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CLINICAL INVESTIGATION **Lung**

GEFITINIB IN COMBINATION WITH IRRADIATION WITH OR WITHOUT CISPLATIN IN PATIENTS WITH INOPERABLE STAGE III NON–SMALL CELL LUNG CANCER: A PHASE I TRIAL

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Purpose: To establish the feasibility and tolerability of gefitinib (ZD1839, Iressa) with radiation (RT) or concurrent chemoradiation (CRT) with cisplatin (CDDP) in patients with advanced non–small cell lung cancer (NSCLC).
Patients and Methods: In this multicenter Phase I study, 5 patients with unresectable NSCLC received 250 mg gefitinib daily starting 1 week before RT at a dose of 63 Gy (Step 1). After a first safety analysis, 9 patients were treated daily with 250 mg gefitinib plus CRT in the form of RT and weekly CDDP 35 mg/m^2 (Step 2). Gefitinib was maintained for up to 2 years until disease progression or toxicity.
Results: Fourteen patients were assessed in the two steps. In Step 1 (five patients were administered only gefitinib and RT), no lung toxicities were seen, and there was no dose-limiting toxicity (DLT). Adverse events were skin and subcutaneous tissue reactions, limited to Grade 1–2. In Step 2, two of nine patients (22.2%) had DLT. One patient suffered from dyspnea and dehydration associated with neutropenic pneumonia, and another showed elevated liver enzymes. In both steps combined, 5 of 14 patients (35.7%) experienced one or more treatment interruptions.
Conclusions: Gefitinib (250 mg daily) in combination with RT and CDDP in patients with Stage III NSCLC is feasible, but CDDP likely enhances toxicity. The impact of gefitinib on survival and disease control as a first-line treatment in combination with RT remains to be determined.

Gefitinib, NSCLC, Chemoradiation, Cisplatin, Phase I study.

INTRODUCTION

Currently, in unresectable Stage III disease, the combination of chemotherapy and RT is the standard treatment approach for patients with good performance status (1). In most patients with NSCLC, epidermal growth factor receptor (EGFR) tyrosine kinase is overexpressed and plays a crucial role in cellular proliferation, inhibition of apoptosis, angiogenesis, metastasis, and chemoresistance (2). Targeting the EGFR pathway is a well-established strategy and can be achieved by either monoclonal antibodies directed against the extracellular domain of the receptor or by small molecules that act by inhibiting EGFR-specific tyrosine kinases (3). Cetuximab, a chimeric IgG1 monoclonal antibody that inhibits EGFR by binding to the extracellular domain, has been studied as a first-line treatment in combination with chemotherapy (4). In head and neck cancer, encouraging results have recently been obtained with a combination of cisplatin and cetuximab in cisplatin-refractory patients (5) and also in combination with irradiation (6).

Gefitinib (ZD1839, Iressa; AstraZeneca; Zug; Switzerland) is the first orally available EGFR-tyrosine kinase inhibitor (TKI) to undergo clinical evaluation. EGFR-targeting agents radiosensitize tumor cells by a variety of mechanisms, including reduction in the proportion of cells in the

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radioresistant S phase by inducing G0/G1 cell cycle arrest, inhibition of RT-induced damage repair, and induction of apoptosis (7). In xenograft tumor models, gefitinib in combination with RT resulted in synergistic growth inhibition (8). Subsequently, Phase I/II studies in different cancer types have been conducted (9–11). A first series investigating the toxicity and safety of combining gefitinib with RT or CRT as a definitive therapy for advanced NSCLC was reported by Stinchcombe *et al.* (12) using a combination of carboplatin, paclitaxel, and high-dose (74-Gy) conformal thoracic RT.

To establish the safety and toxicity profile, we conducted a multi-institutional, Phase I study of gefitinib in combination with RT or CRT in patients with Stage III NSCLC.

METHODS AND MATERIALS

Eligibility criteria

All participating institutions obtained approval by the local ethics committees and the institutional review boards. All patients provided written informed consent. The target population comprised male or female patients with pathologically confirmed Stage III inoperable NSCLC. Patients had to be aged 18–78 years, have a performance status of 0–2 according to the World Health Organization (WHO) status, and a life expectancy of ≥6 months. Patients had to show normal organ and bone marrow function and were checked for adequate pulmonary function Forced exspiratory volume in one second (FEV1 ≥ 80%l). Exclusion criteria were previous RT within the intended treatment volume or prior anti-EGFR therapy.

Study design

The trial was planned with a stepwise design (see Table 1a). Step 1 of the study was to evaluate the safety and tolerability of the combination of gefitinib and RT. The primary endpoint was dose-limiting toxicity (DLT), as defined in the section ''Endpoints.'' The number of patients within a cohort who experienced one or more DLT defined its incidence for a given dose. The incidence of DLT was, in turn, to be used to determine the maximum tolerated dose (MTD). The MTD was defined as the highest dose causing <40% acute DLT and <10% late DLT.

On the basis of our calculations (described under ''Statistical Considerations''), it was planned to include five patients in Step 1 and, if no DLTs were observed, to treat another 12 patients to confirm the results in Step 2. However, in Step 2, only 9 patients were actually included because of slow accrual.

Endpoints

The primary endpoint was DLT, as defined by a Grade 3 or 4 nonhematological toxicity rate <40% for acute and <10% for late toxicities, according to Radiation Therapy Oncology Group recommendations (13). Acute DLT (see Table 1b) had to occur within ≤90 days after initiation of RT; these included any hepatic or renal toxicity of Grade 2 or higher, except reversible Grade 3 liver enzymes elevation, Grade 3 treatment refractory diarrhea, and any other Grade ≥3 nonhematological toxicity, except alopecia, nausea, and vomiting, and any Grade 4 reaction lasting ≥7 days. Any trial drug delay due to treatment-related symptoms of ≥2 weeks or any delay in RT longer than 1 week was considered a DLT-related event (Table 1b). Late DLT was defined as any event considered related to study medication occurring after 90 days of RT and included any Grade ≥3 toxicity or any toxicity Grade <3 that should be considered as a DLT. General toxicity classes sorted by grade and number of events in all patients are provided in Table 2a. Specific monitoring was requested for esophagitis, pericarditis, pneumonitis, spinal cord injuries, and radiculopathy (Table 2b). Secondary endpoints were acute and late toxicity; nature, incidence, and severity of adverse events; incidence of and reasons for trial drug dose interruptions and withdrawals; trial drug exposure; laboratory assessments; physical examination.

Table 1a. Study design

Step	No. of Patients	Gefitinib (mg/d)	Radiotherapy (Gy)	CDDP (mg/m^2/wk)
1	5	250 mg	63 Gy	None
2	9	250 mg	63 Gy	35

Table 1b. Dose-limiting toxicities

Acute DLT (occurring within the first 90 days of the first dose of Gefitinib)
Grade ≥2 hepatic or renal toxicity (except reversible Grade 3 transaminase elevation)
Grade 3 diarrhea despite aggressive antidiarrheal therapy
Other Grade >3 nonhematologic toxicity, excluding alopecia, nausea, vomiting
Late DLT (occurring after the first 90 days of the first dose of AZD1839)
Grade >3 toxicity
Any toxicity Grade <3 that should be considered a DLT, as defined by the principal investigator after review
Either acute or late DLT
Any Grade 4 reaction lasting >7 days
RT treatment delay >1 week
Any delay of gefitinib treatment >2 weeks due to toxicity

Abbreviations: DLT = dose-limiting toxicity; RT = radiation therapy.

Patient evaluation

Initial evaluation included history and physical examination, computer tomography (CT) of the chest, hematology, and blood chemistry profile. During RT or CRT, weekly toxicity assessment was carried out using the National Cancer Institute Common

Table 2a. Toxicity by organ system

	Grade (No. of events in all patients)			
Toxicity (n = 14)	1	2	3	4
Skin and subcutaneous tissues	5	3	0	0
Gastrointestinal disorders	18	2	7	0
Metabolism and nutrition disorders	6	7	1	1
Respiratory, thoracic, and mediastinal disorders	3	1	0	0
Blood and lymphatic system disorders	2	5	2	0
Infections and infestations	1	0	2	0
General disorders	8	1	2	0
Musculoskeletal and connective tissue disorders	1	2	0	0
Nervous system disorders	2	2	1	0
Vascular disorders	0	1	1	0
Eye disorders	0	0	1	0
Reproductive system and breast disorders	1	0	0	0