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Activity of Topotecan 21-Day Infusion in Patients with Previously Treated Large Cell Lymphoma: Long-term follow-up of an Eastern Cooperative Oncology Group Study (E5493)

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Abstract

The purpose of this study was to determine the activity of topotecan given by 21-day continuous infusion in patients previously treated with one prior therapy for a diffuse large cell lymphoma or immunoblastic lymphoma. Patients with appropriate histology and measurable disease who had been treated with one prior chemotherapy regimen were eligible for study. Slides of tumor biopsies were submitted for central review of pathology. Patients were required to have ECOG performance status of 0, 1, or 2 and adequate bone marrow function. Patients were treated with continuous infusion topotecan, 0.4 mg/m²/day × 21 days. Therapy could be escalated to 0.5 and then 0.6 mg/m²/day in subsequent cycles if there was no dose limiting toxicity at the initial dose level. Patients were treated with 2 cycles after achieving complete response or until disease progression or unacceptable toxicity occurred. Thirty seven patients were enrolled, however, only 26 cases were eligible due to performance status of > 2 (2), more than one prior chemotherapy (1), and wrong histology on review (8). Due to the unexpectedly high ineligibility rate, two sets of analysis were done for all the 37 patients enrolled and for the 26 eligible patients, respectively. Of the 37 patients (15 males and 22 females), international prognostic index included 11% low risk, 30% low-intermediate risk; 46% high-intermediate risk, and 8% high risk. The median follow up was 77 months. A total of 136 cycles of therapy were given with a median of 3 cycles per patient. Grade 4 toxicities included: 14% grade 4 thrombocytopenia; 14% grade 4 granulocytopenia, 8% leukopenia, 3% each anemia, hemorrhage, infection, vomiting, thrombosis, liver toxicity, and neuromotor toxicity. The response analysis including all 37 patients showed 5 complete remissions (CR) and 4 partial remissions (PR) for a total response rate of 24% (90% two-stage

confidence interval 13–39%). Median progression free survival (PFS) was 3.7 months, with one and two year PFS of 21% and 6% respectively (90% confidence interval 11–34% and 2–15%). Median overall survival (OS) was 10.5 months, with one and two year OS 41% and 27% respectively (90% confidence interval 27–53% and 16–39%). Analysis including only eligible patient showed similar response rates and survival outcomes. Single agent topotecan has moderate activity for previously treated high grade lymphoma equivalent to that of several newer agents, and should be considered for incorporation into multi-drug salvage chemotherapy programs.

INTRODUCTION

Topotecan, (9-dimethyl-aminomethyl-10-hydroxy-camptothecin) is a semisynthetic camptothecin analog which specifically inhibits the intranuclear enzyme, topoisomerase 1 (1). Topoisomerase 1 is an essential enzyme for DNA plasticity and repair. This enzyme causes single stranded DNA breakage to allow the relief of excess torsional strain of supercoiled DNA and then re-ligation of the DNA to restore continuity of the DNA molecule (2–3). Topotecan has shown schedule dependency in preclinical studies with improved activity with multiday administration. Topotecan is approved for the treatment of ovarian cancer and small cell lung cancer when given at a dose of 1.5 mg/m²/day over 30 minutes daily × 5 (4–5). Hochster et al previously developed a schedule for prolonged infusion topotecan using ambulatory infusion pumps (6). Topotecan was safely administered continuously for 21 days of a 28 day cycle with a recommended phase II dose of 0.53 mg/m²/day. This schedule allows greater dose intensity with less myelosuppression and possibly greater inhibition of the target enzyme topoisomerase I (7–8). In our Phase I study, one patient with previously treated lymphoma responded to therapy and, therefore, the Eastern Cooperative Oncology Group decided to undertake a Phase II study of prolonged topotecan infusion in patients with diffuse large cell lymphoma (IWF Class F) or immunoblastic lymphoma (IWF Class G) who had progressed or relapsed after one prior therapy for treatment of their lymphoma.

METHODS

Eligibility criteria included: histologically confirmed diffuse large cell lymphoma or large cell immunoblastic lymphoma (IWF histology F or G) treated with one prior chemotherapy regimen. Patients had to have fully recovered from any toxicity of prior chemotherapy before entry on study. Adequate organ function including absolute neutrophil count > 1500/ul platelet count > 100,000/ul, creatinine < 1.5 mg/dl or creatinine clearance > 60 ml/min, bilirubin < 2 mg/dl, AST < 5X the upper limit of normal. All blood tests were performed within 2 weeks prior to registration. Patients had to have measurable disease outside of prior radiation portals with at least 2 weeks' interval since completion of any radiotherapy. Patients were required to have measurable disease by physical or radiologic examination including bi-dimensionally measurable disease on CT, ultrasound, or X-ray with one lesion 2 cm in both dimensions considered reproducible by a radiologist, performed within 4 weeks of registration. Patients were required to have pathological material available for central review by a reference ECOG pathologist. Patients were registered centrally with the Eastern Cooperative Oncology Group according to standard procedures including use of a checklist to determine eligibility. Patients could not be pregnant or lactating, have active infection, serious intercurrent illness, history of neoplastic disease other than curably treated non-melanoma skin cancer or cervical carcinoma in situ, and patients could not have a history of HIV infection. Response and toxicity criteria were those of the Eastern Cooperative Oncology Group (9). All patients signed written informed consent as approved by their local institutional review boards.

Treatment

All patients were required to have a central venous access catheter and were treated with continuous infusion topotecan 0.4 mg/m²/day via ambulatory pump (e.g. CADD pump, Pharmacia Deltec, Minneapolis, MN) for the first 21 days of a 28-day treatment cycle. A 50 ml cassette was prepared at the appropriate dose on the basis of the height and weight of the patient. Topotecan was infused at a rate of 7 ml/day using the CADD pump, allowing a 1 ml reserve for delay in refilling the pump. Patients with a maximal Grade 1 toxicity in the first cycle were escalated to 0.5 mg/m²/day in the second cycle and, if this dose produced no greater than Grade 1 toxicity, subsequent cycles were given at a dose of 0.6 mg/m²/day. Patients were treated every 28 days until complete response and then received 2 additional treatment cycles beyond complete response. Patients with stable disease were continued on treatment until disease progression or unacceptable toxicity. In the event of an absolute granulocyte count < 1,000/uL or platelet count < 50,000/uL infusion was stopped and doses were decreased by 0.1 mg/m² in subsequent cycles. If patients were not able to restart treatment after a one-week delay (day 35), dosage was also decreased by 0.1 mg/m² in subsequent cycles. Radiographic evaluation of response was obtained every 2 cycles until the end of therapy and then every 3 months thereafter. Response criteria were those of ECOG; Complete response (CR) included disappearance of all disease including all evaluable disease by physical examination and radiographic CT scanning lasting 4 weeks, plus a negative unilateral bone marrow biopsy. Patients achieving > 50% reduction in measurable disease but less than a CR, also lasting greater than 4 weeks, were considered to have a partial remission (PR).

Statistical Considerations

The primary objective of this Phase II study was to evaluate the response rate of this regimen in relapsed or refractory large cell and immunoblastic lymphoma. This agent was to be considered worthy of further testing if the response rate was > 25%. Accrual would be stopped early if fewer than 2 responders were observed among the first 15 eligible patients. If 2 or more responders were observed then an additional 19 eligible patients would be accrued. Thirty-eight eligible patients were accrued under the assumption that 34 patients would be analyzable. This study continued to the second stage of accrual without stopping since the necessary number of responses were observed among the patients in the first stage. Objective response rate (complete and partial response) is reported along with the exact 90% two-stage confidence interval (CI). Complete response rate is reported with exact 90% confidence interval. The Kaplan Meier method (10) was used to estimate duration of response, disease-free survival, progression free survival and overall survival. Disease free survival was defined as time from documentation of CR to the date of relapse or death. Progression free survival was defined as interval from date of entry on study to date of relapse after a CR, time of progression from PR or stable disease, or date of death from any cause without document of relapse. Overall survival was defined as the time from entry into the study to the date of death from any cause.

RESULTS

Thirty-seven patients were entered from 14 institutions throughout the Eastern Cooperative Oncology Group. Prior chemotherapy regimens consisted mainly of CHOP-like regimens in 29 of the 37 patients (78%) with six having had a variety of other treatments including CDE, ProMACE-MOPP, and other multidrug regimens. Twelve had local radiation in conjunction with chemotherapy. Only one patient received rituximab in addition to CHOP chemotherapy. Among these 37 patients three patients were ineligible by entry criteria for having ECOG performance of 2 or greater (2 patients) or more than one prior chemotherapy regimen (1 patient). Eight patients were determined to have incorrect histology including

one patient with T cell lymphoma, one patient with anaplastic large cell lymphoma, four patients with low grade lymphoma and two patients with nodular large cell lymphoma according to local or central pathologic review. Twenty-six (70%) patients were therefore considered eligible. Due to the unexpectedly high ineligibility rate, two sets of analysis were done for all patients (n=37) and for eligible patients (n=26), respectively. Baseline characteristics are presented in Table 1. Among all the 37 patients, 92% of patients were Caucasian and 59% were female. Using International Prognostic Index (IPI), 11% were considered low risk, 30% were low intermediate risk, 46% were high intermediate risk, and 8% were high risk. The subset of eligible patients has slightly different distribution in IPI (15% low risk, 15% low intermediate risk, 54% high intermediate risk, and 8% high risk).

TREATMENT

A total of 136 cycles of therapy were given to the 37 patients with a median of 3 and a range of 1–17 cycles. Four patients achieved complete response, and completed treatment per protocol. One patient achieved PR, and was taken off study after 6 cycles by error. Twenty-four patients went off study for progression of disease, one for toxicity, three withdrew or refused further therapy, two patients had other complicating disease, and two for other reasons.

TOXICITY

Table 2 summarizes toxicities classified at least possibly treatment related for all 37 patients treated. There were five patients (14%, 90% CI: 5–26%) each with grade 4 granulocytopenia and thrombocytopenia, three patients (8%, 90% CI: 2–20%) with grade 4 leukopenia, and there was 1 case (3%) each of grade 4 anemia, hemorrhage, infection, vomiting, liver toxicity, neuromotor toxicity and thrombosis. Overall Grade 3–4 hematologic toxicity included granulocytopenia in 46% (90% CI: 32–61%), leukopenia in 43% (90% CI: 29–58%), anemia 43% (90% CI: 29–58%), and thrombocytopenia 30% (90% CI: 18–44%).

RESPONSE DATA

Table 3 summarizes the best overall response for all 37 patients as well as the 26 eligible patients. Thirty-three patients had follow up data available due to the fact that 4 patients did not receive more than 1 cycle of treatment. The median follow up was 77 months. Among all 37 patients, 5 patients obtained complete response and 4 patients obtained partial response. Overall objective response rate therefore was 24% (9/37) with a 90% two-stage confidence interval of 13–39%. Complete response rate was 14% (5/37) with 90% confidence interval of 5–26%. Eight of the 9 responders relapsed, with the duration of response ranging from 2 to 29 months. One patient who responded subsequently died without documentation of relapse, and duration of response was censored at the day he was last known to be in remission. The median duration of response was 20 months (90% CI: 3–21 months). For the 26 eligible patients, the overall objective response rate was 27% (7/26) with a 90% two-stage confidence interval of 13–45%. Complete response rate was 19% (5/26) with 90% confidence interval of 8–36%. The median duration of response was 20 months (90% CI: 2–29 months).

Figure 1 shows the Kaplan-Meier curves for progression free survival (PFS). For all patients, the median PFS was 3.7 months (90% CI: 1.8–4.9 months). The one- and two-year PFS rates and 90% confidence interval are 21% (11–34%) and 6% (2–15%), respectively. For eligible patients, the median PFS was 4.4 months (90% CI: 2.2–7.4 months). The one- and two-year PFS rates and 90% confidence interval are 26% (13–42%) and 9% (2–21%), respectively. Figure 2 shows the Kaplan-Meier curves for overall survival. For all patients, the median overall survival was 10.5 months (90% CI: 6.5–13.9 months) with one- and two-year overall survival of 41% (90% CI: 27–53%) and 27% (90% CI: 16–39%), respectively.

For eligible patients, the median overall survival was 12.5 months (90% CI: 7.6–17.8 months) with one- and two-year overall survival of 50% (90% CI:33–65%) and 31% (90% CI:17–46%), respectively.

DISCUSSION

Topotecan, a topoisomerase inhibitor, was developed primarily in a multi-day bolus schedule. We developed a 21-day continuous infusion as a way to take advantage of the schedule dependency of this agent with resulting lower hematologic toxicity. In our Phase I study we observed a response in a patient who had received multiple prior regimens for large cell lymphoma, and that observation led to this multicenter Phase II study. The results of this study, approximately 30% response rate for patients who have failed one prior chemotherapy regimen for large cell or immunoblastic lymphoma, is among the highest reported salvage response rates for a single agent.

Newer single agents with significant activity against refractory and relapsed diffuse large B-cell lymphoma include lenalidomide and rituximab. Two phase II studies of lenalidomide (11,12) have yielded an objective response rate of 35% including complete response rates of 12% (11) and 22% (12), similar to the 19% complete response rate obtained with topotecan in the present study. Phase II studies of rituximab have yielded similar complete and overall response rates in comparable patient populations (13). Phase II studies of bendamustine in relapsed/refractory diffuse large B-cell lymphoma are too early to fully evaluate (14). Other phase II studies suggest that bortezomib is less active in large cell lymphoma than is topotecan in the schedule used in the present study (15).

Other investigators have reported the efficacy of topotecan in the treatment of lymphoma and myelodysplastic syndromes (16). In these lymphoma studies, investigators used daily 30-minute infusion of topotecan alone or with etoposide or paclitaxel. Kraut et al reported the single agent activity ($1.25 \text{ mg/m}^2 \times 5 \text{ days}$) for a mixed group of 29 patients with indolent and aggressive lymphoma and reported a response rate of 17% including 2 CRs (17). MD Anderson investigators treated 71 aggressive lymphoma patients with paclitaxel (200 mg/m^2) and topotecan 1.0 mg/m^2 daily $\times 5$, together with G-CSF, following one or two prior chemotherapy regimens. The overall response rate was 48%, with 31% in patients with primary refractory disease and 65% in those who responded to prior therapy. No CRs were reported (18). Also, topotecan (1.0 to $2.5 \text{ mg/m}^2/\text{day} \times 5 \text{ days}$) was combined with etoposide ($150 \text{ mg/m}^2/\text{day} \times 5 \text{ days}$) and G-CSF for patients with recurrent or refractory aggressive NHL (19). The maximum tolerated dose of topotecan was 2.0 mg/m^2 with dose-limiting mucositis. In 21 patients, those investigators reported 3 CRs and 5 PRs (38%). All responders formed covalent topoisomerase-DNA complexes, compared with only 4/13 non-responders.

Since the publication of our infusion data others have reported the utility of topotecan using 5-day continuous infusion at higher doses than those used in this study. The myelosuppression of the higher dose, shorter infusion leads to prolonged cytopenia and eventual recovery of bone marrow function. The original studies of 10 mg/m^2 infused over 120 hours yielded complete response rates of approximately 28% in patients with MDS (20). These investigators then combined topotecan with ara-C, which led to a 56% complete response rate including those with adverse risk factors (21). This combination, albeit at lower doses, could also be considered for combination salvage therapy of large cell lymphoma using the 21-day topotecan infusion schedule. This regimen may be more easily tolerated than cisplatin based salvage regimens and may be given on an outpatient basis.

In conclusion, topotecan prolonged infusion has very reliable activity in patients with pre-treated aggressive lymphoma. The response rate for the infusion program is similar to the daily $\times 5$ schedules reported from some but not all other studies (17), and does not require the use of growth factor support. Others have used higher dose, shorter infusions for the successful therapy of CMML and MDS. Further investigation of combination drug therapy based on topotecan continuous infusion for the salvage treatment of large cell lymphoma is warranted based on this result.

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Figure 1.
Progression Free Survival

Figure 2.
Overall Survival

Table 1

Baseline Characteristics

Patient Characteristics	All patients (N=37)		Eligible patients (N=26)	
	N	%	N	%
Age (in years)				
Median (Range)	68 (20–80)		68 (20–80)	
Gender				
Male	15	41%	10	38%
Female	22	59%	16	62%
Race				
White	34	92%	25	96%
Black	2	5%	1	4%
Hispanic	1	3%		
B-Symptoms				
Yes	21	57%	14	54%
No	16	43%	12	46%
ECOG Performance Status				
0	12	32%	12	46%
1	25	68%	14	54%
Stage				
I	8	22%	6	23%
II	5	14%	3	12%
III	8	22%	5	19%
IV	16	43%	12	46%
Extranodal Sites				
0	10	27%	7	27%
1	17	46%	11	42%
2	7	19%	6	23%
>2	3	8%	2	8%
Serum LDH *				
< ULN **	1	3%	1	4%
>ULN	34	92%	23	88%
Missing	2	5%	2	8%
IPI ***				
Low Risk	4	11%	4	15%
Low Intermediate Risk	11	30%	4	15%
High Intermediate Risk	17	46%	14	54%
High Risk	3	8%	2	8%
Missing	2	5%	2	8%

* LDH, lactic dehydrogenase;

** ULN, upper limit of laboratory normal;

IPI, International Prognostic Index

Table 2

Grade 3 and Above Toxicities for 37 Treated Patients

Type	Grade	
	3	4
Leukopenia	13	3
Granulocytopenia	12	5
Thrombocytopenia	6	5
Anemia	15	1
Hemorrhage	-	1
Infection	-	1
Nausea	3	-
Vomiting	1	1
Diarrhea	2	-
Stomatitis	1	-
Liver	2	1
Pulmonary	1	-
Local (No Phlebitis)	1	-
Neuro-motor	2	1
Metabolic	1	-
Anorexia	1	-
Fatigue	1	-
Ileus	1	-
Thrombosis	-	1
LDH, elevated	1	-
WORST GRADE	13	12

Table 3

Best Overall Response

Response	All patients (n=37)		Eligible patients (n=26)	
	N	%	N	%
CR	5	14%	5	19%
PR	4	11%	2	8%
SD	8	22%	6	23%
PD	16	43%	10	38%
Uneval [*]	4	11%	3	12%

^{*} These four patients only received one cycle of treatment and went off study due to patient withdrawal or refusal (2), other complicating disease (1), and excessive toxicity (1), respectively.