

ORIGINAL ARTICLE

Phase I study of pemetrexed and concurrent radiotherapy for previously untreated elderly patients with locally advanced non-squamous non-small cell lung cancer

Shinnosuke Takemoto^{1,2}, Yoichi Nakamura³, Minoru Fukuda^{1,4}, Hiroaki Senju¹, Hiroshi Gyotoku¹, Hirokazu Taniguchi¹, Midori Shimada¹, Takaya Ikeda¹, Hiroyuki Yamaguchi¹, Katsumi Nakatomi¹, Nobuyuki Hayashi⁵, Hiroshi Soda⁶ & Hiroshi Mukae¹

1 Department of Respiratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

2 Department of Respiratory Medicine, National Hospital Nagasaki Medical Center, Omura, Japan

3 Division of Thoracic Oncology, Department of Medical Oncology, Tochigi Cancer Center, Tochigi, Japan

4 Clinical Oncology Center, Nagasaki University Hospital, Nagasaki, Japan

5 Department of Radiotherapy, Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan

6 Department of Respiratory Medicine, Sasebo City General Hospital, Sasebo, Japan

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Correspondence

Minoru Fukuda, Clinical Oncology Center, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.

Tel: +81 95 847 1511

Fax: +81 95 841 9613

Email: mifukuda258@nifty.com

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Abstract

Background: Chemoradiotherapy is the standard treatment for locally advanced non-small cell lung cancer (NSCLC); however, it is disputed whether this treatment is suitable for patients aged ≥ 75 . This study was conducted to determine the maximum tolerated dose (MTD) of pemetrexed for use in concurrent radiotherapy for elderly patients with locally advanced non-squamous NSCLC.

Methods: The eligibility criteria were as follows: aged ≥ 75 with inoperable stage IIIA or IIIB non-squamous NSCLC, no history of chemotherapy or radiotherapy, a performance status of 0 or 1, and adequate organ function. The patients were scheduled to receive pemetrexed on days 1, 22, 43, and 64 with concurrent once daily thoracic radiotherapy (60 Gy). The initial pemetrexed dose was 400 (level 1), and it was planned to increase the dose to 500 mg/m² (level 2).

Results: Two patients were enrolled in this trial. In the first case, the patient suffered prolonged leukocytopenia, and treatment was discontinued on day 35. In the second case, febrile neutropenia occurred on day 32, and the patient developed drug-induced pneumonitis and acute respiratory distress syndrome. Both patients experienced dose-limiting toxicities; therefore, the level 1 dose was considered to be the MTD.

Conclusions: During combined treatment with pemetrexed and concurrent radiotherapy, a pemetrexed dose of 400 mg/m² was the MTD; we did not set up a phase II study. Concurrent chemoradiotherapy might be too toxic for elderly patients aged ≥ 75 with locally advanced NSCLC.

Introduction

Lung cancer is the leading cause of cancer death worldwide. It is also the leading cause of cancer death in Japan, with 77 200 deaths from lung cancer occurring in 2015 (20.8% of all cancer deaths).¹ Approximately 80% of all lung cancer cases involve non-small cell lung cancer (NSCLC),² and 34% of NSCLC patients have stage III, locally advanced disease.³ Three meta-analyses of randomized controlled trials

demonstrated that chemoradiotherapy (CRT) was superior to radiotherapy (RT) alone,^{4–6} and phase III trials have suggested that the concurrent administration of these two treatments improves long-term survival compared to sequential strategies.⁷ However, it is unclear whether such combined treatment is suitable for elderly patients. Single agents that only cause mild toxicities may be adequate treatment for elderly patients with unresectable stage III NSCLC.

Table 1 Dose escalation plan

Dose level	Pemetrexed (mg/m ²)
1	400
2	500

Pemetrexed is an antifolate, antitumor agent that exerts its effects by interrupting folate-dependent metabolic processes that are essential for cell replication. It targets thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase.⁸ In elderly patients (i.e. those aged ≥ 75 years) with previously treated NSCLC, pemetrexed monotherapy provided equivalent efficacy to docetaxel monotherapy, which is the standard treatment regimen for elderly NSCLC patients; caused significantly fewer side effects; and was confirmed to be safe and especially effective against non-squamous NSCLC (NSqNSCLC).^{9–12}

Based on these results, we conducted a phase I dose-escalation trial evaluating the utility of combination treatment with pemetrexed and concurrent RT for elderly patients (aged ≥ 75) with locally advanced NSqNSCLC. The aim of this trial was to determine the optimal dose of pemetrexed in this setting (Table 1).

Methods

The trial was conducted in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by the institutional review boards of each participating institution. Written informed consent was obtained from all patients. This study was an independent collaborative (un-sponsored) group study.

Patients and evaluations

The patient eligibility criteria for this study were as follows: aged ≥ 75 ; histologically and/or cytologically confirmed stage IIIA or IIIB NSqNSCLC, inoperable disease, no history of chemotherapy or RT, an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, a life expectancy of 12 weeks or longer, adequate organ function (a leukocyte count of $\geq 4000/\mu\text{L}$, a neutrophil count of $\geq 2000/\mu\text{L}$, a hemoglobin level of ≥ 10 g/dL, a platelet count of $\geq 100\ 000/\mu\text{L}$, a serum bilirubin level of ≤ 1.5 mg/dL, serum alanine aminotransferase and aspartate aminotransferase levels ≤ 2 times higher than the upper limit of normal, and a serum creatinine level of ≤ 1.5 mg/dL), and an oxyhemoglobin saturation (SpO₂) level (as measured by pulse oximetry) of $\geq 95\%$ (in room air); no other form of cancer; and determined by a radiologist as able to undergo RT safely (V20 $\leq 35\%$) (Table 2). The exclusion criteria were as follows: T3N1 disease; having suffered a

Table 2 Patient characteristics

No.	Level	Age	Gender	Histology	TNM	Stage	PS
1	1	87	F	AC	T2aN2M0	IIIA	0
2	1	83	M	AC	T2aN3M0	IIIB	1

AC, adenocarcinoma; PS, performance status; TNM, tumor node metastasis.

myocardial infarction within the previous three months; uncontrolled diabetes mellitus, an active infection, interstitial pneumonia (confirmed by chest X-ray), cerebrovascular disease, symptomatic pericardial effusion, symptomatic superior vena cava syndrome, or a history of significant neurological or psychiatric disorders; severe heart disease, such as uncontrolled angina pectoris, heart failure, hypertension, or arrhythmia; positivity for the hepatitis B surface antigen; or any other complications that made the subject unsuitable for this trial.

Assessment

Before treatment, the patients' complete medical history was taken, and all patients underwent a physical examination, chest RT, chest and abdominal computed tomography (CT), a radionuclide bone scan or positron emission tomography (PET)-CT, brain CT or magnetic resonance imaging, and electrocardiography. Complete blood cell counts and blood biochemistry studies were also conducted and repeated at least twice a week until treatment discontinuation, while other tests were repeated as necessary. Scans or radiographs that were used to assess the treatment response were obtained every 4–6 weeks.

Investigators determined patient response according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. All adverse events were recorded and classified by grade according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Treatment

Treatment commenced within a week of enrollment. The patients were scheduled to receive pemetrexed treatment on days 1, 22, 43, and 64. In addition, 0.5 g oral folic acid was administered daily, and an intramuscular injection of 1 g vitamin B12 was administered every nine weeks; these substances were first administered at least seven days before the start of treatment (Fig 1). We administered an initial pemetrexed dose of 400 mg/m² (level 1) and planned to increase it to 500 mg/m² (level 2). If the patient exhibited a leukocyte count of $< 3000/\mu\text{L}$ or a platelet count of $< 75\ 000/\mu\text{L}$ on the day of therapy, the pemetrexed therapy was postponed until the patient's leukocyte count rose to $\geq 3000/\mu\text{L}$ or their platelet count rose to $\geq 75\ 000/\mu\text{L}$.

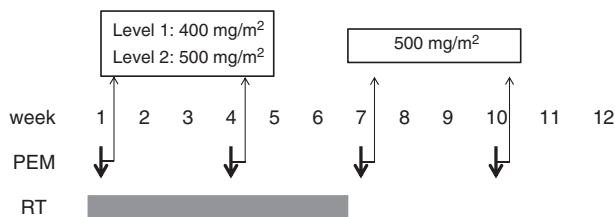


Figure 1 Schema of the planned treatment. PEM, pemetrexed; RT, radiotherapy.

Thoracic RT (once daily for 5 consecutive days of each week, total dose 60 Gy) commenced on day 1. Three-dimensional CT simulations were used for treatment planning. The gross tumor volume (GTV) was defined as the volume of the primary tumor, as demonstrated on the lung window of a CT scan, as well as any metastatic lymph nodes. Metastatic lymph nodes were identified by the oncologists based on their size (≥ 1 cm along the short axis) and 18F-fluorodeoxyglucose (FDG) accumulation on 18F-FDG PET/CT. Cases involving contralateral hilar lymph node metastases were excluded. For this trial, the GTV and the clinical target volume (CTV) for the primary tumor and metastatic lymph nodes were regarded as being the same. Elective nodal regions including the ipsilateral hilar, paratracheal-tracheobronchial, and subcarinal nodal stations were also included in the CTV. The planning target volume (PTV) was defined at the discretion of the radiation oncologist in charge of the case, by adding margins. If a patient had a neutrophil count $< 1000/\mu\text{L}$, RT was discontinued until their neutrophil count increased to $\geq 1000/\mu\text{L}$. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) could be administered if grade 4 leukopenia or neutropenia occurred, and RT was ceased during rhG-CSF treatment.

Outcomes

Dose-limiting toxicities (DLT) were evaluated during treatment and were defined as: grade 4 leukopenia or neutropenia lasting for ≥ 4 days; febrile neutropenia; grade 4 thrombocytopenia; and grade 3 or 4 non-hematological toxicities, except for nausea, vomiting, hair loss, anemia, grade 3 esophagitis lasting two weeks after the last day of RT, and not commencing the second round of pemetrexed until day 35 (Table 3). Our plan regarding dose escalation was to enroll three patients at each dose level, and the dose

would be escalated to the next level if none of the patients experienced DLT. When two or more patients experienced DLT, the associated dose level was defined as the MTD. When one of the three patients developed DLT, an additional three patients were treated at the same level. If none of the additional patients experienced DLT, the dose was escalated to the next level. If one or more of the additional patients experienced DLT, the associated dose level was defined as the MTD. It was decided that the recommended dose of this regimen for a phase II study would be the highest dose level below the MTD. If no DLT was recorded at level 2, it was decided that the recommended dose would be the level 2 dose because it was the recommended dose for chemotherapy alone. If the level 1 dose was shown to be the MTD, we would not carry out a phase II trial because it would indicate that this combination treatment is too toxic for elderly patients.

Results

Two patients were enrolled in this trial at level 1 between September 2012 and May 2014. The first patient was an 87-year-old woman with a PS of 0 and adequate organ function. Although no other toxicities were observed, the patient experienced prolonged leukocytopenia, and treatment was discontinued on day 35. The response and overall survival period were evaluated as a partial response and 909 days, respectively. The second patient was an 83-year-old man. No severe toxicities occurred during the first cycle of pemetrexed. During the second cycle, febrile neutropenia occurred on day 32. RhG-CSF and cefepime were administered immediately; however, the patient exhibited decreased SpO_2 , and areas displaying diffuse ground glass opacity were detected in both lungs on chest CT on day 35. He was diagnosed with drug-induced pneumonitis with acute respiratory distress syndrome and was treated with intensive therapy, including 1000 mg methylprednisolone once a day, but died the next day (day 36). His chest X-ray, RT field, and CT scan before and after treatment are shown in Figure 2. His planned V20 and actual V20 were 23.6% and 19.0%, respectively. His CT showed mild emphysematous bulla, but did not show interstitial pneumonia before treatment. His death was considered to be treatment-related. Tumor shrinkage peaked at more than 30%; however, the duration of the response was not

Table 3 Grades of toxicities and treatment completion

No.	Hb	Leuko	Neutro	Plt	FN	Nausea	Vomiting	AST	ALT	Cr	ILD	Compl	DLT
1	1	2	2	0	0	0	0	0	0	0	0	No	Yes
2	1	4	4	3	3	1	0	2	1	1	5	No	Yes

ALT, alanine aminotransferase; AST, aspartate aminotransferase; compl, completed treatment; Cr, creatinine; DLT, dose-limiting toxicity; FN, febrile neutropenia; Hb, hemoglobin; ILD, interstitial lung injury; Leuko, leukopenia; Neutro, neutropenia; Plt, platelet.

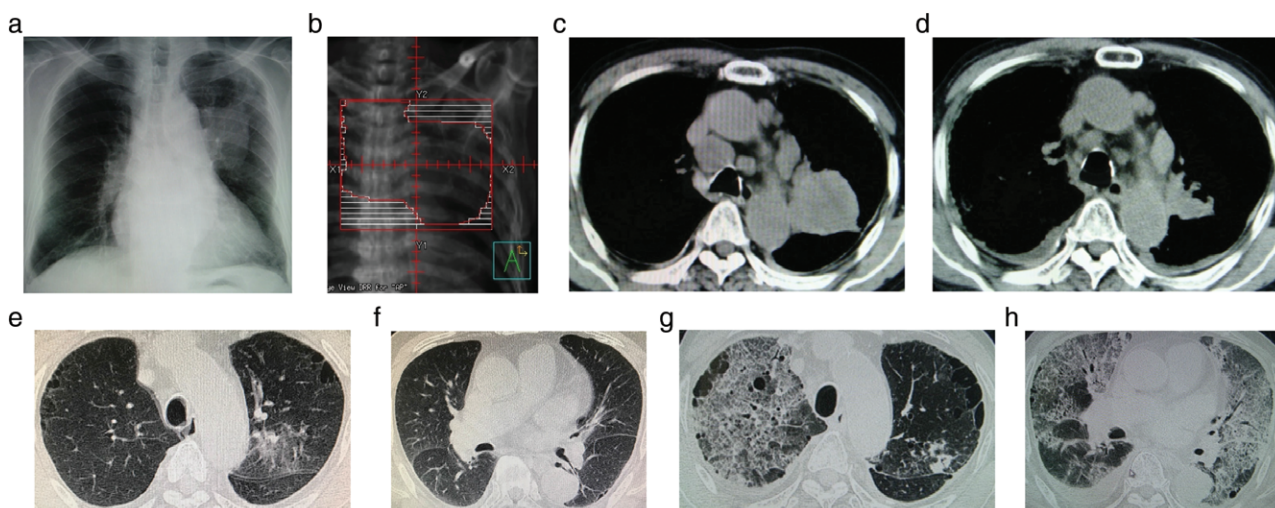


Figure 2 Images of the second patient. Chest X-rays obtained (a) before treatment and (b) planned radiation field. Chest computed tomography scans obtained (c–e) before and (f–h) after treatment.

confirmed, and so the tumor response was defined as not evaluable. Both of the enrolled patients experienced DLT; therefore, the level 1 dose was considered to be the MTD.

Discussion

This phase I study of pemetrexed and concurrent RT determined that a pemetrexed dose of 400 mg/m² is the MTD for previously untreated elderly patients with locally advanced NSqNSCLC. Therefore, according to a previously defined rule we did not conduct a phase II study of this regimen, as it seemed too toxic for this population. We defined elderly people as those aged ≥ 75 years; however, the patients included in this study were considered extremely elderly. It may be necessary to define an upper age limit for further studies involving this patient population.

The administration of thoracic RT to the primary tumor and regional lymph nodes is the conventional treatment for patients with locally advanced, unresectable stage III NSCLC.¹³ As this approach produces five-year survival rates of only 19–36%,³ combined treatment of chemotherapy and thoracic RT was attempted. Meta-analyses of randomized trials have demonstrated that CRT is superior to RT alone, and phase III trials have suggested that the concurrent administration of chemotherapy and RT improves long-term survival compared to sequential strategies.^{4–7} However, it is unclear whether such combined treatment is suitable for elderly patients. In elderly patients with NSCLC, CRT significantly increases the frequency of acute grade 3 or 4 esophageal toxicities compared to sequential CRT.⁷ On the other hand, some studies have reported that CRT is well tolerated and effective, even in elderly populations.^{14,15} Considering these results, a single agent that

causes mild toxicities may be adequate treatment for elderly patients with unresectable stage III NSCLC.

Pemetrexed is an antifolate, antitumor agent that exerts its effects by interrupting folate-dependent metabolic processes that are essential for cell replication. It targets thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides.⁸ Pemetrexed monotherapy has exhibited equivalent efficacy to docetaxel in patients with previously treated NSCLC while causing significantly fewer side effects.⁹ In addition, it has been confirmed as having a slightly different spectrum from other agents used to treat non-squamous and anaplastic lymphoma kinase-positive NSCLC.^{11,16} A meta-analysis of 2671 patients with NSqNSCLC and good PS revealed that the effect of pemetrexed on overall survival did not differ between younger and older patients when cut-off ages of 65 or 70 years were used.¹⁷ Moreover, in elderly patients aged ≥ 75 , pemetrexed was reported to be safe and effective.¹⁰ Pemetrexed is very effective and causes little toxicity in patients with NSqNSCLC, even in elderly populations.^{10,18} However, there is a lack of information about the optimal treatments for elderly patients with locally advanced NSqNSCLC. Recently, Senan *et al.* reported the results of a phase III trial of combination treatment involving pemetrexed or etoposide, combined with cisplatin and thoracic RT, in young and elderly NSqNSCLC patients.¹⁹ Although the pemetrexed arm was not superior to standard CRT, it exhibited a significantly lower incidence of drug-related grade 3 or 4 adverse events, including neutropenia, and thus was considered to display acceptable safety. These findings suggest that pemetrexed and concurrent RT are compatible.

Atagi *et al.* conducted a phase III trial of thoracic RT with or without daily low-dose carboplatin in elderly patients with locally advanced NSCLC, because it was unclear whether CRT improved survival compared to thoracic RT alone.¹⁵ The CRT arm demonstrated a clinically significant benefit over thoracic RT alone in terms of the overall survival period (22.4 vs. 16.9 months; hazard ratio 0.68; stratified one-sided log-rank test, $P = 0.019$). Although CRT seemed feasible and effective in the latter trial and included patients older than 75 years, the cut-off age was 70 years. In our trial, two patients aged 83 and 87 were enrolled; had we enrolled slightly younger patients as per our cut-off, our results may have been different. Care needs to be taken when using combined treatment in extremely elderly patients.

In conclusion, during CRT with pemetrexed, a pemetrexed dose of 400 mg/m² is considered to be the MTD for elderly NSqNSCLC patients. Based on this finding, we did not set up a phase II study. Concurrent CRT may be too toxic for elderly patients aged ≥ 75 with locally advanced NSCLC.

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Disclosure

No authors report any conflict of interest.

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