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Phase II Study of the Addition of Bevacizumab to Standard Chemoradiation for Loco-regionally Advanced Nasopharyngeal Carcinoma: Radiation Therapy Oncology Group (RTOG) Trial 0615

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Abstract

Purpose—We sought to improve the outcomes for loco-regionally advanced nasopharyngeal carcinoma (NPC) by testing the feasibility/safety of adding bevacizumab to chemoradiation.

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Author Contribution

Nancy Y. Lee: PI of the protocol, review of radiation oncology records from institutions, interpretation of the data, writing the paper

Ed Zhang: statistical design, analysis of all data, writing the paper

David.G. Pfister: Review of all med onc records from all institutions, writing the paper

John. Kim: Review of all radiation oncology records from all institutions, writing the paper and helping out with protocol design

Adam.S. Garden: contribution of patients, helping with protocol design and writing the paper

James. Mechalakos: helping to write the physics portion of the protocol and paper

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Anthony.T.C. Chan: translational design and write up of the protocol; writing the paper

K. Kian. Ang: senior who helped design protocol, ensuring protocol is funded through NCI, helping with paper writing

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Patients/Methods—Eligible patients with T2b and/or positive node(s) were prescribed 3 cycles of bevacizumab (15 mg/kg) and cisplatin (100 mg/m²) both given on days 1, 22, and 43 of radiation (70 Gy) using IMRT delivered over 33 days on a daily basis, Monday through Friday. This is followed by 3 cycles of bevacizumab (15 mg/kg), cisplatin (80 mg/m²) both were given on days 64, 85, and 106 and fluorouracil (1000 mg/m²/d) on days 64–67, 85–88, 106–109 after radiation. The primary endpoint was to evaluate the safety of the addition of bevacizumab to chemoradiation, specifically looking at treatment-related Grade 4 hemorrhage and/or any Grade 5 adverse event in the first year. Toxicity during and after treatment were collected along with tumor control endpoints. The analysis was done per protocol. This protocol has completed its target accrual.

Results—There were a total of 46 patients enrolled in this study of whom 44 patients were eligible for analysis. No grade 3–4 hemorrhage or grade 5 adverse events were observed; 9 patients (20.5%) experienced grade 1–2 hemorrhage. Grade 4 adverse events were experienced by the following numbers of patients: leukopenia NOS – 6; lymphopenia – 5; neutrophil count – 5; pharyngolaryngeal pain – 2; hemoglobin – 1; infection with grade 3–4 neutrophils (blood) – 1; infection with grade 3–4 neutrophils [skin (cellulitis)] – 1; tinnitus – 1; thrombosis – 1; radiation mucositis – 1. The most common grade 3 adverse events were radiation mucositis – 33; dysphagia – 25; and mucositis/stomatitis (clinical exam) (pharynx) – 15. Two patients experienced late grade 3 xerostomia. Other late grade 3 adverse events were: dysphagia – 5; hearing impaired – 3; neuralgia NOS – 2; constitutional symptoms (other) – 1; dehydration – 1; fatigue – 1; hearing disability – 1; infection (other) – 1; muscle weakness NOS – 1; peripheral motor neuropathy – 1; peripheral sensory neuropathy – 1; radiation mucositis – 1. With a median follow-up of 2.5 years, the estimated 2-year loco-regional progression-free, distant metastasis-free, progression-free and overall survival (OS) rates were 83.7% (95% confidence interval 72.6–94.9), 90.8% (82.2–99.5), 74.7% (61.8–87.6), and 90.9% (82.3–99.4), respectively.

Conclusion—It was feasible to add bevacizumab to chemoradiation for NPC treatment. The favorable 2-year OS of 90.9% suggests that bevacizumab might delay progression of subclinical disease.

INTRODUCTION

A current standard therapy for patients with loco-regionally advanced nasopharyngeal carcinoma (NPC) is concurrent cisplatin chemotherapy followed by adjuvant chemotherapy (cisplatin and 5-fluorouracil).^{1–5} Although there are debates whether adjuvant chemotherapy is necessary, there is consensus among experts that cisplatin given concurrently with radiation improved overall survival (OS).^{6–10} Since the introduction of intensity-modulated radiation therapy (IMRT), patients are experiencing fewer late toxicities, e.g., xerostomia.^{11,12} Furthermore, an increasing number of centers are reporting superb loco-regional (LR) control [$>90\%$] most likely due to the ability of IMRT to target the irregularly-shaped tumor in a region surrounding by multiple critical tissues such as the brain stem and the optic apparatus when compared to conventional radiotherapy techniques.^{13–17} The excellent LR control reported by single institution experiences has also been reproduced in the multi-institutional setting as evidenced by the results of the phase II RTOG 0225 trial on the use of IMRT with and without chemotherapy in the treatment of NPC.¹⁸ However, with

improved LR control rate, the development of distant metastasis (DM) is still problematic (~30% at 4–5 years) which ultimately results in patient death. Therefore, more effective systemic therapy is needed to further improve OS for these patients.^{15,17,18}

Increased vascular endothelial growth factor-A (VEGF-A) expression has been associated with poor prognosis in squamous cell carcinoma of the head and neck.¹⁹ VEGF has been shown to play an important role in lymph node metastasis through the induction of angiogenesis in NPC.²⁰ Qian, et al. have shown that the levels of serum VEGF were significantly elevated in 65 patients with metastatic NPC.²¹ In another study, overexpression of VEGF was seen in 67% of NPC cases and the higher expression of VEGF in Epstein Barr Virus (EBV) positive tumors was related to higher rates of nodal involvement, recurrence, and lower OS.²² A recent pilot study by Druzgal, et al. analyzed the pre- and post-treatment serum levels of cytokines and angiogenesis factors as markers of outcome in patients with head and neck cancer, of whom 7% had NPC.²³ With a median follow-up of 37 months, patients were more likely to remain disease free when the VEGF level decreased post-treatment than those who continued to have elevated VEGF levels after treatment.

Given that the predominant pattern of failure in loco-regionally advanced NPC in the modern era is distant metastasis and that NPC patients with elevated VEGF have a higher likelihood of recurrence, distant metastases, and decreased survival, this phase II multi-institutional RTOG trial (0615) was launched to test the addition of bevacizumab (as a monoclonal antibody directed against VEGF)²⁴ to the current chemoradiation standard for this group of patients. The hypothesis is that bevacizumab might reduce the rate of DM and improve disease-free survival without significant toxicity as it has done in other disease sites, including colon, renal, and lung cancer.^{25–27} Bevacizumab was chosen because its combination with standard chemotherapy, bevacizumab improves response rate and overall survival in randomized phase III trials in metastatic colorectal and non-small cell lung cancer. Similarly, bevacizumab in combination with chemoradiation for preoperative rectal cancer has shown promising results where one trial reported a 5 year local control and overall survival of 100%.^{28,29,30} We report the feasibility, toxicities, and treatment outcomes of this current trial for loco-regionally advanced NPC.

PATIENTS/METHODS

Study Objectives/Patient Eligibility

Patients with previously untreated stage IIB-IVB NPC, Zubrod 0–1, meeting criteria for blood counts/other tests (e.g., WBC 4,000/ μ l; platelet 100,000/ μ l; serum creatinine of 1.6mg/dl) were eligible. Patients <18 years old, those with a prior (within 3 years) or synchronous malignancy other than non-melanoma skin cancer, and those with T1–2 disease with involvement of retropharyngeal lymph nodes only (N1) were excluded. Tumors close to major blood vessels were not excluded from this study. We did not allow patients who had major bleeds within one month to enroll on this protocol. For details of the inclusion and exclusion criteria, please refer to the supplemental table 1. Pretreatment evaluations consisted of history/physical, dental, nutritional, audiogram, and laboratory studies. Magnetic resonance imaging (MRI) of the nasopharynx/neck was required unless there was a contraindication, i.e., pacemaker in which case a computed tomography (CT) scan of the

nasopharynx/neck was required. Additional tests to evaluate the extent of disease included chest x-ray, alkaline phosphatase, liver function tests, lactate dehydrogenase, and when indicated, liver/bone scans. Positron emission tomography (PET) was optional. The disease was staged according to the 2003 American Joint Committee on Cancer Staging guidelines. All patients signed written informed consents with the study approved by the National Cancer Institute (NCT00408694) and participating centers' Institutional Review Board.

Treatment

IMRT was delivered in 33 fractions using a simultaneous-integrated boost technique.¹⁸ The planning target volume of the gross disease (PTV₇₀) received 70 Gy in 2.12 Gy/fraction, high risk subclinical disease (PTV_{59.4}) received 59.4 Gy in 1.8Gy/fraction, and lower risk subclinical disease (PTV₅₄) 54 Gy at 1.64 Gy/fraction. Radiation therapy was delivered on a daily basis from Monday through Friday over 33 days. The lower neck nodes could be included in extended IMRT fields or irradiated with matching conventional anterior-posterior fields. In the latter scenario, a dose of 50.4 Gy was administered at 1.8 Gy/fraction.

When available, fusion of MRI and/or PET with treatment planning CT images was encouraged to accurately delineate the gross tumor volume (GTV) including the primary disease and nodes >1cm in diameter or nodes with necrotic centers. The high risk subclinical regions included the entire nasopharynx, retropharyngeal nodal regions, skull base, pterygoid fossae, parapharyngeal space, sphenoid sinus, posterior third of the nasal cavity/maxillary sinuses to include the pterygopalatine fossae and level I-V lymph node regions. The level I nodal region was not radiated in the N0 neck.

Bevacizumab (15 mg/kg)³¹ was given concurrently with cisplatin (100mg/m²) on days 1, 22, and 43 followed by adjuvant bevacizumab (15 mg/kg) and cisplatin (80 mg/m²) on day 1, fluorouracil (protracted venous infusion 1000 mg/m²/d) on days 1–4 q4 weeks x3 cycles. Adjuvant therapy starts 3 weeks after chemoradiation on days 64–67, 85–88, 106–109 after radiation.

Guidelines for Dose Modifications During Concurrent chemoradiotherapy

Patients were examined and graded for subjective/objective evidence of developing toxicity according to the CTCAE, v. 3.0 each day that chemotherapy was administered and weekly while receiving radiotherapy. There were no radiotherapy dose modifications. Treatment interruptions are allowed if there was symptomatic mucositis or skin reaction that, in the judgment of the clinician, warranted a break. The treatment was completed as per protocol for treatment breaks up to 14 days. If the break exceeded 14 days, the patient was removed from protocol treatment. The patient would then complete treatment at the discretion of his/her physician but would be followed and included in the analysis.

Chemotherapy dosage modifications were based upon nadir counts and interim non-hematologic toxicities of the preceding cycle for cycles 2–6. The dose modifications for chemotherapy were intended to be permanent (i.e., if the patient's dose was reduced to dose level –1, it remained at the reduced dose level). Cisplatin Dose level reductions were as follows: –1: 80mg/m² and –2: 60mg/m². Chemotherapy must not be administered until the AGC 1,000 and platelets are 100,000. If not, treatment needed to be delayed one week.

If the patient still had not recovered to these parameters in one week, cisplatin should be discontinued. The third dose of cisplatin should be administered within 2 weeks of the end of radiation. If it cannot be administered in this time frame, the dose should be held. Hematologic growth factors for neutropenia or anemia were not allowed during concurrent cisplatin and radiation treatment.

Guidelines for Dose Modifications During Adjuvant Chemotherapy

Cisplatin dose level reductions were as follows: -1: 60mg/m²; -2: 40mg/m²; 5-FU dose reductions were -1: 800mg/m²; -2: 600mg/m². Chemotherapy must not be administered until the AGC 1,000 and platelets are 100,000. If not, delay one week. If the patient still had not recovered to these parameters in one week, adjuvant cisplatin and 5-FU were discontinued. Prophylactic growth factors for neutropenia are not allowed. In the setting of infection, they may be incorporated based on the judgment of the investigator. Growth factors for anemia (e.g., darbepoetin, erythropoietin) may be incorporated based on the judgment of the investigator.

Dose Modifications for NonHematologic Adverse Events During Concurrent & Adjuvant Chemotherapy (4/21/08)

Dosing of chemotherapy would only change if there was a 10% weight loss from baseline. Temperature of 38.5°C with AGC <1000 was an expected potential complication of concurrent chemotherapy and radiotherapy or chemotherapy alone. If neutropenic fever was noted, the chemotherapy dose reduction would be determined by the nadir counts. Specific guidelines for Grade 3 and 4 events can be found in the protocol. In general, chemotherapy was delayed until patients recovered to Grade 1 events.

Treatment Modifications/Delay Guidelines for Bevacizumab (4/21/08)

The dosing date for bevacizumab may be delayed for up to 3 days for logistical reasons (e.g., holiday, patient scheduling conflict). Hypertension is a known and potentially serious adverse event associated with bevacizumab treatment. Patients should have their blood pressure monitored weekly during the first cycle of therapy and prior to each infusion of bevacizumab. Hypertensive medication should be initiated or increased per routine practice. The appropriate interval from discontinuation of bevacizumab to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It was generally recommended that bevacizumab should be discontinued at least 4 weeks prior to major elective surgery. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed. There would be no dose reduction for bevacizumab. Specific guidelines on when bevacizumab should be discontinued can be found in the protocol.

Nutritional evaluation for a prophylactic gastrostomy (PEG) tube placement is **STRONGLY ENCOURAGED**. Prophylactic placement must occur 1 week prior to treatment. For patients who do not have a PEG tube placed prophylactically and who subsequently require placement during treatment, bevacizumab must be stopped at least 1 week prior and for 1 week after the placement of the PEG tube.

Follow-up/Statistical Considerations

Patients underwent weekly examinations during chemoradiation treatments. Follow-up evaluations occurred q3 months during the first 2 years; q6 months during years 3–5; then annually. In addition to tumor/clinical status, acute/late (occurring >90 days after end of RT) normal tissue effects were graded. Both systemic and RT side effects were scored using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Adverse events scored as definitely, probably, or possibly related to protocol treatment (or with unknown relationship) were considered treatment-related.

The primary endpoint was to evaluate the safety of the addition of bevacizumab to chemoradiation, specifically looking at treatment-related Grade 4 hemorrhage and/or any Grade 5 adverse event in the first year. The trial used the multiple testing procedure of Fleming³² with two stages, type I/II errors set at 0.14/0.17, and 5%/15% set as the acceptable/unacceptable rates. The software package used for statistical analysis was SAS version 9.2. The first stage required 14 patients; 3 or more events would be considered unacceptable. Accrual was suspended to evaluate safety in the first stage patients. In the second stage, 4/42 would be considered unacceptable. To allow for up to 10% of patients to be ineligible or not start protocol therapy, the sample size was 46 patients. Secondary endpoints related to adverse events were: Grade 4 hemorrhage and any Grade 5 adverse event after the first year; other Grade 3–5 adverse events, and death during or within 30 days of treatment completion, regardless of cause of death. Another secondary endpoint was to examine the tolerability of the combination of BV to chemoradiation. Namely, during the concurrent phase, to measure the percentage of patients receiving 2 cycles of CDDP and bevacizumab with RT per protocol or with acceptable variation and during the adjuvant phase, the percentage of patients receiving 2 cycles of CDDP, 5FU, and bevacizumab. Tumor volume contouring score and organs at risk contouring score was done remotely as per protocol, acceptable variation, or unacceptable variation.

The rates of tolerability and adverse events were estimated using a binomial distribution along with their associated 95% confidence intervals. OS and PFS were estimated using the Kaplan-Meier method³³ and confidence intervals calculated using Greenwood's formula (see inserted reference). LRP-free and DM-free rates were calculated using the method of cumulative incidence^{34,35} to account for the competing risk of death without failure and confidence interval calculated using method in Gray³⁶. Patients who developed DM were still followed for LR failures. Failure for loco-regional progression-free rate was local or regional recurrence/progression, or death due to study cancer or unknown causes with undocumented site of failure. Failure for distant-metastasis-free rate was distant metastasis. Failure for progression-free survival was local, regional, or distant recurrence/progression, or death due to any cause. For overall survival it is death due to any cause.

This is a RTOG trial that is sponsored by the National Cancer Institution in USA protocol number, NCT00408694. This protocol is supported by grants RTOG U10 CA21661 and CCOP U10 CA37422 from the National Cancer Institute (NCI). The contents of this article are the sole responsibility of the authors and do not necessarily represent the official views of the NCI. The PI along with her co-PI's designed the trial and the sponsor reviewed the trial, made comments. Revisions were done to ensure protocol design was satisfactory to the

NCI governing board. The sponsor did not collect, analyze or interpret the data. The sponsor did not help write the paper. The PI, Dr. Zhang and his team at the RTOG had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Patient Characteristics/Treatment Compliance

From December 13, 2006 to February 5, 2009, 46 patients were accrued from 19 centers in North America and Hong Kong of whom 44 patients (44/46; 95.7%) were eligible for analysis (1 did not start protocol therapy; 1 had WBC outside protocol range). The study was closed briefly in early 2008 for a planned adverse event analysis but reopened after for two months in the absence of Grade 4 hemorrhages and Grade 5 adverse events reported. This current dataset was created on 6/15/2011. Table 1 lists the pretreatment patient/tumor characteristics.

Table 2 lists actual treatments delivered. Forty-three patients (43/44; 97.7%) received IMRT. Fourteen of 44 patients (14/44; 31.8%) had major deviation for tumor volume contouring. Only 12 of 44 patients (12/44; 27.3%) were scored per protocol for chemotherapy delivery; of these 9 (9/12; 75.0%) patients had protocol/allowed modifications and/or delays of their chemotherapy. Of the 32 patients (32/44; 72.7%) scored not per protocol, 19 (19/32; 59.4%) received 80% of the protocol dose and 13 (13/32; 40.6%) received <80%. All patients received at least 2 cycles of cisplatin concurrent with RT and only 1 patient (1/44; 2.2%) received < 2 cycles of bevacizumab concurrent with IMRT. The concurrent and adjuvant phases were both tolerable in 30 patients (30/44; 68.2%) of the patients. Eight patients (8/44; 18.2%) did not receive any adjuvant therapy.

Failure Pattern

Median follow-up for surviving patients was 2.5 years (range 1.0–3.6). Four patients (4/44; 9.1%) had LR failures and five (5/44; 11.4%) had DM as first site of failure. Three other patients died (3/44; 6.8%), one (1/44; 2.2%) from unknown cause and two (2/44; 4.5%) from NPC without having the patterns of relapse reported. Figure 1 A–D shows the cumulative incidence curves for LRPF and DMF and Kaplan-Meier curves for PFS and OS along with 2-year estimated rates for all endpoints with 95% confidence intervals..

Adverse Events

There were no Grade 5 adverse events observed and no deaths occurred within 30 days of treatment completion. No patients experienced grade 3–4 hemorrhage but 9 (9/44; 20.54%) had grade 1–2 hemorrhage at least possibly related to protocol therapy. Five patients (5/44; 11.4%) experienced at least 1 Grade 4 non-hematologic adverse event [(1/44 (2.2%) radiation mucositis, 2/44 (4.5%) pharyngolaryngeal pain, 1/44 (2.2%) neutropenia, and 1/44 (2.2%) thrombosis)]. Overall, 77.3% of patients (34/44) experienced acute grade 3–4 mucositis, 13.6% (6/44) experienced grade 3 radiation dermatitis, and 4.5% (2/44) grade 3 late xerostomia. Table 34 and Supplemental Table 1 summarize adverse events while Table 45 summarizes all reported hemorrhages. Four patients (4/44; 9.1%) required a feeding tube

before protocol therapy. At 1 and 2 years after the start of treatment, 12.2% (5/41) and 5.6% (2/36) required a feeding tube.

DISCUSSION

Hemorrhage is a well-known complication of bevacizumab. No Grade 3 or 4 hemorrhages were observed in this trial. Nine patients had grade 1 and 1 grade 2 hemorrhage. Besides hemorrhage, no other unusual toxicities associated with the addition of bevacizumab to cisplatin and/or fluorouracil was noted in this group of patients. In terms of worst non-hematologic toxicity, 5 patients (11.4%) experienced grade 4 while the majority of the patients (79.5%) experienced grade 3 toxicity. Furthermore, as noted in Table 3 no excessive, unexpected late effects were observed with the addition of bevacizumab to chemoradiation for these patients. Of note, only one patient died in this cohort without documentation of disease progression hence suggesting that bevacizumab did not have any unwarranted toxic deaths.

This phase II trial showed that 30 (68.2%) patients received 3 cycles of concurrent cisplatin. This compares favorably to the compliance rates to cisplatin during radiation, i.e., 63% in the Intergroup 0099 trial, 71% in the Singapore trial, and 52% in the Hong Kong NPC-9901 trial.^{1,2,10} The compliance of bevacizumab during concurrent chemoradiation was also surprisingly good: 70.5% received 3 cycles and 97.7% received at least 2 cycles. The addition of bevacizumab did not impede RT delivery where all but 1 patient (65.72 Gy) received the prescribed 70 Gy. The compliance to 3 cycles of adjuvant cisplatin was 47.7% in this RTOG study versus 46%, 55%, 57%, and 76% in the RTOG 0225, Intergroup 0099, Singapore, and Hong Kong NPC-9901 trials, respectively. Despite bevacizumab given in the adjuvant setting, 75% of the patients received at least 2 cycles and 52.3% received 3 cycles. Overall, the investigators felt that it was feasible to add bevacizumab to chemoradiation for NPC and there was no major compromise in the delivery of current chemoradiation standard.

The use of IMRT to target irregularly-shaped tumors in a confined space surrounded by multiple critical normal tissues, reported LR control rates from single institutions have been in excess of 90% for NPC, even in patients presenting with advanced loco-regional disease.^{13–16,37} RTOG 0225 has also demonstrated the transportability of IMRT from single institutions to the multi-institutional setting and reproduced the superb loco-regional treatment outcomes.¹⁸ Consequently, DM has become the main cause of death. Therefore, the RTOG initiated this phase II study to test whether it was feasible to add a biologic therapy to the present chemoradiation standard for loco-regionally advanced NPC at risk for distant failure. Bevacizumab was added during both the concurrent and adjuvant phases of chemotherapy. The reason for combining bevacizumab with the concurrent phase of chemoradiotherapy is to enhance the effect of cisplatin in potentially sterilizing distant micrometastases from the very beginning of treatment since compliance to the adjuvant phase has been rather low. Two study chairs reviewed all target volume delineations independently and found major deviations in 31.8% of the cases. This number is higher than expected as RTOG 0225 has shown that with proper training and guidelines from RTOG, majority of cases had minor variation. Further assessment revealed that major deviations

were mostly associated with delineation of level V neck nodes or the skull base encompassed in the elective irradiation target volumes. This could explain the lower than expected 2-year loco-regional progression-free rate of 84% versus other series at 90%. This emphasizes the importance of attention to accurate target delineation to ensure no marginal misses when using high precision radiotherapy techniques.

Although the addition of bevacizumab did not seem to result in any unusual grade 3–4 events, the toxicity still seemed substantial and compliance to protocol treatment was not ideal. Since not all loco-regionally advanced NPC recur after standard chemoradiation, questions have been raised as to whether bevacizumab should be incorporated in the management of local-regionally advanced NPC. If one can identify a cohort of patients at high risk for recurrence, these patients can perhaps derive the greatest benefit with the addition of a biologic therapy to the current standard. Efforts in identifying the patient at high risk for recurrence with the standard chemoradiation regimen are sought. The protocol was designed to perform collateral translational studies, i.e., testing VEGF expression in attempt to further identify the patients at risk for recurrence. Due to the limited samples that we have obtained so far from the various RTOG institutions, we have not begun doing any collateral studies. Unfortunately, the RTOG was not given the permission to make collection of biospecimens mandatory by central and institutional review boards. However, we will continue to encourage institutions to send all these biospecimens to our headquarter tissue bank. We plan to perform VEGF assay with and correlate with clinical outcomes. Therefore, the current standard of care for loco-regionally advanced disease remains chemoradiation and any additional biologic therapy should be done in a protocol setting. One interesting finding from the current trial is that although the 2-year PFS was 74.7%, the 2-year OS was surprisingly high at 90.9%. The higher OS when compared to historical controls could also be due to better detection of recurrent disease with sophisticated imaging such as PET scans so that salvage, i.e., re-irradiation, chemotherapy can be done in a timely fashion. Please also note that the comparison is limited by changes in AJCC staging for NPC as well as the ability to improve upon staging using MRI and/or PET scans in the current series versus historical controls. Nonetheless, the prolongation of OS in this cohort of patient when compared to traditional chemoradiation only is worth further studying. Could bevacizumab also have prolonged the OS in this patient population despite having active disease? The size of this phase II trial is too small to make a firm conclusion and validation in a phase III randomized of the results is needed to confirm the findings.

The question on who should receive bevacizumab in addition to chemoradiation needs to be addressed. Recent data has shown that pre-treatment and particularly post-treatment circulating EBV DNA correlated with cancer stage, clinical outcome, and prognosis in patients with endemic NPC.^{39,40–45} In two large studies, post-treatment EBV DNA level has been shown to be the most significant prognostic factors for both progression-free survival and overall survival with hazard ratios ranging 11.9 to 34.5.^{43,46} Persistently elevated or rising EBV DNA has been shown to predate clinical recurrence by 3 to 7 months.^{43,46–48} There is now strong evidence that circulating EBV DNA level is a reliable marker of the extent of subclinical disease^{43,49} and, therefore, can be used to select patients for more intensive therapy.

However, the level of post-treatment EBV DNA that correlates with a complete response varies by center. Chan et al.⁴⁶ reported that a levels below 500 copies/ml are suggestive of achieving complete response in patients treated with chemoradiation. Lin et al.⁴³ reported that undetectable plasma EBV DNA after 40 cycles of PCR were strongly correlated with complete response. Due to the extreme sensitivity of the quantitative PCR detection method, many factors can affect the final results. These include the calibration of the PCR instrument, the DNA extraction method, the reference standard and operator variability. Therefore, assay standardization and interlaboratory assay harmonization would need to be accomplished before one can reliably employ EBV DNA level as an integral biomarker for directing treatment decision in multi-institutional clinical trial. Our current thought is that intensification of adjuvant systemic therapy, such as the addition of bevacizumab or other agent(s), is only warranted for patients with persistent detectable circulating EBV titer. We have therefore initiated a project to compare and harmonize EBV DNA measurement approaches among four different laboratories (2 laboratories in Taiwan, 1 in Hong Kong, and 1 in Stanford University, USA). Completion of this project will enable us to initiate a multi-institutional and intercontinental trial incorporating post-chemoradiation EBV DNA level as a mean to direct patients toward the most appropriate therapy.

In summary, RTOG 0615 has demonstrated that it was feasible to deliver bevacizumab to the current chemoradiation standard with chemotherapy delivery appearing similar to that observed in other chemoradiotherapy studies in advanced NPC not including bevacizumab. A favorable 2 year OS rate of 90.9% was achieved. Coupled with the prognostic information that can be obtained from post-chemoradiation EBV DNA once the interlaboratory validation studies are done, it is the hope that the next RTOG trial for NPC can incorporate circulating EBV DNA level as an integral biomarker for directing patients to receiving different therapy intensity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Since the introduction of IMRT with the ability to target the skull base without injury the critical structures, the predominant pattern of failure of locoregionally advanced NPC has been distant as evidenced by several single institution as well as multi-institutional studies. Efforts by the RTOG in search of additional agent to combat distant metastasis were done over the past several years. There is both preclinical and clinical evidence that NPC patients with elevated VEGF are at risk for recurrence. Bevacizumab, a monoclonal antibody directed against VEGF has been shown to improve response rate and overall survival in randomized phase III trials in metastatic colorectal and non-small cell lung cancer. Bevacizumab in combination with chemoradiation for preoperative rectal cancer has also shown promising results where one trial reported a 5 year local control and overall survival of 100%. Therefore, RTOG 0615 was initiated with first the primary endpoint of ensuring safety and tolerability with the addition of bevacizumab to current standard chemoradiation for NPC and second to test the hypothesis that bevacizumab might reduce the rate of distant metastasis and improve disease-free survival without significant toxicity as it has done in other disease sites, including colon, renal, and lung cancer. We reported that it was feasible to add bevacizumab to the current standard treatment for NPC. Furthermore, the 2 year distant metastasis-free rate of 90% is so encouraging for this group of patients.

The findings of all the trials especially since Intergroup 0099 has progressively shown that we have better locoregional control (RTOG 0225) using IMRT and now even better distant metastasis free rate (current trial) and resulting in a high overall survival of 90% at 2 years. The higher OS when compared to historical controls could also be due to better salvage, i.e, re-irradiation and chemotherapy. Nonetheless, the higher distant metastasis-free rate at 2 years is encouraging for this disease. Although the results are encouraging from this current trial, the standard of care is still concurrent chemoradiation. We feel that not all patients will need the addition of bevacizumab to the current standard. This study tells us that it was safe and feasible. The issue is to identify who is at risk of distant metastasis and failure and hence these are the patients who should receive the largest benefit from the addition of bevacizumab to current standard.

Fig 1.

A. Locoregional progression-free rate in patients with nasopharyngeal cancer treated with intensity-modulated radiation therapy, chemotherapy, and bevacizumab.

B. Distant Metastasis-Free Rate in patients with nasopharyngeal cancer treated with intensity-modulated radiation therapy, chemotherapy, and bevacizumab.

C. Progression-free survival Rate in patients with nasopharyngeal cancer treated with intensity-modulated radiation therapy, chemotherapy, and bevacizumab.

D. Overall Survival Rate in patients with nasopharyngeal cancer treated with intensity-modulated radiation therapy, chemotherapy, and bevacizumab.

Table 1**Pretreatment Characteristics (n=44)**

<hr/>		
Age (years)		
Median		48.5
Min - Max		18–63
Q1 -Q3		39–56
Gender		
Male	29 (65.9%)	
Female	15 (34.1%)	
Race		
Asian	23 (52.3%)	
Black or African-American	2 (4.5%)	
White	16 (36.4%)	
More than one race	2 (4.5%)	
Unknown	1 (2.3%)	
Ethnicity		
Hispanic or Latino	3 (6.8%)	
Not Hispanic or Latino	38 (86.4%)	
Unknown	3 (6.8%)	
Zubrod performance status		
0	33 (75.0%)	
1	11 (25.0%)	
Primary site		
Nasopharynx, NOS	43 (97.7%)	
Posterior superior wall	1 (2.3%)	
Histology		
WHO I	4 (9.1%)	
WHO Ma (or II)	8 (18.2%)	
WHO lib (or III)	32 (72.7%)	
T stage		
T1	12 (27.3%)	
T2a	4 (9.1%)	
T2b	3 (6.8%)	
T3	15 (34.1%)	
T4	10 (22.7%)	
N stage		
N0	5 (11.4%)	
N1	8 (18.2%)	
N2	26 (59.1%)	
N3a	2 (4.5%)	
N3b	3 (6.8%)	
Overall AJCC stage		

IIB	5 (11.4%)
III	24 (54.5%)
IVA	10 (22.7%)
IVB	5 (11.4%)

Q1 = first quartile; Q3 = third quartile; NOS = not otherwise specified; AJCC = American Joint Committee on Cancer.

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Table 2**Protocol Treatment Delivered (n=44)**

Type of radiation therapy administered	
3DCRT	1 (2.3%)
IMRT	43 (97.7%)
Radiation dose (Gy)	
Median	69.96
Min - Max	65.72 – 70
Q1 - Q3	69.96 – 70
Concurrent cisplatin cycles	
2	14 (31.8%)
3	30 (68.2%)
Concurrent bevacizumab cycles	
1	1 (2.3%)
2	12 (27.3%)
3	31 (70.5%)
Adjuvant cisplatin cycles	
0	11 (25.0%)
1	3 (6.8%)
2	9 (20.5%)
3	21 (47.7%)
Adjuvant 5-FU cycles	
0	8 (18.2%)
1	3 (6.8%)
2	9 (20.5%)
3	24 (54.5%)
Adjuvant bevacizumab cycles	
0	8 (18.2%)
1	3 (6.8%)
2	10 (22.7%)
3	23 (52.3%)

Q1 = first quartile; Q3 = third quartile.

Table 3

Number of Patients with Treatment-Related Adverse Events by Category and Grade

Category	Any time (n=44) Grade					Acute (n=44) Grade					Late (n=44) Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Allergy/immunology	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0
Auditory/ear	0	19	6	1 ^a	0	0	16	4	1	0	0	12	3	0	0
Blood/bone marrow	1	7	7	9 ^b	0	1	7	7	9	0	2	2	0	0	0
Cardiac arrhythmia	0	2	0	0	0	0	2	0	0	0	0	0	0	0	0
Cardiac general	2	0	3	0	0	2	0	3	0	0	0	0	0	0	0
Coagulation	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0
Constitutional symptoms	4	18	17	0	0	4	19	16	0	0	10	9	2	0	0
Dermatology/skin	11	20	9	0	0	12	18	9	0	0	16	5	0	0	0
Endocrine	0	4	1	0	0	1	1	1	0	0	0	3	0	0	0
Gastrointestinal	0	5	38	1 ^c	0	0	5	38	1	0	9	21	7	0	0
Hemorrhage/bleeding	8	1	0	0	0	5	1	0	0	0	3	0	0	0	0
Infection	0	8	7	1 ^d	0	0	8	7	1	0	0	0	1	0	0
Lymphatics	4	4	1	0	0	3	2	1	0	0	3	2	0	0	0
Metabolic/laboratory	4	6	12	0	0	4	6	12	0	0	3	2	0	0	0
Musculoskeletal/soft tissue	5	10	4	0	0	4	7	4	0	0	9	6	1	0	0
Neurology	20	8	2	0	0	14	7	1	0	0	16	4	1	0	0
Pain	4	15	17	2 ^e	0	4	15	16	2	0	5	8	2	0	0
Pulmonary/upper respiratory	10	7	6	0	0	9	7	6	0	0	7	0	0	0	0
Sexual/reproductive function	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Syndromes	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Vascular	0	1	0	1 ^f	0	0	1	0	1	0	0	0	0	0	0

Includes adverse events where relationship to protocol treatment is missing.

Adverse events were graded with CTCAE version 3.0.

The late period is defined as > 90 days after the end of treatment.

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- g* tinnitus – 1.
- h* leukopenia NOS – 6; lymphopenia – 5; neutrophil count – 5; hemoglobin – 1.
- c* radiation mucositis – 1.
- d* infection with grade 3–4 neutrophils (blood) – 1; infection with grade 3–4 neutrophils [skin] (cellulitis) – 1.
- e* pharyngolaryngeal pain – 2.
- f* thrombosis – 1.

Table 4

Hemorrhages

Patient ID	Type of Hemorrhage	Grade	Relationship to Treatment	Days from Start of RT
A	Epistaxis	1	Possible	765
B	Epistaxis	1	Probable	52
C	Lower gastrointestinal hemorrhage	1	Possible	415
D	Urogenital hemorrhage	1	Unrelated	55
E	Hemorrhage, GI: Upper GI NOS	2	Probable	138
	Lower gastrointestinal hemorrhage	2	Probable	138
F	Hemorrhage, GI: Upper GI NOS	1	Possible	35
G	Hemorrhage, Pulmonary/upper respiratory: Pharynx	1	Definite	55
H	Epistaxis	1	Definite	49
I	Epistaxis	1	Probable	498
J	Epistaxis	1	Possible	46
	Hemorrhage, GI: Upper GI NOS	1	Possible	46