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A phase II evaluation of ixabepilone in the treatment of recurrent/persistent carcinosarcoma of the uterus, an NRG Oncology/Gynecologic Oncology Group study[☆]

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Abstract

Background—The primary objectives were to determine the objective response rate (ORR) and safety profile of ixabepilone in women with recurrent or persistent uterine carcinosarcoma (UCS). Secondary objectives included progression-free survival (PFS) and overall survival (OS). Exploratory translational objectives included characterization of class III beta tubulin expression and its association with response, PFS, and OS.

Methods—Patients had measurable disease; up to two prior chemotherapeutic regimens were allowed, but must have included a taxane. Women received ixabepilone 40 mg/m² as a 3 hour IV infusion on day 1 of a 21 day cycle. Treatment was continued until disease progression or unacceptable toxicity occurred.

Results—Forty-two women were enrolled, with 34 eligible and evaluable. Median age was 68 years. ECOG performance status was 0 in 56% of women, 38% had received radiation, and 15% had received 2 lines of chemotherapy. Overall ORR was 11.8% (4/34, 90% CI 4.2–25.1%); all were partial responses. Stable disease for at least 8 weeks was achieved in 8 patients (23.5%). Median PFS and OS were 1.7 mo and 7.7 mo, respectively, with a median follow-up of 37 mo. Six month PFS was 20.6%. Major grade 3 toxicities were neutropenia (47%), fatigue (15%), dehydration (15%), hypertension (15%), and hyponatremia (15%); grade 2 peripheral neuropathy was reported in 18%. In this small sample size, class III beta tubulin expression in the primary tumor was not associated with the response to ixabepilone, PFS, or OS.

Conclusion—In this cohort of women, single agent ixabepilone showed modest but insufficient clinical activity.

Keywords

Ixabepilone; Carcinosarcoma

1. Introduction

Uterine carcinosarcoma is a rare aggressive neoplasm characterized by malignant epithelial and mesenchymal elements. Previously considered and categorized with uterine sarcomas, more recent data suggest it is more accurately described as a de-differentiated carcinoma [1,2]. While this histologic type accounts for fewer than 5% of all uterine malignancies, it is associated with a high incidence of extra uterine disease at the time of diagnosis, as well as

high recurrence rates despite the aggressive use of adjuvant therapy, including chemotherapy and radiation. Previous studies have identified cisplatin, carboplatin, ifosfamide, and paclitaxel as agents with significant clinical activity in the chemotherapy naïve population. Response rates (RR) with these agents, either single agent or in combination, range from 20 to 54%[3–9], yet, five year survival rates are poor, ranging from 35 to 62%[3–5,10,11].

For women who relapse after first line treatment, there is a paucity of known active agents. The Gynecologic Oncology Group (GOG) has formally evaluated novel therapies for these women and only paclitaxel has demonstrated moderate activity with a response rate of 17%; however, the eligibility for this trial required no prior taxane therapy [12]. Topotecan, gemcitabine with docetaxel, oral trimetrexate, thalidomide, imatinib mesylate, and pazopanib have all been investigated as second line regimens and appear to have minimal or limited activity [13–18].

The epothilones are a novel class of non-taxane microtubule stabilizers with unique properties obtained by fermentation of the myxobacterium *Sorangium cellulosum* [19,20]. The cytotoxic activity of epothilones, like those of the taxanes, has been linked to suppression of cell growth by promoting accelerated assembly of stable microtubules, which consequently leads to cell cycle arrest at the G2-M transition, and eventual cell death [19,21]. Mechanistically, epothilone B disrupts microtubule dynamics by stabilizing the microtubule against depolymerization, thereby enhancing microtubule polymerization. Ixabepilone (BMS-247550) is a semi-synthetic analog of epothilone B specifically designed to overcome the metabolic instability of the natural product as demonstrated in preclinical models. It binds to the same site on beta tubulin as paclitaxel and, in preclinical models, appears to be a more potent polymerizer of tubulin than paclitaxel [19,20,22,23]. The tubulin polymerizing activity of epothilone Bis two to 10 times more potent than either paclitaxel or docetaxel [24–27]. Apreclinical study evaluating the activity of patupilone, another epothilone B analog, in two uterine carcinosarcoma cell lines similarly found increased sensitivity compared to paclitaxel [28].

Tubulin, the major building block of microtubules, functions as structural and mobile elements in mitosis, intracellular transport, and in the cytoskeleton. Studies have shown that increased tumor expression of a particular tubulin isotype, class III beta-tubulin, correlates with poor clinical outcomes in patients with various malignancies [29–31]. These include breast, ovarian, and gastric cancers, as well as non-small cell lung cancer. Studies suggest that the poor clinical outcomes in the setting of class III beta-tubulin overexpression are related to resistance to the tubulin-binding chemotherapeutic agents, taxanes and vinca alkaloids, commonly used in the treatment of these malignancies. There are limited reports on class III beta-tubulin expression in uterine serous carcinoma that similarly show it to be associated with poor prognosis and a marker for both paclitaxel resistance and sensitivity to epothilones [32]. Levels of expression of class III beta-tubulin in uterine carcinosarcomas have not been extensively studied.

In both Phase I and II clinical trials, objective responses with ixabepilone have been shown in a broad range of tumor types, both those considered to be sensitive, as well as those considered relatively insensitive to taxanes [33]. Treatment with ixabepilone generated

objective responses in patients with large cell and non-Hodgkin's lymphoma, peritoneal, endometrial, vulvar, head and neck, ovarian, cervical, colon, breast and lung carcinomas, mesothelioma and melanoma [34]. A phase II study in recurrent or persistent endometrial carcinoma, GOG-129P, demonstrated objective responses in 12% of patients and stable disease in 60% [35]. In light of the previous activity seen in other tumor types, as well as the known activity of microtubule agents-like taxanes-in this disease site, we initiated a national, multiinstitutional phase II, non-comparative trial of ixabepilone in women with recurrent or persistent uterine carcinosarcoma (UCS) who were previously treated with a taxane. The primary objectives were to determine the objective response rate (ORR) by RECIST 1.1 and side effect profile of ixabepilone in this patient population. Secondary objectives included defining the duration of progression-free survival (PFS) and overall survival (OS). Exploratory translational objectives involved characterization of class III beta tubulin expression and its association with response, PFS, and OS.

2. Materials & methods

2.1. Patient selection/eligibility

Eligible women had histologically confirmed advanced, persistent, or recurrent uterine carcinosarcoma and measurable disease defined by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) [36]. The GOG Pathology Committee performed histologic confirmation by central review. All women must have received one prior cytotoxic chemotherapy regimen for management of their disease. For women who had not received a taxane as part of their initial management, a second, taxane containing regimen was required to be eligible. Finally, women were allowed to receive one non-cytotoxic regimen for management of recurrent or persistent disease; these agents could include monoclonal antibodies, cytokines, and small molecule inhibitors of signal transduction. Additional eligibility included a GOG performance status of 0–2, and adequate bone marrow, renal, and hepatic functions. Grade 2 or greater neuropathy was exclusionary. Patients signed an approved informed consent. The protocol was approved by the Institutional Review Board of each participating GOG institution.

2.2. Treatment

All patients had baseline imaging within four weeks of starting therapy. History and physical examination, and assessment of toxicity was performed for each cycle of therapy. Ixabepilone was supplied by the National Cancer Institute (IND#59699, NSC#710428) and administered at 40 mg/m² intravenously over 3 h on day one of each 21 day cycle. Body surface area was capped at 2.0 m². Recommended premedication for ixabepilone infusions included an H1 and H2 antagonist 30–60 min prior to infusion to reduce the risk of hypersensitivity reactions.

Hematologic treatment decisions were based on the absolute neutrophil count (ANC), and subsequent cycles of therapy were initiated when the ANC was 1500 cell/mcl and platelet count was 100,000/mcl. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria Version 4.0 (CTCAEv4) [37]. Subsequent doses were modified for grade 4 or febrile neutropenia, grade 4 thrombocytopenia, grade 2 or greater peripheral neuropathy,

grade 2 or greater renal toxicity, grade 3 or greater elevation in liver function, or other grade 2 non hematologic toxicities that required a delay in therapy. Treatment could be held for up to three weeks, and two dose reductions were permitted (32 mg/m², 25 mg/m²) prior to removal from the study. Treatment was continued until progressive disease or adverse effects prohibited further therapy.

Patients did not receive prophylactic growth factors (i.e. filgrastim, sargramostim, or pegfilgrastim) unless they experienced recurrent febrile neutropenia and/or recurrent documented grade 4 neutropenia that persisted for seven days despite dose reductions. Patients were allowed to receive erythropoietin, iron supplements, and/or transfusions as clinically indicated for anemia.

2.3. Quantification of class III beta tubulin expression

Immunohistochemistry (IHC) was performed on formalin-fixed paraffin-embedded tissue sections on a Dako Autostainer. High pH antigen retrieval was performed followed by incubation with the primary antibody, anti (β-tubulin isotype III (Sigma-Aldrich® T5076; produced in mouse). An Envision + Dual Link System (Peroxidase polymer (Dako) with a DAB chromogen) was then used to stain the sections. The EnVision + Dual Link System-HRP is a two-step IHC staining technique which uses a peroxidase labeled polymer which is conjugated with secondary antibodies (goat anti-mouse) followed by incubation with a DAB chromogen. Scoring of the IHC staining was based on the percentage of tumor cells showing beta III tubulin expression increased in intensity in comparison to background staining. Ascore of zero was designated when b 1%(none), 1 when 1–10%(mild/focal), 2 when N 10%(moderate), or 3 when N50%(strong) of tumor cells showed over expression, respectively (Fig. 1).

2.4. Evaluation criteria

Response assessments were performed by imaging every two cycles (every six weeks). Response and progression were based on RECISTv 1.1. Patients who received at least one dose of ixabepilone were considered evaluable for both toxicity and efficacy. Symptomatic deterioration was defined as global deterioration in health status attributable to the disease that required a change in therapy without objective evidence of progression of disease.

OS was defined as the observed length of life from entry into the study to death or to the date of last contact. PFS was defined as the duration of time from the entry into the study to the date of progression, death, or last contact, whichever occurs first.

2.5. Statistical methods

The primary objective of this study was to assess the activity of ixabepilone in women with persistent or recurrent uterine carcinosarcoma as measured by the frequency of patients who have an objective tumor response. The null hypothesis (H0) relating to uninteresting levels of activity was determined from an analysis of a historical dataset based on a similar population of patients, where the activity levels were believed to be inactive to modestly active. The null hypothesis specified that the probability of a patient experiencing a tumor

response would be 5% Clinically interesting probabilities of response was determined to be 25%

To evaluate this hypothesis, we employed an optimal, but flexible, two-stage study design that used an early stopping rule intended to limit patient accrual to inactive treatments [38,39]. During the first stage, the accrual was 19 eligible and evaluable patients, but permitted to range from 15 to 22 patients; observation of at least one out of the 19 patients with objective tumor responses would prompt continuation to the second stage of accrual. During the second stage, the overall study accrual would be 34 eligible and evaluable patients, but permitted to range from 30 to 37 patients. If five or more out of the 34 patients had objective responses, the regimen would be considered worthy of further investigation. The average type I and II error rates for this study were design were approximately 5% The average probability of early termination when the agent was inactive was 53% Kaplan-Meier method was used to estimate the median of PFS and OS [40]. The associations of class III beta tubulin expression with response, PFS, or OS were explored by a Spearman's rank correlation coefficient or univariate Cox proportional hazards model [41]. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Patient characteristics

Forty-two women were enrolled over a three year period. The first stage of accrual was achieved over 18 months following activation; the second stage accrued over a 10 month period. Eight patients were deemed ineligible, six due to wrong cell type (14%), one due to inadequate pathology, and one because of a second primary cancer. Thirty-four women were therefore eligible for response and toxicity. Patient demographics are listed in Table 1. The median age was 68 years (range 52–81 years). Twenty-four percent (N = 8) were African-American. Performance status was 0 in 56% of women. All had previously undergone surgery, 38% had previous radiation, and 15% received two prior lines of chemotherapy.

3.2. Adverse events

All reported adverse events by highest grade as assessed by CTCAE v4 are listed in Table 2. The major, grade 3 or 4 toxicities were neutropenia (47%), decreased white blood cell (44%), anemia (15%), fatigue (15%), dehydration (15%), hypertension (15%), and hyponatremia (15%). Febrile neutropenia occurred in 6% of patients. Grade 2 or 3 peripheral neuropathy was reported in 21%

There were six deaths reported during the period of active treatment or within 30 days of last study treatment. Four of these women received only one cycle of study treatment. One death possibly related to therapy occurred nine days following treatment; the patient experienced progressive weakness with nausea, vomiting, diarrhea, dehydration, and hypotension. Two deaths were directly attributed to progressive disease. Three additional deaths were related to respiratory failure/distress; these were not felt to be directly related to study treatment, but more likely to symptomatic deterioration, rapidly declining performance status, and likely progressive disease.

3.3. Treatment response and survival

The median number of cycles delivered was two (range 1–10). There were four patients (11.8%) with confirmed partial response (90% confidence interval [CI]: 4.2–25.1%); there were no complete responses (Table 3). Eight patients (23.5%) had stable disease as their best response, and 16 (47.1%) experienced progressive disease. Seven women (20.6%) survived progression-free for at least 6 months (PFS $\geq$ 6 months). Seven women received only one cycle of protocol directed therapy, and they were included in the evaluation of ORR and adverse event reporting. According to the study decision rules, the study did not meet its prespecified objectives. With a median follow up of 37 months, median PFS and OS were 1.7 (90% CI: 1.3–2.8) and 7.7 months (90% CI: 4.4–11.1), respectively (Fig. 2).

3.4. Translational results

Translational specimens were received from 34 enrolled patients. Five specimens were excluded based on ineligible cell type, and two specimens did not contain adequate tissue for immunohistochemical processing. The primary tumor was submitted in all cases and therefore was the tissue type selected for comparative analysis of class III beta tubulin expression in the remaining 27 specimens. Fifteen specimens demonstrated no or only focal/mild overexpression of class III beta tubulin; twelve specimens revealed moderate to strong overexpression.

An arbitrary significance level of 0.05 was used to classify individual statistical hypothesis test results as interesting and worthy of further investigation. There were no interesting associations of class III beta tubulin expression in the primary tumor with tumor response, PFS, or OS. The Spearman's rank correlation coefficient for class III beta tubulin expression score with tumor response was 0.08. The hazard ratios of high beta tubulin expression (score $\geq$ 1) versus low beta tubulin expression (score $\leq$ 1) for PFS and OS were 0.89 (95% CI: 0.4–1.97) and 0.73 (95% CI: 0.32–1.66), respectively.

4. Discussion

Successful treatment of uterine carcinosarcoma continues to be a challenge in both the adjuvant and recurrent settings. Current adjuvant treatment paradigms for this disease now include combination chemotherapy. While ifosfamide and paclitaxel is considered the most active regimen based on the phase III trial GOG-161, the use of ifosfamide is cumbersome and can result in significant toxicity [5]. The combination of carboplatin and paclitaxel demonstrated a promising response rate of 54% in a non-comparative phase II trial in chemotherapy naive women with advanced or recurrent measurable disease [8]. PFS and OS in these adjuvant studies was still only 5.8 or 7.6 months, and 13.5 or 14.7 months, respectively. A randomized phase III trial comparing ifosfamide and paclitaxel to carboplatin and paclitaxel, GOG-261, has completed accrual and analysis of endpoints is ongoing; eligibility for this study again required no prior chemotherapy, but included all stages of disease without measurable tumor, as well as recurrent measurable disease. Therefore, there is a continuing need for clinical trials in the recurrent setting.

The more recent clinical studies in the recurrent setting, where women have received prior chemotherapy and approximately 20–40% had undergone radiation, reveal a different and more refractory patient population than previously studied [12–18]; in this study 15% of women had received two prior lines of chemotherapy and 38% had received radiation. Both novel cytotoxics and biologic targeted approaches have thus far been unsuccessful in demonstrating any significant antitumor activity. The extremely aggressive pattern of recurrence and progression with this tumor provide a seemingly small window of opportunity to administer potentially effective therapies. In this study, four women (12%) only received one cycle of treatment and subsequently died within 30 days of their last treatment; unfortunately, this is not a unique occurrence. In most of the GOG trials in this clinical setting, 16–57% of the participating women received less than two cycles of the prescribed treatment [13–17].

While timely patient accrual to this trial was quite successful despite its relative rarity, histologic exclusions occurred in 14% of the enrolled patients and are not uncommon given the complex pathologic appearance of this tumor. For this reason, central pathology review should continue to be included in the eligibility criteria for these clinical trials. With regard to the translational objectives of the study, class III beta tubulin did not show any significant associations with demographic or pathologic characteristics, nor did it correlate with treatment or survival outcomes. Quantification of class III beta tubulin was challenging. First, all of the tumors expressed class III beta tubulin to some extent, and many of the tissue sections available for review had little background normal endometrial tissue for relative comparison. Second, because these are biphasic tumors, the two components invariably stained differently, with the epithelial/carcinomatous component staining much more strongly than the stromal/sarcomatous component.

In conclusion, in this phase II study, ixabepilone did not meet the prespecified endpoints to warrant further investigation in carcinosarcoma. Future studies should be aimed at understanding the molecular characteristics and potential driver mutations that occur in this uncommon disease in the hope of identifying targeted therapies. Clinical trial participation should continue to be encouraged.

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HIGHLIGHTS

- Prospective Phase II trial of ixabepilone in recurrent or persistent uterine carcinosarcoma
- The objective response rate of nearly 12% did not meet the predefined criteria for clinical activity.
- Median progression free survival was 1.7 months and median overall survival was 7.7 months.

Fig. 1.
Examples of class II beta tubulin IHC expression.

Fig. 2.
Progression Free (PFS) and Overall survival (OS).

Table 1

Patient demographics.

Characteristic	Ixabepilone	
	n	%
Age (years)		
50–59	7	20.6
60–69	13	38.2
70–79	12	35.3
80–89	2	5.9
Ethnicity		
Hispanic	1	2.9
Non-Hispanic	30	88.2
Undeclared	3	8.8
Race		
American Indian	1	2.9
African American	8	23.5
White	25	73.5
Performance status		
0	19	55.9
1	11	32.4
2	4	11.8
Number of prior regimens		
1	29	85.3
2	5	14.7
Prior radiation		
Yes	13	38.2
No	21	61.8
Prior surgery		
Yes	34	100.0
Total	34	100.0

Table 2

All reported adverse events by highest grade assessed by CTCAE v 4 without regard to attribution.

System Organ Class	Ixabepilone (n = 34)										
	No. and (%) of patients by grade										
	1	2	3	4	5						
Overall highest grade	2 (5.9)	4 (11.8)	15 (44.1)	7 (20.6)	6 (17.6)						
Blood and lymphatic system disorders	14 (41.2)	3 (8.8)	3 (8.8)	3 (8.8)	0 (0.0)						
Cardiac disorders	2 (5.9)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)						
Ear and labyrinth disorders	6 (17.6)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)						
Eye disorders	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)						
Gastrointestinal disorders	11 (32.4)	8 (23.5)	6 (17.6)	0 (0.0)	0 (0.0)						
General disorders and administration site conditions	6 (17.6)	12 (35.3)	8 (23.5)	0 (0.0)	1 (2.9)						
Immune system disorders	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)						
Infections and infestations	1 (2.9)	3 (8.8)	2 (5.9)	1 (2.9)	0 (0.0)						
Injury, poisoning and procedural complications	2 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)						
Investigations	6 (17.6)	7 (20.6)	10 (29.4)	9 (26.5)	0 (0.0)						
Metabolism and nutrition disorders	6 (17.6)	4 (11.8)	11 (32.4)	1 (2.9)	0 (0.0)						
Musculoskeletal and connective tissue disorders	14 (41.2)	4 (11.8)	1 (2.9)	0 (0.0)	0 (0.0)						
Neoplasms benign, malignant and Unspecified	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.9)						
Nervous system disorders	10 (29.4)	12 (35.3)	2 (5.9)	1 (2.9)	0 (0.0)						
Psychiatric disorders	5 (14.7)	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)						
Renal and urinary disorders	10 (29.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)						

Isabepilone (n = 34)					
System Organ Class	No. and (%) of patients by grade				
	1	2	3	4	5
Reproductive system and breast disorders	3 (8.8)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	10 (29.4)	4 (11.8)	2 (5.9)	0 (0.0)	3 (8.8)
Skin and subcutaneous tissue disorders	4 (11.8)	14 (41.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	1 (2.9)	2 (5.9)	7 (20.6)	1 (2.9)	0 (0.0)

Table 3

Patient response and progression-free survival status.

Characteristic	Ixabepilone	
	n	%
Response by RECIST 1.1		
Partial response	4	11.8
Stable disease	8	23.5
Increasing disease	16	47.1
Indeterminate	6	17.6
PFS N 6 months		
Yes	7	20.6
No	27	79.4
Total	34	100.0