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ORIGINAL ARTICLE

Phase II study of 9-aminocamptothecin in previously treated lymphomas: results of Cancer and Leukemia Group B 9551

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Abstract
Purpose To evaluate the efficacy and toxicity of the topoisomerase I inhibitor, 9-aminocamptothecin (9-AC), in patients with relapsed lymphoma and to correlate 9-AC plasma concentrations with response and toxicity.
Methods Eligible patients had relapsed Hodgkin lymphoma (HL) treated with one or two prior regimens, low grade non-Hodgkin's lymphoma (NHL) treated with one or two prior regimens, or aggressive NHL treated with one prior regimen. The first nine patients received 9-AC dimethylacetamide 0.85 mg/m^2 per day intravenously over 72 h every 2 weeks and the remaining 27 patients received 9-AC/colloidal dispersion 1.1 mg/m^2 per day. Patients received a minimum of three cycles unless progression or intolerable toxicity occurred. Responding patients received two cycles past best response with a minimum of six cycles.
Results CALGB 9551 accrued 37 patients from April 1996 through October 2000; one patient with HD, 18 patients with indolent lymphoma, and 17 patients with aggressive lymphoma. The overall response rate was 17%, with response rates of 11% (2 partial responses) in patients with indolent histologies and 23% (1 complete response, 3 partial responses) in patients with aggressive histologies. The patient with HD did not respond. Response rates were similar for both drug formulations. The median remission duration for the six responders was 6.5 months, with one remission lasting longer than 12 months. Significant grade 3 and 4 toxicities included neutropenia (66%), anemia (31%), and thrombocytopenia (36%), with 20% of patients experiencing grade 3 or 4 infection. No treatment related deaths occurred. Steady state serum concentrations did not correlate with patient response or toxicity.
Conclusion Single agent 9-AC has modest activity in aggressive non-Hodgkin's lymphomas.

Keywords Relapsed non-Hodgkin's lymphoma · 9-Aminocamptothecin (9-AC) · Topoisomerase I inhibitor · Pharmacokinetics

Introduction

Camptothecins are cytotoxic agents which target topoisomerase I and thereby inhibit DNA and RNA synthesis. The camptothecin analogs, topotecan and irinotecan hydrochloride (CPT-11) have activity in heavily pretreated patients with relapsed lymphoma. In a Japanese multi-center phase II study of irinotecan 40 mg/m^2 per day as a 72 h continuous infusion in patients with relapsed lymphoma, the overall response rate in non-Hodgkin's lymphoma (NHL) was 42% (26/62), including 12 complete responses (CR) [1, 2]. None of four patients with Hodgkin's lymphoma (HL) responded. The principal adverse effects were myelosuppression and gastrointestinal symptoms including diarrhea, nausea, vomiting, anorexia, and abdominal pain. Investigators

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at MD Anderson Cancer center treated 22 patients with NHL with irinotecan, 300 mg/m^2 every 21 days [3]. Eight patients (36%) responded, including patients with indolent and aggressive histologies. A phase II consortium study of topotecan in 32 patients with relapsed lymphoma demonstrated a response rate of 17%, with four of the five responders having aggressive histology [4]. Another phase II study of topotecan in 71 patients with lymphoma at MD Anderson Cancer Center revealed an overall response rate of 48, with 31% of patients with primary refractory disease and 65% of patients with relapsed disease responding [5]. These favorable results indicated that the camptothecins might be an important class of drugs in the treatment of lymphoma.

9-aminocamptothecin (9-AC), a water insoluble camptothecin derivative, was selected for clinical evaluation based on its broad activity in preclinical studies [6–8]. As compared to irinotecan, there appeared to be no gastrointestinal toxicities with 9-AC. Clinical trials of 9-AC were delayed compared with other camptothecin analogs because of complex formulation requirements. The solubility of 9-AC is greatly enhanced in a dimethylacetamide (DMA) vehicle. An alternative formulation of 9-AC, a lyophilized colloidal dispersion (CD), revealed enhanced water solubility, a similar growth inhibition pattern, and slightly improved toxicity profile, with regard to neutropenia, compared with the original DMA formulation [9]. Because phase I studies of 9-AC/CD were completed after activation of CALGB 9551, the study was amended to include this new formulation.

Phase I studies of 9-AC/DMA as a 72 h infusion repeated either every 2 or 3 weeks, reported a maximum tolerated dose (MTD) for the 2-week schedule of 0.85 mg/m^2 per day, and 1.08 mg/m^2 per day for the 3-week schedule [10, 11]. The dose-limiting toxicity (DLT) in both phase I studies was neutropenia without granulocyte colony-stimulating factor (G-CSF), and neutropenia and thrombocytopenia with G-CSF. Dosing recommendations for 9-AC/CD were 1.1 mg/m^2 per day for 3 days for the 2-week schedule and 1.3 mg/m^2 per day for 3 days for the 3 week schedule [9, 12]. Similar to the DMA formulation, neutropenia was the DLT and little non-hematologic toxicity was demonstrated with 9-AC/CD.

Wilson et al. [13] at the National Cancer Institute (NCI) treated 45 patients with relapsed or refractory lymphomas with 9-AC/DMA 0.96 mg/m^2 per day for 3 days with or without G-CSF. Cycles were repeated every 3 weeks with 0.01 mg/m^2/h increment escalations or reductions based on toxicity. Patients had received a median of two prior chemotherapy regimens (range 1–6), with one-third of patients not responding to their most recent chemotherapy regimen. Six patients had previously undergone high dose therapy with autologous stem cell rescue. Of 40 assessable patients, the overall response rate was 25%, with similar response rates for indolent (3/12 PR) and aggressive (6/25 PR) lymphomas. In chemotherapy-sensitive patients, the response rate was 32% compared with 8% in chemotherapy-resistant patients. G-CSF did not increase dose-intensity secondary to dose-limiting thrombocytopenia.

CALGB 9551 was designed to test 9-AC in a less heavily pretreated group of patients than those treated in the NCI phase II study. The objectives of this protocol were to evaluate the response rate, response duration, and the toxicity of 9-AC in previously treated patients with NHL and HL. Correlating 9-AC plasma concentrations with toxicity and response was a secondary objective.

Patients and methods

Eligible patients included those with relapsed or refractory HL or NHL. One or two prior chemotherapy regimens were allowed for patients with HL and indolent lymphoma (small lymphocytic, follicular grade I/II), while patients with aggressive lymphoma (follicular large cell, diffuse small cleaved, diffuse mixed, or diffuse large cell) had failed only one prior regimen. The study required a CALGB performance status of 0–2. Patients with CNS or HIV-related lymphomas were excluded. Chemotherapy or radiation therapy was not allowed within 3 weeks prior to study entry; nitrosoureas, melphalan, and mitomycin were not allowed within the past 6 weeks. Previous allogeneic or autologous transplant or prior camptothecins were not allowed. All participating patients signed an informed consent in accord with guidelines for the protocol as approved by the Human Studies Committee of all participating institutions.

9-AC was supplied by the Cancer Treatment Evaluation Program, NCI. Initially, 9-AC was administered in dimethylacetamide (DMA) solvent at 0.85 mg/m^2 per day (total dose 2.55 mg/m^2) as a continuous infusion on days 1–3 and repeated every 2 weeks. In February 1997, the formulation was changed to a colloidal dispersion (CD) based on preliminary phase I data. The dose of 9-AC/CD was 1.1 mg/m^2 per day (total dose 3.3 mg/m^2) as a continuous infusion on days 1–3 and repeated every 2 weeks. If the absolute neutrophil count (ANC) following cycles 1 and 2 of treatment was greater than 1,000/μL, the dose was escalated to 1.3 mg/m^2 per day for subsequent cycles.

In the absence of intolerable toxicity or clear progression of disease, patients received a minimum of three cycles. Partial responders or complete responders were treated for two cycles past their best response, with a minimum of six cycles for partial and complete responses. Patients were restaged after the third and sixth cycles. Complete response was defined as the disappearance of all measurable disease for at least 4 weeks, and partial response was defined as a

reduction of greater than 50% in the sum of products of the perpendicular diameters of all measurable lesions lasting more than 4 weeks. Stable disease consisted of less than a 50% reduction and less than a 25% increase in the sum of the products of the two perpendicular diameters of all measured lesions, and the appearance of no new lesions. Progressive disease or relapse required an increase in the product of two perpendicular diameters of any measurable lesion by 25% or more over the initial size on study entry. A treatment failure was defined as progressive disease, failure to respond, or death from any cause.

Pharmacokinetics and pharmacodynamics

Blood samples for pharmacokinetic studies were required during cycle one only, with the first sample collected prior to initiation of the infusion on day 1 and the second sample within the last 4 h of the 72 h infusion. Total 9-AC/CD concentrations were measured by HPLC using a modification of the method by Takimoto et al. [14]. The 72 h steady state concentration (Css) of total drug, as well as Css adjusted for pretreatment serum bilirubin and albumin, were correlated with response and toxicity, including only adverse events reported during cycle 1 and nadir cell counts collected during cycle 1. Regression models were used to examine the relationship of 9-AC and adjusted 9-AC with the nadir cycle 1 counts, the nadir counts as a proportion of the pre-treatment count, and the proportion of the pre-treatment count adjusting for the pre-treatment count as a covariate in the model. Using Wilcoxon Rank Sums test (nonparametric alternative to the *t* test), mean levels of 9-AC and adjusted 9-AC were compared between patients with and without grade 3+ adverse events for each of the hematologic toxicities.

Statistical analysis

For each histologic group (indolent vs. aggressive), a two-stage design was used. The design was based on approximately 90% power to detect a difference between a response (CR or PR) rate of 20 and 40% for indolent histologies, and 10 and 30% for aggressive histologies. The critical values to continue to stage II was at least 4 responders out of 17 treated in the indolent histology group and at least 3 responders out of 18 treated in the aggressive histology group.

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson. Statistical analyses were performed by CALGB statisticians. As part of the quality assurance program of the CALGB, members of the Data Audit Committee visit all participating institutions at least once every 3 years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 16 patients (43.2%) of the 37 patients under this study.

Results

CALGB 9551 accrued a total of 37 patients from April 1996 through October 2000. One patient had no follow-up or toxicity forms submitted and was excluded from the analysis due to insufficient data. Of the remaining 36 patients, 1 had HL, 18 had indolent NHL (3 small lymphocytic, 6 follicular grade I, 7 follicular grade II, 2 missing data), and 17 had aggressive NHL (11 diffuse large cell, 2 follicular large cell, 1 diffuse small cleaved, 1 diffuse mixed, 2 missing data). The protocol was closed prematurely due to slow accrual and low response rate. All patients met the eligibility criteria for the protocol. Patient characteristics of the 35 patients with NHL are listed in Table 1. Seventy-two percent of patients were over age 60. Nine patients received the DMA formulation and 27 received the CD formulation. The median number of cycles administered was three and ranged from 1 to 15, with 22 patients (63%) receiving three or more cycles.

Table 1 Patient Characteristics

Characteristic	Indolent NHL ($n = 18$)	Aggressive NHL ($n = 17$)	All
Gender			
Male	10 (56%)	11 (65%)	21 (65%)
Age			
40–59	7 (39%)	2 (12%)	9 (26%)
60–69	8 (44%)	5 (29%)	13 (37%)
70–89	3 (17%)	10 (59%)	13 (37%)
Stage			
I	3 (17%)	2 (12%)	5 (14%)
II	1 (6%)	2 (12%)	3 (9%)
III	2 (11%)	1 (6%)	3 (9%)
IV	12 (67%)	12 (71%)	24 (69%)
B symptoms	13 (72%)	13 (76%)	26 (74%)
Performance status			
0	11 (65%)	6 (35%)	17 (50%)
1	4 (24%)	7 (41%)	11 (32%)
2	2 (12%)	4 (24%)	6 (18%)
Missing	1	0	

Response and survival

The overall response rate was 17% with one complete response (CR). The patient with HL had stable disease. The response rate (RR) was 11% (2 PR) for patients with indolent NHL and 23% (1 CR, 3 PR) for aggressive histologies, $P = 0.40$. The median response duration was 6.5 months (range 2–102 months). The longest remission was in an 80-year-old woman with relapsed, diffuse large cell lymphoma 7 years after treatment with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy who achieved a CR with 9-AC and relapsed 8.5 years following treatment. All 9-AC responders had received only one prior chemotherapy regimen, and all had achieved a response to previous therapy (3 CR, 1CRu, 2 PR). Of the six responders, five were treated with the CD formulation (RR 18.5%), and one with the DMA formulation (RR 11.1%) ($P = 0.61$). The failure-free survival (FFS) at one year with 95% confidence intervals (CI) was 0.03 (0.00–0.08), Fig. 1. One and two-year overall survival (OS) rates were 0.69 (0.54–0.84) and 0.61 (0.44–0.77), respectively. Figure 2 shows the OS by histology. Eight patients are alive with a median follow-up of 8.7 years (range 2.4–10.8 years).

Toxicity

No treatment-related deaths occurred; however, 94% of patients experienced a grade 3 or 4 toxicity (Table 2). Grade 3 and 4 hematologic toxicities were common including neutropenia (66%), anemia (31%), and thrombocytopenia (36%). Twenty percent of patients had a grade 3 or 4 infection. Significant non-hematologic toxicities included primarily nausea, vomiting, and malaise/fatigue. The incidence of grade 3 or 4 neutropenia (78% vs. 33%, $P = 0.036$) and thrombocytopenia (44% vs. 11%, $P = 0.11$) was higher among patients receiving the CD formulation than the DMA formulation. Nine of the 22 patients receiving three or more cycles required a dose-reduction secondary to hematologic toxicity. Only one patient was dose escalated after cycle 3, and required de-escalation after cycle 4.

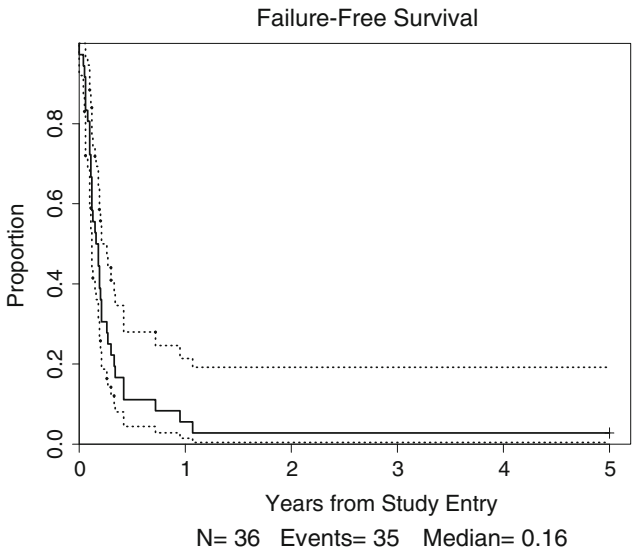

Fig. 1 Failure-free survival and 95% confidence intervals for all patients

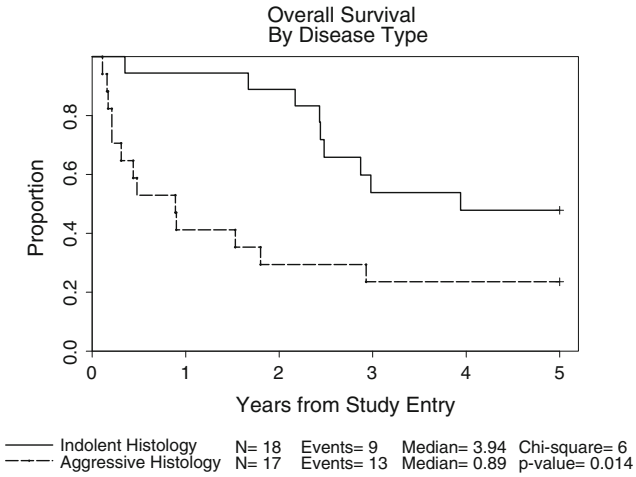

Fig. 2 Overall survival by disease type

Table 2 Toxicity

	Grade of toxicity				
	0	1	2	3	4
	n (%)	n (%)	n (%)	n (%)	n (%)
WBC	5 (14)	7 (19)	7 (19)	9 (25)	8 (22)
Platelets	11 (31)	6 (17)	6(17)	6 (17)	7 (19)
Hemoglobin	2 (6)	11 (31)	12 (33)	11 (31)	0 (0)
Granulocytes/bands	6 (17)	1 (3)	5 (14)	8 (22)	16 (44)
Lymphocytes	12 (33)	0 (0)	5 (14)	9 (25)	10 (28)
Infection	28 (78)	1 (3)	0 (0)	6 (17)	1 (3)
Nausea	13 (36)	15 (42)	5 (14)	2 (6)	1 (3)
Vomiting	22 (61)	7 (19)	3 (8)	2 (6)	2 (6)
Anorexia	23 (64)	7 (19)	5 (14)	1 (3)	0 (0)
Hypotension	31 (86)	3 (8)	1 (3)	1 (3)	0 (0)
Phlebitis/thrombosis	35 (97)	0 (0)	0 (0)	1 (3)	0 (0)
Edema	32 (89)	3 (8)	0 (0)	1 (3)	0 (0)
Motor	33 (92)	2 (6)	0 (0)	1 (3)	0 (0)
Cortical	33 (92)	0 (0)	1 (3)	2 (6)	0 (0)
Skin	31 (86)	2 (6)	2 (6)	1 (3)	0 (0)
Fever w/o infection	26 (72)	3 (8)	6 (17)	0 (0)	1(3)
Malaise/fatigue	18 (50)	14 (39)	2 (6)	2 (6)	0 (0)
Prothrombin time	35 (97)	0 (0)	0 (0)	1 (3)	0 (0)
Maximum toxicity	0 (0)	1 (3%)	1 (3)	12 (33)	2 (6)

Pharmacokinetics

Pharmacokinetic data were obtained for 33 patients. The median 9-AC plasma concentration was 34.8 ng/mL, with a range of 7.9–304.7 ng/mL. 9-AC concentration did not correlate with patient response, with a median value of 29.3 ng/mL (range 18.1–142.1) for the six responders, and 38.1 ng/mL (range 7.9–304.7) for the non-responders. Likewise, raw and adjusted (for bilirubin/albumin) 9-AC levels were not associated with hematologic toxicities, including grade 3 or 4 neutropenia and thrombocytopenia. The median concentration was 30.0 versus 50.0 ng/mL for patients with and without grade 3/4 neutropenia and 40.6 versus 34.0 ng/mL for patients with and without grade 3/4 thrombocytopenia. All six patients with grade 3/4 infections had 9-AC concentrations above the median (38.1–90.6).

Discussion

9-AC has modest activity in refractory and relapsed lymphoma. Results were similar to those seen in the NCI Phase II study of 9-AC, despite selection of less heavily pretreated patients for the current study. As with topotecan, a trend toward higher response rates was seen in patients with aggressive histologies compared to patients with indolent NHL. Hematologic toxicities were significant, particularly with the 9-AC/CD formulation. The recommended phase II dose of 9-AC/CD, while nearly 30% higher than that recommended for 9-AC/DMA, was thought to have a similar toxicity profile. In fact, Phase I studies suggested there might be less thrombocytopenia with the CD formulation. Because of the increased hematologic toxicity seen in the current trial, any further evaluation of this drug should include reconsideration of the appropriate 9-AC/CD dose.

Plasma concentrations of 9-AC did not appear to correlate with toxicity or response, in contrast to previous pharmacokinetic studies in patients with solid tumors [15]. However, pharmacodynamic analysis was likely limited by small patient numbers, low response rates, and severe hematologic toxicity in most patients.

The combination of topoisomerase I and topoisomerase II inhibitors has also been explored in lymphoma based on preclinical studies that demonstrated an additive or even synergistic effect when topoisomerase I and II inhibitors were administered sequentially [16–18]. A decrease of topoisomerase I levels results in a significant increase in topoisomerase II levels and vice versa. Higher levels of the topoisomerase enzyme may enhance the activity of an inhibitory agent. CALGB conducted a Phase II study of sequential administration of doxorubicin (D1) and topotecan (D3–5) in relapsed aggressive lymphoma [19]. The response rate in 25 evaluable patients was 20%, including 2/2 patients with Burkitt's lymphoma. Kancherla et al. reported a 38% response rate in 22 patients with recurrent, aggressive NHL treated with concurrent topotecan and etoposide (days 1–5 every 21 days) and Crump et al. reported an 18% response rate in 22 patients with relapsed, aggressive lymphoma treated with sequential topotecan (D1–5) and etoposide (D6–10) [20, 21]. Topotecan has also shown significant activity in combination with the tubulin inhibitor paclitaxel in relapsed or refractory aggressive NHL [22].

9-AC is no longer in clinical development. While preclinical studies of 9-AC demonstrated much stronger topo I inhibitory activity than topotecan or irinotecan, Phase I and II clinical studies in colon cancer and head and neck cancer failed to demonstrate significant activity [8]. While the drug has modest activity in aggressive lymphomas, the use in lymphoma alone could not sustain continued development of this poorly soluble molecule. The minimal activity and hematologic toxicity of single agent topoisomerase I inhibitors at current doses and schedules does not warrant further investigation of these agents in NHL.

This study also demonstrates the feasibility of administering untested agents to patients with lymphoma earlier in the course of the disease, even if additional active agents are available. Trials of new agents should be considered in patients in first or second relapse with indolent lymphomas or in patients with aggressive lymphomas in first or second relapse who are not transplant candidates. The 5-year survival rates in this trial are similar to results with "standard of care" therapies for similar patients; 48% for patients with relapsed, indolent NHL and 24% for patients with relapsed or refractory aggressive NHL who are not transplant candidates. Use of an inactive agent prior to an active agent is unlikely to affect survival.

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