Phase II study of fosaprepitant + 5HT3 receptor antagonist + dexamethasone in patients with germ cell tumors undergoing 5-day cisplatin-based chemotherapy: A Hoosier Cancer Research Network Study

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Abstract

Purpose

A phase III study adding aprepitant to a 5HTT3 receptor antagonist plus dexamethasone in germ cell tumor (GCT) patients treated with 5 day cisplatin combination chemotherapy demonstrated a significant improvement in complete response (CR) (J Clin Onc 30:3998-4003, 2012). Fosaprepitant has demonstrated non-inferiority compared to aprepitant in single day cisplatin chemotherapy and is approved as a single-dose alternative. This single arm phase II study is the first clinical trial evaluating fosaprepitant in patients receiving multi-day cisplatin regimen.

Methods

GCT patients receiving 5 day cisplatin combination chemotherapy were enrolled. Fosaprepitant 150 mg was given IV on days 3 and 5. A $5HT_3$ antagonist days 1-5 (days 1, 3, 5, if palonosetron) plus dexamethasone 20 mg days 1, 2, and 4 mg po bid days 6, 7, 8 was administered. Rescue antiemetics were allowed. The primary objective was to determine the CR rate – no emetic episodes or use of rescue medications. Accrual of 64 patients was planned with expected CR>27%.

Results

65 patients were enrolled of whom 54 were eligible for analysis. Median age was 33. 51 patients received BEP (bleomycin, etoposide, cisplatin) chemotherapy. CR was observed in 13 (24.1%) patients (95% Agresti-Coull binomial C.I. 14.5%, 37.1%).

Conclusion

The data in this phase II study, in contrast to our prior phase III study, appears to indicate a lower CR rate with the substitution of fosaprepitant for aprepitant. It is unknown whether the substitution of fosaprepitant for aprepitant provides the same benefit in multi-day cisplatin that was achieved with single day cisplatin.

-**Keywords**: germ cell tumor, testicular cancer, fosaprepitant, chemotherapy-induced nausea and vomiting

Introduction

Germ-cell tumors (GCTs) represent the most common carcinoma in men ages 15 to 35 years. There is an estimated 8,430 new cases to be diagnosed in the United States in 2015 [1]. The introduction of cisplatin-based combination chemotherapy has established testicular cancer as a model for a curable neoplasm [2]. Acute and delayed nausea and vomiting is a universal adverse effect of cisplatin chemotherapy. Despite significant progress in the prevention of chemotherapy-induced nausea and vomiting (CINV), emesis continues to be associated with a significant deterioration in quality of life in patients treated with combination chemotherapy [3]. The addition of the brain-penetrant neurokinin-1 receptor antagonist (NK1-RA) aprepitant, to a 5-hydroxytryptamine-3 receptor antagonist (5HT3-RA) and dexamethasone improved the prevention of CINV in patients receiving highly emetogenic single-day cisplatin chemotherapy [4-6]. In the Hoosier Cancer Research Network (HCRN), a phase III study was conducted with a 5HT3-RA plus dexamethasone plus either aprepitant or placebo in a randomized double-blind placebo controlled study of patients receiving 5 day cisplatin-based combination chemotherapy. This study demonstrated a significant improvement in complete response (CR) rate of 42% versus 13% ($P<0.001$) favoring aprepitant [7].

Although the oral capsule is appropriate for many patients, the availability of an intravenous (IV) formulation would provide further convenience and flexibility. Fosaprepitant is a water-soluble prodrug of aprepitant available in IV formulation. It is rapidly converted to the active form

(aprepitant) by phosphatase enzymes and is expected to provide the same aprepitant exposure in regards to AUC and hence similar antiemetic effect [8].

A randomized, double-blind phase III study was conducted to assess the efficacy and safety of fosaprepitant in the prevention of CINV in cisplatin-naive patients who were treated with chemotherapy regimens that included single-day cisplatin ≥ 70 mg/m^2 [9] enrolled over 2,200 patients and demonstrated that a single dose of intravenous fosaprepitant was non-inferior to standard 3-day oral aprepitant. Here we report the results of the first clinical trial evaluating fosaprepitant in patients receiving multi-day cisplatin combination chemotherapy.

Methods

Patient Selection

Eligible patients were ≥ 15 years of age with histologically or cytologically confirmed diagnosis of germ cell tumor who were scheduled to receive a standard 5 day cisplatin based chemotherapy regimen. Prior chemotherapy was allowed and patients did not have to be chemotherapy naive. Patients had to be without nausea or vomiting for 24 hours before study entry and no antiemetic use for 72 hours prior to starting protocol therapy. Absolute neutrophil count ≥ 1,500 cells/μL, WBC count ≥ 3,000 cells/μL, platelet count ≥ 100,000 cells/μL, AST and ALT ≤ 3 x upper limit of normal, bilirubin ≤ 1.5 x upper limit of normal, and creatinine less than 2 mg/dL were required. Patients should have had an ECOG performance status of 0-2 and no active central nervous system (CNS) metastasis.

This single arm HCRN phase II study was conducted from 2013 to 2015 after approval by each site's institutional review board. Informed consent was obtained from all individual participants included in the study.

Study design and treatment regimen

All participating patients received germ cell combination chemotherapy utilizing cisplatin 20mg/m^2 x 5 days. All patients received an anti-emetic regimen consisting of dexamethasone 20mg orally daily on days 1 and 2 then 4mg orally BID (twice daily) on days 6, 7, and 8. A 5HT3-RA was administered to all patients 30 minutes before starting chemotherapy: ondansetron 8mg orally BID on days 1 to 5 or palonosetron 0.25mg IV on days 1, 3, and 5. Fosaprepitant 150mg was administered IV on days 3 and 5 over 20-30 minutes (Table 1). Patients were permitted to take rescue therapy of the treating investigator's choice for nausea and/or emesis/retching based on clinical circumstances. No additional doses of 5HT3-RA, dexamethasone, or fosaprepitant were given during the acute or delayed treatment periods. Patients who required rescue therapy were permitted to continue the study at the discretion of the treating investigator and in consultation with the patient.

The primary endpoint was complete response (CR) of both acute (days 1 through 5) and delayed (days 6 through 8) CINV, defined by no emetic episodes or use of rescue medications. Secondary endpoints included incidence of emetic episodes via patients logs (days 1 through 8), use of rescue medications (days 1 through 8), patient's self-reported assessment of nausea (days 1 through 8) using a 0-100mm visual analog scale (VAS), safety, and toxicity.

Study visits and assessment procedures

In the pre-study period, all pertinent demographics (age, gender, height, and weight) and medical data (site and stage of disease, ECOG performance status, laboratory values, medications, and prior oncologic therapies) were recorded.

All patients were provided a diary inclusive of days 1 through 8 of the chemotherapy cycle. Patients were asked to complete a daily log of any episodes of vomiting or retching and the time of these episodes beginning with day 1 and daily through day 8. The use of rescue therapy, defined as any medication taken to treat established nausea or emesis, was also recorded. On days 1 through 8, patients rated nausea by using a 100-mm horizontal VAS ranking their nausea for the prior 24 hours from no nausea to the worst nausea with a measurement of 0-100mm. A VAS score of 0 to 5mm was considered as no nausea.

Statistical Methods

The CR rate of aprepitant in GCT patients receiving 5 day cisplatin-based combination chemotherapy was 42% [7]. We expected fosaprepitant to have similar CR rate. A one-sided score test was used to compare the CR rate of fosaprepitant with the historical data of aprepitant. Denoting the CR rate of fosaprepitant as p, the hypotheses are H_0: $p \leq 27\%$ versus H_A: $p \geq 27\%$. A CR rate of fosaprepitant that is no worse than 15% lower than aprepitant was considered worth further investigation. Enrollment of 64 patients was required to attain a power of 0.80 with type I error level as 0.05.

Continuous variables were summarized by mean, median, and range. Categorical variables were summarized by frequencies and percentages. Overall CR was tested according to the aforementioned hypotheses. In addition, 95% confidence interval of Agresti-Coull type was constructed for the overall CR. Adverse events were summarized by their grades and types.

Results

Patient characteristics

From January 2013 till May 2015, patients with GCT who were scheduled to receive 5 day cisplatin chemotherapy were enrolled. A total of 65 patients were enrolled on study. One patient had a reaction to the infusion and was taken off study. 10 patients were not evaluable because they did not complete the VAS on all 8 days. Hence, 54 patients were evaluable and eligible for analysis Demographic and treatment data are listed in Table 1. Median age was 33 (range 15-66). All patients were Caucasian and male. Eastern Cooperative Oncology Group (ECCOG) Performance Status was 0 in 59 (92.2%) patients, 1 in 4 (6.2%) patients, and 2 in 1 (1.6%) patient. Chemotherapy regimen consisted of BEP (bleomycin, etoposide, cisplatin) in 51 (79.7%) patients, EP (etoposide, cisplatin) in 10 (15.6%) patients, VeIP (vinblastine, ifosfamide, cisplatin) in 2 (3.1%) patients, and cisplatin/epirubicin in 1 (1.6%) patient. All evaluable patients received fosaprepitant 150mg IV on days 3 and 5. Among evaluable patients, 4 received ondansetron and and 50 received palonosetron. All evaluable patient received 5 days of dexamethasone. Among evaluable patients, 50 (92.6%) were chemotherapy-naïve. Table 2 depicts patient and treatment characteristics.

Efficacy Endpoints

Primary and secondary endpoints were analyzed in the 54 evaluable patients. Complete response (CR), defined by no emetic episodes and no use of rescue medications, was observed in 13 (24.1%) patients in the overall treatment period day 1-8 (95% Agresti-Coull binomial C.I. 14.5%, 37.1%). This was insufficient to reject the null hypothesis H0: $p \leq 27\%$ ($p=0.68$). CR was observed in 16 (29.6%) patients during the acute phase (days 1 through 5) and 25 (46.3%)

patients in the delayed phase (days 6 through 8). Figure 1 depicts the percentage of CR in the acute, delayed, and overall phases. Sixteen (29.6%) patients had at least one emetic episode. Total number of emetic episodes was 29. Nine patients had 1 emetic episode; 2 patients had 2 episodes; 4 patients and 3 episodes and 1 patient had 4 emetic episodes. The largest number of emetic episodes occurred on days 3, 5, and 7 with 5 patients having an emetic episode on each of these days. The fewest number of emetic episodes occurred on days 1 and 6 with 2 patients having an emetic episode on these days. Figure 2 depicts a histogram indicating the percentage of patients who had emetic episodes on days 1 through 8. Thirty-seven (68.5%) patients received rescue medications. Rescue medications consisted of Lorazepam, Prochlorperazine, Promethazine, or Dexamethasone. Lorazepam was the most common rescue medication used. There were 225 episodes in 47 patients of reported nausea >5mm on the VAS in the 8 day reporting period. Figure 3 depicts the median VAS score on days 1 through 8. No patient had a change in their planned cisplatin-based combination chemotherapy schedule.

Safety

Sixty-four patients were evaluable for toxicity. Administration of fosaprepitant was well tolerated. There was a total of 7 grade III or IV toxicity events on this study that were possibly, probably, or definitely related to study drug. Two patients had grade III toxicity consisting of leukopenia and thrombocytopenia. Four patients had grade IV toxicity consisting of leukopenia and neutropenia. One patient had grade IV toxicity consisting of febrile neutropenia. There was no cases of reaction at the infusion site attributable to fosaprepitant infusion on this study.

Discussion

Severe CINV were common adverse events associated with certain chemotherapeutic regimens and forced a substantial number of patients to delay or even refuse potentially curative therapy [10]. Despite the compelling advances made in recent years, CINV continues to be among the most distressing and feared adverse effects of chemotherapy [11]. Prior to the introduction of ondansetron, the first $5HT_3$ receptor antagonist, the typical patient with testicular cancer would experience a median of 10 emetic episodes on day 1 of a 5 day cisplatin-based chemotherapy course, 5 episodes on day 2, and decreasing emetic episodes on later days [12]. The introduction of ondansetron was fundamental in preventing acute nausea and vomiting associated with cisplatin-based chemotherapy [13,14]. More recently, this trend has been reversed in multi-day cisplatin as patients experience more severe symptoms of CINV on later days of the chemotherapy cycle (days 3-5) as well as delayed CINV on days 6-8 [15].

The addition of dexamethasone in phase III studies resulted in further improvement in the prevention of acute CINV [16]. Delayed CINV was not adequately controlled by $5HT_3$ receptor antagonists and dexamethasone [17].

Aprepitant, a NK1-RA, demonstrated efficacy in controlling both acute and delayed CINV and hence it was combined with previous antiemetic regimens. Aprepitant was initially given for 5 days [18] but eventually a 3 day course was deemed sufficient [6]. Aprepitant proved to be efficacious in preventing CINV in a randomized double-blind placebo-controlled trial which enrolled cisplatin-naïve patients who were treated with chemotherapy regimens including cisplatin ≥ 70 mg/m^2 administered on a single day [6]. In the HCRN, a phase III study was conducted to test the efficacy of aprepitant in patients undergoing a 5-day cisplatin-based

combination chemotherapy regimen [7]. In this randomized double-blind placebo-controlled crossover study, 42% of patients achieved a CR, defined as no emetic episodes and no use of rescue medications, with aprepitant compared to 13% with placebo ($p < 0.001$).

An intravenous formulation of a NK1-RA was developed. Fosaprepitant is a water-soluble phosphoryl prodrug of aprepitant which when administered intravenously, rapidly converts to aprepitant within 30 minutes of administration [19]. A phase III trial compared single dose fosaprepitant 150mg IV in combination with granisetron 40 μg/kg IV and dexamethasone to a control regimen of placebo, granisetron, and dexamethasone [20]. Complete response, defined by no emesis and no rescue therapy, was higher in the fosaprepitant arm than in control arm; 64% vs. 47% ($p = 0.0015$). Fosaprepitant was more effective than control regimen in both acute and delayed phases. A phase III randomized, double-blind, non-inferiority study was conducted comparing fosaprepitant to aprepitant in chemotherapy-naïve patients receiving cisplatin ≥ 70 mg/m^2 [9]. A single dose of intravenous fosaprepitant was shown to be non-inferior to standard 3-day oral aprepitant in preventing CINV in patients receiving single-day cisplatin. However, there is a paucity of data with fosaprepitant in patients receiving a 5-day cisplatin combination chemotherapy regimen.

The HCRN conducted this single arm phase II study as a first evaluation of fosaprepitant in patients receiving 5-day cisplatin-based combination chemotherapy for GCT. We have used dexamethasone only on days 1 and 2 of the acute phase in an attempt to decrease the adverse effects of corticosteroids. Patients with GCT who are receiving three to four cycles of cisplatin combination chemotherapy will be subjected to high doses of dexamethasone which will put them at risk for hyperglycemia, anxiety, agitation, insomnia, gastrointestinal irritation, and peptic ulcer disease. We attempt to avoid the potential long-term adverse effects of dexamethasone in

this young patient population such as obesity, avascular necrosis of the hip, and cataracts [21-23].

In the phase II study reported here, fosaprepitant combined with dexamethasone and 5HT3-RA was very well tolerated with minimal grade III or IV toxicities. However, the CR rate observed in this study appears to be significantly lower than our previous study with aprepitant. Fosaprepitant had a CR rate of 24.1% on this study compared to a CR rate of 42% with aprepitant [7]. While there may be several factors that contributed to the low CR rate, a notable one is that 15% of the patients were not evaluable for the primary endpoint due to incomplete patient logs.

To the best of our knowledge, this is the first clinical trial evaluating fosaprepitant in patients receiving 5-day cisplatin-based chemotherapy regimens for GCT. The data in this small phase II study, in contrast to our prior phase III study, appears to indicate a significantly lower CR rate with the substitution of fosaprepitant for aprepitant.

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-All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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-Conflicts of interest:

Nabil Adra: none

Costantine Albany: none

Mary J. Brames: none

Somer Case-Eads: none

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Figure 1. Percentage of complete response (CR) in acute, delayed, and overall phase

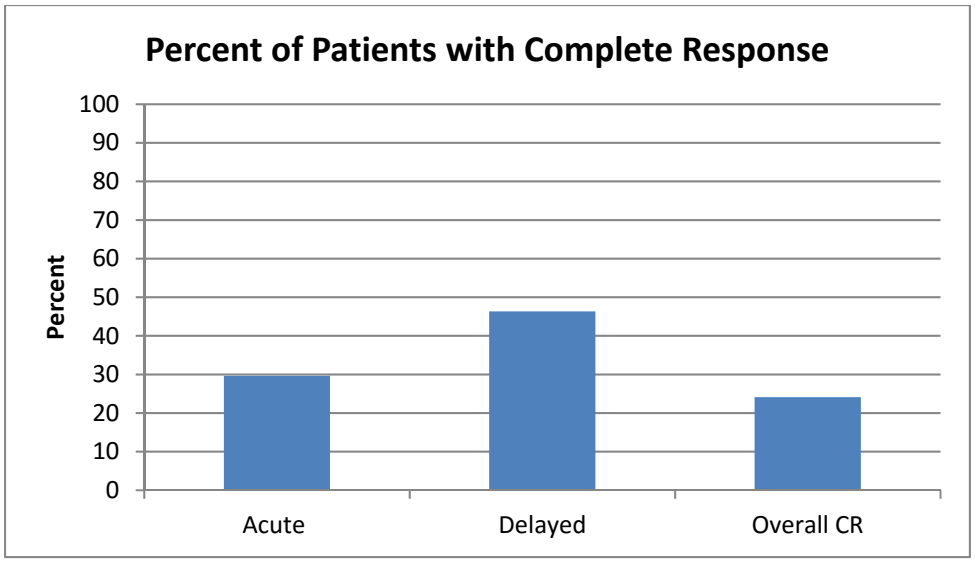

Figure 2. Percentage of patients with emetic episodes on days 1 through 8

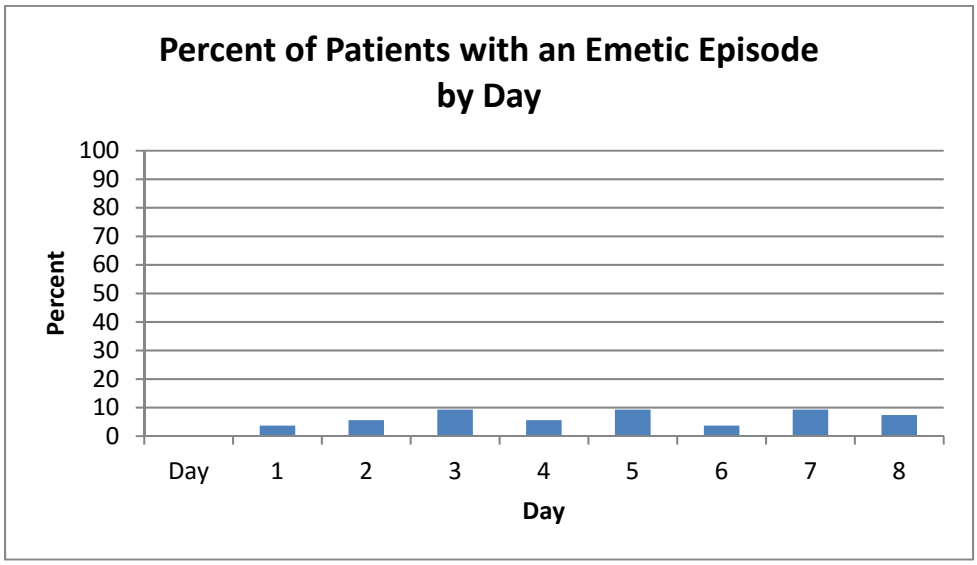

Figure 3. Median VAS (visual analog scale) score on days 1 through 8

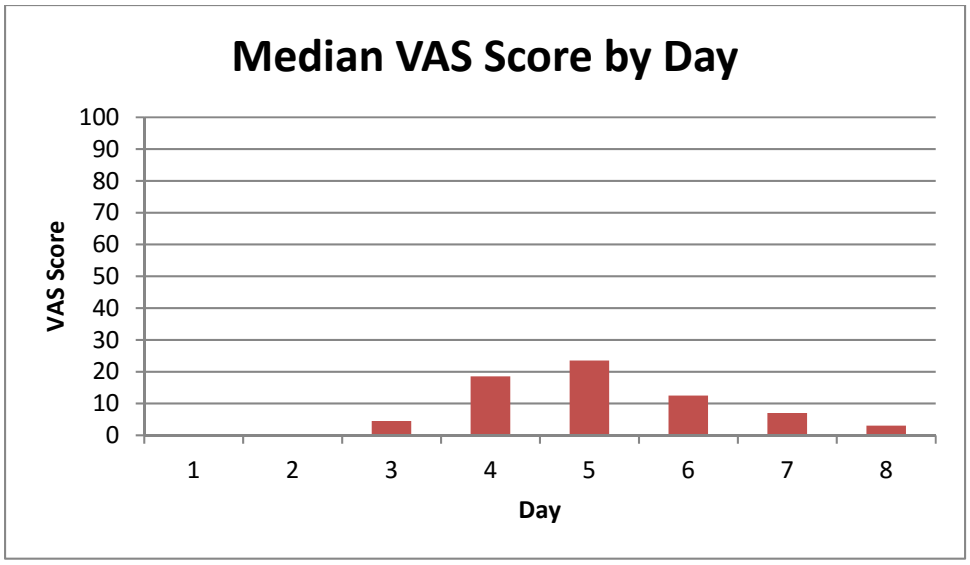

Table 1: Study Drug Schedule

Day 1	Day 2	Day 3	Day 4	Day 5	Days 6–8
Dexamethasone 20 mg PO	Dexamethasone 20 mg PO	Fosaprepitant 150 mg IV	-	Fosaprepitant 150 mg IV	Dexamethasone 4 mg PO BID
Palonosetron 0.25 mg IV		Palonosetron 0.25 mg IV	-	Palonosetron 0.25 mg IV	

*Alternatively, ondansetron 8mg PO BID can be utilized on days 1 to 5 if palonosetron is not available.

Abbreviations: PO, orally; IV, intravenous; BID, twice daily

Table 2. Patient and Treatment Characteristics

	All patients (n=64)		Evaluable Patients (n=54)	
	Median	**Range**	**Median**	**Range**
Age	33	15-66	33	15-66
	n	**%**	**n**	**%**
Sex				
Male	64	100.0	54	100.0
Race				
Caucasian	64	100.0	54	100.0
Ethnicity				
Non-Hispanic	61	95.3	51	94.4
Hispanic	3	4.7	3	5.6
ECOG PS				
0	59	92.2	51	94.4
1	4	6.2	2	3.7
2	1	1.6	1	1.9
Stage				
I	27	42.2	23	42.6
II	24	37.5	21	38.9
III	11	17.2	9	16.7
IS	1	1.6	1	1.9
Unknown	1	1.6	0	0.0
Prior Chemotherapy				
Yes	5	7.8	4	7.4
No	59	92.2	50	92.6
Chemotherapy Regimen				
BEP	51	79.7	43	79.6
EP	10	15.6	8	14.8
VeIP	2	3.1	2	3.7
Cisplatin/Epirubicin	1	1.6	1	1.9

BEP=bleomycin, etoposide, cisplatin; EP=etoposide, cisplatin; VeIP=vinblastine, ifosfamide, cisplatin