Available online at www.sciencedirect.com

SCIENCE DIRECT

Gynecologic Oncology 98 (2005) 217 – 221

Gynecologic Oncology

www.elsevier.com/locate/ygyno

Phase II evaluation of topotecan in carcinosarcoma of the uterus: A Gynecologic Oncology Group study

David Scott Miller[a,*], John A. Blessing[b], Jeanne Schilder[c], Adnan Munkarah[d], Yi Chun Lee[e]

[a]*Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Texas, Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., J7.124, Dallas, TX 75390-9032, USA*

[b]*Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY 14263, USA*

[c]*Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, IN 46202, USA*

[d]*Division of Gynecologic Oncology, Wayne State University, Detroit, MI 48201, USA*

[e]*Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, State University of New York Health Science Center at Brooklyn, Brooklyn, NY 11203, USA*

Received 5 November 2004
Available online 22 June 2005

Abstract

Objectives. To estimate the antitumor activity of topotecan in patients with persistent or recurrent carcinosarcoma (malignant mixed mullerian tumors) of the uterus and to determine the nature and degree of toxicity of topotecan in this cohort of patients.

Materials and methods. Eligible patients had measurable advanced or recurrent carcinosarcoma of the uterus. Topotecan at a target dose of 1.5 mg/m^2 was administered IV daily for 5 days, every 3 weeks, until progression of disease or adverse affects prohibited further therapy.

Results. Twenty-seven member institutions entered 51 patients. Of the patients entered, 48 were eligible. Patient characteristics included a median age of 65, with 33% having prior radiation and 92% having prior chemotherapy. Twenty-six patients (54%) had a performance status (PS) of 0, 18 (38%) had a PS of 1, and four (8%) had a PS of 2. Patients received from 1 to 21 (with a median of 2) courses of treatment. The most frequently observed grade 4 toxicities were neutropenia seen in 35 (73%) patients, leukopenia in 14 (29%), and thrombocytopenia in 10 (21%). Three (6%) patients developed neutropenic sepsis and died shortly after their first treatment cycle. There were five (10%) complete responses; 13 (27%) patients maintained stable disease, 26 (54%) experienced increasing disease, and reassessment did not occur in four (8%).

Conclusion. Topotecan at this dose and schedule does not appear to have major activity in patients with advanced or recurrent uterine carcinosarcoma previously treated with chemotherapy.

Keywords: Uterine neoplasms; Carcinosarcoma; Topotecan; Camptothecin; Topoisomerase-1 inhibition

Introduction

Advanced or recurrent carcinosarcoma of the uterus portends a grim prognosis. The Gynecologic Oncology Group (GOG) has embarked on a series of phase II trials to identify potentially active cytotoxic agents for the treatment of advanced or recurrent carcinosarcoma [1–12]. To date, only two cytotoxic drugs, cisplatin and ifosfamide, have demonstrated definite activity in this disease [2,4,7,12]. Topotecan is a semi-synthetic derivative of camptothecin and is an antitumor drug with topoisomerase 1-inhibitory activity. It is approved by the FDA for second line treatment of ovarian and small cell lung cancers. Results from preclinical studies showed that it is active against several sarcoma and gynecologic cancer cell lines [13,14]. Thus, a phase II non-comparative trial of topotecan was initiated in patients with advanced uterine carcinosarcoma.

* Corresponding author. Fax: +1 214 648 8404.
E-mail address: david.miller@utsouthwestern.edu (D.S. Miller).

0090-8258/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2005.05.015

Materials and methods

Eligible patients had histologically confirmed advanced, persistent, or recurrent uterine carcinosarcoma (malignant mixed mullerian tumors) and measurable disease defined as tumors that could be assessed in at least two dimensions by palpation, X-ray, computerized tomography, or ultrasound. They must have failed local therapeutic measures and be considered incurable but have received no more than one prior chemotherapy regimen.

Patients with a history of other invasive malignancy within the previous 5 years, other than non-melanoma skin cancer, were excluded. Also required was a GOG performance status (PS) of 0–2, as well as granulocytes >1500/mcl, platelets >100,000/mcl, creatinine >1.5 mg%, creatinine clearance >20 ml/min as well as adequate liver function including bilirubin <1.5× institutional normal, along with SGOT and alkaline phosphatase <3× institutional normal. They were to have recovered and be without infection. Patients provided written informed consent consistent with current institutional, state, and federal regulations prior to study entry.

Topotecan was to be given at an intended dose of 1.5 mg/m^2/day given as a 30-min intravenous infusion for 5 days every 3 weeks. Following two patient deaths due to neutropenic sepsis after the first cycle, the protocol was amended in July 1999 so that the beginning dose was adjusted for age, previous pelvic radiation, and creatinine clearance (Table 1) [15]. Subsequent doses were modified for grade 4 granulocytopenia, grade 3 thrombocytopenia, or grade 4 non-hematologic toxicity. Use of growth factors was permitted only for patients who had febrile neutropenia or delay in recovery of granulocytes beyond day 22. Patients were to undergo history, physical, and laboratory evaluation prior to each cycle of topotecan and, for tumor/s measurable only by computerized tomography or MRI, such tests were to be performed every 6 weeks. Hematologic parameters were to be monitored weekly. Patients who received at least one dose of topotecan were evaluable for toxicity, and those who survived at least 4 weeks were evaluable for response.

Response was determined according to standard GOG criteria [16]. The minimum treatment was one course, and patients were to remain on study until disease progression or adverse affects prohibited further therapy. The study was designed to test the hypothesis that the true response rate was 0.10 versus the alternative that it was 0.30. A two-stage sampling plan was employed that featured accrual of 25 patients in the first stage. The hypothesis that the true response rate was 0.30 would be rejected if fewer than four responses were noted. Observation of four or more responses would indicate a second stage of accrual for that regimen with an additional accrual of approximately 15 patients. The hypothesis that the response rate was 0.30 would be rejected if fewer than eight responses were noted. This design featured a size of 0.04 and power of 0.93.

Table 1
Basis for initial topotecan dosing

Creatinine clearance (ml/min)[a]	Not high risk (mg/m^2/day)	High risk (mg/m^2/day)
>60	1.5	1.5
40–59	1.5	1.0
20–39	0.75	0.5

Note. Initial dosage was determined by renal function, age, and history of prior radiation according to the table above. High risk is defined as, age > 70 years; or prior abdominal or pelvic radiation therapy.

[a] Creatinine clearance was measured or estimated by the method of Cockroft-Gault or Jeliffe.

Results

From June 1998 to November 1999 and September 2000 to July 2001, this phase II trial was open to member institutions of the Gynecologic Oncology Group. Fifty-one patients were entered from 27 GOG member institutions. Three patients were histologically ineligible because of wrong cell type (2) or stage (1); the remaining 48 constitute the basis of this report. Patient characteristics are displayed in Table 2. Per protocol guidelines, patients received initial doses as follows: 1 received 0.5 mg/m^2; 6 received 1.0 mg/m^2; 11 received 1.25 mg/m^2; and 30 received 1.5 mg/m^2. Fourteen patients received only one, eleven received two, and the remaining twenty received more than two cycles. All of the four who were inevaluable for response received one course. The most common toxicities greater than or equal to grade 1 were neutropenia, leukopenia, anemia, and/or thrombocytopenia, seen in 91% of patients, and GI, seen in 40% of patients (Table 3). The median WBC for those 44 patients who experienced leukopenia was 1150 (range: 100–3570). Among the 35 patients experiencing thrombocytopenia, the median platelet nadir was 46,700 (range: 500–146,000). The most frequent grade 4 adverse effects were neutropenia (73% of patients), leukopenia (29% of patients), and thrombocytopenia (21% of patients). Three patients developed neutropenic sepsis and died shortly after their first treatment cycle. The only commonalities of these patients were previous radiation therapy, impaired calculated creatinine clearance (42–75 ml/min), and renal failure at presentation with their neutropenic sepsis. Following the first two cases and review by the GOG Data Safety Monitoring Board, the protocol was amended so that the starting dose of topotecan was adjusted for age, previous pelvic radiation, and creatinine clearance (Table 1) [15].

The total response rate was 10%, with five patients achieving a complete response and none experiencing a partial response (95% confidence interval [CI]: 3.5%–22.7%) with a median response duration for the complete responders of 8.3 months. Tumor remained stable in 13 (27%) patients, 26 (54%) patients experienced increasing disease, and response could not be assessed in four patients (8%). According to GOG response criteria, these latter