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A Phase II Trial of Bevacizumab + Cetuximab + Cisplatin with Concurrent Intensity Modulated Radiation Therapy (IMRT) for Patients with Stage III/IVB Head and Neck Squamous Cell Carcinoma (HNSCC)

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Abstract

Background—To evaluate the efficacy and tolerability of the addition of two monoclonal antibodies, bevacizumab and cetuximab, to two cycles of high-dose cisplatin administered concurrently with IMRT for HNSCC.

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Methods—Patients with newly diagnosed stage III/IVB (M0) HNSCC received cetuximab (400 mg/m^2 loading dose, followed by 250 mg/m^2 weekly), bevacizumab (15 mg/kg, days 1 and 22), and cisplatin (50 mg/m2, days 1, 2, 22, and 23) concurrently with IMRT (70 Gy). The primary endpoint was progression free survival (PFS). Secondary endpoints were overall survival (OS) and safety and tolerability.

Results—Among 30 patients enrolled, the primary tumor site was oropharynx in 25 patients (p16 immunohistochemistry was positive in 17, negative in 1, and not done in 6 of the oropharynx tumors). Median age was 57 years (range, 38–77 years) and 27 patients had clinical stage IVA disease. All patients completed the full planned dose of radiation therapy. The most common ≥ grade 3 adverse events were lymphopenia, mucositis (functional), and dysphagia. With a median follow up of 33.8 months, 2 year PFS was 88.5% (95% CI, 68.1–96.1) and 2 year OS was 92.8% (95% CI, 74.2–98.1%)

Conclusion—The addition of bevacizumab and cetuximab to two cycles of cisplatin, given concurrently with IMRT, was well tolerated and was associated with favorable efficacy outcomes in this patient population.

INTRODUCTION

Large randomized studies established the regimen of three cycles of bolus cisplatin administered concurrently with radiation therapy for locally/regionally advanced HNSCC.[1,2] The only molecularly targeted agent which has surpassed investigational status in the treatment of HNSCC is cetuximab, a chimeric monoclonal antibody that targets the extracellular domain of epidermal growth factor receptor (EGFR). Cetuximab modestly improves efficacy when combined with radiation therapy for locally/regionally advanced HNSCC,[3,4] and modestly improves overall survival when added to platinum + 5-fluorouracil chemotherapy for recurrent/metastatic disease.[5]

Vascular endothelial growth factor-A (VEGF-A), a cental regulator of tumor angiogenesis, is targeted by the monoclonal antibody bevacizumab. Increased VEGF-A expression is associated with poor prognosis in HNSCC,[6] and inhibition of angiogenesis is a potent radiosensitization strategy pre-clinically.[7] However, in a phase II combined modality study that called for three cycles of bevacizumab and cisplatin administered concurrently with radiation therapy for stage II/IVB HNSCC, we found only half of patients were able to receive the full planned 3 cycles of both drugs due to cumulative adverse events.[8] To improve tolerability in HNSCC combined modality clinical trials that incorporate bevacizumab, a heuristic next step would be to reduce exposure to the cytotoxic agent cisplatin.

Preclinical and early clinical studies support a model in which cross-talk between EGFR and VEGF pathways enhances tumor growth and angiogenesis in HNSCC.[9] In phase II clinical study for 46 patients with advanced HNSCC, the combination of cetuximab and bevacizumab yielded an objective response rate of 16% and a disease control rate of 73%.[9] These data suggest that the combined inhibition of VEGF and EGFR may yield additive efficacy in HNSCC.

During the protocol-writing phase, we proposed that the combination of cetuximab and bevacizumab may improve efficacy, and that the third cycle of cisplatin may be omitted without compromising efficacy. Here we report the mature results of a non-randomized phase II study in which patients with locally/regionally advanced HNSCC received two cycles of bolus cisplatin, plus two cycles of bevacizumab, and weekly cetuximab,[4,3] administered concurrently with radiation therapy.

METHODS

Patient Eligibility and Baseline Assessment

The study was approved by the local Institutional Review Board, and all subjects provided written informed consent. Patient selection criteria and pre-treatment evaluation, including computed tomography (CT) or magnetic resonance imaging (MRI) scan of tumor site and whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) scan, were essentially as described in our prior phase II study of bevacizumab plus chemoradiation.[8] A significant difference is that the current study did not mandate pre-treatment placement of a percutaneous gastrostomy (PEG) tube, but this was allowed at the discretion of the investigator.

Study Objectives and Treatment Plan

The primary endpoint of the study was to determine the 2-year progression-free survival (PFS) for patients with locally or regionally advanced HNSCC treated with concurrent IMRT + cisplatin + bevacizumab + cetuximab. Secondary endpoints were to determine median overall survival (OS) and to describe the safety and tolerability of the regimen.

The cetuximab schedule was a loading dose (400 mg/m^2 on day minus 7) followed by weekly dosing (250 mg/m^2 on days 1, 8, 15, 22, 29, 36, and 43).[3] Two cycles of cisplatin (50 mg/m^2 on days 1, 2, 22, 23) and bevacizumab (15 mg/kg on days 1 and 22) were planned. Day 1 refers to the first day of radiation therapy. Guidelines for cisplatin and bevacizumab treatment modifications were as previously described.[8] Bevacizumab and/or cetuximab doses could be delayed do to adverse events, but dose reductions for bevacizumab and/or cetuximab were not allowed. Concurrent intensity-modulated radiation therapy (IMRT) was delivered on a standard schedule of one fraction per day (excluding weekends and holidays) to a total dose of 7000 cGy over 33 to 35 treatment days. High risk subclinical disease received 5940 to 6300 cGy while the lower risk subclinical disease received 5400 to 5600 cGy.

Evaluation During Study and Response Assessment

Adverse events were graded using the NCI Common Terminology Criteria for Adverse Events, Version 3.0. Acute toxicities were defined as those occurring from date of registration until 30 days after completion of therapy. Routine laboratory studies (complete blood cell count, basic metabolic panel with magnesium) were obtained weekly during the treatment period. CT or MRI scan of tumor site and whole-body FDG-PET scan were repeated approximately 3 – 4 months after the completion of chemoradiation. Neck surgery was not offered to patients who had a complete clinical and radiographic response, but could

be offered to patients without complete response. For patients who maintained active follow-up, planned surveillance included clinic visits approximately every 3 months for 2 years, and every 6 months thereafter.

Statistical Considerations

Time endpoints were measured from the start of treatment until the first reported distant or local/regional failure or until death from any cause. Second malignancies that were not upper aerodigestive squamous cancers were not scored as events. Patients with persistent local-regional persistent disease at the time of post-treatment imaging could undergo salvage surgery. Patients who underwent complete resection of persistent disease at salvage surgery, and thereby achieved status of no evidence of disease, were considered to be progression-free. Patients with any unresectable disease after chemoradiation would be considered to have experienced disease progression. PFS data was censored at the time of last follow-up for patients without distant or local/regional failure. The protocol contained an early stopping rule for unanticipated toxicity. The regimen would be deemed worthy of further study if 2-year PFS was 70%. With a sample size of 30 subjects, the statistical design yields a 3% type 1 error rate and 84% power.

RESULTS

Patient Characteristics and Treatment Delivery

30 subjects were enrolled between December 14, 2009 and June 18, 2013. Patient characteristics are summarized in Table 1. It was a predominantly male population with median age of 57 years (range, 38–77 years). The most common clinical stage was IVA, and the most primary tumor site was oropharynx. Positive p16 immunohistochemistry, a surrogate marker for HPV-related oropharynx cancer, was detected in 71% (17/24) of oropharynx cancers. Only 23% (7/30) of the study subjects had tobacco histories of more than 10 pack-years. Twenty patients were treated at MSKCC Main Campus in New York City, and 10 patients were treated at regional network sites.

All 30 patients completed the prescribed course of radiation therapy (70 Gy). Both planned cycles of bevacizumab were received by 28 patients; two patients receive only 1 cycle of bevacizumab. Both cycles of cisplatin were administered at full dose for 24 patients. Three patients received cycle 2 of cisplatin with 50% dose reduction, and three patients received only one cycle of cisplatin. Eighteen patients received all 8 planned cetuximab infusions, including the loading dose. Cetuximab infusions were administered for 7 or 6 weeks for 5 and 4 patients, respectively. One patient each received 5, 4, and 0 weeks of cetuximab. The latter patient experienced a cetuximab hypersensitivity reaction during the loading dose attempt, but remained on study to receive both cycles of bevacizumab and cisplatin at full dose.

Acute Toxicities and Late Functional Outcomes

Table 2 lists acute adverse events, regardless of attribution, that occurred in ≥ one-third of patients at any grade, and/or were ≥ grade 3 in at least 2 patients. The most common adverse events of any grade, occurring in 29 patients each, were mucositis (clinical exam), fatigue,

and low hemoglobin. The most common adverse events ≥ grade 3 were lymphopenia, mucositis (functional), and dysphagia. There were 3 episodes of neutropenic fever, but there were no grade 5 events. Fifteen patients underwent placement of percutaneous gastrostomy tube.

The Performance Status Scale for Head and Neck Cancer Patients (PSS-HN)[10] was used to evaluate post-treatment speech and swallowing function for 23 patients. PSS-HN scores for these patients were obtained at a median of 3.1 months after completion of treatment (range, 1.0 to 14.8 months). PSS-HN scores are summarized in Table 3. Median scores for eating in public, understandability of speech, and normalcy of diet were 100, 100, and 80, respectively.

Efficacy

Three patients experienced recurrent disease. One was a 63 year-old male never-smoker with base of tongue squamous cell cancer, stage IVA, p16 positive. Cycle one of cisplatin was complicated by neutropenic fever, and cycle two of cisplatin was given with a 50% dose reduction. Approximately 12 months after completion of treatment, he was found to have recurrent neck disease, and this was cytologically confirmed. A second patient with disease recurrence was a 57 year-old man with hypopharynx squamous cell cancer, stage IVA. Approximately 7 months after completion of treatment, imaging studies and physical exam demonstrated evidence of local/regional disease recurrence; tissue confirmation was not obtained due to rapid clinical decline. The third patient to experience treatment failure was a 66 year-old woman with right tonsil squamous cancer, stage IVA. She had a 25 pack-year tobacco history; p16 status of tumor was not obtained. She developed cytologically confirmed lung metastases approximately 3 months after completion of treatment.

One patient with hypopharynx carcinoma underwent neck surgery 3.2 months after the final radiation treatment, and surgical pathology findings were notable for one level 2 neck node with persistent squamous carcinoma. Because he was rendered disease-free by this salvage surgery, this did not meet criteria for a progression event per the statistical methods. A patient with base of tongue carcinoma underwent resection of persistent level 2 neck node 3.7 months after completion of radiation therapy, and pathology finding were non-malignant cells only.

Regarding the primary endpoint of the study, 2 year PFS was 88.5% (95% CI: 68.1–96.1%) and was unchanged after 3 years (Figure 1A). At a median follow up of 33.8 months (range, 4.8 to 55.5 months), median PFS was not reached. Overall survival at 2 years was 92.8% (95% CI: 74.2–98.1%) and was stable after 3 years (Figure 1B). Median overall survival was not reached.

DISCUSSION

This phase II study describes safety and encouraging efficacy with the addition of two monoclonal antibodies, bevacizumab and cetuximab, to two cycles of cisplatin administered concurrently with intensity-modulated radiation therapy in locally/regionally advanced HNSCC. Both planned cycles of bevacizumab were completed by 93% of study subjects,

and all completed the planned radiation therapy. The most common ≥ grade 3 adverse events were lymphopenia, functional mucositis, and dysphagia. Regarding the primary endpoint of the study, 2 year PFS was 88.5%.

The current study adds to the published experience of numerous non-randomized phase II studies in which bevacizumab was added to various combined modality regimens for locally/regionally advanced HNSCC.[8,11–14] Key results from five of these studies have recently been summarized recently.[14] Two studies combined bevacizumab with erlotinib, an orally administered EGFR inhibitor, during radiation therapy for locally/regionally advanced HNSCC. Yoo and colleagues combined bevacizumab, erlotinib, and weekly cisplatin with concurrent twice-daily radiation therapy; 3- year estimated PFS was 82%.[13] Hainsworth and colleagues conducted a prospective trial of bevacizumab plus induction chemotherapy, followed by radiation therapy given concurrently with weekly paclitaxel, bevacizumab, and erlotinib. Estimated 3 year PFS was 71%.[12] A central limitation of these studies, and the current study, is the lack of a randomized design to test the null hypothesis regarding the efficacy of bevacizumab. A single institution non-randomized trial with a relatively small sample size, such as the current study, does not provide a direct comparison with the efficacy of standard of care treatment.

The favorable efficacy outcomes in the current study are probably influenced, at least in part, by the favorable prognostic features of the study population. 80% of the patients on this study had oropharynx cancer, and the oropharynx cancers that were available for testing were predominantly HPV-related. The study population had relatively few patients (23%) with greater than 10 pack-years of tobacco history. After the design of the study, data from RTOG 0129 demonstrated that the combination of HPV-related cancer and ≤ 10 pack-year tobacco history defines a group of patients with a favorable prognosis in oropharynx cancer studies.[15] RTOG 0129 also demonstrated no significant efficacy advantage for three cycles of cisplatin (concurrent with standard fractionation) versus two cycles of cisplatin (concurrent with accelerated fractionation),[15] which is consistent with the results of this study in which high efficacy was achieved with only two planned cycles of concurrent cisplatin.

As this study was nearing completion of accrual, negative data regarding the combination of cisplatin + cetuximab, given concurrently with radiation therapy, emerged from the RTOG 0522 trial.[16] The negative RTOG 0522 data do not address the hypothesis of potential added activity with the addition of bevacizumab to the cisplatin/cetuximab/radiation combination. There are signals of potentially useful clinical efficacy with combined EGFR and VEGF blockade from several HNSCC studies in the locally/regionally advanced setting[12,13] and in the recurrent/metastatic setting,[9,17] albeit in non-randomized studies. The negative RTOG 0522 data underscore the need for predictive biomarkers to guide the development of targeted therapy regimens. Potential predictive biomarkers for combined EGFR and VEGF inhibition have been described.[17] Further interrogation of potential biomarkers would be an essential part of any future development effort regarding combined EGFR and VEGF inhibition in HNSCC.

The role of bevacizumab in HPV-related tumors warrants further study. In pre-clinical studies with cervical cancer cell lines, transfection with constructs expressing HPV E6 and E7 upregulates VEGF expression and enhances angiogenesis.[18] The clinical benefit of bevacizumab in HPV-related cancers was established in a randomized phase III trial for patients with advanced cervical cancer, in which the addition of bevacizumab to standard chemotherapy increased overall survival by 3.7 months.[19] In recurrent/metastatic HNSCC, the results of ECOG 1305 are awaited regarding standard chemotherapy with our without bevacizumab.[20] The impact of bevacizumab among patients with HPV-related cancers in ECOG 1305 could help elucidate if sensitivity to bevacizumab may be a general characteristic of HPV-related malignancies.

In conclusion, the current study adds to a growing body of literature which demonstrates that bevacizumab is well tolerated when added to radiation-based therapy for locally/regionally advanced HNSCC. Favorable efficacy results were observed in this single-arm study, but a larger randomized study would be needed to assess the efficacy of this regimen conclusively. Targeting angiogenesis with bevacizumab may be appropriate for de-intensification trials that seek to reduce exposure to conventional cytotoxic agents for patients with HPV-related oropharynx cancer.

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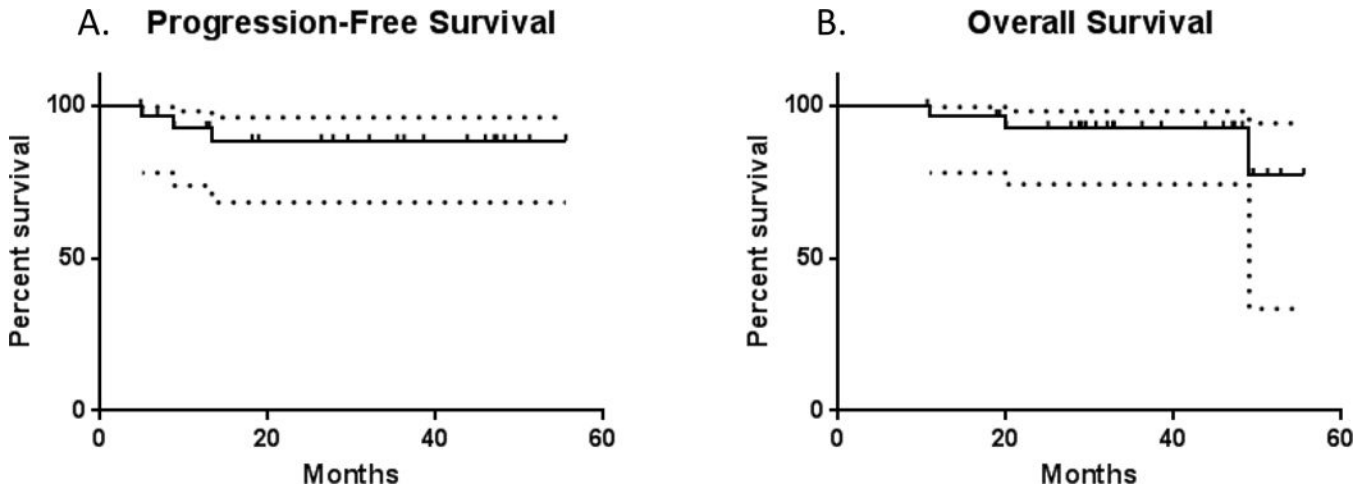

Figure 1.

The Kaplan-Meier plots illustrate (A) Progression Free Survival and (B) Overall Survival. The dotted lines indicate 95% confidence intervals.

Table 1

Patient characteristics

Patient Characteristic	Summary
Age, median (range)	57 years (38–77 years)
Gender (M/F)	27/3
Karnofsky Performance Status, median (range)	90 (80–100)
Subsite, N subjects (%)	
Oropharynx	24 (80)
Tonsil	11
Base of tongue	13
Hypopharynx	3 (10)
Larynx	2 (7)
Oral cavity	1 (3)
Tumor (T) classification, N subjects (%)	
1	7 (23)
2	14 (47)
3	7 (23)
4	2 (7)
Node (N) classification, N subjects (%)	
0	2 (7)
1	2 (7)
2a	3 (10)
2b	19 (63)
2c	4 (13)
3	0
Overall Stage, N subjects (%)	
III	3 (10)
IVA	27 (90)
p16 status, N subjects (%), oropharynx only	
Positive	17/24 (71)
Negative	1/24 (4)
Unknown/insufficient material for assay	6/24 (25)
Tobacco Pack-Years, N subjects (%)	
0 to ≤ 1 pack year	14 (47)
> 1 to ≤ 10 pack years	8 (27)
>10 to ≤ 20 pack years	1 (3)
>20 pack years	6 (20)
Unknown	1 (3)

Table 2

Summary of Adverse Events (N= 30 subjects)

Adverse Event	Number of patients (%)		
	Any Grade	Grade	Grade 4
Mucositis- clinical exam	29 (97)	6 (20)	1 (3)
Fatigue	29 (97)	3 (10)	0
Low hemoglobin	29 (97)	1 (3)	0
Nausea	28 (93)	6 (20)	0
Constipation	28 (93)	0	0
Lymphopenia	27 (90)	16 (53)	11 (37)
Weight loss	27 (90)	4 (13)	0
Dysphagia	26 (87)	9 (30)	1 (3)
Leukopenia	26 (87)	7 (23)	1 (3)
Rash, acne/acneiform	26 (87)	3 (10)	0
Hypoalbuminemia	25 (83)	0	0
Pain- throat/pharynx/larynx	24 (80)	4 (13)	0
Mucositis- functional	23 (77)	11 (37)	0
Hyponatremia	23 (77)	3 (10)	0
ALT elevation	22 (73)	2 (7)	0
Thrombocytopenia	19 (63)	1 (3)	0
Vomiting	17 (57)	2 (7)	0
Hypomagnesemia	17 (57)	0	0
AST elevation	15 (50)	0	0
Pain - headache	14 (47)	0	0
Diarrhea	13 (43)	0	0
Neutropenia	12 (40)	2 (7)	1 (3)
Creatinine elevation	12 (40)	2 (7)	0
Cough	12 (40)	0	0
Hyperkalemia	12 (40)	0	0
Hypokalemia	11 (37)	3 (10)	0
Fever (without neutropenia)	10 (33)	0	0
Epistaxis	10 (33)	0	0
Thrombosis/embolism	6 (20)	5 (17)	0
Hypophosphatemia	6 (20)	3 (10)	0
Febrile neutropenia	3 (10)	3 (10)	0
Pain – abdomen	3 (10)	3 (10)	0
Allergic reaction/hypersensitivity	3 (10)	2 (7)	0

Table 3

Summary of results obtained after chemoradiation with the Performance Status Scale for Head and Neck Cancer Patients (N=23 patients)

Function	Median	Range	No. patients with score of 100 (%)
Eating, median (range)	100	25 – 100	14/23 (61)
Speech, median (range)	100	75 – 100	18/23 (78)
Diet, median (range)	80	30 – 80	8/23 (35)