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Phase II evaluation of eribulin mesylate (E7389, NSC 707389) in patients with metastatic or recurrent squamous cell carcinoma of the head and neck: Southwest Oncology Group trial S0618

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Summary

Purpose—Eribulin mesylate, an halichondrin B analog, binds to tubulin and microtubules and possesses broad anti-cancer activity. We conducted a multi-institutional Phase II trial to evaluate the response rate of eribulin mesylate in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN).

Experimental Design—Forty eligible patients who had not received prior chemotherapy for metastatic or recurrent SCCHN were enrolled with the following characteristics: 29 male, 11 female; median age 61.2 years; Zubrod Performance Status of 0 (48%) and 1 (53%). Thirty-three patients (83%) had metastatic disease. Primary tumor sites included: 38% oropharynx, 30% lip/oral cavity, 15% larynx, 10% hypopharynx, 5% other/unknown and 3% nasopharynx. Patients received eribulin mesylate at 1.4 mg/m² on Days 1 and 8 of an every 21-day cycle.

Results—Common Grade 3 and 4 toxicities included: lymphopenia (15%), leukocytopenia (13%), neutropenia (10%), hyponatremia (5%), fatigue (5%), diarrhea (5%) and dyspnea (5%), with one treatment-related death due to pulmonary hemorrhage. Among 40 assessable patients, two confirmed partial responses were observed, for an estimated confirmed response rate of 5%

(95% confidence interval: 1–17%). The estimated median progression-free survival is 3 months (95% confidence interval: 1–3 months) and estimated median overall survival is 7 months (95% confidence interval: 5–10 months).

Conclusions—Eribulin mesylate given on Days 1 and 8 of a twenty-one day cycle in metastatic or recurrent SCCHN was well tolerated, but did not result in a clinically significant median PFS. Studies of other agents should be considered in this setting.

Keywords

Eribulin mesylate; Head and neck cancer

Introduction

Head and neck cancers account for 6% of all cancers worldwide, with nearly 48,000 new cases in the United States each year. For patients with recurrent or metastatic disease, the prognosis is extremely poor. Standard cisplatin-based therapy for recurrent and/or metastatic squamous cell carcinoma of the head and neck provides a response rate of 30–40% and a median survival of 6 to 9 months [1]. Patients experiencing disease progression on platinum-based palliative chemotherapy have a dismal prognosis, with a median survival of approximately 100 days with conventional chemotherapy [2] and 178 days with single-agent anti-Epidermal Growth Factor Receptor (EGFR) inhibitor, cetuximab [3]. Novel agents are desperately needed to improve the overall survival in patients with metastatic and recurrent head and neck cancer.

The halichondrin class of pharmaceuticals was first isolated by Uemura and Hirata from the western Pacific sponge *Halichondria okadai* [4]. Several members of the class showed potent cytotoxicity against the NCI-60 cell line panel [5], including halichondrin B; however, manufacture of these compounds was limited by the small supply of the marine sponge. Fortunately, several synthetic analogues show similar potency to the parent compound [5,6]. One of these is eribulin mesylate (Fig. 1), which induces mitotic spindle disruption by binding to tubulin and inhibiting tubulin polymerization [5]. Its effect appears to be unique among mitotic spindle toxins (such as vinca alkaloids, taxanes, and colchicine); it decreases normal microtubule-dependent spindle tension at the kinetochores, which prevents the signal for mitotic checkpoint passage, thus arresting mitosis [7,8]. It also has a 5- to 10-fold increased potency when compared to other tubulin-based antimitotic agents [4,9]. It has a wide therapeutic window in breast, melanoma and non-small cell lung cancer mice xenograft models with >95% tumor suppression occurring over a 4-fold dosing range (0.25–1.0 mg/kg) without evidence of significant toxicity [9].

The successful completion of several Phase I studies established the maximum tolerated dose (MTD of 1.4 mg/m² on Day 1 & 8 of an every-21-day schedule) and described adverse events as per the Common Toxicity Criteria for Adverse Events (CTCAE) Version 3.0 [10]. Common Grade 3 and 4 events in multiple studies included: neutropenia, febrile neutropenia, hypoglycemia, hypophosphatemia, fatigue, peripheral neuropathy and elevation of alkaline phosphatase [10–14]. Several Phase II trials have demonstrated responses in patients with breast [11,15,16], non-small cell lung [17,18] and prostate cancers [19,20], with Phase III trials ongoing.

Rational for treatment of head and neck cancer patients

Recurrent head and neck cancer is incurable, but recent progress in treating this disease has evolved through the addition of taxanes and EGFR inhibitors to cisplatin [1,21,22]. Because other spindle toxins have proven activity in the treatment of head and neck cancer [1,21,23],

eribulin mesylate was chosen to investigate its utility in patients with metastatic or recurrent SCCHN not previously treated with chemotherapy.

Materials and methods

Eligibility criteria

Patients were required to have head and neck cancer that was metastatic or recurrent following definitive therapy and not amenable to curative salvage therapy (radiation or surgery). Patients must not have received prior chemotherapy for recurrent or newly diagnosed metastatic disease.

Patients who had received chemotherapy in conjunction with definitive therapy and had recurred were eligible provided the last dose of chemotherapy was received at least 6 months prior to registration, and the last dose of targeted therapy (i.e. EGFR inhibitor) was received at least 2 weeks prior to registration. Patients may have received only one induction or adjuvant regimen. This study required consenting adult patients over the age of 18 years to have measurable disease per RECIST [24], a Zubrod Performance Status of 0 or 1, adequate hematologic (absolute neutrophil count (ANC) $\geq 1,500/\text{mm}^3$ and platelet count $\geq 100,000/\text{mm}^3$), adequate hepatic (serum bilirubin and liver enzymes (SGOT AND SGPT) ≤ 2 times the institutional upper limit of normal (IULN)) and adequate renal (serum creatinine ≤ 2 times IULN) functions. Patients were excluded if they: had active or prior CNS metastasis, were pregnant or nursing, were known to be HIV-positive and on combination antiretroviral therapy, or had prior malignancy (excluding adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which they were complete remission, or any other cancer from which they were disease-free for 5 years).

Treatment

Patients were to receive eribulin mesylate at $1.4 \text{ mg}/\text{m}^2$ on Days 1 and 8 of an every 21-day cycle. The drug was to be delivered at a concentration between 0.025 mg/ml and 0.05 mg/ml and administered as an IV bolus over three to 5 min. Anti-emetic choice was left to the discretion of the treating physician, although no specific antiemetics or premedications were required.

Dose modifications

Eribulin mesylate administration required an ANC $\geq 1,500/\text{uL}$ and platelet count $\geq 100,000/\text{uL}$ on Day 1 of each treatment cycle. Dose level modifications were: Level-1 was $1.1 \text{ mg}/\text{m}^2$ and Level-2 was $0.8 \text{ mg}/\text{m}^2$. Dose was decreased by one dose level for Grade 3/4 ANC or platelets on Day 8, or any Grade 3/4 non-hematologic toxicity (excluding Grade 3 nausea, vomiting, diarrhea of brief duration (<3 days), and fever without neutropenia). Dose modifications were based on the toxicity requiring the largest dose reduction. Doses held on Day 8 during a course of therapy were omitted.

Assessments and reason for removal from study

All adverse events were graded according to the National Cancer Institute's Common Toxicity Criteria (CTCAE), version 3.0. Responses were evaluated after every two cycles of therapy according to RECIST [24]. Patients were removed from protocol treatment for any of the following: progressive disease, symptomatic deterioration, unacceptable toxicity, general or specific changes in the patient's condition rendering the patient unsuitable for further treatment, treatment delay >3 weeks or patient's request to withdraw from the study at any time for any reason.

Statistics

The main objective of this study was to assess the response probability (confirmed complete and partial responses) in patients with advanced or recurrent SCCCHN when treated with eribulin mesylate. Secondary objectives were to evaluate progression-free and overall survival probability, as well as qualitative and quantitative toxicities of this regimen. It was assumed that eribulin mesylate would not be of further interest if the true confirmed response probability was less than 5%, while a true confirmed response probability of 20% or more would be of considerable interest. A two-stage design was used for patient accrual. For the initial stage, 20 eligible patients would be accrued. If no confirmed responses were observed, the study would be terminated with the conclusion that eribulin mesylate is inactive in this setting. However, if at least one confirmed response was seen among the first 20 patients, an additional 20 eligible patients would be accrued. Five or more confirmed responses out of 40 would be considered evidence that eribulin mesylate warrants further study, provided other factors, such as adverse events, PFS and overall survival were also favorable.

This design had a significance level of 5% and a power of 92%. Forty patients would be sufficient to estimate progression-free survival at any particular time point (for example 4-month PFS) and overall survival at any particular time point to within 15% (95% confidence interval). Forty patients would also be sufficient to estimate adverse event rates to within 15% (95% confidence interval). An adverse event with at least 5% probability of occurring had an 87% chance to be seen at least once. Overall survival and progression-free survival estimates were calculated using the method of Kaplan-Meier²³, and 95% confidence intervals for their medians were constructed using the method of Brookmeyer-Crowley²⁴. Exact binomial confidence intervals were calculated for response outcomes.

Results

From June 2006 to December, 2007 a total of 42 patients were enrolled; 20 in the first stage and after an adequate number of responses, 22 in the second stage of the trial. Of the 42 patients, 2 were ineligible, one who did not have documented evidence of measurable disease by RECIST, and one due to inadequate hematologic function. Patient characteristics are listed in Table 1, and summarized as follows: 29 were male, 11 female, with a median age of 61.2 years, and Zubrod Performance Status of 0 in 48% and 1 in 53%. Thirty-three (83%) patients had metastatic disease (3 newly diagnosed), while 7 (18%) had recurrent/persistent non-metastatic disease. Tumor sites included: oropharynx 38%, lip/oral cavity 30%, larynx 15%, hypopharynx 10%, other/unknown 5% and nasopharynx 3%. Twenty patients (50%) had received prior adjuvant/induction chemotherapy, while 33 (83%) had received prior radiotherapy.

All patients received at least one cycle of treatment (defined as having received at least some amount of study drug during that cycle) with a median number of cycles of 3.5 (range: 1–28 cycles). Seventeen patients (43%) required some kind of dose modification. All 40 eligible patients were evaluable for toxicity. Table 2 summarizes CTCAE toxicities at least possibly related to eribulin mesylate that were observed in 10% or more of the patients or had a severity of Grade 3 or worse. Common Grade 3 and 4 toxicities included: lymphopenia (15%), leukocytopenia (13%), neutropenia (10%), hyponatremia (5%), fatigue (5%), diarrhea (5%) and dyspnea (5%). There was one treatment-related death due to pulmonary hemorrhage in a subject with a metastasis encasing the pulmonary artery at initiation of treatment.

Best responses as assessed according to RECIST, are shown in Table 3. Two patients could not have their exact response determined, one who died due to non-disease-related causes

prior to the first follow-up disease assessment and the other due to inadequate follow-up assessments. However, neither patient was responding to treatment. Among 40 assessable patients, two confirmed partial responses were observed, for an estimated confirmed response rate of 5% (95% confidence interval: 1–17%), one patient had an unconfirmed partial response, and 48% of patients had stable disease. The two patients who had confirmed partial responses received 5 and 17 cycles of therapy. The estimated median progression-free survival is 3 months (95% confidence interval: 1–3 months) and estimated median overall survival is 7 months (95% confidence interval: 5–10 months) as seen in Fig. 2a and b.

Discussion

The need for novel effective therapies for recurrent or metastatic SCCHN spurred us to investigate eribulin mesylate in this setting. It has a unique mechanism of action, excellent preclinical efficacy in a variety of tumor cell lines and reported activity in non-small cell lung cancer (both Day 1 and 8, as well as Day 1, 8, and 15 schedules) [17,18], breast cancer (both Day 1 and 8, as well as Day 1, 8, and 15 schedules) [11,25] and taxane-naïve metastatic prostate cancer (Day 1 and 8) [19,20]. The decrease in toxicity seen with the compound in heavily pre-treated breast cancer lent credence to the study of eribulin mesylate in SCCHN. The study population's characteristics were representative of this patient group: oropharyngeal cancers were the most common primary site and the majority had recurrent disease after definitive therapy. Single-agent eribulin mesylate was well tolerated in our study, with expected hematologic toxicity. Non-hematologic toxicity was mild, with the exception of one treatment-related pulmonary hemorrhage in a patient with a metastasis encasing the pulmonary artery at initiation of treatment. However, despite the excellent tolerability of the drug, eribulin mesylate failed to show clinically significant activity in SCCHN. Perhaps cancers of squamous histology are not as sensitive to eribulin mesylate as other tumor types (i.e. adenocarcinoma of the breast or prostate, or nonsmall cell lung cancer), although this has not been reported previously with this compound or family of compounds. Alternatively, the fact that the majority of patients on this study were pretreated with radiation and chemotherapy may have created a more therapy-resistant population in which few therapies would be successful.

Traditionally, recurrent and metastatic SCCHN has been an extremely difficult disease to treat, because of the frailty of the population and the lack of efficacious agents. Cytotoxic chemotherapeutic agents such as methotrexate, cisplatin, 5-fluorouracil, bleomycin, paclitaxel, docetaxel, pemetrexed, and irinotecan provide a disappointing single-agent RR of between 15 to 30% and a median PFS of 3 to 5 months [1,26]. Trials using combination chemotherapy provided a slight improvement in RR and median overall survival (OS), over single-agent studies. For example, in similar populations to the present study, SWOG trial S9902 evaluating carboplatin and docetaxel had a RR of 25% and a median OS of 7.4 months [27], while Glisson et al. using cisplatin and docetaxel had a 40% RR and a median OS of 9.6 months [28] and randomized Phase III ECOG study E1395 revealed no difference in survival between cisplatin and 5-fluorouracil versus cisplatin and paclitaxel (RR 29% versus 26%, median OS of 8.7 versus 8.1 months) [23]. Eribulin mesylate does not achieve the same RR, median OS or PFS as these and other recent studies of recurrent SCCHN [23,27-30].

In addition, the successful emergence of EGFR inhibitors, both monoclonal antibodies [21,22,31,32] and tyrosine kinase inhibitors [33,34], has revolutionized therapy in metastatic and recurrent head and neck cancer. The EXTREME trial by Vermorken and colleagues in metastatic and recurrent SCCHN used platinum-5-fluorouracil in combination with or without weekly cetuximab, an EGFR directed chimeric monoclonal antibody. The

experimental arm of the study improved RR by 15% and median OS was prolonged by 2.7 months, compared to the control arm, thus setting a new standard for results of trials in recurrent or metastatic SCCHN. While eribulin mesylate was well tolerated, and showed mild activity in this population, studies such as EXTREME make the utility of eribulin mesylate less notable in this population. In conclusion, eribulin mesylate, while a promising novel spindle toxin in other disease states, is not recommended for future study in refractory or metastatic head and neck cancer.

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Fig. 2.

a Progression free survival of all evaluable patients treated with E7389. **b** Overall survival of all evaluable patients treated with E7389

Table 1

Patient characteristics of 40 eligible patients treated with E7389

Age		
Median (range)	61.2	(44.0, 87.1)
Sex		
Male	29	73%
Female	11	28%
Hispanic		
Yes	2	5%
No	35	88%
Unknown	3	8%
Race		
White	33	83%
Black	5	13%
Asian	1	3%
Unknown	1	3%
Performance status		
0	19	48%
1	21	53%
Primary site		
Lip/oral cavity	12	30%
Nasopharynx	1	3%
Oropharynx	15	38%
Hypopharynx	4	10%
Larynx	6	15%
Other/unknown	2	5%
Disease type		
Metastatic	33	83%
Non-metastatic	7	18%
Disease status		
Newly diagnosed	3	8%
Persistent	2	5%
Recurrent	33	83%
Not reported	2	5%

Table 2

CTCAE toxicities that were at least possibly related to E7389, seen in at least 10% of the study population or at least once with severity of Grade 3 or worse

Adverse event	Grade					
	0	1	2	3	4	5
ALT	38	2	0	0	0	0
AST	36	4	0	0	0	0
Alkaline phosphatase	35	5	0	0	0	0
Alopecia	28	8	4	0	0	0
Anorexia	36	3	1	0	0	0
Constipation	35	5	0	0	0	0
Dehydration	37	0	2	1	0	0
Diarrhea	31	5	2	2	0	0
Dry mouth	38	1	0	1	0	0
Dyspnea	37	1	0	2	0	0
Fatigue	20	8	10	2	0	0
GI Inf, 0-2 ANC: gums	38	0	2	0	0	0
GI Inf, 3-4 ANC: gums	39	0	1	0	0	0
GI Inf, Unk ANC: gums	39	0	0	1	0	0
GI pain: oral cavity	38	0	2	0	0	0
Hemoglobin	20	9	10	1	0	0
Hyperglycemia	34	3	2	1	0	0
Hypoalbuminemia	34	3	3	0	0	0
Hypocalcemia	36	4	0	0	0	0
Hypokalemia	36	3	0	1	0	0
Hyponatremia	36	2	0	2	0	0
Leukocytes	28	5	2	4	1	0
Lung hemorrhage: bronchopulmonary	39	0	0	0	0	1
Lymphopenia	31	1	2	5	1	0
Mucositis, clinical: oral cavity	36	2	2	0	0	0
Mucositis, functional: oral cavity	38	1	0	1	0	0
Nausea	26	9	5	0	0	0

Adverse event	Grade					
	0	1	2	3	4	5
Neuropathy-sensory	35	3	1	1	0	0
Neutrophils	27	3	6	3	1	0
Pneumonitis	39	0	0	1	0	0
Rash	39	1	0	0	0	0
Skin infection with Grade 0–2 neutrophils	39	0	1	0	0	0
Skin infection with Grade 3–4 neutrophils	39	0	0	1	0	0
Vomiting	36	2	2	0	0	0
Weight loss	32	3	5	0	0	0
Maximum grade any adverse event	3	5	18	12	1	1

Table 3

Best response of study population to E7389

Complete response	0	0%
Partial response	2	5%
Unconfirmed complete response	0	0%
Unconfirmed partial response	1	3%
Stable/no response	19	48%
Increasing disease	16	40%
Early death	1	3%
Assessment inadequate	1	3%