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ORIGINAL ARTICLE

Carboplatin with weekly docetaxel and ifosfamide in advanced head and neck cancers: a phase I Brown University Oncology Group dose escalation study (HN-93)

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Abstract
Purpose A phase I study was performed to determine the maximally tolerated dose of carboplatin, ifosfamide, and docetaxel in advanced head and neck cancers.
Methods Carboplatin (week 1) was administered with weekly docetaxel and ifosfamide for 3 weeks in an every 4-week cycle. Restaging was done after two cycles, while dose level escalation was done in cohorts of three patients.
Results Fifteen patients (recurrent/metastatic disease, $n = 8$; bulky locally advanced disease, $n = 7$) were enrolled. No dose-limiting toxicities were observed. Toxicities included grade 3 neutropenia and anemia ($n = 2$, each), and grade 2 thrombocytopenia ($n = 3$). The final level of carboplatin AUC = 6 (week 1) with docetaxel 30 mg/m^2 per week and ifosfamide 1,000 mg/m^2 per week was chosen for further evaluation.
Conclusions This novel regimen of carboplatin with weekly docetaxel and ifosfamide has a favorable toxicity profile and is active in this setting. Phase II study results are awaited.

Keywords Docetaxel · Carboplatin · Ifosfamide · Recurrent · Metastatic · Head and neck

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Introduction

In the United States, an estimated 48,010 new cases and 11,260 deaths due to head and neck cancers were estimated in 2009 [1]. Though some patients with recurrent squamous cell cancers of the head and neck (HNSCC) can undergo salvage surgery, most patients with recurrences and all patients with distant metastases are incurable and are associated with short survival outcomes [2]. The platinum analogues, cisplatin and carboplatin, and the taxanes, docetaxel and paclitaxel, are among the most active agents in this setting.

Weekly schedules of docetaxel in patients with recurrent or metastatic HNSCC have shown maintained activity but reduced hematologic toxicity [3–5]. Ifosfamide is an alkylating agent that has activity in head and neck cancers, and upon weekly evaluation has been well tolerated when given for 3 of 4 weeks [6, 7]. The combination of cisplatin and docetaxel is synergistic and has yielded high response rates in the setting of locally advanced, recurrent, or metastatic HNSCC [8–10]. Carboplatin has a superior therapeutic index and more predictable individualized dosing than cisplatin and has been successfully used in head and neck trials at the Brown University Oncology Group [11, 12].

Triplet chemotherapy regimens have evaluated the addition of taxanes to the cisplatin–fluorouracil regimen in the setting of recurrent and metastatic HNSCC [13, 14]. Shin et al. evaluated two triplet chemotherapy regimens for metastatic head and neck cancer. The TIP and TIC

regimens consist of paclitaxel, ifosfamide, and cisplatin or carboplatin, respectively [15, 16]. Both these regimens demonstrated impressive response rates but had a high incidence of toxicities with the TIC regimen having less grade 2/3 toxicities than TIP. In order to obviate the toxicities with these conventional schedules and increase dose-intensity with possibly efficacy, we conducted a phase I/II study evaluating weekly administration of docetaxel and ifosfamide with every 4-week carboplatin. This report pertains to the phase I portion of the study where the primary objective was to determine the maximum tolerated dose (MTD) of this combination. The secondary objectives were to determine the toxicities and feasibility of this regimen.

Materials and methods

Eligibility

Patients were enrolled at Brown University Oncology Group (BrUOG) member institutions. Patients who were 18–80 years old with histologically documented squamous cell carcinoma of the head and neck were eligible. A written informed consent was obtained prior to enrollment. Patients presenting with metastatic disease, recurrent disease after primary therapy, or patients presenting with bulky disease that would be potentially resectable after chemotherapy given in a neoadjuvant fashion were eligible for therapy upon this study.

Other eligibility criteria included normal bone marrow function (hemoglobin $\geq$ 8 g/dl, absolute neutrophil count $\geq$ 1,800 cells/mm^3, platelet count $\geq$ 100,000 cells/mm^3), normal renal function (serum creatinine level $\leq$2.0 mg% and a calculated creatinine clearance, using the Cockcraft–Gault formula, >30 ml/min), and normal hepatic function (LFT <3 times the upper limit of normal, bilirubin level less the upper limit of normal). Patients were required to have an ECOG performance status 0–2, no history of prior malignancy except for basal cell carcinoma. Pregnant, lactating women, or those not practicing contraception were not eligible to participate in this study. Patients were required to have no peripheral neuropathy and to have a life expectancy of at least 3 months at enrollment.

Treatment plan

All patients were assessed by a complete clinical history and physical examination, blood counts, serum chemistries, urinalysis, and electrocardiogram. Computed tomography scans of the head and neck, chest, and abdomen were performed prior to beginning chemotherapy. Patients were staged by physical and radiological evaluation according to the American Joint Committee on Cancer criteria.

Table 1 Dose escalation levels

Dose level	Carboplatin (week 1)	Docetaxel (weeks 1, 2, 3) (mg/m^2)	Ifosfamide (weeks 1, 2, 3) (mg/m^2)
Level 1	AUC = 5	20	1,000
Level 2	AUC = 5	25	1,000
Level 3	AUC = 5	30	1,000
Level 4	AUC = 5	35	1,000
Level 5	AUC = 6	30	1,000

In this phase I study, patients received escalating doses of weekly docetaxel IV over 1 h for 3 of 4 weeks in each cycle. They also received ifosfamide given IV weekly along with Mesna for 3 of 4 weeks. Carboplatin IV over 30–60 min was given on week one of the every 4-week cycle (Table 1). A fifth dose level was added in attempt to maximize the carboplatin dose when no MTD was seen at the originally planned four dose levels.

The occurrence of any of the events described below *during cycle one* of treatment was considered to be a dose-limiting toxicity (DLT) during the phase I portion of the study. Hematologic toxicity consisting of febrile neutropenia lasting >48 h on antibiotics or with sepsis or documented bacteremia for a pathogenic species, platelet counts <20,000/μl, absolute neutrophil count (ANC) <500/μl lasting >7 days, ANC and platelets that had not recovered to 1,000/μl and 75,000/μl, respectively, by completion of the cycle or patient receiving <75% of planned chemotherapy dose was considered as a DLT. Non-hematologic toxicity consisting of any grade 3 or more toxicity (except alopecia, myalgias and arthralgia) during induction chemotherapy was considered a DLT.

Patients with locally advanced disease went onto receive definitive chemoradiotherapy for local control and/or organ preservation. Patients with bulky or recurrent cancer who demonstrated clinical and/or radiological decrease in tumor size after completing two cycles of chemotherapy were eligible to proceed to surgery or radiotherapy for local control if deemed feasible.

Treatment modifications

Toxicity grading was based on the National Cancer Institute Common Toxicity Criteria. Patients were evaluated for hematologic and non-hematologic toxicity by weekly complete blood counts and chemistries. A treatment cycle was begun with all three drugs administered at full doses only if the granulocyte count was >1,800/μl, and platelet count was >100,000/μl. For mid-cycle hematologic toxicity, the doses of docetaxel and ifosfamide were reduced to 50% for granulocyte count of 1,000–1,799/μl and/or platelet count of 75,000–99,999/μl. Both docetaxel and ifosfamide were

withheld if the granulocyte and/or platelet levels dropped below 1,000/μl and 75,000/μl, respectively. Colony stimulating factors were not used. For grade 2 neurologic toxicity, docetaxel was held, while ifosfamide and carboplatin were given at 50% dose; for any grade 3 neurologic toxicity, all three drugs were held. Therapy was resumed when toxicity reverted to grade 1 or better. For elevated bilirubin levels, docetaxel was withheld till the levels normalized and then resumed at 75% of planned dose; carboplatin and ifosfamide were not held for elevated bilirubin levels.

Treatment evaluations

Clinical and radiologic responses were assessed after completing two cycles of chemotherapy. Tumor response criteria were based on bidimensional measurements, and World Health Organization criteria were used to define complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Survival was measured since the time of patient registration until death or the last day of follow-up.

The purpose of the study was to evaluate the feasibility and the MTD of this regimen. A clinically meaningful feasibility rate would be a 75% rate of completion for the planned therapy from initiation till first restaging. Dose escalation was performed with an underlying DLT rate of <20%. An estimated total of 15–30 patients were planned for accrual to complete this phase I study.

Results

Patient characteristics

Fifteen patients were enrolled upon the study and are assessable for response, survival, and toxicity. Detailed patient characteristics are listed in Table 2. There were eight patients with recurrent/metastatic cancers, and seven patients had bulky stage 4 (non-metastatic) cancers. Of the eight patients in the recurrent/metastatic group, six patients had local recurrences, and two patients had lung metastases. Of the seven patients presenting with bulky stage 4 (non-metastatic) disease, five patients had T4 primary tumors, and the other two patients had N3 nodes; overall N2–N3 tumors were present in five of seven patients in this group.

Dose escalation and treatment delivery

Three patients were treated at each dose level, and cohort expansion was not required. A total of 34 cycles (median—2 cycles, range 2–4 cycles) of chemotherapy were delivered during the phase I portion of this study. Reasons for discontinuation of therapy included progression ($n = 5$), stable disease ($n = 2$), patient choice ($n = 1$), unrelated illness ($n = 1$), or completion of required protocol therapy ($n = 6$).

Table 2 Patient characteristics

Characteristic	Number (%)
Patients	15 (100)
Age (range 39–70 years)	
Median	56
Sex	
Men	10 (67)
Women	5 (33)
ECOG performance status	
0	3 (20)
1	12 (80)
Disease status	
Recurrent/metastatic	8 (53)
Bulky locally advanced	7 (7)
Prior therapy	
Radiotherapy	2
Chemoradiotherapy	5

Toxicity

Traditional severe hematologic toxicities and gastrointestinal toxicities were not commonly encountered upon this study (Table 3). Two patients developed grade 3 anemia, two patients developed grade 3 neutropenia, and two patients developed grade 2 thrombocytopenia. All patients at dose level 5 reported nausea with two patients having grade 2 nausea, likely reflecting the higher carboplatin dose. Grade 2 diarrhea was seen in three patients.

Other toxicities included non-neutropenic infections (two patients), grade 2 urticaria (one patient), grade 1 neuropathy (one patient), and venous thrombosis (two patient).

Response

Among all patients who completed the required two cycles of therapy, evidence of clinical benefit (disease remission or stabilization) was seen in the majority of patients. Of this patient cohort, 13 patients have expired, and 2 patients are alive at time of reporting.

Discussion

Results of recent randomized trials have demonstrated improved outcomes with triplet chemotherapy regimens in comparison with standard doublet regimens in patients with advanced head and neck cancer [17, 18]. While associated

Table 3 Major observed toxicities in all patients

Toxicity	Grades	Level 1	Level 2	Level 3	Level 4	Level 5
Neutropenia	1–2	0	1	2	2	0
	3–4	0	0	1	0	1
Thrombocytopenia	1–2	1	0	2	1	1
	3–4	0	0	0	0	0
Anemia	1–2	2	2	2	3	3
	3–4	1	0	1	0	0
Nausea/vomiting	1–2	2	0	0	0	3
	3–4	0	0	0	0	0
Diarrhea	1–2	1	1	1	1	1
	3–4	0	0	0	0	0
Neuropathy	1	0	1	0	0	0
	2	0	0	0	0	0

with impressive efficacy, triplet chemotherapy regimens in the recurrent/metastatic setting have been associated with major toxicities. The traditional approach in this setting has been to incorporate a taxane into the standard platinum–fluorouracil doublet regimen. Alternatively, MD Anderson Cancer Center investigators have evaluated the highly active regimen of platinum, taxane, and ifosfamide in this setting. This traditional every 3-week approach of using a triplet combination of platinum, paclitaxel, and ifosfamide (TIC and TIP regimens) has been notable for major toxicities [15, 16].

The goal of our phase I study was to establish the MTD of the combination of carboplatin (given every 4 weeks) in combination with ifosfamide and docetaxel, both given weekly for 3 weeks. Our results demonstrate that this schedule is feasible with a very favorable toxicity profile. In this study, no patient developed grade 4 neutropenia or neutropenic fever. Hematologic toxicity consisted of grade 3 neutropenia (13%) or grade 2 anemia and thrombocytopenia (13% each). There were no grade 3/4 gastrointestinal toxicities with the most significant toxicities being grade 2 diarrhea in 3 (20%) patients and grade 2 nausea in 2 (13%) patients. Peripheral neuropathy occurred as grade 2 foot drop in one patient which subsequently improved. Accordingly, dose level 5 (carboplatin AUC = 60) was chosen for further testing in the phase II component of this study.

In the MD Anderson Cancer Center experience, substituting carboplatin for cisplatin conferred a much improved toxicity profile with reduced hematologic toxicity, neutropenic fever, gastrointestinal toxicity, and neuropathy. However, the TIC regimen was still associated with a 30% incidence of neutropenic fever in the absence of growth factor support. In contrast, the lack of any episode of neutropenic fever or any grade 4 hematologic toxicity is very promising. Similarly, the lack of any grade 3/4 gastrointestinal toxicity in this cohort was extremely encouraging.

Clinical benefit was obtained with disease responses, and stabilization seen in patients with head and neck cancers of various primary sites. In conclusion, this phase I study demonstrated the feasibility and tolerability of this triplet regimen. Further accrual of patients on the phase II component of this study has been completed, and final results will be forthcoming soon.

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