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ORIGINAL REPORT

Epidermal Growth Factor Receptor Inhibitor Gefitinib Added to Chemoradiotherapy in Locally Advanced Head and Neck Cancer

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ABSTRACT

Purpose
Assess efficacy and toxicity of gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, added to, and in maintenance after, concurrent chemoradiotherapy (CCRT) in locally advanced head and neck cancer (LA-HNC) and correlate outcomes with *EGFR* gene copy number alterations.

Patients and Methods
Patients with stage III to IV LA-HNC received two cycles of carboplatin/paclitaxel induction chemotherapy (IC) followed by split-course CCRT with fluorouracil, hydroxyurea, twice daily radiotherapy (FHX), and gefitinib (250 mg daily) followed by continued gefitinib for 2 years total. The primary end point was complete response (CR) rate after CCRT. *EGFR* gene copy number was assessed by fluorescent in situ hybridization.

Results
Sixty-nine patients (66 with stage IV disease, 37 with oropharynx primary tumors, and 67 with performance status 0 to 1) were enrolled with a median age of 55 years. Predominant grade 3 or 4 toxicities during IC and CCRT were neutropenia (n = 20) and in-field mucositis (n = 59) and dermatitis (n = 23), respectively. CR rate after CCRT was 90%. After median follow-up of 3.5 years, 4-year overall, progression-free, and disease-specific survival rates were 74%, 72%, and 89%, respectively. To date, one patient has developed a second primary tumor in the aerodigestive tract. In 31 patients with available tissue, high *EGFR* gene copy number was associated with worse overall survival ($P = .02$).

Conclusion
Gefitinib can be administered with FHX and as maintenance therapy for at least 2 years, demonstrating CR and survival rates that compare favorably with prior experience. High *EGFR* gene copy number may be associated with poor outcome in patients with LA-HNC treated with this regimen.

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INTRODUCTION

Locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) is a global public health issue, with more than 500, 000 cases diagnosed per year.[1] Primary therapy for LA-SCCHN often uses a multimodality approach consisting of concurrent chemoradiotherapy (CCRT) with or without surgery.[2] The administration of induction chemotherapy (IC) has recently gained prominence as supported by meta-analysis data.[3] In addition, phase III trials have demonstrated that the addition of a taxane to cisplatin and fluorouracil yields improvements in complete response rates, survival, and larynx preservation.[4-6]

An association between epidermal growth factor receptor (EGFR) expression and survival has been noted in SCCHN.[7] A randomized study demonstrated that the addition of cetuximab to radiotherapy improves overall survival (OS),[8] whereas phase I studies have demonstrated the feasibility of administering EGFR inhibitors concurrently with chemoradiotherapy.[9-11] Gefitinib is an EGFR small-molecule tyrosine kinase inhibitor (TKI) with radiosensitizing properties consistently demonstrating tumor growth delay and enhancement of apoptosis

in preclinical models.[12] Furthermore, single-agent activity has been demonstrated in recurrent and metastatic disease.[13]

Previous investigations have demonstrated that patients with LA-SCCHN have high survival and organ preservation rates after therapy with sequential carboplatin/paclitaxel IC and CCRT with paclitaxel/fluoruracil/hydroxyurea and hyperfractionated radiotherapy (TFHX).[14] We hypothesized that gefitinib, as a targeted agent, would be well tolerated and a less toxic radiation enhancer than paclitaxel. Furthermore, we hypothesized that administration of gefitinib as a maintenance agent would be feasible with the potential to decrease failure rates. We therefore undertook a phase II study to incorporate gefitinib into a standard chemoradiotherapy regimen in patients with LA-SCCHN.

PATIENTS AND METHODS

Treatment-naive patients, 18 years or older with Eastern Cooperative Oncology Group performance status ≤ 2, were required to have histologically confirmed SCCHN, stage III (only tongue base or hypopharyngeal primaries) or IV, without evidence of metastatic disease, and intact organ function as previously described.[14] Postoperative patients were eligible only if surgery was organ-preserving, consisting of simple excision of a primary lesion or selective neck dissection. Institutional review board approval was obtained, and all patients provided informed consent.

IC consisted of two cycles of paclitaxel (100 mg/m^2 days 1, 8, and 15) and carboplatin (area under the curve of 6, day 1) as previously described.[14] CCRT, scheduled to begin 1 to 2 weeks after the last dose of paclitaxel, consisted of 4 to 5 14-day cycles (5 days of 500 mg of hydroxyurea orally every 12 hours, 600 mg/m^2/d of continuous-infusion fluorouracil, and 1.5 Gy of radiation twice per day followed by 9 days without therapy) based on extent of preprotocol surgery as previously described.[14] Gefitinib (AstraZeneca, London, United Kingdom), 250 mg every day orally, was begun on the first day of radiotherapy and continued for a maximum of 2 years. Radiotherapy and surgical guidelines are described fully in the Appendix, online only.

Laboratory Analyses

Fluorescent in situ hybridization (FISH), detection of human papillomavirus (HPV) DNA, and EGFR immunohistochemistry (IHC) methods are fully described in Appendix (online only). Tumor biopsy was performed and tissue collected as previously described.[15] FISH was performed using the LSI Locus Specific Identifier DNA Probes (Abbot Molecular, Des Planes, IL). Tumors with an *EGFR:CEP7* signal ratio less than 2 were considered nonamplified, whereas those with a ratio of ≥ 2 were considered amplified. The alterations in *EGFR* signals due to alterations in chromosome 7 copy number were classified as previously described,[16] and FISH positive was defined by amplification or high polysomy. For HPV analysis, in situ hybridization was performed according to manufacturer's guidelines using the Benchmark automated slide-staining system (Ventana Medical Systems, Tucson, AZ). For IHC, rabbit primary antibody (Santa Cruz Biotechnology, Santa Cruz, CA, catalog no. sc-03) was applied at 1:75 dilution and scored on a 0 to 3+ scale.

Statistical Considerations

The primary end point was complete response (CR) rate achieved 1 month after CCRT using Response Evaluation Criteria in Solid Tumors (RECIST). Patients who achieved a CR at the primary site, either clinically or radiologically (by computed tomography [CT] or magnetic resonance imaging), had that confirmed with biopsy whenever possible. Patients with less than CR at the primary site underwent biopsy. If this was negative, the patient was considered a complete responder. If this was positive or not performed, response was scored as the worst of either clinical or radiologic response assessment. Patients with less than CR in the neck underwent neck dissection, and the same algorithm was followed as for primary site response assessment. The overall response assessment consisted of both primary site and neck nodes using the worst response categorization in these areas. All patients who received at least one dose of therapy and had measurable disease, including those with incompletely resected disease before study entry, were assessed for response. All patients who received at least one dose of therapy were included in survival analyses. The study was conducted as a single arm, two-stage, noninferiority phase II trial with a total sample size of 59 evaluable patients, which was sufficient to detect a 15% lower CR rate than 80% achieved with TFHX historical controls[14] and α and β of 0.05 and 0.20, respectively. During the first stage, 25 evaluable patients were recruited, with a plan to terminate if ≤ 16 CRs were observed; otherwise, an additional 34 patients would be recruited. The new treatment would be deemed not inferior to historical if ≥ 45 CRs were observed. The false-negative rate in the first stage was less than 0.05.

OS, progression-free survival (PFS), and disease-specific survival (DSS) were calculated using the Kaplan-Meier product-limit estimate and expressed as probabilities with 95% CIs. Univariate and multivariate analyses of patient and disease factors including age, race, sex, weight loss, performance status, stage, and tumor site in relation to failure risk were conducted using Cox proportional hazards regression models. *EGFR* status was evaluated for prognostic effect on OS and PFS by the log-rank test. Further detailed statistical analysis is provided in the Appendix (online only).

RESULTS

Patients Characteristics

From February 2003 to October 2004, 70 patients signed consent at three participating institutions, although one patient withdrew before initiating therapy and is not included in any analyses (Fig 1, Table 1, and Appendix Table A1, online only). As expected, the majority of HPV-positive tumors (15 of 17) were from oropharynx primary sites. Conversely, of the 22 oropharynx tumors for which tissue was available for HPV testing, 68% were HPV positive. Ten patients underwent surgery to remove all gross disease before initiating study and were thus unevaluable for response.

Treatment Delivery and Toxicity

The frequency and grade of adverse events observed during IC and CCRT are presented in Table 2. All patients, except two, completed both cycles of IC, and 57 patients did so within the scheduled 8 weeks. One patient voluntarily withdrew from study during IC, and another was diagnosed with a duodenal ulcer. As expected, the most frequent toxicity encountered during IC was neutropenia. Twelve patients required dose modification during IC, in the majority of cases for neutropenia (10 of 12).

The predominant toxicity observed during CCRT was radiation mucositis, which had a characteristic pattern, with a plateau in intensity midway through treatment and gradual abatement (Fig 2). Typical EGFR TKI toxicity was also observed, including rash and diarrhea, but neither was dose-limiting. Sixty-six of 69 patients were treated with intensity-modulated radiotherapy techniques, whereas 64 received all intended radiotherapy fractions as scheduled. Two patients declined to receive gefitinib during chemoradiotherapy, whereas 46 of 67 received 90% of all planned doses of systemic agents as scheduled. Twelve subjects received RBC transfusion at some point during CCRT. There were four treatment-related deaths during or immediately after CCRT: two from bacterial sepsis without neutropenia, one cardiac event, and one sudden death after planned neck dissection.

After completion of radiotherapy, patients were eligible to continue on gefitinib alone. The median duration of gefitinib maintenance therapy was 667 days. Nine subjects never received gefitinib after CCRT (four patients died during or after CCRT, one patient had progressive disease, three patients voluntarily refused, and one patient

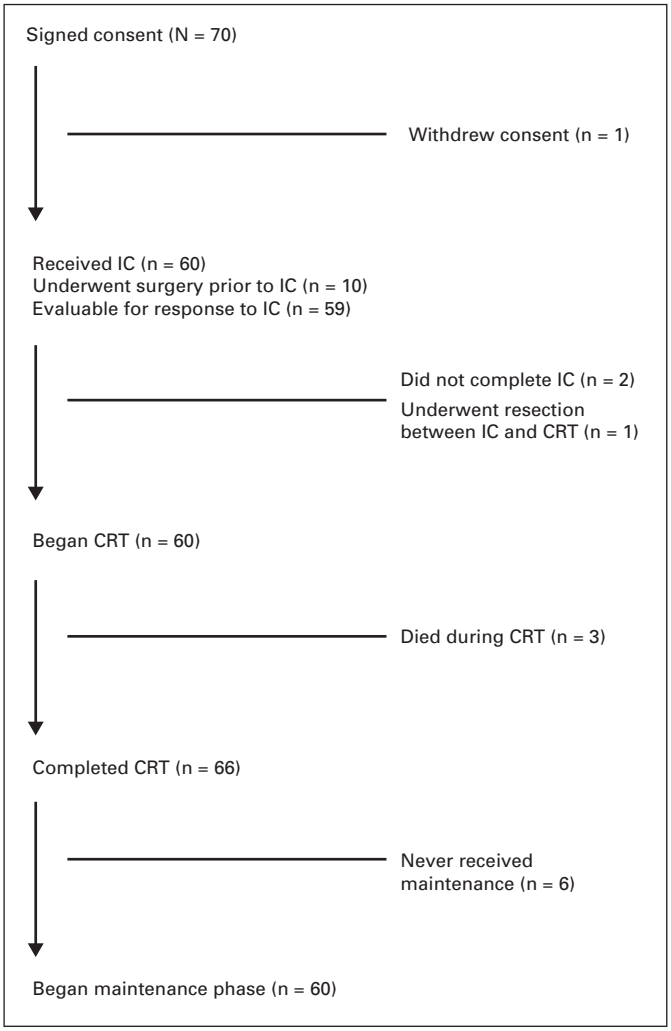

Fig 1. Flow diagram of all patients who signed informed consent. IC, induction chemotherapy; CRT, chemoradiotherapy.

developed respiratory failure secondary to exacerbation of chronic obstructive pulmonary disease. This latter patient underwent CT scanning, which demonstrated no evidence of interstitial lung disease, but this patient did not restart gefitinib). Forty-eight of the 60 patients who began maintenance were able to complete 2 years of gefitinib; 12 patients discontinued gefitinib maintenance for elevated liver transaminases (n = 3), rash (n = 2), diarrhea (n = 1), xerostomia (n = 1), nausea (n = 1), comorbid illness (n = 2), voluntary refusal (n = 1), and disease recurrence (n = 1).

Institutional policies regarding gastrostomy tube placement included placement only when necessary. Nine patients underwent gastrostomy tube insertion before initiating therapy, whereas 25 patients required gastrostomy tube placement during or shortly after therapy, and 35 patients never required feeding tubes. In patients who survived at least 1 year from completion of CCRT, 11 patients still required a gastrostomy tube to maintain nutrition. Three of these patients were able to swallow, and another two required tube maintenance secondary to disease recurrence. In total, five patients underwent esophageal dilation to address dysphagia; three of these patients never required tube placement.

Table 1. Patient and Tumor Characteristics

Characteristic	No.	%*
Total entered onto study	69	
Age, years		
Median	55	
Range	49-64	
Sex		
Male	55	80
Female	14	20
Treating institution		
UC	55	80
NSUHS	8	12
OCA	6	9
Performance status		
0	48	70
1	19	28
2	2	3
Race		
White	58	84
Hispanic	1	1
Black	10	15
Alcohol consumption		
None	14	20
Mild	20	29
Moderate	17	25
Heavy	17	25
Unavailable	1	2
Tobacco use		
Never	16	23
Pipe or cigar	2	3
< 20 pack-years	18	26
20-40 pack-years	20	29
> 40 pack-years	12	17
Unavailable	1	1
Weight loss before study entry		
None	43	62
< 5% body weight	8	12
5%-10% body weight	9	13
> 10% body weight	5	7
Unavailable	4	6
Primary site		
Oral cavity	10	15
Oropharynx	37	53
Hypopharynx	6	9
Supraglottic larynx	6	9
Glottic larynx	2	3
Nasopharynx	4	6
Sinus	1	1
Unknown	3	4
Stage		
III	3	4
IVa	56	81
IVb	10	15
Human papillomavirus status		
Positive	17	25
Negative	21	30
Unavailable	31	45
Feeding tube before therapy		
Yes	9	13
No	60	87

Abbreviations: UC, University of Chicago; NSUHS, North Shore University Health System; OCA, Oncology Care Associates.
*Can add to more than 100% in some categories due to rounding.

Table 2. Number of Patients With Respective Toxicity Grade Observed During Induction Chemotherapy and Concurrent Chemoradiotherapy Listed by Frequency (n = 69)

	Grade										
	1		2		3		4		5		
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	Total (n)
Induction Chemotherapy											
Neutropenia	12	17	25	36	16	23	4	6			57
Fatigue	43	62	6	9	0	0	0	0			49
Alopecia	19	28	24	35	—		—				43
Pain	26	38	6	9	1	1	0	0			33
Nausea	22	32	3	4	1	1	0	0			26
Neurotoxicity	17	25	3	4	0	0	0	0			20
Diarrhea	13	19	1	1	0	0	0	0			14
Anorexia	12	17	1	1	0	0	0	0			13
Vomiting	5	7	1	1	1	1	0	0			7
Mucositis	5	7	3	4	0	0	0	0			8
Constipation	7	10	1	1	0	0	0	0			8
Infection	1	1	3	4	4	6	0	0			8
Fever	3	4	1	1	0	0	0	0			4
Thrombocytopenia	24	35	3	4	1	1	2	3			30
Concurrent Chemoradiotherapy											
Mucositis	0	0	10	14	52	75	7	10	0	0	69
Radiation dermatitis	16	23	26	38	20	29	3	4	0	0	65
Pain	16	23	25	36	11	16	1	1	0	0	53
Fatigue	35	51	12	17	4	6	0	0	0	0	51
Nausea	32	46	10	14	5	7	0	0	0	0	47
Neutropenia	18	26	21	30	7	10	4	6	0	0	50
Anorexia	20	29	12	17	4	6	1	1	0	0	37
Vomiting	27	39	5	7	3	4	1	1	0	0	36
EGFR-related rash	19	28	10	14	3	4	0	0	0	0	32
Thrombocytopenia	27	39	3	4	1	1	0	0	0	0	31
Infection	4	6	12	17	11	16	1	1	2	3	30
Diarrhea	21	30	2	3	1	1	0	0	0	0	24
Constipation	18	26	5	7	1	1	0	0	0	0	24
Neurotoxicity	10	14	0	0	2	3	0	0	0	0	12
Fever	11	16	0	0	1	1	0	0	0	0	12
Palmar-plantar erythrodysesthesia	8	12	1	1	0	0	0	0	0	0	9

Other long-term toxicities included two patients who required surgery for osteoradionecrosis of the mandible, whereas another patient underwent hyperbaric oxygen for bone exposure.

Efficacy

Ten patients who underwent resection of disease before initiating therapy were inevaluable for response (Fig 1). Fifty-nine patients were evaluable for response to IC (Fig 1), and consistent with prior studies, the overall response rate was 90%, with seven CRs (Appendix Table A2, online only). CR was observed in 52 patients after CCRT (Appendix Table A2), including one patient who underwent surgical resection of gross disease between IC and CCRT and is included in the response analysis to CCRT as stable disease. Neck dissection was performed on 36 patients after completion of CCRT; 32 patients were pathologically free of disease. Of the four patients with evidence of cancer in the neck dissection specimen, three have died of disease.

With a median follow-up of 3.54 years (range, 0.3 to 4.7 years), there have been 18 deaths and 10 patients with documented progressive disease: two local only, one regional only, two locoregional, one regional with distant metastasis, and four distant metastatic only, yielding 4-year OS and PFS rates of 74% (95% CI, 62% to 83%) and 72% (95% CI, 60% to 81%), respectively (Fig 3A and 3B). In addition, the 4-year DSS rate was 89% (95% CI, 77% to 95%; Fig 3C), with eight patients dying of SCCHN. One subject underwent laryngectomy for recurrent disease and is disease-free. The causes of non-SCCHN–related mortality were treatment related (four described above), respiratory disease (three unrelated to treatment with no evidence of interstitial lung disease on CT scan), cardiac disease (one patient), and second malignancy (one patient with hepatocellular carcinoma and one patient with esophageal carcinoma). One patient with local progression underwent salvage laryngectomy and is alive, whereas one patient is alive with pulmonary metastases. No patients developed a second primary SCCHN or lung cancer.

Univariate and multivariate analyses were performed to assess whether patient or disease characteristics were associated with OS or PFS (Appendix Table A3, online only). In univariate analysis, increasing age, black race, and nonoropharynx primary tumors were consistently associated with worse outcome. Appendix Figure A1 (online only) displays OS, PFS, and DSS in patients with oropharynx and nonoropharyx primary tumors. In multivariate analysis, only age and race were associated with both outcomes, whereas patients with nonoropharynx primary tumors maintained a statistically significantly worse PFS.

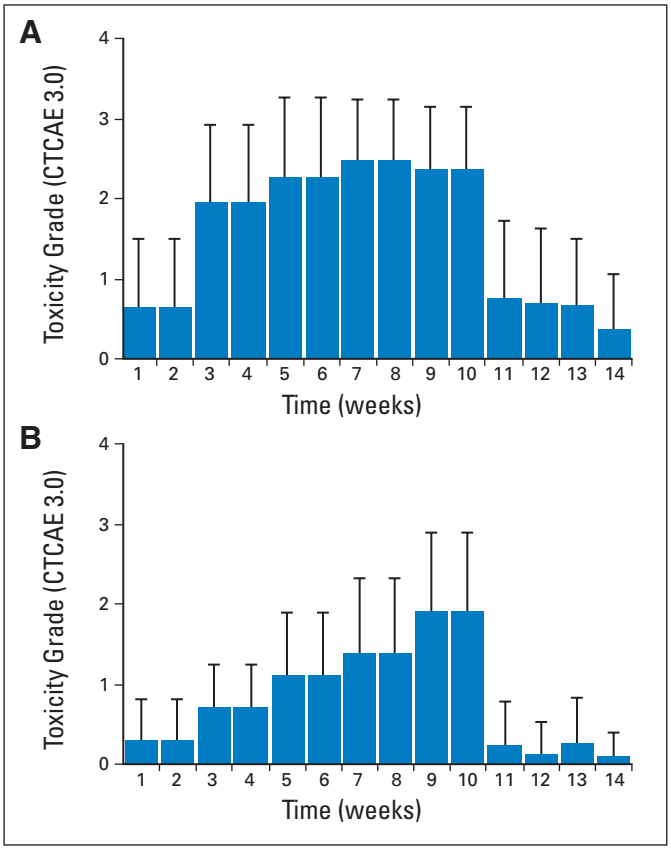

Fig 2. Mean toxicity grade of (A) acute in-volume mucositis and (B) dermatitis over time. The planned duration of chemoradiotherapy was 7 to 9 weeks. Toxicities were graded on a weekly basis starting from initiation of concurrent chemoradiotherapy to at least 4 weeks after completing chemoradiotherapy. Common Terminology Criteria of Adverse Events (CTCAE) version 3.0 was used to grade toxicity. Error bars represent standard deviation.

Laboratory Correlatives

EGFR protein expression and, more recently, gene copy number have been suggested as negative prognostic markers in patients with SCCHN.[7,16-18] We hypothesized that administration of an EGFR inhibitor within a chemoradiotherapy platform would abrogate the negative consequences of increased EGFR expression. Tumor tissue collected before initiating treatment was adequate for EGFR FISH and IHC analysis in 31 and 21 patients, respectively (Appendix Table A4, online only). Quantification of *EGFR* gene copy number displayed a great deal of intra- and inter-tumor heterogeneity (Fig 4). *EGFR* amplification was present in three cases, whereas 10 cases had elevated *EGFR* copy number per cell due to chromosome 7 polysomy. There was a statistically significant association between *EGFR* gene copy number and IHC staining intensity (Appendix Table A5, online only; $P = .02$). We grouped patients with *EGFR* amplification and high polysomy together as previously described and defined these samples as *EGFR* FISH positive. *EGFR* status was not associated with patient sex, race, age, primary tumor site, prior alcohol or tobacco use, or weight loss before study entry. Moreover, when examining a relationship between *EGFR* status and outcome, there was no association between gene copy number and response to chemoradiotherapy; however, we found that *EGFR* FISH-positive status was associated with shorter OS time ($P = .021$), as well as a trend toward earlier time to recurrence ($P = .067$; Appendix Table A6, online only).

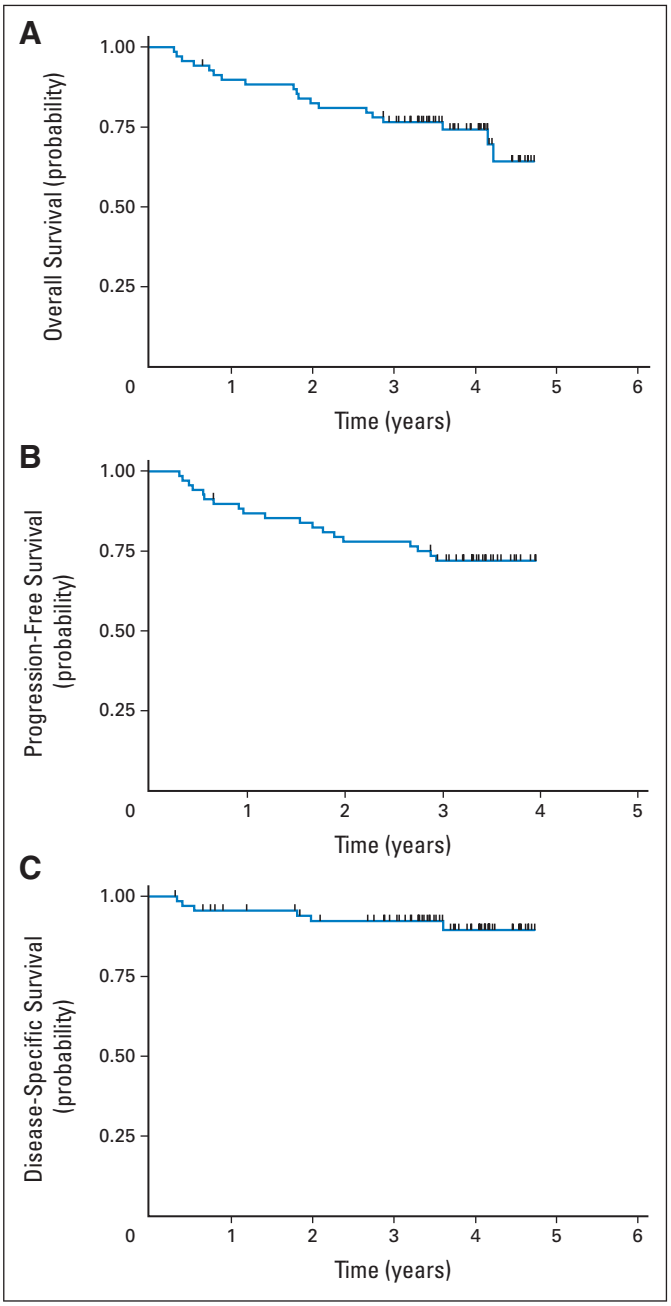

Fig 3. Kaplan-Meier survival curves. Survival estimates of (A) overall survival, (B) progression-free survival, and (C) disease-specific survival for all patients.

DISCUSSION

This multi-institutional phase II study in LA-SCCHN reports the efficacy, toxicity, and correlative results of EGFR TKI administration with chemoradiotherapy. The observed CR rate and other efficacy outcomes compare favorably with our prior experience,[14] with dramatically reduced rates of neuropathy and myelosuppression (any grade neuropathy 36% *v* 17% and grade 3 to 4 neutropenia 30% *v* 16%, respectively, for paclitaxel- and gefitinib-containing regimens).

Since initiation of the present study, further data have been reported for administering EGFR inhibitors in LA-SCCHN[8,9,11,19,20]

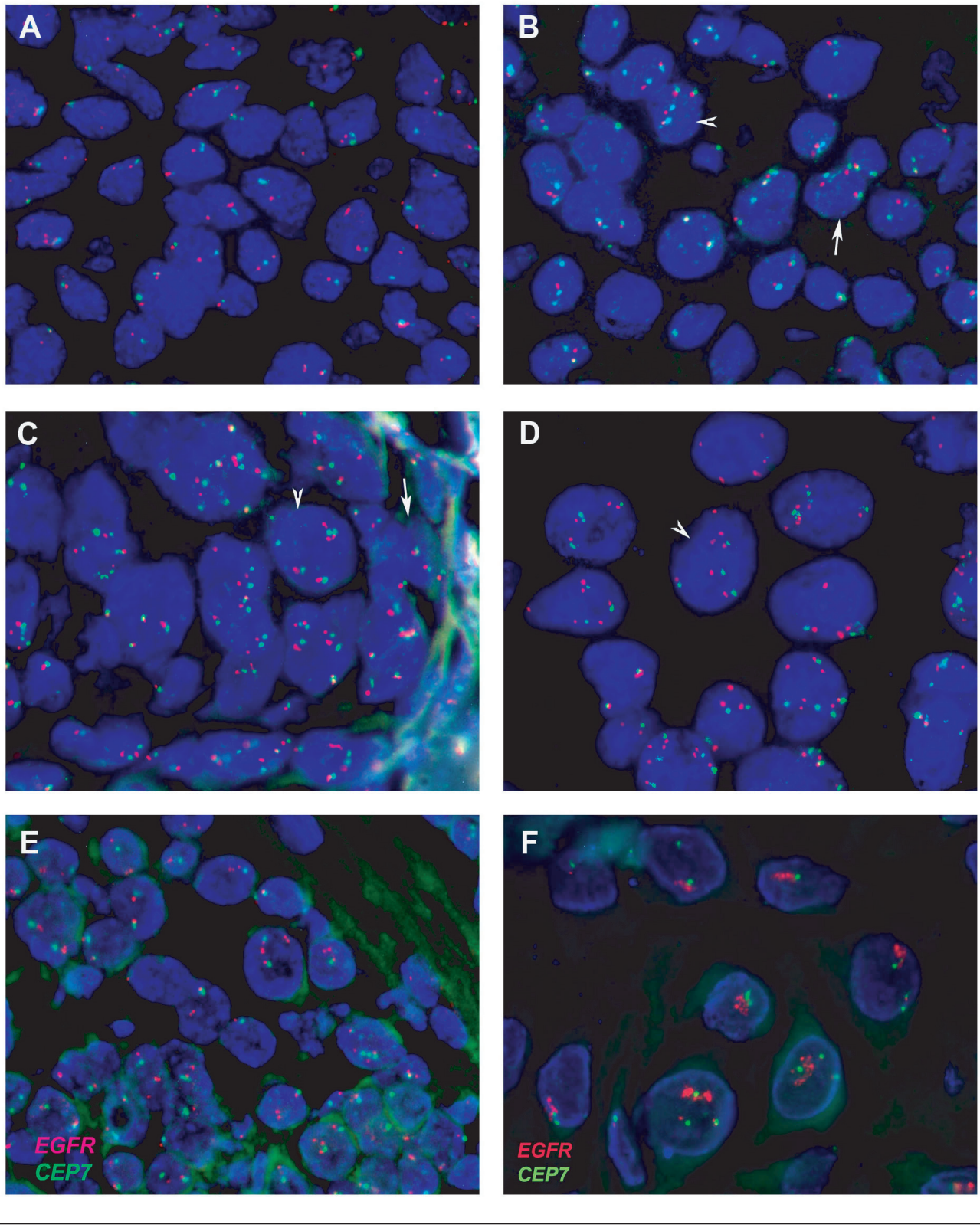

Fig 4. Photomicrographs (×1,200) for *EGFR* (red) and *CEP7* (green). (A) Disomy. (B) *EGFR* trisomy in 15% (arrow) and tetrasomy in 2% of cells (arrowhead), classified *EGFR* fluorescent in situ hybridization (FISH) negative. (C) Cells are trisomic (arrow) or highly polysomic (arrowhead), classified *EGFR* FISH positive. (D) High polysomy in 83% (arrowhead), classified *EGFR* FISH positive. (E, F) Low and high *EGFR* amplification, classified *EGFR* FISH positive.

supporting feasibility, whereas promising preliminary data have been presented combining cetuximab or panitumumab with platinum-based chemoradiotherapy platforms. Argiris et al[21] reported 88% 2-year survival in 39 patients receiving cisplatin/docetaxel/cetuximab IC followed by cisplatin/cetuximab/radiotherapy and continuing cetuximab for a maximum of 6 months. The Eastern Cooperative Oncology Group[22] observed a 76% 1-year survival in 60 patients with unresectable LA-SCCHN receiving cisplatin/cetuximab/radiotherapy. A phase I study combining panitumumab with concurrent paclitaxel, carboplatin, and radiotherapy demonstrated tolerability, and after a median follow-up of 21 months, 95% of patients remained disease-free.[23] Cumulatively, these data suggest a genuine improvement in efficacy when EGFR inhibitors are added to chemoradiotherapy regimens, and we await ongoing phase III trials to establish the validity of this hypothesis.

The optimal dose of gefitinib in SCCHN has been controversial. Single-arm phase II studies in recurrent or metastatic SCCHN suggested that 500 mg was more efficacious than 250 mg,[13,24] the standard dose in lung cancer, and a phase III study comparing gefitinib to methotrexate in recurrent or metastatic SCCHN confirmed a higher response rate of 500 mg compared with 250 mg.[25] The current study was planned and completed before availability of the phase III data, and one could speculate that 500 mg would have been more effective. However, in the context of CCRT, it is unclear whether the higher dose is indicated, especially considering its greater associated toxicity. Moreover, four treatment-related deaths were observed on this study, and any measure that further increased toxicity should be undertaken with caution. One could argue that efforts now need to concentrate on reducing toxicity of CCRT regimens in selected patients.

Acute in-volume radiation toxicity observed during this study was manageable and comparable with that encountered during TFHX. It is notable that acute mucositis and dermatitis associated with FHX regimens have a unique pattern, with a peak midway through treatment, a plateau lasting to the end of radiotherapy, and then a gradual abatement (Fig 2). This contrasts with regimens administering uninterrupted single daily or accelerated fractionated radiation that peak late or after completion of treatment. Several investigators have suggested that measuring the highest grade toxicity during treatment can be misleading without reflecting duration of and recovery from adverse effects.[26] In this study, we measured acute mucositis and dermatitis as a function of time during and after treatment, which allows more thorough evaluation, and we believe that these metrics will serve as better indicators of toxicity, allowing valid comparisons between regimens.

Gefitinib was feasibly administered in the majority of patients during the maintenance phase, with overall excellent adherence. The study design does not allow determination of this component's contribution to survival; however, it is intriguing to note that with 42 months median follow-up, only 10 patients have had disease recurrence. As a cautionary note, however, similar attempts in locally advanced non–small-cell lung cancer in which gefitinib was also administered after CCRT did not improve survival.[27]

EGFR gene copy number was a poor prognostic feature in this study, associated with shorter PFS and OS. We anticipated that *EGFR* FISH-positive patients would benefit most from EGFR TKI, with the hypothesis that their cancers depend on EGFR signaling for growth and survival. Recently, an analysis of associations between *EGFR* gene copy number and outcomes in a phase III study in recurrent or metastatic SCCHN adding cetuximab to platinum/FU chemotherapy found no predictive value of this parameter.[28] Moreover, another randomized in similar patients found that patients with high EGFR expression by IHC fared worse when receiving cetuximab as compared with those with moderate or low expression.[29] Finally, the randomized study comparing gefitinib to methotrexate in patients with recurrent or metastatic SCCHN reported that high *EGFR* gene copy number portended a poorer prognosis but was not predictive of EGFR TKI efficacy.[25] Taken together with our study, *EGFR* gene copy number has prognostic value in SCCHN but may not help in selecting patients for treatment with EGFR inhibitors. The search for validated predictive biomarkers in this arena is still ongoing.

There are inherent limitations to comparing our results with historical controls, which is especially relevant with the realization that the majority of oropharynx primary tumors are HPV related.[30] These cancers are also being detected with increasing frequency and carry a better prognosis.[30] Within our study samples evaluated for HPV, 68% of oropharynx tumors were positive, an incidence consistent with large epidemiologic and retrospective series. Extrapolation to the entire study population approximates 25 patients or 36% (68% of 37 oropharynx tumors) being HPV positive. Along those lines, survival in patients with oropharynx tumors was significantly higher than in those with nonoropharynx. Without knowing the incidence of HPV positivity in prior studies, it is difficult to draw definitive conclusions comparing regimens. Moreover, although the sample size in the nonoropharynx subgroup does not allow adequately powered comparisons with older regimens, the efficacy observed in these patients is encouraging.

This study confirms the feasibility of administering an EGFR TKI with chemoradiotherapy and as maintenance to patients with LA-SCCHN. In addition, we found promising efficacy of this approach, highlighted by a 72% 4-year survival rate. Further pursuit of combination EGFR TKI and chemoradiotherapy is warranted, and randomized studies assessing the contribution of such agents (eg, lapatinib) are being pursued.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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