Abstract

Purpose: It is known that EGFR activation up-regulates VEGF which has been correlated with resistance to anti-EGFR agents. The purpose of this PD study was to investigate effects of the EGFR inhibitor erlotinib (E) with the VEGF antibody bevacizumab (B) in recurrent or metastatic HNC.

Patients and Methods: Phase III trial of fixed dose erlotinib (E) given orally (150 mg) daily with escalation of bevacizumab (B) to a maximum of 15 mg/kg for 3 weeks and continued at 15 mg/kg in the phase II portion. Patients were randomized to receive the initial bevacizumab dose on either day 1 or day 15. Serum VEGF and TGFα levels were quantified by ELISA. Pre-treatment (n=12) and post-treatment (n=5) biopsies taken after 2 weeks of treatment (E alone or E + B) were analyzed by immunofluorescence and laser scanning cytometry (LSC).

Results: Serum VEGF levels were decreased following E or E + B treatments (p=0.007), but TGFα levels were increased (p=0.079) and no correlation with clinical response or progression-free survival (PFS) was observed. Paired tissue samples showed that E or E + B treatments reduced expression of pERK by 47% (p=0.05) and pERK/ERK ratio by 53% (p=0.04). Furthermore, E or E + B treatments increased apoptosis in tumor cells (pre: 1.05%, post: 7.98%; p=0.03) and in endothelial cells (pre: 0%, post: 14.43%; p=0.09). At baseline, higher pEGFR/EGFR and pKDR/KDR ratios correlated with a complete response (CR) (CR>non-CR; p=0.09 and p=0.002, respectively). Using a second anti-pKDR antibody, we confirmed that higher pKDR/KDR ratio also correlated with CR (p=0.02). Of note, higher pKDR/KDR ratio correlated with a complete tumor response (p=0.04) and better PFS (p=0.18).

Conclusions: Compared to erlotinib (E) alone, erlotinib + bevacizumab (E+B) treatment showed an increased inhibition of survival factors, e.g. pEGFR/EGFR and pKDR/KDR ratios appear to predict a complete response to E + B. The promising E + B efficacy and predictive biomarkers warrant further validation in larger patient cohorts.

Background

More than 40,000 patients per year are diagnosed with metastatic squamous cell carcinoma of the head and neck (SCCHN).

Almost 100% of SCCHN overexpress EGFR.

A phase III SCCHN trial with combined treatment of an EGFR inhibitor, erlotinib (150 mg daily), and an anti-VEGF mAb, bevacizumab (15 mg/kg every 3 weeks) showed the combined therapy to be well-tolerated with a 15% overall response rate and a median survival of 6-8 months.

Study Design

Phase I: Fixed standard dose of erlotinib (150 mg daily), escalating dose of bevacizumab to 15 mg/kg.

Phase II: 1st stage (n=22) and 2nd stage (n=24) design, and correlative laboratory studies (Fig. 1, below).

Patients and Methods

Pre-treatment (n=12) and pre-/post-treatment (day 15) of paired biopsies (n=5) were obtained (Fig. 1).

Out of 12 pre-treatment biopsies, 2 showed a complete response (CR), 1 a partial response (PR), 7 a stable disease (SD), and 2 a progressed disease (PD).

Table 1. Clinical response and treatment options of the pre-/post-paired biopsies.

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Pre (n=5)</th>
<th>Post (n=5)</th>
<th>% Target Inhibition</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>100%</td>
<td>0%</td>
<td>100%</td>
<td>0.002</td>
</tr>
<tr>
<td>Non-CR</td>
<td>0%</td>
<td>100%</td>
<td>100%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Serum VEGF and TGFα levels were increased (p=0.097) and no correlation with RR, survival, or PFS.

Expression of pEGFR, EGFR, pKDR, KDR, pERK, ERK and TUNEL was determined by immunofluorescence and quantified by laser scanning cytometry (LSC).

Results

Serum Markers

Serum VEGF (n=28) decreased (p=0.057) and TGFα increased (p=0.097) after treatment. There was no correlation with RR, survival, or PFS.

Tissue Markers

Decreased pERK/ERK ratio (53%) was significantly associated with erlotinib ± bevacizumab treatment (Table 2).

Apoptosis increased in tumor (TC) and endothelial cells (EC) with significant levels detected in TC (Table 2 and Figure 2).

Conclusions

Serum levels of VEGF and TGFα did not correlate with RR, survival, or PFS.

Decreased pERK/ERK ratio was associated with erlotinib or erlotinib ± bevacizumab treatment with significance found only in erlotinib-treated patients.

Apoptosis increased in tumor (TC) and endothelial cells (EC) with significant levels detected in TC.

Higher pEGFR/EGFR and pKDR/KDR ratios in baseline tumor biopsies predicts CR with significance found for pKDR/KDR.

The promising clinical efficacy of erlotinib + bevacizumab and predictive biomarkers warrant further validation studies with larger patient cohorts.

Acknowledgements

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