	7	1
Sepsis, bacterial	16	0	0	2	2
Pneumonia, bacterial	16	0	0	3	1
Abscess	15	0	0	5	0
Other bacterial	19	0	0	0	1
Unknown etiology infections	8	0	0	12	0
Allergic reaction	19	0	1	0	0
Diffuse skin	14	0	4	0	2
Stomatitis/mucositis	18	1	0	1	0
Abdominal pain	19	0	0	1	0
Diarrhea	18	0	2	0	0
CNS	19	0	0	1	0
Fungal Infection	17	0	0	3	0

ANC = absolute neutrophil count; APC = absolute phagocyte count; CNS = central nervous system