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A phase II evaluation of gefitinib in the treatment of persistent or recurrent endometrial cancer: A Gynecologic Oncology Group study ☆

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HIGHLIGHTS

- Gefitinib was evaluated in a phase II trial of advanced endometrial cancer.
- One patient achieved a complete response, though gefitinib did not demonstrate significant clinical activity overall.
- The levels of a soluble truncated form of EGFR, sEGFR, positively correlated with overall survival.

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ABSTRACT

Background. A phase II trial was performed to evaluate the efficacy and safety of gefitinib in patients with persistent/recurrent endometrial cancer.

Methods. Women with histologically confirmed persistent/recurrent endometrial cancer were treated with 500 mg oral gefitinib daily until progression or severe toxicity, with progression-free survival (PFS) at six months as the primary endpoint. Tumor expression of total epidermal growth factor receptor (EGFR), estrogen receptor (ER), progesterone receptor A (PRA) and B (PRB), Ki67, pEGFR and activated extracellular signal-regulated kinase (pERK) were examined pre- and post-treatment. EGFR was sequenced, and serum concentrations of soluble EGFR (sEGFR) at baseline also were examined.

Results. Of 29 patients enrolled, 26 were evaluable for efficacy and toxicity. Four patients experienced PFS ≥6 months, and one had a complete response which was not associated with an EGFR mutation. The concentration of sEGFR in pretreatment serum was positively correlated with overall survival (OS), but not with responsiveness to gefitinib in this small patient cohort. Expression of tumor biomarkers was not associated with PFS or OS. Co-expression of ER with PRA in primary and recurrent tumors, and pEGFR with pERK in primary tumors was observed.

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Conclusions. This treatment regimen was tolerable but lacked sufficient efficacy to warrant further evaluation in this setting. The possible association between serum sEGFR concentrations and OS, and temporal changes in expression of pEGFR and pERK and the documented CR of one patient are interesting and warrant additional investigation.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, with an estimated 47,130 cases and 8010 deaths expected in 2012 [1]. While most patients present with early stage disease and are cured by treatment, the prognosis for patients who relapse is poor, and traditional chemotherapeutic regimens for relapsed patients result in low response rates [2–4]. For these patients, biologically targeted therapeutics are enticing experimental regimens.

The epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase that regulates many basic facets of cell and tissue function including cellular growth, survival, differentiation, and migration [5]. EGFR is often overexpressed or mutated in adult solid tumors. Efforts over the last two decades to design EGFR tyrosine kinase inhibitors culminated with FDA approval of the orally active drugs gefitinib and erlotinib for treatment of non small cell lung cancer (NSCLC) and erlotinib for treatment of pancreatic cancer. While methods for stratifying patients most likely to benefit from gefitinib treatment are still being optimized, mutations in EGFR to date appear to be the best predictive marker of responsiveness for NSCLC patients [6]. Moreover, an alternate isoform of EGFR, designated sEGFR, present in both tumor tissue and in circulation, also has been shown to have clinical utility in cancer patients [7–14] and is being studied as a predictive marker of responsiveness to treatment in cancer patients [15].

In vitro and *in vivo* studies of endometrial cancer have implicated EGFR as an important regulator of cell proliferation and survival [16–21]. However, tumor EGFR expression has been associated with adverse outcomes in endometrial cancer only in some studies [19,22–24], whereas in others, EGFR is not a significant marker of survival [25–28]. Serum sEGFR concentrations have not previously been examined in endometrial cancer patients.

Gefitinib has substantial growth inhibitory and apoptotic inductive activity in a number of *in vitro* and *in vivo* studies using tumor cell lines and xenografts, including those of endometrial origin [17,29–33]. Only one study thus far has reported on the efficacy of an EGFR tyrosine kinase inhibitor (i.e. erlotinib) for the treatment of patients with endometrial cancer [34]. Gefitinib is safe and well tolerated with some associated dermatological and gastrointestinal adverse events.

The primary endpoint of this phase II clinical trial was progression-free survival (PFS) at six months for daily oral gefitinib (500 mg) as a treatment for recurrent or persistent endometrial cancer. Overall survival (OS) was included as a secondary endpoint. The potential prognostic and predictive clinical utility of several candidate biomarkers previously associated with steroid receptor and EGFR signal transduction pathways in endometrial cancer were evaluated.

Materials and methods

This was a Gynecologic Oncology Group (GOG) sponsored non-randomized, multicenter phase II open-label trial, designated GOG 229C, which evaluated the efficacy and safety of gefitinib (supplied by AstraZeneca, Cheshire, UK) in 26 evaluable patients with endometrial carcinoma who had persistent or recurrent disease following front-line chemotherapy and higher priority protocols. Clinical and laboratory toxicities were monitored and graded according to the National Cancer Institute Common Toxicity Criteria (CTC) Version 2.0. All adverse events were recorded and graded according to the CTC, Version 2.0 (http://ctep.info.nih.gov). Radiographic studies were performed at two-month intervals. All patients who progressed were followed to assess OS.

Eligibility

Patients with histologically confirmed, recurrent or persistent endometrial carcinoma after at least one chemotherapeutic regimen, and with at least one measurable lesion (at least 20 mm by palpation, X-ray, CT scan, or MRI, or at least 10 mm by spiral CT scan) were eligible for this trial. Each patient provided written consent for the protocol including the translational research component with annual Institution Review Board approval at each of the participating institutions and laboratories in accordance with local, state, and federal regulations and guidelines.

Study design and treatment plan

Gefitinib was administered at a dose of 500 mg per day orally. Each 28 day period was considered a cycle. If side effects were not severe and requirements for monitoring toxicity were met, patients were eligible to remain on the study agent until progression.

Management of toxicity

In general, gefitinib was withheld in patients with grade 2 or greater toxicities until resolution, and patients were then restarted on a reduced dose of 250 mg/day. No dose reductions below 250 mg were allowed. If toxicities did not resolve to grade ≤ 1 or baseline after two weeks of withholding gefitinib (≥ 15 days) for any toxicity, the patient was removed from study.

On-study evaluation

Details are provided in the Supplemental Methods.

Biological samples

Archived formalin-fixed, paraffin-embedded (FFPE) primary tumor tissue from the initial hysterectomy, and serial pre- and post-treatment biopsies (core biopsies or final needle aspirates) of recurrent or persistent tumor were required for this protocol. Patients also were asked to provide serum samples prior to gefitinib treatment. See Supplemental Methods for additional details.

Analysis of EGFR mutation status

Genomic DNA was extracted from FFPE tumor tissue using a TrimGen DNA purification kit (TrimGen Corp, Sparks, MD) according to the kit instructions. EGFR exons 18–21 were amplified by polymerase chain reaction (PCR) as published previously and the amplicons sequenced as described in Supplemental Methods [35].

Analysis of serum sEGFR concentrations

Twenty-four (of 26 evaluable) patients provided baseline serum samples prior to gefitinib treatment for sEGFR quantitation. Serum sEGFR was quantitated by acridinium-linked immunosorbent assay as previously described [36,37].