Original Study

Phase I Study of Lapatinib and Pemetrexed in the Second-Line Treatment of Advanced or Metastatic Non–Small-Cell Lung Cancer With Assessment of Circulating Cell Free Thymidylate Synthase RNA as a Potential Biomarker

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Abstract

In this dose-escalation study we assessed safety and efficacy of lapatinib and pemetrexed in 18 patients with advanced or metastatic non–small-cell lung cancer (NSCLC). The primary outcome was identification of the optimal treatment regimen. Lapatinib and pemetrexed was well tolerated and 1250 mg/500 mg (respectively) was determined as the optimal dose level; suggesting potential use for lapatinib combination therapy in NSCLC.

Introduction: Lapatinib is a dual tyrosine kinase inhibitor that targets epidermal growth factor receptor and HER2. We report on a dose-escalation study of lapatinib combined with pemetrexed in second-line treatment to evaluate the safety and efficacy in advanced or metastatic non–small-cell lung cancer (NSCLC) and an exploratory study in which circulating cell-free thymidylate synthase ribonucleic acid (cfTSmRNA) was measured in all patients and compared with clinical benefit. **Patients and Methods:** Eligible patients had stage IIIB or IV NSCLC after 1 previous line of chemotherapy and an Eastern Cooperative Oncology Group performance status of 0 to 2. Three dose levels (DLs) of lapatinib (daily)/pemetrexed (every 21 days) were evaluated: DL0, 1250 mg/400 mg; DL1, 1250 mg/500 mg; and DL2, 1500 mg/500 mg, respectively. The primary outcome was identification of the optimal treatment regimen. **Results:** Eighteen patients were treated (DL0: n = 4; DL1: n = 8; DL2: n = 6). The most common adverse events (any grade) were diarrhea (61%), rash (44%), nausea (33%), anemia, and fatigue (both 28%). DL1 was determined as optimal after 3 dose-limiting toxicities (DLTs) during the first cycle of DL2 (Grade 3 diarrhea and mucositis, Grade 4 lymphocytopenia); no other DLTs were observed. Partial response was detected in 4 patients. cfTSmRNA was at the limit of detection and was not measurable in all patients. Nonsignificant trends were observed, suggesting that higher levels of cfTSmRNA are associated with poorer outcome. Confirmatory studies are required. **Conclusion:** Lapatinib and pemetrexed was well tolerated, and data suggest a similar response rate to pemetrexed monotherapy.

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Introduction

Non–small-cell lung cancer (NSCLC) continues to be the most common cause of cancer-related deaths, with worldwide mortality rates declining in men but increasing in women.[1-3] Nearly half of patients with NSCLC present with advanced disease, for which the 5-year relative survival rate is 3.7%.[4] Epidermal growth factor receptor (EGFR) mutation analysis has informed treatment decisions and EGFR tyrosine kinase inhibitors are now the standard of care for a patient with an EGFR-mutated tumor.[4] Platinum-based combination treatments remain the first choice in non–EGFR-mutated tumors and optimal combinations are influenced by histology. Adenocarcinomas have better outcomes when treated with pemetrexed in combination with platinum, whereas squamous cell carcinoma (SCC)/not otherwise specified (NOS) tumors respond to other platinum combinations, such as platinum and gemcitabine or taxanes.[4,5] Currently, options for second-line treatment are limited to single agents; these treatments have low response rates and only benefit a small proportion of patients.[4,6]

Recent efforts to improve the efficacy of second-line therapy have focused on targeted agents against 2 oncogenes known to be associated with lung cancer: EGFR and human epidermal growth factor receptor 2 (HER2). Amplification and/or overexpression of EGFR and HER2 are reported in 30% to 84% and 16% to 23% of patients with NSCLC, respectively.[7-9] In NSCLC, irrespective of the line of treatment, therapy with an EGFR-specific agent can lead to compensatory upregulation of EGFR and HER2, potentially leading to drug resistance.[8,10] A potential alternative treatment strategy under investigation considers HER2-specific agents. Trastuzumab, a humanized antibody against HER2 that inhibits cell proliferation,[11] when tested in combination with gemcitabine and cisplatin in the first-line setting for NSCLC was not associated with greater response rates or improved survival compared with gemcitabine and cisplatin doublet treatment.[12,13] Trastuzumab treatment can induce EGFR overexpression in trastuzumab-resistant breast cancer cell lines, a potentially compensatory response similar to that seen in single-agent EGFR inhibitor therapy.[14]

Lapatinib is a dual tyrosine kinase inhibitor that targets EGFR and HER2, with modest efficacy in solid tumors as a monotherapy.[15,16] In vitro tumor growth and assessments in mouse models of lung cancer with positive HER2 amplification have demonstrated that lapatinib substantially reduced cell proliferation.[17] In a phase I dose-escalation study in heavily pretreated patients, lapatinib was associated with stable disease in 2 cases of NSCLC.[15] Although in a phase II trial, second-line single-agent lapatinib induced only 1 partial response, the favorable tolerability profile of lapatinib suggests that it could be combined with another agent that is active for the treatment of NSCLC,[18] such as pemetrexed, a cytotoxic antifolate inhibitor of thymidylate synthase (TS [an enzyme required for the synthesis of the DNA component, deoxythymidine monophospate; and hence essential for cellular division and DNA repair]), which has been demonstrated as well tolerated and has few toxicities overlapping with lapatinib.[18,19]

Increased levels of tumor TS are associated with reduced antitumor activity of pemetrexed, and differential sensitivity to pemetrexed reported in adenocarcinomas and SCCs have been attributed to greater levels of TS expression in SCC and a very small proportion of NOS tumors.[5,20,21]

Cell line experiments have demonstrated synergy between antifolates and EGFR inhibitors.[22,23] Giovannetti et al[23] reported increasing cellular TS levels in NSCLC cell lines in response to exposure to pemetrexed; paradoxically, TS levels decreased in cells treated with pemetrexed and erlotinib in combination. Similar effects have been observed in breast cancer cell lines treated with a combination of lapatinib and the antifolate, capecitabine.[24] Whether a similar effect is observed in vivo is yet to be confirmed, but these data raise the possibility that EGFR inhibitors might sensitize tumors to TS inhibitors irrespective of EGFR mutation status. EGFR mutations conferring sensitivity to EGFR tyrosine kinase inhibitors are most common in adenocarcinoma and rare in patients with other tumor types (such as SCC/NOS).[25] Patients with SCC/NOS would in theory be more likely to benefit from any synergistic effects that the drug combination has, and would be less likely to respond to either drug as a single agent.

Monitoring changing tumor TS levels is clearly desirable; however, obtaining repeated tumor samples that reflect the current molecular status of tumors is not clinically feasible. There is accumulating evidence that circulating cell free (cf)[26] ribonucleic acid (RNA), extracellular nucleic acid which is shed from cells during normal cellular turnover that can be isolated from plasma or serum, has potential as such a biomarker.[27-30] Circulating cfTSmRNA of patients with colorectal cancer has been compared with that of control subjects; in patients with cancer, cfTSmRNA was detected more frequently and its presence was associated with higher tumor TS levels.[31]

We report on a phase I dose-escalation study of lapatinib in combination with pemetrexed in the second-line setting to evaluate the safety and efficacy of this nonplatinum combination regimen in patients with advanced or metastatic NSCLC. To investigate cfTSmRNA as a potential biomarker in NSCLC, circulating cfTSmRNA was measured in exploratory analyses in all patients participating in the study.

Patients and Methods

This was a phase I dose-escalation study of lapatinib and pemetrexed for second-line treatment of advanced or metastatic NSCLC (GlaxoSmithKline study number EGF109462; ClinTrials.gov NCT00528281). The study was conducted in accordance with Good Clinical Practice, all applicable regulatory requirements, and the guiding principles of the Declaration of Helsinki. Ethics committees at the participating institutions approved the study protocol. All patients provided written informed consent before study entry.

Eligible patients were $\geq$ 18 years of age with histologically or cytologically confirmed advanced (incurable stage IIIb or IV) NSCLC at diagnosis or relapsed after curative surgery; had received 1 previous cytotoxic chemotherapy regimen; had an Eastern Cooperative Oncology Group performance status of 0 to 2; had normal cardiac ejection fraction; and had a measurable lesion defined according to the Response Evaluation Criteria in Solid Tumors (RECIST).