Pediatr Blood Cancer 2014;61:431–435

Phase II Trial of Clofarabine With Topotecan, Vinorelbine, and Thiotepa in Pediatric Patients With Relapsed or Refractory Acute Leukemia

Neerav Shukla, MD,* Rachel Kobos, MD, Thomas Renaud, MD, Laurel J. Steinherz, MD, and Peter G. Steinherz, MD

Background. Outcomes for children with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) are dismal. In an effort to improve outcomes, we performed a phase I/II study of a novel clofarabine based combination regimen called TVTC. Herein, we report the response rates of patients in the phase II portion of the study. ***Procedure.*** Seventeen patients with R/R ALL, AML, or biphenotypic leukemia were enrolled. Sixteen patients were evaluable for response. Patients were treated at the maximum tolerated dose (MTD) from the phase I portion of the study (clofarabine 40 mg/m^2/day IV × 5 days, topotecan 1 mg/m^2/day IV continuous infusion × 5 days, vinorelbine 20 mg/m^2/week IV × 3 weeks, thiotepa 15 mg/m^2/day IV × 1 day). The primary endpoint was overall response rate (ORR), defined as CR or CR without platelet recovery (CRp). ***Results.*** The ORR was 69% (10 CR, 1 CRp). Among the 11 responders, 9 (82%) proceeded to hematopoietic stem cell transplantation. The most common grade 3+ non-hematologic toxicities were febrile neutropenia (82%) and transient transaminase elevation (47%). ***Conclusions.*** TVTC demonstrates significant activity in patients with R/R acute leukemia. The activity in R/R AML patients was very encouraging, with 8 of 12 (67%) patients achieving a CR/CRp. Patients with high risk *de novo* AML may benefit from incorporation of TVTC therapy into frontline treatment regimens. This regimen warrants further exploration in a larger cohort of patients with R/R leukemia. Pediatr Blood Cancer 2014;61:431–435. © 2013 Wiley Periodicals, Inc.

Key words: clofarabine; leukemia; refractory; relapsed; pediatric

INTRODUCTION

Significant progress has been made in the survival rates of both acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) over the past 4 decades. Current 5-year survival rates are approximately 85% for children with ALL, and 55% for those with AML [1,2]. Unfortunately, patients with relapsed disease have dismal outcomes [3,4]. Hematopoietic stem cell transplantation (HSCT) following a repeat remission state offers these patients the best chance at survival [4,5]. For a relapse regimen to be effective, it must be able to induce a remission state and allow for a safe and efficient transfer to HSCT.

Clofarabine (2-chloro-9-[2-deoxy-2-fluoro-β-D-arabinofluronosyl] adenine) is a deoxyadenosine analog, similar in structure to fludarabine and cladribine, but rationally modified to enhance cytotoxic activity [6]. Following cellular entry, clofarabine becomes activated by cytosolic kinases to its active form, clofarabine triphosphate [7]. A phase I study of clofarabine as a single agent in children with relapsed leukemia identified a maximum tolerated dose (MTD) of 52 mg/m^2 per day for 5 days [8]. Subsequent phase II studies at the identified MTD established activity against relapsed/refractory (R/R) ALL and AML, with overall response rates of 30% and 26%, respectively [9,10].

A number of ongoing and completed clinical trials have been designed to evaluate the feasibility, toxicity, and efficacy of clofarabine in combination with other chemotherapeutic agents [11–20]. We previously conducted a protocol for children with R/R leukemia using a reinduction regimen of topotecan, vinorelbine, thiotepa, and gemcitabine (TVTG), resulting in a 30% remission rate [21]. In an effort to improve on the results of this regimen, we created the TVTC protocol, a phase I/II protocol for children with R/R leukemia wherein we replaced gemcitabine with clofarabine. Our rationale with this approach was twofold: (1) to introduce previously unutilized chemotherapeutic agents to R/R leukemia patients in an effort to circumvent the issue of drug resistance and (2) to avoid further anthracycline exposure to minimize short-term and long-term cardiac toxicity. In the phase I portion of this study, the MTD of clofarabine was 40 mg/m^2/day for 5 days [16]. In this report, we describe the efficacy of the phase II portion of the TVTC protocol, in terms of response rates and ability to bridge patients to HSCT.

METHODS

Patient Eligibility

Patients with R/R ALL or AML were eligible for this study. Inclusion criteria required ≥20% bone marrow blasts, age between 1 and 29 years, and a Karnofsky performance status or Lansky performance status of ≥70. Patients with ALL were eligible if they met one of the following criteria: refractory to induction with 2 or more regimens; relapsed <24 months after first remission on a high-risk protocol or refractory to one standard reinduction regimen; second or greater relapse. Patients with AML were eligible if they met one of the following criteria: refractory to initial induction; any relapse. Other eligibility criteria included adequate hepatic (conjugated serum bilirubin ≤2 mg/dl, aspartate aminotransferase and alanine aminotransferase ≤4× ULN), renal (normal serum creatinine for age or creatinine clearance >60 ml/minute per 1.73 m^2), and cardiac function (echocardiogram with ejection fraction >50%). Exclusion criteria included prior clofarabine treatment, uncontrolled systemic infections, <14 days since completion of previous cytotoxic therapy (<7 days if patient demonstrated rapidly progressive disease and had recovered from

Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, New York

Grant sponsor: Sanofi/Genzyme

Conflict of interest: Neerav Shukla and Peter Steinherz have participated as members of a Genzyme advisory board and have received honoraria and research support for clinical studies.

*Correspondence to: Neerav Shukla, Memorial Sloan-Kettering Cancer Center, Box 197, 1275 York Avenue, New York, NY 10065.
E-mail: shuklan@mskcc.org

Received 23 August 2013; Accepted 29 August 2013

DOI 10.1002/pbc.24789
Published online 24 September 2013 in Wiley Online Library (wileyonlinelibrary.com).

any toxicities from that therapy), and symptomatic central nervous system (CNS) disease. Patients with asymptomatic CNS were eligible to enroll on study.

The study protocol was approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) institutional review board. Parents or guardians provided informed consent and patients 7 years or older provided assent. The study was conducted in accordance with the basic principles of the Declaration of Helsinki. This study was registered at www.clinicaltrials.gov as #NCT00462787. N.S. analyzed and interpreted the data. All authors had access to the primary clinical trial data.

Treatment

Patients were treated at the MTD based on the phase I portion of this study (Fig. 1). Topotecan was given as continuous infusion, at a dose of 1 mg/m^2/day on Days 0–4 (120 hours). Vinorelbine was given as intravenous push, over 6–10 minutes, at a dose of 20 mg/m^2, once a week, on Days 0, 7, and 14. Thiotepa was given as intravenous infusion administered at a dose of 15 mg/m^2 over 4 hours on Day 2. Clofarabine was administered intravenously, over 2 hours, at a dose of 40 mg/m^2, on 5 consecutive days, on Days 3–7. Dexamethasone was given on Day 3 as prophylaxis against capillary leak syndrome. Intrathecal cytarabine and hydrocortisone was administered to all patients within 7 days of starting therapy. Additional weekly intrathecal doses of cytarabine and hydrocortisone were given to patients with asymptomatic CNS disease. Patients underwent a BM aspirate on Day 14 of the first induction cycle, and again following count recovery.

Patients who did not exhibit disease progression or significant toxicity were eligible to continue to repeat cycles of TVTC chemotherapy until consolidation with HSCT was available.

Response and Toxicity Criteria

Efficacy of the protocol was evaluated by response rates and successful transition to HSCT. A patient's best response after one cycle of TVTC was used to determine overall response rate (ORR). ORR was defined as the sum of complete remission (CR) and complete remission excepting platelets (CRp). CR was defined as M1 marrow (<5% blasts) and recovery of peripheral counts (platelets $\geq 75 \times 10^9$/L and absolute neutrophil count $\geq 1 \times 10^9$/L). CRp was defined as CR, except for recovery of platelet count to $<75 \times 10^9$/L. Partial remission (PR) was defined as a BM with >5% and <25% blasts with recovery of platelet and neutrophil counts. Partial response with marrow aplasia (PRa) was defined as a hypocellular marrow with <5% blasts and without hematopoietic recovery.

Adverse events (AEs) were graded by the investigator using the National Cancer Institute common Terminology Criteria for AE

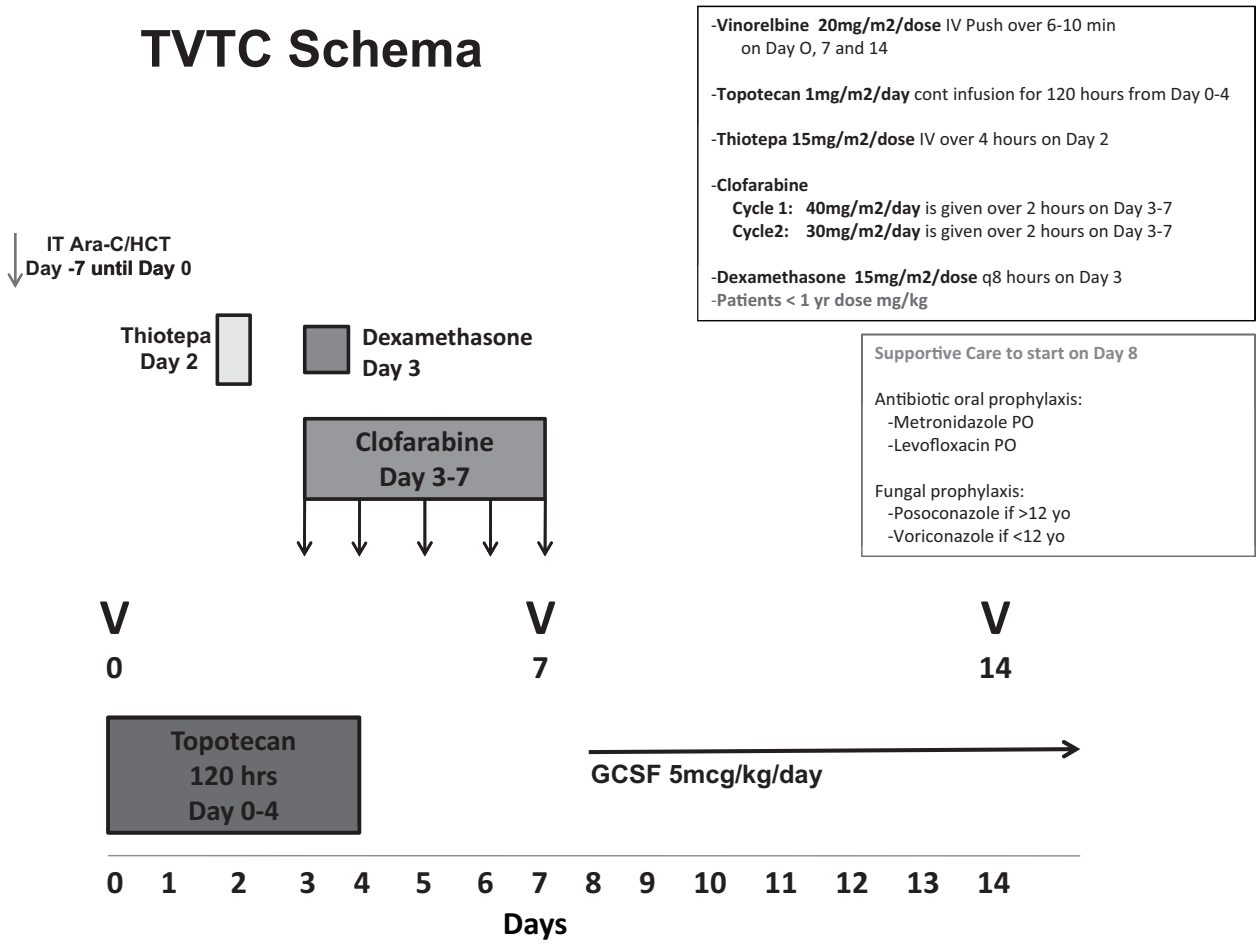

Fig. 1. Protocol Schema for TVTC.

Version 3.0. Data were monitored by the Data and Safety Monitoring Plans of MSKCC as approved by the NCI. Both the Data and Safety Monitoring Committee for Phase I and Phase II clinical trials and the Data and Safety Monitoring Board for Phase III clinical trials monitored the trial with regards to compliance, data verification, audits, and therapeutic response assessment.

Statistics

For the phase II portion of this study, descriptive statistics were performed. Qualitative data are reported in terms of absolute frequencies and percentages, and quantitative data in terms of medians with minimum and maximum values. Data analyses for patients are current as of August 2013.

RESULTS

Patients

A total of 17 patients were enrolled on the phase II portion of this trial (Table I). Twelve patients had AML, 4 patients had B-precursor ALL, and 1 patient had biphenotypic leukemia. The median age was 10 years, with a range from 8 months to 24 years. As the majority of patients had AML, most patients were previously treated with 1 prior regimen (82%). High-risk cytogenetics were found in 41% of the patients. One patient with pre-B ALL had refractory disease to three prior induction attempts, with 4.6% aberrant blasts by flow cytometric evaluation. An IRB waiver was obtained to enroll him onto the study. Because he had less than 20% blasts upon enrollment, he was not evaluable for response.

Response

Of the 16 patients evaluable for response, 10 achieved CR and 1 achieved CRp for an ORR of 69% (Table II). CR or CRp was achieved in 67% (8/12) of patients with AML, 67% (2/3) of patients with ALL, and 100% (1/1) of patients with biphenotypic leukemia. Two patients had no evidence of blasts on marrow evaluation following one cycle of TVTC, but failed to achieve hematopoietic recovery (PRa). One of these patients proceeded directly to HSCT without count recovery, and is currently alive 41+ months post-transplant.

Of the 11 patients with CR or CRp, 9 patients (82%) proceeded directly to HSCT in remission (Table III). Four of the 9 (44%) received a single cycle of TVTC; 5 of the 9 (55%) patients received 2 cycles prior to HSCT. No patients received more than 2 cycles of therapy.

The patient with refractory pre-B ALL to 3 prior regimens, with 4.6% residual disease by flow cytometry, achieved minimal residual disease negativity following TVTC. He is alive in remission for over 2 years following HSCT.

Toxicity

Sixteen (94%) patients experienced at least one grade 3 or higher non-hematologic toxicity (Table IV). Febrile neutropenia was observed in 14 (82%) of patients. Infectious etiologies of bacterial sepsis were identified in 8 (47%) patients and included *Streptococcus viridans*, *Escherichia coli*, *Vancomycin-resistant Enterococcus faecium* (VRE), *Pseudomonas aeruginosa*, *Listeria monocytogenes*, and *Coagulase-negative staphylococci*. The patient with *L. monocytogenes* sepsis also had meningitis, manifested by generalized clonic–tonic seizures.

TABLE I. Patient Demographics (n = 17)

Characteristic	No. of patients	% of patients
Age (years)		
Median	10	n/a
Range	<1–24	n/a
Sex		
Male	8	47
Female	9	53
Race		
Asian	2	12
Black	2	12
Hispanic	2	12
White	11	64
Immunophenotype		
AML	12	70
B-precursor ALL	4	24
Biphenotypic	1	6
Prior regimens		
1 regimen	14	82
2 regimens	1	6
3 regimens	2	12
Refractory to prior regimen	3	18
Prior HSCT	1	6
High risk cytogenetics		
Monosomy 7 AML	2	12

continued

Two patients achieved a complete remission following one cycle of TVTC, but were unable to receive a second cycle or proceed to HSCT due to toxicity. The first (Pt ID #7) was a 12-year-old female with relapsed FLT3 ITD positive AML who developed abdominal mucormycosis. She recovered following surgical and medical management, but relapsed during her recovery. The other was a 16-year-old male (Pt ID #8) with relapsed MLL-rearranged ALL who had severe septic shock from *P. aeruginosa* sepsis. He eventually recovered after more than a month of intensive medical management, but had a leukemic relapse before being able to transition him to HSCT.

There was one toxicity related death in this cohort of patients. He was a 25-year-old male who had a PRa following his first cycle of TVTC. After admission to the intensive care unit for VRE sepsis and severe neutropenic enterocolitis, he died of a sudden cardiac arrest 45 days after starting TVTC. Post-mortem evaluation revealed no evidence of leukemia. There were no cases of veno-occlusive disease, although only one patient on the study had a previous HSCT. Capillary leak syndrome was not observed in any patients.

DISCUSSION

This phase II study of clofarabine combined with topotecan, vinorelbine, and thiotepa was conducted to evaluate a regimen with novel agents which patients had not been previously exposed to. The two primary objectives were: (1) achieve a marrow remission and (2) successfully transition patients to HSCT. The study

TABLE II. Efficacy Data

Outcome	No. of patients	% of patients
ORR (CR + CRp)[a]	11/16	69
CR	10	63
CRp	1	6
PRa	2	12
PD	3	19
ORR by immunophenotype[a]		
AML	8/12	67
Pre-B ALL	2/3	67
Biphenotypic	1/1	100

demonstrated substantial efficacy with an ORR of 69% in patients with R/R leukemia. This response rate compares very favorably to other published combination studies using clofarabine (14–67%) [11–15,19,20]. Furthermore, the regimen proved to be tolerable in the majority of cases, as 82% of patients who achieved a CR or CRp were able to proceed directly to HSCT.

The majority of patients in the phase II portion of this study had R/R AML. This regimen proved to be highly effective in this population, with 67% achieving a CR or CRp. Furthermore, all but one of the patients who achieved a CR/CRp proceeded directly to HSCT. Two additional AML patients developed aplastic marrows with no evidence of leukemia involvement. One of those patients died of an acute cardiac arrest. The other went forward to HSCT and has been in remission for over 3 years. Only 2 of the 12 AML patients had completely refractory disease to TVTC.

Only 3 patients with pre-B ALL were evaluable for response on the phase II portion of this study. Although 2 of the 3 (67%) patients achieved a CR, a larger cohort of patients needs to be treated to evaluate the efficacy of TVTC in patients with R/R pre-B ALL. Although patients with T-cell ALL were eligible, no patients were enrolled during the phase II portion of this study.

Febrile neutropenia and infectious complications were frequently observed on this regimen. Due to the high number of infections, we later incorporated an aggressive prophylactic anti-microbial regimen for all patients. The regimen consists of levofloxacin, metronidazole, and voriconazole. Posaconazole replaced voriconazole for our older patients. Since the incorporation of this anti-microbial regimen, we have seen much fewer infectious complications, with only one of our last six patients enrolled onto the protocol having a documented bacterial or fungal infection. The remainder of the toxicity profile on this study compared favorably to other published clofarabine combination studies.

Furthermore, we have successfully administered this regimen on an outpatient basis for the majority of our patients. The topotecan infusion was usually started on a Friday, and continued for 5 days using a portable infusion pump. Patients came to our urgent care center on the following Sunday for the 4-hour infusion of thiotepa. Clofarabine was given Monday through Friday on an outpatient basis. Although the majority of patients required hospital admission for febrile neutropenia, most patients were safely able to spend a considerable portion of their therapy as outpatients.

One of the most attractive qualities of clofarabine in the treatment of relapsed or refractory pediatric AML is the lack of demonstrable cardiac toxicity. There is an increased risk of left ventricular dysfunction with cumulative doses of $\geq 300\,mg/m^2$ of doxorubicin-equivalent anthracycline dosing, with worsening deficits as the dose increases [22,23]. Current AML protocols use significant doses of anthracycline therapy for all patients. The demonstration of mitoxantrone activity in relapsed AML has led to its incorporation into *de novo* protocols, raising the anthracycline exposure even higher [24]. Current Children's Oncology Group (COG) protocols use $>400\,mg/m^2$ doxorubicin-equivalent doses of anthracyclines for children with AML. Therefore, the vast majority of relapsed patients have already reached their maximum lifetime limit of reasonable anthracycline exposure. Developing an effective clofarabine based protocol for AML patients may provide a useful alternative to further anthracycline exposure and minimize the risk of future ventricular dysfunction.

Very few phase II clofarabine based multi-agent regimens have been evaluated for efficacy in children with AML. In our study, the ORR in patients with AML was 67%. Furthermore, 7 of the 8 responders (88%) successfully transitioned to HSCT in remission. Cooper et al. [20] recently reported on the efficacy of the phase II portion of COG protocol AAML0523, which evaluated a regimen of clofarabine ($52\,mg/m^2/day \times 5$ days) combined with cytarabine ($1\,mg/m^2/day \times 5$ days) in 46 patients with R/R AML. They demonstrated an ORR of 46%, with 76% of responders proceeding

TABLE III. Characteristics of Responders (N = 11)

Patient ID	Age (years)	Sex	Immunophenotype	Cytogenetics	Best response	Cycles of TVTC	Went Directly for HSCT	Days between Day 1 of TVTC and HSCT	OS (months)
7	12	F	AML	Monosomy 7, trisomy 8	CR	1	Yes	113	7.2
8	16	M	Pre-B ALL	MLL translocation—t(4;11)(q21;q23)	CR	1	No	n/a	8.5
9	7	F	Biphenotypic	no abnormality found	CR	2	Yes	119	69.9+
10	<1	M	AML	MLL translocation—t(10;11)(p12;q23)	CR	2	Yes	78	59.6+
12	7	F	Pre-B ALL	57XX, del (7)(p13p15)	CR	2	Yes	76	50.66
13	4	M	AML	trisomy 6	CR	2	Yes	93	7.5
15	7	F	AML	t(1;12), del(6q), add(18p)	CR	2	Yes	124	14.9
17	11	F	AML	FLT3 ITD	CR	1	No	n/a	12.1
19	15	F	AML	del 5q	CR	1	Yes	49	37+

TABLE IV. Grade ≥3 Non-Hematologic Adverse Events in Two or More Patients

Adverse event	Grade ≥3	Grade 3	Grade 4	Grade 5
Febrile neutropenia	14 (82%)	14	0	0
Increased ALT	8 (47%)	8	0	0
Typhlitis	3 (18%)	2	1	0
Hyperbilirubinemia	2 (11%)	2	0	0
Hypotension	2 (11%)	0	2	0
Increased AST	2 (11%)	2	0	0
Pain	2 (11%)	2	0	0

to HSCT. Miano et al. reported on the efficacy of clofarabine ($40\,mg/m^2/day \times 5$ days) combined with cyclophosphamide ($440\,mg/m^2/day \times 5$ days) and etoposide ($100\,mg/m^2/day \times 5$ days) in 16 patients with R/R AML. The ORR in patients with AML was 44%, with 57% of responders proceeding to HSCT [11].

This study using the TVTC regimen is the most effective pediatric phase II, clofarabine based trial against R/R leukemia reported to date. Accrual numbers were limited by the fact that this was a single institution study. However, given the efficacy of this protocol along with the high rate of successful HSCT following recovery, this regimen warrants further evaluation in a cooperative group setting. Furthermore, incorporation of the regimen should be strongly considered in future therapeutic protocols in patients with newly diagnosed AML who have poor responses to induction chemotherapy.

ACKNOWLEDGMENTS

N.S. performed the research, designed the research study, analyzed the data, and wrote the paper, R.K. performed the research, T.R. performed the research L.J.S. performed the research, and P.G.S. performed the research and designed the research study. Funding support for this clinical trial was provided in part by Sanofi/Genzyme. We would like to thank Joseph Olechnowicz for editing this manuscript.

REFERENCES

1. Pui CH, Mullighan CG, Evans WE, et al. Pediatric acute lymphoblastic leukemia: Where are we going and how do we get there? Blood 2012;120:1165–1174.
2. Rubnitz JE, Inaba H. Childhood acute myeloid leukaemia. Br J Haematol 2012;159:259–276.
3. Gaynon PS, Childhood acute myeloid leukaemia. Br J Haematol 2005;131:579–587.
4. Sander A, Zimmermann M, Dworzak M, et al. Consequent and intensified relapse therapy improved survival in pediatric AML: Results of relapse treatment in 379 patients of three consecutive AML-BFM trials. Leukemia 2010;24:1422–1428.
5. Oliansky DM, Camitta B, Gaynon P, et al. Role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of pediatric acute lymphoblastic leukemia: Update of the 2005 evidence-based review. Biol Blood Marrow Transplant 2012;18:505–522.
6. Bonate PL, Arthaud L, Cantrell WR Jr, et al. Discovery and development of clofarabine: A nucleoside analogue for treating cancer. Nat Rev Drug Discov 2006;5:855–863.
7. Parker WB, Shaddix SC, Chang CH, et al. Effects of 2-chloro-9-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl)adenine on K562 cellular metabolism and the inhibition of human ribonucleotide reductase and DNA polymerases by its 5′-triphosphate. Cancer Res 1991;51:2386–2394.
8. Jeha S, Gandhi V, Chan KW, et al. Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemia. Blood 2004;103:784–789.
9. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol 2006;24:1917–1923.
10. Jeha S, Razzouk B, Rytting M, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute myeloid leukemia. J Clin Oncol 2009;27:4392–4397.
11. Miano M, Pistorio A, Putti MC, et al. Clofarabine, cyclophosphamide and etoposide for the treatment of relapsed or resistant acute leukemia in pediatric patients. Leuk Lymphoma 2012;53:1693–1698.
12. Inaba H, Bhojwani D, Pauley JL, et al. Combination chemotherapy with clofarabine, cyclophosphamide, and etoposide in children with refractory or relapsed haematological malignancies. Br J Haematol 2012;156:275–279.
13. Abd Elmoneim A, Gore L, Ricklis RM, et al. Phase I dose-escalation trial of clofarabine followed by escalating doses of fractionated cyclophosphamide in children with relapsed or refractory acute leukemias. Pediatr Blood Cancer 2012;59:1252–1258.
14. Inaba H, Rubnitz JE, Coustan-Smith E, et al. Phase I pharmacokinetic and pharmacodynamic study of the multikinase inhibitor sorafenib in combination with clofarabine and cytarabine in pediatric relapsed/refractory leukemia. J Clin Oncol 2011;29:3293–3300.
15. Hijiya N, Thomson B, Isakoff MS, et al. Phase 2 trial of clofarabine in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. Blood 2011;118:6043–6049.
16. Steinherz PG, Shukla N, Kobos R, et al. Remission re-induction chemotherapy with clofarabine, topotecan, thiotepa, and vinorelbine for patients with relapsed or refractory leukemia. Pediatr Blood Cancer 2010;54:687–693.
17. Locatelli F, Testi AM, Bernardo ME, et al. Clofarabine, cyclophosphamide and etoposide as single-course re-induction therapy for children with refractory/multiple relapsed acute lymphoblastic leukaemia. Br J Haematol 2009;147:371–378.
18. Hijiya N, Gaynon P, Barry E, et al. A multi-center phase I study of clofarabine, etoposide and cyclophosphamide in combination in pediatric patients with refractory or relapsed acute leukemia. Leukemia 2009;23:2259–2264.
19. Cooper TM, Razzouk BI, Gerbing R, et al. Phase I/II trial of clofarabine and cytarabine in children with relapsed/refractory acute lymphoblastic leukemia (AAML0523): A report from the Children's Oncology Group. Pediatr Blood Cancer 2013;60:1141–1147.
20. Cooper T, Alonzo TA, Gerbing R, et al. AAM L0523: A report from the Children's Oncology Group on the efficacy of clofarabine in combination with cytarabine in pediatric patients with relapsed acute myeloid leukemia. The American Society of Hematology 53rd annual meeting 2012 (3604) 2012.
21. Kolb EA, Steinherz PG. A new multidrug reinduction protocol with topotecan, vinorelbine, thiotepa, dexamethasone, and gemcitabine for relapsed or refractory acute leukemia. Leukemia 2003;17:1967–1972.
22. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol 2005;23:2629–2636.
23. Steinherz LJ, Steinherz PG, Tan CT, et al. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 1991;266:1672–1677.
24. Wells RJ, Adams MT, Alonzo TA, et al. Mitoxantrone and cytarabine induction, high-dose cytarabine, and etoposide intensification for pediatric patients with relapsed or refractory acute myeloid leukemia: Children's Cancer Group Study 2951. J Clin Oncol 2003;21:2940–2947.