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Ifosfamide and Vinorelbine Is an Effective Reinduction Regimen in Children With Refractory/Relapsed Hodgkin Lymphoma, AHOD00P1: A Children's Oncology Group Report

Tanya M. Trippett^{1,*}, Cindy L. Schwartz², R. Paul Guillerman³, Alan S. Gamis⁴, Sharon Gardner⁵, Shirley Hogan⁶, Wendy B. London⁷, Lu Chen⁸, and Pedro de Alarcon⁹

¹Memorial Sloan Kettering Cancer Center, New York, New York

²MD Anderson Cancer Center, Houston, Texas

³Texas Children's Cancer Center at Baylor College of Medicine, Houston, Texas

⁴The Children's Mercy Hospital & Clinics, Kansas City, Missouri

⁵New York University Hospital, New York, New York

⁶University of Mississippi Medical Center, Jackson, Mississippi

⁷Boston Children's Hospital/Dana Farber Cancer Institute, Boston, Massachusetts

⁸Children's Oncology Group - Statistics and Data Center, Arcadia, California

⁹St. Jude Midwest Affiliate, University of Illinois College of Medicine, Peoria, Illinois

Abstract

Background—We assessed the safety and efficacy of ifosfamide and vinorelbine (IV) as a less toxic and effective reinduction regimen for pediatric patients with relapsed or refractory Hodgkin Lymphoma.

Procedure—This multi-center Children's Oncology Group phase II pilot study enrolled patients <30 years of age with biopsy-proven Hodgkin Lymphoma in relapse or refractory disease after front-line therapy. Treatment consisted of ifosfamide 3,000 mg/m² intravenous infusion over 24 hr on Days 1–4 and vinorelbine 25 mg/m²/dose intravenous push on Days 1 and 5 of each 21 day cycle with cytokine support. The study endpoints included estimation of key toxicities (cardiac, hepatic, or renal toxicity or toxic death), the rate of successful peripheral stem cell harvesting, and response after two cycles of therapy.

Results—Sixty-six patients received a median of two cycles of IV. Sixty-four of 66 were heavily pretreated, 4 had refractory disease, 55% were male and 79% had nodular sclerosis HL. The primary toxicities were hematologic. Harvested peripheral stem cells were sufficient for

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*Correspondence to: Tanya M. Trippett, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. trippet1@mskcc.org.

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autologous transplantation in 46 of 54 patients for whom stem cell collection was attempted. The overall response rate (72%; 95% CI 59–83%) permitted the majority of patients to undergo subsequent stem cell transplantation.

Conclusions—IV is a safe and effective re-induction regimen for salvage of pediatric patients with relapsed or refractory Hodgkin Lymphoma with an excellent response rate and success of post chemotherapy stem cell harvest. It avoids the use of etoposide, an agent associated with secondary malignancy after stem cell transplantation.

Keywords

hodgkin lymphoma; ifosfamide; re-induction; relapse; vinorelbine

INTRODUCTION

Combined modality, chemotherapy and radiotherapy, have resulted an event-free survival of 80–90% of pediatric patients with Hodgkin lymphoma (HL) and an overall survival rate of 90–95%. Although patients who relapse after single modality therapy (radiation or chemotherapy) may be cured with the inclusion of the alternate modality alone or in combination [1,2], those who are initially treated with combined modality therapy benefit from high dose therapy with stem cell rescue [3,4]. Unfortunately, progression during induction therapy or relapse within 12 months of therapy has been associated with a poor prognosis [3,4]. Improvements in retrieval re-induction chemotherapy followed by high-dose chemotherapy and autologous stem cell reconstitution may improve event-free survival (EFS) and overall survival (OS) [5]. In addition, new re-induction regimens should be considered that reduce the toxicities associated with the more standard regimens such as ifosfamide, carboplatin (or cisplatin), and etoposide (ICE). ICE has been widely used as a re-induction regimen for patients with relapsed/refractory HL [6,7–14]. It is effective but the risk of myelodysplastic syndrome and treatment-related secondary leukemia associated with the combination of alkylating agents and epipodophyllotoxins in pediatric Hodgkin lymphoma patients [15] encourages the search for less toxic re-induction regimens.

Vinorelbine, a semi-synthetic vinca alkaloid, has demonstrated marked single agent clinical activity (50%) in patients with recurrent HL with limited toxicities including granulocytopenia as the dose-limiting toxicity and reversible peripheral neuropathy in 20% of patients [16,17]. The mechanism of action of vinorelbine is similar to, but more selective than, that of the vinca alkaloids; inhibition of microtubule formation occurs but there is only limited inhibition of neural axonal formation, thereby diminishing the incidence of neurotoxicity at the pediatric maximum tolerated dose (MTD) of 30 mg/m²/week [18]. Twenty adult patients receiving ifosfamide and vinorelbine (IV) for refractory/recurrent HL [16], achieved an overall response rate of 80% (40% CR and 40% PR). The main toxicity was Grade 3–4 neutropenia (65%) without report of Fanconi's tubular dysfunction.

In this study, our goal was to evaluate the safety and efficacy of IV as a novel re-induction regimen for children and adolescents with relapsed/refractory HL.

METHODS

Patients

Patients with biopsy proven relapsed or refractory HL were enrolled between May 2001 and March 2006. Eligibility criteria included the following: age less than 30 years; Karnofsky performance score $\geq 60\%$ (patients > 16 years) or Lansky play scale $\geq 60\%$ (patients ≤ 16 years); life expectancy of at least 2 months; no chemotherapy within 2 weeks of the start of therapy (3 weeks for nitrosourea containing therapy); and adequate bone marrow, hepatic, renal, and cardiac function. Key exclusion criteria included serious intercurrent infection or known hypersensitivity to E.coli-derived proteins, filgrastim, or any component of filgrastim. Patients were considered minimally treated if they were stage I or IIA at diagnosis and were initially treated with radiation therapy only, with Pediatric Oncology Group Protocol P9426, or with less than four cycles of conventional chemotherapy with or without radiation therapy. All other patients were considered heavily treated.

Approval of the protocol was required by the Institutional Review Board of the participating sites in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained in accordance with institutional assurance policies of the US Department of Health and Human Services and in accordance with the Declaration of Helsinki from all patients or parents/legal guardians.

Study Design and Treatment

This was a multi-center, open-label, non-randomized phase II pilot study. A 21-day cycle consisted of ifosfamide $3,000 \text{ mg/m}^2/\text{day}$ via continuous intravenous infusion over 24 hr on Days 1–4 and vinorelbine $25 \text{ mg/m}^2/\text{dose}$ intravenous push on Days 1 and 5. Filgrastim $5 \mu\text{g/kg/day}$ was administered subcutaneously starting on Day 6 of each cycle of therapy until recovery of neutrophil count. Subsequent cycles of IV were initiated when: ANC $\geq 1,000/\mu\text{L}$ 48 hr after discontinuation of filgrastim and platelet count $\geq 75,000/\mu\text{L}$. Supportive care included continuous hydration and administration of MESNA for uroprotection ($3,000 \text{ mg/m}^2/\text{day}$ via continuous intravenous infusion on Days 1–5).

There were two phases of the study: (1) establishment of an acceptable induction success rate defined as the patients who complete induction without primary toxicity and adequate response permitting hematopoietic stem cell transplantation; and (2) expansion of enrollment for more accurate estimates of response rate.

Patient Evaluation

Patient histories, physical exams with assessment of Karnofsky performance status/Lansky play scale scores, hematology and serum chemistry profiles were performed at baseline and prior to each cycle. Baseline kidney function was assessed by 24 hr urine collection for creatinine clearance or a radionuclide glomerular filtration rate study. Adverse events were assessed on a continuous basis.

Response Assessment

Tumor imaging and response assessment were performed in all evaluable patients by CT scan and gallium scintigraphy or [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) scan at baseline and after every 2 cycles of therapy. Response criteria were adapted with some modification from criteria from the Cotswolds Meeting [19], the International Workshop to Standardize Response Criteria for Non-Hodgkin Lymphomas, and the RECIST criteria [20]. CR was defined by gallium or FDG-PET negativity, at least 80% reduction in the product of the perpendicular diameters (PPD) of each site of measurable disease or return involved nodes to normal size on CT, and resolution of palpable lymphadenopathy and all focal lesions of the liver or spleen. Very good partial response (VGPR) required at least 60% reduction in the PPD of each nodal mass. Partial response (PR) required at least 50% reduction in the PPD of each site of measurable disease. Progressive disease (PD) was defined as at least 50% increase in the PPD of any involved site or development of new lesions. Stable disease (SD) was defined as less than a PR, but without meeting criteria for PD. Best response was defined as the single best response at any evaluation. Patients were defined as responders to IV if they achieved a PR, VGPR, or CR. Nonresponders included those with SD or PD.

Toxicity Assessment

Toxicity was assessed according to NCI Common Toxicity Criteria version 2.0. Course-specific toxicity rates were estimated for all grade 3 or 4 toxicities.

Stem Cell Harvesting

Autologous peripheral blood stem cells (PBSC) were collected during hematopoietic recovery following IV. Hematologic parameters for PBSC harvesting were a rising ANC of at least $1,000/\mu\text{L}$. The definition of a successful PBSC mobilization was the ability to harvest at 5×10^6 CD34+ cells/kg within five collection days. Bone marrow harvesting or repeat stem cell mobilization/collection was reserved for patients who failed to achieve the designated cell dose at the investigators discretion. Patients with bone marrow involvement at the time of study entry were required to have absence of bone marrow involvement on repeat bone marrow biopsies prior to stem cell collection. If persistent bone marrow disease was noted, the patient was removed from the study.

Statistical Analysis

Response assessment—A two-stage rule was used for assessment of response. An induction success rate of 70% was the acceptable performance level for IV. A Bayesian monitoring rule with prior density Beta on the probability P of induction success was used in the initial cohort to evaluate whether observed interim and final induction success rates were consistent with this target. Operationally, this rule required and achieved a minimum of seven responses in the first 12 patients and 16 responses in the first 25 patients to continue with the study. The study accrual was expanded after the initial cohort in order to establish a more precise estimate of the overall response rate with standard error on the order of $\pm 6\%$.

Event-free (EFS) and overall survival (OS) probability estimates at 5 years were calculated by the Kaplan-Meier method. EFS was measured from the date of enrollment until date of relapse, progressive disease, second malignancy, death from any cause, or date of last contact if no event occurred. OS was measured from the date of enrollment until the date of death from any cause or date of last contact. Standard errors were reported according to Peto [21].

Toxicity Assessment

The primary toxicity endpoint was defined as the occurrence of at least one of the following: Toxic death was defined as any death predominantly attributable to treatment-related toxicities or complications, occurring during or within one month of the completion of therapy. Five or more toxic deaths (of 65 patients) would have been considered unacceptable. This rule provided 95% power to detect a death rate less than 3%, a null hypothesis of a 12% toxic death rate, and Type I error rate of 9.7%. Toxic death was counted as a treatment failure in the response analysis. In the event of a first toxic death, review of the event and the progress of all patients were mandated.

Cardiac, hepatic, or renal toxicity resulting in termination of reinduction therapy, or persistent inadequate cardiac, hepatic, or renal function one month after the completion of therapy. Inadequate function was defined as: Cardiac: Shortening fraction <27% by echocardiogram; Ejection fraction <50% by radionuclide angiogram. Hepatic: SGOT (AST) or SGPT (ALT) >5 × normal; Total bilirubin >3× normal. Renal: Serum creatinine 3× normal; GFR <60 ml/minute/1.73 m². Hematologic: Delay of >2 weeks in the start of re-induction cycle two or in hematologic recovery after cycle two secondary to severe myelosuppression, infection, or sepsis. Secondary toxicity endpoints included all other non-hematologic grades 3 or 4 toxicities.

RESULTS

Patients

Of the 66 patients enrolled on study, all were deemed eligible. Sixty-four of 66 patients were heavily pretreated. Characteristics of the patients enrolled on study are summarized in Table I.

Toxicity

The toxicity profile was acceptable according to the established parameters of the study. The incidence of grade 3 or 4 toxicities reported by cycle of IV is summarized in Table II. Hematologic toxicity was the predominant toxicity for all patients with neutropenia being predominant after all cycles. The incidence of thrombocytopenia was approximately 50%. There were no treatment delays. There was no evidence of nephrotoxicity, cardiotoxicity, or significant hepatic toxicity. The incidence of neuropathic pain was minimal (2.1%) One patient demonstrated symptoms of neurotoxicity including hallucinations and somnolence attributed to ifosfamide administration. There were no toxic deaths reported on this study.

Peripheral Stem Cell Harvesting

Fifty-four of 66 patients underwent peripheral stem cell harvesting and were evaluable. Of those, 46 had “successful harvest” with data on collection days and CD34 counts. Of the patients, 26 (56%) had successful harvests according to criteria in this study (5×10^6 CD 34+ cells/kg within 5 collection days) and 42 patients (78%) according to conventional standards of 2×10^6 cells/kg (Table III). The majority of patients with a successful harvest according to the criteria of this study required a total of two collections for a successful PBSC harvest. The median number of CD34+ cells/kg collected was 5.4×10^6 cells/kg (range: $0.7\text{--}35.3 \times 10^6$ cells/kg). Based on available data reported during follow-up, forty-four of 61 patients underwent peripheral stem cell transplantation after IV, with 39 autologous and 5 allogeneic.

Response to Re-induction with IV

Sixty-one patients were evaluable for response after 2 cycles of IV; five were inevaluable for the following reasons: withdrawal by parents’ choice [1], in-evaluable by protocol violation steroid therapy added for nausea [1], transfer to a non-participating institution [1], and delayed response evaluation (two patients achieving partial response after 3 cycles and CR after 4 cycles). None of the patients were removed because of toxicity or disease progression. The response data are shown in Table IV. Sixteen patients (26.2%) achieved a complete response and 28 patients (45.9%) achieved at least a partial response, yielding an overall response rate (ORR) of 72% (95% CI 59–83%). Six patients (10%) experienced PD during the first 2 cycles; two patients after cycle 1 and the remaining four patients after cycle 2.

The median time of follow-up among patients without a reported EFS event was 5.31 years (range 0.15–8.80 years). 5-year EFS and OS for patients on this study are shown in Figure 1. There were 28 patients with reported first events (24 relapse/progression, two with second malignancies, and two patients who died). The 5-year EFS was 57.2% (95% CI 44.0%–68.3%). A total of 17 deaths were reported. The 5-year OS was 73.9% (95% CI 60.3%–83.4%).

DISCUSSION

Combination chemotherapy of IV is a safe and effective reinduction regimen for children and adolescents with relapsed/refractory Hodgkin lymphoma with an ORR after two cycles of IV of 72% (95% CI 59–83%). This study was designed specifically for evaluating a salvage treatment regimen for children and adolescents with relapsed or refractory Hodgkin lymphoma. Comparison of reinduction regimens is complicated by studies that combine efficacy data for HL with non-Hodgkin lymphoma and by the overall limited numbers of HL patients enrolled on studies for recurrent disease. Nonetheless, the reported response rate and outcome data after IV are comparable to previously reported historical data with ICE in adults and children with relapsed/refractory HL as well as to other retrieval approaches studied in our legacy groups. In the largest historical series of adult and pediatric combined with HL treated with standard ICE, a response rate of 80% was reported after two cycles of therapy and a 5-year EFS of 55% [6,22].

As was seen in adult trials of IV, the toxicity profile of IV was favorable. The predominant toxicity reported was reversible neutropenia but this did not lead to treatment delays between cycles. No significant non-hematologic toxicity was reported and there were no toxic deaths. The two second malignancies reported as first EFS events included one patient with AML and another with cervical cancer. The report of cervical cancer is likely not relevant to treatment with this regimen. The one event of AML may be attributable to the initial therapy or this regimen.

A distinct advantage of this regimen over other regimens studied in children such as ICE, DECAL [23], and APE [24] is that IV does not include etoposide. The use of etoposide during salvage therapy has been associated with secondary leukemias in patients with HL. [15] The success of our IV regimen provides an alternative regimen that has an acceptable profile of acute toxicities especially reversible myelosuppression, similar or better efficacy, without an additive risk of etoposide-induced secondary malignancy. This is a significant advantage in this setting where the majority of patients undergo subsequent stem cell transplantation.

Documenting success in stem cell mobilization in children after salvage therapy is critical for ensuring the utility of a new regimen such as IV. Stem cell mobilization data has been described in adult patients receiving combination therapy with IV and other chemotherapeutic agents including gemcitabine and prednisone [25,26]. The majority of patients were able to mobilize peripheral stem cells despite prior heavy pre-treatment with alkylating agents in the population of patients enrolled on study. Although the study set a higher bar (5×10^6 cells/kg) for “successful” stem cell mobilization in a particularly heavily pretreated population of patients, most transplant centers now consider a cell dose of 2×10^6 cells/kg an acceptable yield after stem cell mobilization.

In conclusion, the results of this study have demonstrated that IV is an effective and safe re-induction regimen for pediatric patients with relapsed/refractory HL. Further studies using this combination to augment intensity of therapy for newly diagnosed high risk patients receiving frontline therapy who have a slow early response to therapy are being conducted in the Children’s Oncology Group. In the relapsed setting, IV meets the criteria for consideration as a standard pediatric re-induction approach prior to high dose therapy with stem cell transplantation.

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Fig. 1. AHOD01P1, Event-free (EFS) and Overall Survival (OS) rates from study entry. The 5-year EFS and OS rates were 57.2% (95% CI, 44.0%, 68.3%) and 73.9% (95% CI, 60.3%, 83.4%) respectively.

TABLE I**Patient Characteristics**

Characteristics	N = 66 (%)
Age (years)	
0–4	0/66(0)
5–9	3/66 (4.5)
10–14	18/66 (27)
15–19	42/66 (64)
20–29+	3/66 (4.5)
Sex	
Male	36/66 (55)
Female	30/66 (45)
Race	
White	47/66 (71)
Black	9/66 (14)
Other	9/66 (14)
Unknown	1/66 (1)
Institutional Pathology at study entry	
Nodular Sclerosis (NS)	36/66 (70)
Mixed Cellularity (MC)	4/66 (6)
Lymphocyte Predominant (LPHD)	0/66 (0)
Not classifiable into one of the above categories	16/66 (17)
Presence of B symptoms at study entry	
No	53/66 (83)
Yes	11/66 (17)
Unknown	2/66
Disease status at study entry	
1st relapse post chemotherapy	59 (89)
2nd or subsequent relapse	3 (5)
Progressive disease/primary induction failure	4 (6)

TABLE II

Toxicity Profile by Cycle

Toxicity	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	(N = 66)		(N = 64)		(N = 26)		(N = 4)	
	n	%	n	%	n	%	n	%
Allergy/Immunology-Other	1	1.5	0	0.0	0	0.0	0	0.0
Hemoglobin (Hgb) *	12	18.2	40	62.5	12	46.2	2	50.0
Leukoocytes (total WBC) *	52	78.8	52	81.3	21	80.8	3	75.0
Lymphopenia	1	1.5	3	4.7	0	0.0	0	0.0
Neutrophils/granulocytes (ANC/AGC) *	53	80.3	51	79.7	19	73.1	3	75.0
Platelets *	20	30.3	31	48.4	14	53.8	2	50.0
Transfusion: Platelets	1	1.5	5	7.8	3	11.5	0	0.0
Transfusion: pRBCs	5	7.6	6	9.4	5	19.2	1	25.0
Left ventricular function *	0	0.0	0	0.0	0	0.0	0	0.0
Fever (in the absence of neutropenia)	1	1.5	1	1.6	0	0.0	0	0.0
Nausea	4	6.1	0	0.0	1	3.8	0	0.0
Stomatitis/pharyngitis	1	1.5	0	0.0	0	0.0	0	0.0
Vomiting	1	1.5	1	1.6	1	3.8	0	0.0
Febrile neutropenia ^{1]}	12	18.2	6	9.4	3	11.5	0	0.0
Infection with grade 3 or 4 neutropenia ^{2]}	4	6.1	4	6.3	3	11.5	0	0.0
Infection without neutropenia	0	0.0	2	3.1	0	0.0	0	0.0
Acidosis *	0	0.0	1	1.6	0	0.0	0	0.0
Hypocalcemia *	0	0.0	1	1.6	0	0.0	0	0.0
Hypokalemia *	3	4.5	5	7.8	3	11.5	0	0.0
Hyponatremia	1	1.5	0	0.0	0	0.0	1	25.0
Hypophosphatemia *	1	1.5	2	3.1	0	0.0	0	0.0
Confusion	1	1.5	0	0.0	0	0.0	0	0.0
Hallucinations	1	1.5	0	0.0	0	0.0	0	0.0
Mood alteration-anxiety, agitation	1	1.5	0	0.0	0	0.0	0	0.0

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Toxicity	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	n	%	n	%	n	%	n	%
Abdominal pain or cramping	2	3.0	0	0.0	0	0.0	0	0.0
Myalgia (muscle pain)	1	1.5	0	0.0	0	0.0	0	0.0
Neuropathic pain	1	1.5	0	0.0	0	0.0	0	0.0
Creatinine [*]	0	0.0	0	0.0	0	0.0	0	0.0
Proteinuria [*]	0	0.0	0	0.0	0	0.0	0	0.0
Urinary Electrolyte wasting [*]	0	0.0	1	1.6	1	3.8	0	0.0

^{*} = Target toxicities;
¹ = Fever of unknown origin without clinically or microbiologically documented infection;
² = Documented clinically or microbiologically.

TABLE III

Peripheral Stem Cell Harvesting

Patients with successful PBSC harvest (s)		N = 46
Total harvest	5×10^6 CD 34+ cells/kg	26
1 collection		13
2 collections		9
3 collections		3
8 collections		1
Total harvest	$<5 \times 10^6$ CD 34+ cells/kg	20
1 collection		1
2 collections		3
3 collections		7
4 collections		4
5 collection		3
6 collections		1
12 collections		1

TABLE IV

Response After Two Cycles of IV

Response	Evaluable Pts after cycle 2 N = 61(%)
Complete Response (CR)	16 (26.2)
Partial Response (PR)	28 (45.9)
Stable Disease (SD)	11 (18.0)
Progressive Disease (PD)	6 (9.8)