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Clinical trial evaluating efficacy and safety of pemetrexed based chemotherapy regimen versus ramucirumab plus erlotinib in Chinese patients with lung cancer: A preliminary investigation

Qin Mei[1], Lingjun Ye[1], Chunyou Chen[2] and Hao Lin[1]*
[1]Department of Medical Oncology, The First People's Hospital of Wenling, Wenling, Zhejiang, China
[2]Department of Neurology, The First People's Hospital of Wenling, Wenling, Zhejiang, China

Abstract: To carry out a preliminary clinical trial to compare the effectiveness and safety of pemetrexed based chemotherapy regimen in combination of cisplatin versus ramucirumab plus erlotinib in Chinese patients with metastatic non-small-cell lung cancer (NSCLC). Patients with confirmed diagnosis of NSCLC were randomly (1:1 ratio) grouped and treated intravenously with a mixture of pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) plus Best Supportive Care (BSC), or ramucirumab (8 mg/kg) intravenously (IV) + erlotinib 25 mg/day. Overall survival (OS), overall response rate (ORR), progression free survival (PFS), and the safety were assessed. Pemetrexed based chemotherapy regimen in combination of cisplatin showed significantly higher OS (14.4 months *vs*. 10.47 months, $p<0.05$) and PFS (9.5 months *vs*. 5.1 months) than ramucirumab plus erlotinib. Objective response was also favorable in the patients treated with pemetrexed based chemotherapy regimen, when compared with those given ramucirumab plus erlotinib. Pemetrexed based chemotherapy regimen found more effective to ramucirumab plus erlotinib in improving OS, PFS and ORR, and it offers greater clinical benefits than ramucirumab plus erlotinib in Chinese NSCLC patients. Pemetrexed based chemotherapy regimen in combination of cisplatin appears to be better choice of drug for the treatment of Chinese patients with advanced stage of lung cancer.

Keywords: Pemetrexed based chemotherapy regimen, ramucirumab, erlotinib, cisplatin, lung cancer.

INTRODUCTION

Metastatic non-small-cell lung cancer (NSCLC) is a leading cause of cancer-related mortality worldwide (Aberle *et al*., 2011). The disease is highly prevalent among Asian countries (Aberle *et al*., 2011; Siegel, 2016; Hoffman, 2000; Torre, 2015). There are several approved treatment modalities in Asian countries. Currently, surgery is the typical treatment for resectable NSCLC patients (Franco, 2018). However, 20 to 30 % of subjects with NSCLC develop relapse in spite of surgical removal of cancerous cells (Aberle *et al*., 2011; Siegel, 2016; Hoffman, 2000; Torre, 2015; Chang, 2013; Escudier, 2007; Hellmann, 2015). Recently, nivolumab, oral multikinase inhibitor and newer agents such as nintedanib and ramucirumab have been identified as new therapeutic options for NSCLC patients (Morabito, 2018). Several lines of clinical evidence from pivotal studies have suggested that pemetrexed based chemotherapy regimen should be used as the first line therapy, in addition to crizotinib for NSCLC (Hoffman, 2000; Torre, 2015; Chang, 2013; Escudier, 2007; Hellmann, 2015).

Ramucirumab is a recombinant human receptor-targeted monoclonal antibody that selectively binds to the extracellular domain of vascular endothelial growth factor receptor-2 (VEGFR-2) and inhibits activation of VEGFR-2 (Hu, 2018; Gould, 2014; Han, 2018; Lu, 2003; Zhu, 2003) and is commonly used in several types of solid cancers. In REACH study (Zhu, 2015), second-line treatment with ramucirumab did not significantly improve survival over placebo in patients with advanced hepatocellular carcinoma. However, treatment with ramucirumab in lung cancer is not well established. In larger studies such as REACH and REACH-2 trials (Zhu, 2015; Andrew, 2018), ramucirumab was well tolerated, with a safety profile consistent with its established profile. Pemetrexed belongs to the anti-folate class of cytotoxic agents. It is effective and well tolerated in lung cancer patients after epidermal growth factor receptor (EGFR) - tyrosine kinase inhibitor (TKI) failure, and has been recommended as the 1st line treatment for NSCLC due to its favorable efficacy and safety profile (Gould, 2014; Han, 2018). Erlotinib, an EGFR inhibitor has been found effective in improving clinical outcome in patients with NSCLC (Yongsheng, 2012).

There are no studies on direct comparison of pemetrexed based chemotherapy regimen and ramucirumab plus erlotinib in Chinese patients with NSCLC. Comparison of efficacy and safety of pemetrexed based chemotherapy regimen versus ramucirumab plus erlotinib in Chinese NSCLC patients has not been carried out till date. Thus, the present trial was designed to evaluate, for the first time, the effectiveness and safety of pemetrexed-based regimens relative to ramucirumab plus erlotinib in Chinese patients with NSCLC. In the current clinical trial,

**Corresponding author:* e-mail: LoganMartinjjm@yahoo.com

it has been hypothesized that ramucirumab, a mixed inhibitor of VEGFR, in combination of erlotinib, a EGFR inhibitor may show a better survival benefit as compared to pemetrexed based chemotherapy regimen in combination of cisplatin in Chinese patients with NSCLC. The purpose of the current clinical trial was to evaluate efficacy and safety of pemetrexed based chemotherapy regimen in combination of cisplatin and ramucirumab plus erlotinib in Chinese patients with NSCLC.

MATERIALS AND METHODS

Study design, patients and ethics

Patients with confirmed diagnosis of NSCLC, with ECOG (Eastern Cooperative Oncology Group) Performance Status (PS) in the range of 0-1 and who had metastases were recruited in this trial. The primary objective of this study was to compare the effectiveness and safety of pemetrexed based chemotherapy regimen and ramucirumab plus erlotinib in Chinese patients with NSCLC. Efficacy parameters such as overall survival (OS), overall response rate (ORR) and progression free survival (PFS) were assessed after pemetrexed based chemotherapy regimen and ramucirumab plus erlotinib treatments. The safety of pemetrexed based chemotherapy regimen and ramucirumab plus erlotinib treatments was also assessed, in addition to survival time with respect to disease progression. Written consent was obtained from each enrolled subject. The trial protocol and other essential trial-related documents were approved by the Institutional ethics committee of The First People's Hospital of Wenling vide approval number: IEC/FPHW-2019/273/12. Each patient was instructed to provide information on demography, medical history and family history using a pre-designed form as per our screening protocol before enrollment in the screening program.

Trial drug administration

Patients with confirmed diagnosis of NSCLC were randomly grouped and treated intravenously with a mixture of pemetrexed (500 mg/m2) and cisplatin (75 mg/m2) plus Best Supportive Care (BSC), or ramucirumab (8 mg/kg) intravenously (IV) + erlotinib 25 mg/day orally in a 1:1 ratio on Day 1 of each 21-day cycle for 4 cycle or until disease progression, development of unacceptable toxicity; protocol noncompliance; or withdrawal of consent by the patient or sponsor/investigator decision occurred. Each enrolled subject was received supplementation of folic acid and vitamin B_{12} as a part of BSC. Pemetrexed (500 mg/m^2) administered as an intravenous infusion over 10 minutes. Cisplatin (75 mg/m^2) infused over 2 hours beginning approximately 30 minutes after the end of pemetrexed administration. Ramucirumab (8mg/kg) administered by intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent ramucirumab (8mg/kg) infusions may be administered over 30 minutes.

Efficacy assessment

Using Response Evaluation Criteria in Solid Tumors (RECIST) Criteria, overall survival (OS) and progression free survival (PFS) were recorded for each patient using CT scan and/or magnetic resonance imaging (MRI). The number of patients with partial response (PR), complete response (CR), stable diseases (SD) or progressive diseases (PD) was recorded. Moreover, OS and PFS were recorded for each patient. The survival time of patients was assessed from date of diagnosis of lung cancer to date of death due to lung cancer, or date lost to follow up. The primary trial endpoints were comparison of as OS, overall response rate (ORR), and PFS after pemetrexed based chemotherapy regimen and ramucirumab plus erlotinib treatments, to determine which treatment was more effective in improving these parameters. The secondary trial endpoint was comparison of safety of pemetrexed based chemotherapy regimen and ramucirumab plus erlotinib treatments.

Safety assessment

The incidence and severity of drug-induced liver injury in subjects with and without liver metastasis were evaluated based on laboratory criteria. Treatment-related adverse events (TEAEs) or serious AEs (SAEs) referred to any event considered to be causally related to the trial drug according to the physician's subjective judgment. No re-escalation was done for the patients who needed dose reductions. In addition, patients who were serially and repeatedly subjected to treatment were monitored for evidence of cumulative toxicity. Serious adverse events were followed up until recovery, death, or loss to follow-up, if a causal relation with the investigational drug could not be ruled out.

STATISTICAL ANALYSIS

Since the present investigation was designed as a preliminary study, a formal calculation of sample size was not carried out. Analyses of population were applied to those who received at least one dose of either pemetrexed based chemotherapy regimen in combination of cisplatin or ramucirumab plus erlotinib treatments. Patients who received at least one dose of either pemetrexed based chemotherapy regimen in combination of cisplatin or ramucirumab plus erlotinib treatments were included in safety analysis. Comparison of PFS and OS and response was made between both treatment groups using a log-rank test. Results were considered significant if $p < 0.05$. Data analysis was conducted using Sigma Plot (ver 11.0).

RESULTS

Baseline characteristics of subjects and drug exposure

A total of 150 patients were enrolled in this study from Jan 2017 to March 2019. They were randomly allocated to Ramucirumab plus Erlotinib (n=75) or pemetrexed based chemotherapy regimen (n=75). Both treatment

groups had similar demographics and baseline characteristics. The demography and clinical features of all recruited patients are table 1.

Treatment efficacy

Pemetrexed based chemotherapy regimen showed significantly higher OS and PFS than ramucirumab plus erlotinib (OS: median = 14.4 and 10.5 months, respectively; $p < 0.05$; PFS: median = 9.5 and 5.1 months, respectively). Objective response was also favorable in the patients treated with pemetrexed based chemotherapy regimen, when compared with those given ramucirumab plus erlotinib. Pemetrexed based chemotherapy regimen was found to be more effective to ramucirumab plus erlotinib in improving OS, PFS and ORR, and it offers greater clinical benefits than ramucirumab plus erlotinib

Table 1: Demographic data for patients treated with pemetrexed based chemotherapy regimen (n=75) and ramucirumab plus erlotinib (n = 75)

Characteristic	Ramucirumab plus Erlotinib (n=75) n (%)	Pemetrexed based chemotherapy regimen (n=75), n (%)
Age (years), mean (SD)	45.5 (3.4)	46.7 (5.6)
Gender, n (%)		
Male	49 (65)	45 (60)
Female	26 (35)	30 (40)
KS status, n (%)		
=<50%	50 (67)	55 (73)
>50%	25 (33)	30 (40)
Previous use of anti-VEGF agents, n (%)		
Yes	60 (80)	62 (83)
No	15 (20)	13 (17)
Previous use of anti-EGFR agents, n (%)		
Yes	66 (88)	65 (87)
No	14 (19)	15 (20)
Initial Pathological Diagnosis, n (%)		
Histopathological	35 (47)	33 (44)
Cytological	25 (33)	32 (43)
Biochemical Assay and Imaging	15 (20)	10 (13)
ECOG Performance Status, n (%)		
0	40 (53)	45 (60)
1	35 (47)	35 (47)
Duration of Disease, median (range) months	0.42 (0.31-0.76)	0.52 (0.33-0.81)

Abbreviation: K-*ras* = mutations in the Kirsten *ras*; n = number of patients; VEGF = vascular endothelial growth factor; EGFR = epidermal growth factor receptor; ECOG= Eastern Cooperative Oncology Group. Pemetrexed based chemotherapy regimen = Pemetrexed + cisplatin

Table 2: Comparison of efficacy between Pemetrexed based chemotherapy regimen (n=75) and ramucirumab plus erlotinib (n=75) in patients with lung cancer.

Variable	Ramucirumab plus Erlotinib (n=75)	Pemetrexed based chemotherapy regimen (n=75)
OS		
Median (months)	10.5	14.4
HR (95% CI) Probability value	0.52 (0.3-0.7) p<0.001	
Progression-free survival		
Median (months)	5.1	9.5
HR (95% CI), Probability value	0.62 (0.4-0.7) p<0.001	
ORR		
CR	5	9
PR	17	37
SD	43	34
PD	10	5

Abbreviation: CR = Complete response; CI = confidence interval; OS = Overall survival; PR = partial response; SD = stable disease; PD = progressive disease; HR = Hazard ratio; n = number of patients in each category.
Pemetrexed based chemotherapy regimen = Pemetrexed + cisplatin

in Chinese patients with NSCLC. These results are table 2.

Safety and tolerability

In the ramucirumab plus erlotinib group, the most common treatment-related adverse events (TEAEs) were neutrophil count decreased, white blood cell count decreased and neutropenia followed by Diarrhea, fatigue and aspartate aminotransferase increased (table 3). Laboratory abnormalities were higher in the ramucirumab plus erlotinib group than in the pemetrexed based chemotherapy regimen group. Majority of the hepatotoxicity events in patients treated with ramucirumab plus erlotinib group were of grade 1 or 2.

The patients who were treated with pemetrexed based chemotherapy regimen showed significantly higher OS than ramucirumab plus erlotinib. The 6 months survival was 18% and 8% among patients treated with pemetrexed based chemotherapy regimen and ramucirumab plus erlotinib, respectively. Overall survival outcome was favorable in the patients treated with pemetrexed based chemotherapy regimen, when compared with those given ramucirumab plus erlotinib. Based on the above Kaplan-Meier (KM) curve, pemetrexed based chemotherapy regimen was found to be more effective to ramucirumab plus erlotinib in improving survival outcome, and it offers greater clinical benefits than ramucirumab plus erlotinib in Chinese patients with NSCLC (fig. 1).

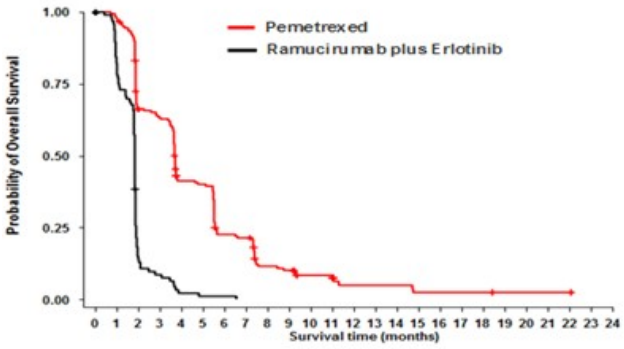

Fig. 1: Overall survival in lung cancer patients treated with pemetrexed based chemotherapy regimen (n=75) and Ramucirumab plus Erlotinib (n=75).

The patients who were treated with pemetrexed based chemotherapy regimen showed significantly delayed PFS than ramucirumab plus erlotinib. Overall progression free survival outcome was favorable in the patients treated with pemetrexed based chemotherapy regimen, when compared with those given ramucirumab plus erlotinib. The 6 months progression free survival was 21% and 12 % among patients treated with Pemetrexed based chemotherapy regimen and ramucirumab plus erlotinib, respectively. Based on the above KM curve, pemetrexed based chemotherapy regimen was found to be more effective to ramucirumab plus erlotinib in improving survival outcome, and it offers greater clinical benefits than ramucirumab plus erlotinib in Chinese patients with NSCLC (fig. 2).

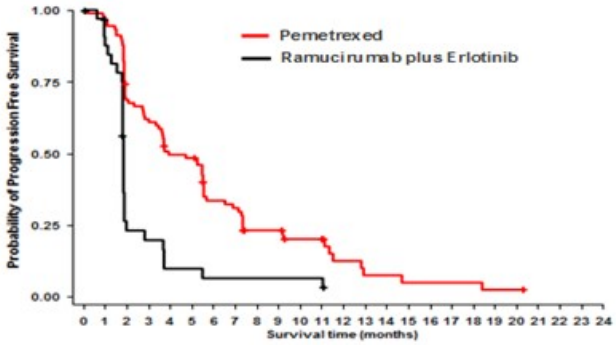

Fig. 2: Progression free survival in lung cancer patients treated with pemetrexed based chemotherapy regimen (n=75) and Ramucirumab plus Erlotinib (n=75).

DISCUSSION

The current investigation is the first trial carried out to compare the efficacy and safety of compare the effectiveness and safety of pemetrexed based chemotherapy regimen in comnibnation of cisplatin versus ramucirumab plus erlotinib in Chinese patients with NSCLC. No direct comparison of pemetrexed based chemotherapy regimen in combination of cisplatin versus ramucirumab plus erlotinib was performed. Thus, the present trial was designed to evaluate, for the first time, the effectiveness and safety of pemetrexed based chemotherapy regimen relative to ramucirumab plus erlotinib in Chinese patients with NSCLC. In the current clinical trial, it has been hypothesized that ramucirumab, a mixed inhibitor of VEGFR, in combination erlotinib, a EGFR inhibitor may show a better survival benefit as compared to pemetrexed based chemotherapy regimen in combination of cisplatin in Chinese patients with NSCLC. The purpose of the current clinical trial was to evaluate efficacy and safety of pemetrexed based chemotherapy regimen in combination of cisplatin and ramucirumab plus erlotinib in Chinese patients with NSCLC.

Pemetrexed based chemotherapy regimen in combination of cisplatin showed significantly greater OS and PFS than ramucirumab plus erlotinib treatment. The objective response was also favorable among the patients treated with pemetrexed based chemotherapy regimen, when compared with ramucirumab plus erlotinib. The present trial results showed that Pemetrexed based chemotherapy regimen were superior to ramucirumab plus erlotinib in improving OS, PFS and ORR, and it offered significantly greater clinical benefits for advanced stage liver cancer patients than ramucirumab plus erlotinib. The results of the present trial may help clinicians to select appropriate treatment modalities for advanced stage liver cancer patients. These results are consistent with previous reports

Table 3: Treatment-related adverse events in lung cancer patients treated with pemetrexed based chemotherapy regimen (n=75) and ramucirumab plus erlotinib (n=75).

Preferred term	Ramucirumab plus Erlotinib (n=75), n (%)	Pemetrexed based chemotherapy regimen (n=75), n (%)
Neutrophil count decreased	21 (28)	13 (17)
White blood cell count decreased	11 (15)	6 (8)
Neutropenia	13 (17)	6 (8)
Diarrhea	8 (11)	6 (8)
Fatigue	6 (8)	3 (4)
Hepatic hemorrhage	3 (4)	1 (1)
Wound complication	2 (3)	4 (5)
Aspartate aminotransferase increased	11 (15)	5 (7)
Hypothyroidism	2 (3)	1 (1)

Abbreviation: AEs = adverse events; n = number of patients in each category. Pemetrexed based chemotherapy regimen = Pemetrexed + cisplatin

(Rosell, 2002; Shepherd, 2001). In general, pemetrexed based chemotherapy regimen or ramucirumab plus erlotinib treatment were well-tolerated in the patients with advanced stage of solid cancer (Rosell, 2002; Shepherd, 2001). Earlier, ramucirumab in combination with Chemotherapy (FOLFOX regimen) has been tested in patients with advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma (Garcia, 2014; Yoon, 2016; Qin, 2013) or metastatic colorectal cancer (Garcia, 2014). To the best of our knowledge, this is the first trial to test Pemetrexed based chemotherapy regimen versus ramucirumab plus erlotinib in patients with NSCLC. In the present trial, the best overall response including disease control rate and ORR was favorable for the patients who were treated with Pemetrexed based chemotherapy regimen as compared to ramucirumab plus erlotinib treatment.The present trial results showed that pemetrexed based chemotherapy regimen were superior to ramucirumab plus erlotinib in improving OS, PFS and ORR, and it offered significantly greater clinical benefits for NSCLC patients than ramucirumab plus erlotinib. The results of the present trial may help clinicians to select appropriate treatment modalities for NSCLC. In general, pemetrexed based chemotherapy regimen and ramucirumab plus erlotinib were well-tolerated in the NSCLC patients. The finding pertaining to pemetrexed based chemotherapy regimen is consistent with previous reports which showed that it is efficacious and of acceptable safety profile in patients with NSCLC. Indeed, pemetrexed based chemotherapy regimen has been recommended as first line therapy for NSCLC. Due to its good efficacy and safety profile, the present trial also showed that pemetrexed based chemotherapy regimen was efficacious in the treatment of patients with ACL.In REACH study, the most common severe TEAE of ramucirumab in Asians patients with metastatic liver cancer were hypertension. Safety of ramucirumab therapy for Asians was similar to non-Asians (Park, 2016). In the present clinical trial, the most common grade ≥3 TEAEs (occurring in ≥5% of patients) after administration of ramucirumab with FOLFOX regimen were hypertension followed by increased aspartate aminotransferase concentration and thrombocytopenia. This is in consistent with REACH trial (Park, 2016), with similar safety profile. Nonetheless, most of these TEAEs are common in patients with HCC due to underlying malignancies and liver diseases. Despite of some differences in clinical trial design such as different setting and line of treatment between present clinical trial and REACH trial, the toxicities of ramucirumab-FOLFOX4 are more likely to be associated with chemotherapy.

Limitations of the study

The present trial was conducted at single hospital in China; therefore, results may not be generalized to other population. Due to low sample size of present study, large clinical trial with appropriate sample size warranted to design the efficacy and safety of pemetrexed based chemotherapy regimen in comination of cisplatin in Chinese patients to further confirm the finding of this trial.

CONCLUSION

The present trial results showed superior efficacy combination of pemetrexed based chemotherapy regimen compared to ramucirumab plus erlotinib treatment in Chinese patients with metastatic liver cancer. The results of present trial may help clinician to select appropriate therapeutic intervention for the patients with metastatic liver cancer. However, large clinical trial is needed to confirm generalizability of present finding before clinical use.

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