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Squamous cell carcinomas of the skin responsive to erlotinib: 5 cases

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Key words: epidermal growth factor receptor; epidermal growth factor receptor inhibitor; erlotinib; squamous cell carcinoma of the skin.

INTRODUCTION
Epidermal growth factor receptor inhibitors (EGFRi) are a class of targeted antineoplastics used for the palliative treatment of aggressive squamous cell cancers of skin (SCCS). Most reports describe the monoclonal antibody, cetuximab, or the small molecule, gefitinib.1-6 Response rates of SCCS to EGFRi are high, with complete response (CR) not uncommon. The molecular basis for susceptibility of SCCS to EGFRi remains unknown. A report found no EGFR mutations in SCCS of patients treated with gefitinib.1 Erlotinib is an orally available EGFRi approved for the treatment of lung and pancreatic cancer. Here we describe the courses of 5 patients with recurrent/unresectable or metastatic SCCS who had palliative benefit from erlotinib. We also report the results of EGFR mutational analysis of their archived tumors. One of these patients was reported on previously in an abstract.2

METHODS
Institutional Review Board approval was obtained for chart review and archival tumor analysis. Specimens were analyzed using the ResponseDX test (Response Genetics Inc, Los Angeles, CA).

CASE SERIES
Case 1
A 60-year-old man with a history of remote Hodgkin’s disease and multiple SCCS had metastases to parotid and neck lymph nodes. Intravenous cisplatin and 5-fluorouracil produced no response. He began gefitinib in May 2004 with resolution of 1 disease site and stability of others, which were later resected. In March 2006 he discontinued using gefitinib after local progression. Resection was attempted followed by various ineffective medical treatments. In August 2007 he began erlotinib, 150 mg daily, with docetaxel, 75 mg/m² every 3 weeks, receiving 8 cycles through February 2008 with response and clinical benefit. He continued with erlotinib monotherapy until progression in May 2008. Erlotinib and taxanes were ineffective, and he died in January 2009.

Case 2
A 54-year-old nonimmunosuppressed man with SCCS of the face received radiation followed by orbital exenteration and right side of the neck dissection. He developed a submental mass and posterior cervical adenopathy within 6 months and was treated with cisplatin and radiation. Two months after radiation, his submental mass recurred, and he began erlotinib at 150 mg daily with CR (Fig 1). There was skepticism that this mass had actually been
Case 2
A 60-year-old nonimmunosuppressed man with a history of a remote prior oral cancer had a rapidly growing SCCS of the lip. Erlotinib was started at 150 mg daily while surgery was arranged. His tumor regressed completely by day 14 (Fig 1). On resection, only a 2-mm focus of tumor remained. Five months later he had recurrence lateral to his previous site. He began erlotinib at 75 mg daily (prior treatment caused a rash) and had CR, leaving defects in the skin where the tumor had been. He then received neck dissections in June 2005 followed by radiation and carboplatin but suffered clinical progression in the skin. Imaging showed multiple new lung nodules, which proved to be SCCS on biopsy. Immunosuppression was switched from tacrolimus to sirolimus, and he began erlotinib at 150 mg daily. Follow-up computed tomography showed a marked reduction in the size and number of lung metastases. Unfortunately, his extrapulmonary cancers responded only transiently, and he died from their continued progression. Computed tomography performed shortly before his death 7 months later showed no evidence of progressive cancer or pneumonitis in his lungs.
radiation with concurrent erlotinib, discontinuing
the erlotinib February 2009. Ten months later he had
a recurrence in the contralateral neck and restarted
erlotinib, 75 mg daily, with CR. On progression
5 months later, his dose was increased to 150 mg
with CR producing an extensive cavity in the tissues
of his neck. Because of declining performance status,
he discontinued his cancer treatment in September
2010 and died 1 month later.

RESULTS—MUTATIONAL ANALYSIS
All 5 tumor specimens were found to contain
wild-type EGFR.

DISCUSSION
In these patients with incurable SCCS, erlotinib
produced responses lasting months with palliative
benefit and low toxicity. It is not known why EGFRi
is active against SCCS. These EGFRi-responsive
tumors did not contain mutant EGFR. Perhaps the
normal EGFR pathway is important to SCCS because
of nonmutational amplification. Overexpression of
EGFR could explain the patient in case 5, whose
tumors progressed during erlotinib treatment but
again responded completely to a double dose.
Increased EGFR gene copy number has been
reported in SCCS.7,8

The mechanistic target of rapamycin (mTOR)
pathway is downstream from EGFR, and treatment
with the mTOR inhibitor, sirolimus, has been associ-
ated with a reduced rate of new SCCS in transplant
patients as well as regression of some established
cancers.9 The mechanism by which sirolimus
accomplishes this is not known. One explanation is
that sirolimus accomplishes this by attenuating the
EGFR pathway. Other treatments operating along the
mTOR/EGFR axis might be beneficial for persons
suffering advanced or metastatic SCCS.

Even though erlotinib is less expensive and does
not require an infusion center, cetuximab is often
cheaper for the patient because of differences in
insurance coverage. Nevertheless, erlotinib should
be considered for off-label use in palliating advanced
SCCS.

REFERENCES
(ZD 1839) in a patient with advanced cutaneous squamous