Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Am J Clin Oncol. Author manuscript; available in PMC 2020 January 06.

Published in final edited form as:

Am J Clin Oncol. 2008 December ; 31(6): 557–560. doi:10.1097/COC.0b013e318172d5de.

High Incidence of Oral Dysesthesias on a Trial of Gefitinib, Paclitaxel, and Concurrent External Beam Radiation for Locally Advanced Head and Neck Cancers

Hadley Sharp, MD[*], **John C. Morris, MD**[†], **Carter Van Waes, MD**[‡], **David Gius, MD, PhD**[*], **Theresa Cooley-Zgela, RN**[*], **Anurag K. Singh, MD**[§]

[*]Radiation Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland; [†]Metabolism Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland; [‡]Head and Neck Surgery Branch, National Institutes of Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, Maryland; [§]Department of Radiation Medicine, Roswell Park Cancer Institute, Buffalo, New York.

Abstract

Objectives: To report a high incidence of oral mucosal dysesthesia occurring in patients on a pilot study of the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (Iressa) in combination with paclitaxel (Taxol) and external beam radiation therapy for the treatment of locally advanced squamous cell carcinoma of the head and neck.

Methods: Nine patients were enrolled on a pilot phase I trial of oral gefitinib 250 mg/d with 6 weekly doses of paclitaxel (36 or 45 mg/m^2) and concurrent radiation therapy [66–76 Gray (Gy)]. All had stage III/IVA-B squamous cell carcinoma of the head and neck. Patients were evaluated twice weekly by physicians and daily by nursing for adverse events.

Results: Six of 9 patients (67%) developed a grade 3 “burning” quality oral dysesthesia. These patients received at least 50 Gy (range 50–70 Gy) to the oral tongue. The patients without grade 3 oral dysesthesia received less than 50 Gy radiation to the oral tongue. The oral dysesthesia was exacerbated by the ingestion of neutral pH liquids such as water. Of the 6 patients, all eventually developed common toxicity criteria grade 3/4 mucositis; however, symptoms continued after resolution of the mucositis. Gabapentin (Neurontin) was administered to 2 patients as a treatment for painful mucosal neuropathy. Both patients had near resolution of symptoms despite the evolution of oral mucositis.

Conclusions: Development of “burning”-type oral dysesthesia occurred in patients treated with the combination of gefitinib, paclitaxel, and external beam radiation of the oral tongue. This dysesthesia was improved by the use of gabapentin.

Reprints: Anurag K. Singh, MD, Department of Radiation Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263. anurag.singh@roswellpark.org.

H. S. is a Howard Hughes Medical Institute-National Institutes of Health research scholar.

The authors have no relationship with organizations that would influence the results reported in this manuscript.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Concurrent treatment with chemotherapy and radiation therapy has become the standard of care for locally advanced squamous cell carcinomas of the head and neck (SCCHN).[1] Yet, even with aggressive treatment, long-term outcomes remain suboptimal.[2] Efforts to improve these outcomes have prompted evaluation of novel agents and targeted therapies in combination with chemoradiation therapy.[3]

The epidermal growth factor receptor (EGFR), overexpressed in more than 90% of SCCHN, [4] represents a potential target for modulation of tumor sensitivity. EGFR is a cellular transmembrane receptor with tyrosine kinase (TK) signaling activity. EGFR-dependent signaling is involved in cancer cell proliferation, resistance to apoptosis, angiogenesis, tumor invasion, and metastasis. Several drugs targeting EGFR including the monoclonal antibody cetuximab (Erbitux) and the small molecule EGFR-specific TK-inhibitor, gefitinib (Iressa) exhibited antitumor activity in the laboratory and in the clinic.[5–8] Gefitinib, a small molecule EGFR-selective TK inhibitor that blocks epidermal growth factor autophosphorylation and activation, is approved for the third-line treatment of chemotherapy-resistant nonsmall cell lung cancer.[9] Preclinical studies suggest that EGFR inhibition enhances the sensitivity of tumor cells to certain chemotherapy agents and radiation.[8,10–13]

We report the occurrence of moderately severe oral dysesthesias occurring in patients receiving treatment on a protocol evaluating the use of oral gefitinib in combination with paclitaxel and radiation for locally advanced SCCHN. The dysesthesia appeared to be responsive to treatment with anticonvulsant agent gabapentin.

PATIENTS AND METHODS

Initial Evaluation, Eligibility, and Accrual

Patients were treated on a National Cancer Institute Institutional Review Board-approved protocol. Eligibility included biopsy-proven SCCHN, age ≥18 years, American Joint Committee on Cancer stages III-IVA-B, Eastern Cooperative Oncology Group performance status ≤2, no prior radiation or chemotherapy ≥4 weeks since major surgery, and the ability to provide informed consent. Patients were initially evaluated with a medical history, physical examination, and routine hematological and serum chemistry laboratory studies. All patients underwent detailed tumor staging with chest radiography and contrast enhanced computed to mography scan, magnetic resonance imaging if indicated and nasopharyngoscopy. Gastrostomy tubes were routinely offered to all patients.

Chemotherapy

Gefitinib (Iressa) was started on day 1 as a single daily dose (250 mg), administered orally or via gastric feeding tube, and continued until completion on the same day that the radiation therapy was completed. Paclitaxel was administered as a weekly bolus for 6 weeks beginning on day 8 before the first dose of radiation was administered. The first 3 patients received 36 mg/m^2 whereas the remaining 6 patients received 45 mg/m^2.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Radiation Therapy

External beam radiation therapy began within 6 hours of the first paclitaxel dose. Median doses of 54 to 57.6 Gy, 60 to 64 Gy, and 66 to 70 Gy were delivered to the low-risk clinical tumor volume, high-risk clinical tumor volume and boost/gross tumor volume, respectively in 27 to 36 fractions. The maximum prescription dose ranged from 66.6 to 72 Gy. Computed tomography volume based (3-dimensional) planning techniques, including intensity modulated radiation therapy for some portion of the treatments, were used with every attempt made to protect normal tissues and vital structures.

Response Evaluation

Patients were evaluated for toxicity twice weekly by physicians and daily by nursing. Patients were evaluated with a history, physical examination, and nasopharyngoscopy after therapy as follows: monthly for 3 months; every 3 months until 12 months; every 4 months during the second year; and every 6 months during years 3 and 4. Toxicity was documented according to common toxicity criteria (CTC) version 2.0. Dose limiting toxicity was defined as any nonhematological CTC grade 3 or 4 adverse event or Radiation Therapy Oncology Group grade 4 mucosal toxicity possibly, probably or definitely related to any treatment component of the study.

Statistical Methods

Acute toxicity was the major end point of this study. Simple descriptive statistics including range, percent incidence, and mean were used to describe findings.

RESULTS

Between August 2004 and December 2005, 9 patients median age 48.5 (range, 27–77 years) were enrolled. All had histologically confirmed American Joint Committee on Cancer stage III/IV SCCHN. Table 1 summarizes patients' stage at presentation. Median follow-up was 15 months (range 5–34).

Six of the 9 patients (67%) developed grade 3 "burning" quality generalized oral dysesthesia. The dysesthesia was exacerbated by the ingestion of neutral pH liquids such as water. Patients with dysesthesia also developed some dysarthria. There was no dysphagia or odynophagia per se; however, the dysesthesia was sufficient to cause patients to use their gastrostomy tubes almost exclusively for nutritional support. These 6 patients received at least 50 Gy (range 50–70 Gy) to the oral tongue. The 3 patients without oral dysesthesia received less than 50 Gy radiation to the oral tongue.

The dysesthesia was both temporally and symptomatically very distinct from classic radiation-induced mucositis. Of the 6 patients, all eventually developed CTC grade 3/4 mucositis. Oral dysesthesia began in the second week of radiation treatment. The earliest mucositis was observed during the third week of radiation. Therefore, oral dysesthesia preceded development of mucositis by 7 to 10 days. Moreover, the dysesthesia persisted well after resolution of the mucositis and was present at the 4-week follow-up when mucositis had resolved. Dysesthesia did resolve in all patients by the 3-to 6-month follow-up.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Two patients were empirically treated with gabapentin (Neurontin) for their painful mucosal dysesthesia. Both patients who received gabapentin had near resolution of dysesthesia symptoms despite the evolution of oral mucositis consistent with their concurrent chemoradiation therapy. See Table 2 for symptom and treatment information for each patient enrolled in the trial.

DISCUSSION

We report a high incidence (67%) of oral dysesthesias, an unanticipated toxicity, on a phase I trial of combination daily oral gefitinab and weekly intravenous paclitaxel for 6 weeks with concurrent radiation therapy for advanced SCCHN. Dysesthesias occurred in all patients receiving a minimum of 50 Gy to the oral tongue. This is the first report of an unusual toxicity from the therapeutic combination of gefitinib, paclitaxel, and radiation.

Chemotherapy and concurrent radiation for advanced SCCHN is associated with a number of short and long-term oropharyngeal sequelae, that may significantly impact on a patient's quality of life.[14] Factors implicated in increased mucosal sensitivity to radiation and cytotoxic chemotherapy include high cellular turnover rates of the oral mucosa, the presence of a diverse and complex microflora in the mouth, and recurrent local trauma during normal oral function. With irradiation fields including the oral cavity, 90% to 100% of patients will see some degree of oral complication.[15]

Oral dysesthesias have been associated with a variety of agents including chemotherapy and radiation.[16–21] In the absence of clinical mucositis, however, oral dysesthesia during radiation to the tongue is uncommon. Similarly, oral dysesthesia is not a known side effect of either paclitaxel or gefitinib. Mucositis was a dose limiting toxicity in early studies with paclitaxel and radiation for head and neck cancers.[22,23]

Gefitinib alone is well tolerated. A skin rash and diarrhea were noted in some patients, but the hallmarks of cytoxic therapy including bone marrow depression, neurotoxicity, and nephrotoxicity were absent.[24,25] With concurrent chemotherapy, including with paclitaxel, gefitinib did not exhibit novel toxicities that were not seen with monotherapy.[26,27]

Radiation therapy for head and neck cancer combined with gefitinib has not been reported. However, radiation therapy with cetuximab, another EGFR receptor inhibitor, has been reported and did not produce oral dysesthesias.[28]

The oral dysesthesia (burning tongue pain) reported here occurs before and persists after visible indication of inflammation in the mucosa has resolved. Thus, this dysesthesia was both temporally and symptomatically very distinct from classic radiation-induced mucositis. The absence of obvious nociceptive stimulation and impulse production separated from afferent input, suggesting neuronal hyperexcitability, was consistent with a neuropathic process.[29]

After the initial 4 patients experienced dysesthesia, an empirical trial of gabapentin, a γ-aminobutryic acid analogue was initiated. Gabapentin was initially developed as an anticonvulsant drug to diminish the neuronal hyperexcitability of epilepsy. Gabapentin has

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

also been used in neuropathic pain syndromes, which also demonstrate neuronal hyperexcitablity, and has been found to be effective in the treatment of neuropathic pain.[30] Though the exact mechanism underlying this analgesia remains unclear, gabapentin, possibly through interaction with the alpha2delta subunit of voltage-gated calcium channels, inhibits hyperalgesia and allodynia evoked by a variety of neural insults, including peripheral trauma, diabetes, and chemotherapy.[31,32]

On this study, patients who received gabapentin experienced substantial resolution of their dysesthesia. Contrasting with the substantial salutary effect on dysesthesias, gabapentin had minimal effect on symptoms associated with mucositis. This observation is consistent with the experience of Bar Ad et al, who found that routine use of gabapentin prevented need for narcotics in only 10% of head and neck cancer patients with grade 2 to 3 mucositis from concurrent cisplatin based chemotherapy and intensity modulated radiation therapy.[33]

The excellent response of the dysesthesia, compared with minimal response of mucositis symptoms, to gabapentin further supports a neuropathic origin for the dysesthesia. Possibly, the combination of paclitaxel, gefitinib, and radiation therapy may have—by activating quiescent nociceptors in peripheral nerves or enhancing the local release of inflammatory mediators—heightened the sensitivity of peripheral sensory nerves causing dysesthesia which was then ameliorated by gabapentin.[34,35]

Optical coherence tomography has been used in animal models to demonstrate neuroplasticity and to attempt to elucidate the mechanisms of neuropathic pain.[36] Using optical coherence tomography in humans, it may be possible to develop a better understanding of the pain mechanism during this phenomenon. A better understanding of the mechanism underlying the development of this oral dysesthesia may lead to a more complete knowledge of the interaction between chemotherapy, different EGFR TK inhibitors, and radiation therapy.

Acknowledgments

Supported in part by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Center for Cancer Research.

REFERENCES

1. Budach W, Hehr T, Budach V, et al. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer. 2006;6:28. [PubMed: 16448551]
2. Bernier J, Vermorken JB, Koch WM. Adjuvant therapy in patients with resected poor-risk head and neck cancer. J Clin Oncol. 2006;24:2629–2635. [PubMed: 16763276]
3. Bernier J, Bentzen SM. Radiotherapy for head and neck cancer: latest developments and future perspectives. Curr Opin Oncol. 2006;18:240–246. [PubMed: 16552235]
4. Grandis JR, Tweardy DJ. Elevated levels of transforming growth factor alpha and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer. Cancer Res. 1993; 53:3579–3584. [PubMed: 8339264]
5. Jermann M, Stahel RA, Salzberg M, et al. A phase II, open-label study of gefitinib (IRESSA) in patients with locally advanced, metastatic, or relapsed renal-cell carcinoma. Cancer Chemother Pharmacol. 2006;57: 533–539. [PubMed: 16052341]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

6. Cappuzzo F, Finocchiaro G, Metro G, et al. Clinical experience with gefitinib: an update. Crit Rev Oncol Hematol. 2006;58:31–45. [PubMed: 16531062]
7. Felip E, Rosell R. Clinical experience with erlotinib in non-small-cell lung cancer. Drugs Today (Barc). 2006;42:147–156. [PubMed: 16628257]
8. Harari PM, Huang S. Radiation combined with EGFR signal inhibitors: head and neck cancer focus. Semin Radiat Oncol. 2006;16:38–44. [PubMed: 16378905]
9. Ciardiello F Epidermal growth factor receptor inhibitors in cancer treatment. Future Oncol. 2005;1:221–234. [PubMed: 16555994]
10. Mamot C, Rochlitz C. Targeting the epidermal growth factor receptor (EGFR)–a new therapeutic option in oncology? Swiss Med Wkly. 2006; 136:4–12. [PubMed: 16597093]
11. Lynch T Jr, Kim E. Optimizing chemotherapy and targeted agent combinations in NSCLC. Lung Cancer. 2005;50(suppl 2):S25–S32.
12. Hennemann B Palliative chemotherapy of head and neck cancer: present status and future development. Laryngorhinootologie. 2006;85:172–178. [PubMed: 16547892]
13. Dowell JE. Epidermal growth factor receptor mutations in non-small cell lung cancer: a basic science discovery with immediate clinical impact. Am J Med Sci. 2006;331:139–149. [PubMed: 16538075]
14. Sciubba JJ, Goldenberg D. Oral complications of radiotherapy. Lancet Oncol. 2006;7:175–183. [PubMed: 16455482]
15. Herrstedt J Prevention and management of mucositis in patients with cancer. Int J Antimicrob Agents. 2000;16:161–163. [PubMed: 11053801]
16. Savage NW, Boras VV, Barker K. Burning mouth syndrome: clinical presentation, diagnosis and treatment. Australas J Dermatol. 2006;47: 77–81; quiz, 82–73. [PubMed: 16637799]
17. Haneke E Psychological aspects of glossodynia (author's transl). Dtsch Med Wochenschr. 1978;103:1302–1305. [PubMed: 679825]
18. Naylor GD, Marino GG, Shumway RC. Glossodynia after radiation therapy and chemotherapy. Ear Nose Throat J. 1989;68:751–757. [PubMed: 2693056]
19. Gowda A, Goel R, Berdzik J, et al. Hypersensitivity reactions to oxaliplatin: incidence and management. Oncology (Williston Park). 2004;18:1671–1675; discussion, 1676, 1680, 1683–1684. [PubMed: 15648298]
20. Rios-Buceta L, Buezo GF, Penas PF, et al. Palmar-plantar erythrodysaesthesia syndrome and other cutaneous side-effects after treatment with Tegafur. Acta Derm Venereol. 1997;77:80–81. [PubMed: 9059693]
21. Fracasso PM, Blessing JA, Molpus KL, et al. Phase II study of oxalipltin as second-line chemotherapy in endometrial carcinoma: a gynecologic oncology group study. Gynecol Oncol. 2006;103:523–526. [PubMed: 16712905]
22. Hoffmann W, Belka C, Schmidberger H, et al. Radiotherapy and concomitant weekly 1-hour infusion of paclitaxel in the treatment of head and neck cancer–results from a phase I trial. Int J Radiat Oncol Biol Phys. 1997;38:691–696. [PubMed: 9240634]
23. Steinberg L, Hassan M, Olmsted L, et al. A phase I trial of radiotherapy and simultaneous 24-hour paclitaxel in patients with locally advanced head and neck squamous cell carcinoma. Semin Oncol. 1997;24(suppl 19):51–56.
24. Forsythe B, Faulkner K. Overview of the tolerability of gefitinib (IRESSA) monotherapy: clinical experience in non-small-cell lung cancer. Drug Saf. 2004;27:1081–1092. [PubMed: 15554744]
25. Veronese ML, Algazy K, Bearn L, et al. Gefitinib in patients with advanced non-small cell lung cancer (NSCLC): the expanded access protocol experience at the University of Pennsylvania. Cancer Invest. 2005;23:296–302. [PubMed: 16100941]
26. Fountzilas G, Pectasides D, Kalogera-Fountzila A, et al. Paclitaxel and carboplatin as first-line chemotherapy combined with gefitinib (IRESSA) in patients with advanced breast cancer: a phase I/II study conducted by the Hellenic Cooperative Oncology Group. Breast Cancer Res Treat. 2005;92: 1–9. [PubMed: 15980985]
27. Czito BG, Willett CG, Bendell JC, et al. Increased toxicity with gefitinib, capecitabine, and radiation therapy in pancreatic and rectal cancer: phase I trial results. J Clin Oncol. 2006;24:656–662. [PubMed: 16446337]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

28. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006; 354:567–578. [PubMed: 16467544]

29. Pjevic M, Patarica-Huber E, Radovanovic D, et al. Neuropathic pain due to malignancy: mechanisms, clinical manifestations and therapy. Med Pregl. 2004;57:33–40.

30. Jensen T Anticonvulsants in neuropathic pain: rationale and clinical evidence. Eur J Pain. 2002;6:61–68. [PubMed: 11888243]

31. Cheng JK, Chiou LC. Mechanisms of the antinociceptive action of gabapentin. J Pharmacol Sci. 2006;100:471–486. [PubMed: 16474201]

32. Gilron I, Flatters S. Gabapentin and pregabalin for the treatment of neuropathic pain: a review of laboratory and clinical evidence. Pain Res Manag. 2006;11:16A–29A.

33. Bar Ad V, Dutta P, Both S, et al. Gabapentin for the treatment of pain related to radiation-induced mucositis, in patients with head and neck cancers treated with concurrent chemoradiation using intensity modulated radiation therapy (IMRT). Int J Radiat Oncol Biol Phys. 2007;69: S426–S427.

34. Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature. 2001;413:203–210. [PubMed: 11557989]

35. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science. 2000;288:1765–1769. [PubMed: 10846153]

36. Ooi Y, Satomura Y, Seki J, et al. Optical coherence tomography reveals in vivo cortical plasticity of adult mice in response to peripheral neuropathic pain. Neurosci Lett. 2006;397:35–39. [PubMed: 16386846]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

TABLE 1.

Characteristics of Primary Disease in Patients Enrolled in Trial

Patient	1	2	3	4	5	6	7	8	9
Location of primary	Laryngeal $T_3N_0M_X$	Ant. oral tongue $T_3N_1M_0$	Hypopharyngeal $T_3N_2M_X$	Oropharyngeal $T_2N_3M_1$	Oral tongue and oral pharyngeal tonsil $T_2N_2M_X$	Base of tongue $T_3N_3M_0$	Oropharyngeal tonsil $T_2N_2M_0$	Oral tongue $T_3N_2M_0$	Base of tongue and soft palate $T_4N_3M_X$
Side	L	R	L	R	R	B	L	R	L
Neck level treated	II-IV	II-IV	II-V	II-V	I-V	II-V	I-V	I-V	I-V

Am J Clin Oncol. Author manuscript; available in PMC 2020 January 06.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

TABLE 2.

Treatment and Symptom Information for 9 Patients Enrolled in Trial

Patient	1	2	3	4	5	6	7	8	9
Conventional vs. IMRT	IMRT	IMRT	Con. then IMRT	IMRT	IMRT	IMRT	IMRT	IMRT	IMRT
Dose to oral tongue (Gy)	14–35	72	0	7–42	50	70	56–70	70	56–70
Symptoms									
Dysesthesia	Slight	X	—	—	X	X	X	X	X
Mucositis	—	X	—	—	X	X	X	X	X
Gabapentin prescribed	—	—	—	—	—	—	—	X	X