JBUON 2013; 18(4): 899-907
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Third-line therapy in advanced non-small cell lung cancer

Zhen Ying Geng[1,2], Shun Chang Jiao[1], Shi Cui Liu[2], Ying Li[1], Zhe Feng Liu[1], Guo Qing Zhang[1], Li Jie Wang[1], Feng Qu[2]

[1]*Department of Medical Oncology, PLA General Hospital, Haidian District, Beijing;* [2]*Medical College of Nankai University, TianJin, China*

Summary

Purpose: *With the improvements in first- and second-line treatments in non-small cell lung cancer (NSCLC), there is an increasing number of patients who receive third-line therapy. No other standard choice for third-line therapy aside from erlotinib is possible. This study investigated the efficacy and safety of single-agent chemotherapy, epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), doublet chemotherapy and chemo-targeted therapy as third-line treatment in advanced NSCLC.*

Methods: *This study included 233 stage IIIb or IV NSCLC patients who were retrospectively reviewed to explore the differences in survival between different treatments.*

Results: *The median progression free survival (PFS) in the EGFR-TKIs, single-agent, doublet and chemo-targeted groups was 3.83, 2.72, 2.86 and 3.29 months, respectively (p = 0.073). The median OS from the initiation of the third-line treatment was 11.16, 8.24, 8.49 and 9.33 months in the 4 groups (p=0.02). The rates of grade III-IV toxicities were 16.4, 27.6, 57.3 and 44.0% (p <0.001), respectively with the third-line treatment, and overall survival (OS) was prolonged in patients who never smoked (p=0.040), had adenocarcinoma (p=0.034), had good ECOG performance status (PS) (p=0.012) and achieved disease control after both first-and second-line treatments (p =0.031).*

Conclusion: *Patients with advanced NSCLC who never smoked, had adenocarcinoma, have good PS, and good disease control from the first- and second-line therapies could benefit more with third-line treatment. EGFR-TKIs and chemo-targeted therapy showed increased OS compared with single-agent and doublet chemotherapy.*

Key words: *chemotherapy, non-small cell lung cancer, prognosis, targeted therapy, third-line treatment*

Introduction

Lung cancer is one of the most life-threatening malignancies and the leading cause of cancer-related mortality [1]. About 80% of all lung cancer patients have NSCLC, and 40–50% of them have advanced disease on presentation [2].The prognosis of advanced NSCLC remains poor, but in line with progress in clinical research, it is improving. Two-drug third-generation platinum-based regimens are the standard first-line therapy, with the exception that gefitinib is selected for patients who are positive for EGFR mutation. Pemetrexed, docetaxel and gefitinib are the standard agents used in second-line therapy; pemetrexed plus cisplatin/carboplatin is also a tolerable chemotherapy regimen [3]. Many studies have shown that second-line chemotherapy will give patients a survival benefit and improved quality of life [4,5]. However, there have been relatively fewer clinical studies regarding third-line therapy as compared with first-and second-line therapy. Erlotinib is currently the only drug that has been approved for third-line treatment [6]. Recently, second-line therapy was given to 40–60% of patients and 20–30% of patients could receive third-line or further therapy [6]. However, there are few prospective studies that addressed the role of third-line treatment in NSCLC, and there are also few retrospective analyses [7,8]. Analysis of efficacy and prognostic factors for third-line treatment of advanced NSCLC is a noteworthy problem. Based on this we conducted a retrospective study to investigate the efficacy and survival of third-line treatment in advanced NSCLC patients.

Correspondence to: Shun Chang Jiao, MD. Department of Medical Oncology, PLA General Hospital, 28 Fuxing Road, Haidian District, Beijing, 100853, China. Tel: +86 010 66939761 Fax: +86 010 68236546, E-mail: chenwencw163@163.com
Received: 04/05/2013; Accepted: 16/05/2013

Methods

This study was conducted after approval of the hospital's Ethics Committee. We included all consecutive patients with NSCLC who had received at least 3 lines of systemic antineoplastic treatment between January 1, 2003 and December 31, 2007 at the General Hospital of the Chinese People's Liberation Army. All chemotherapy courses were administered in this hospital, and were consistent with standardized guidelines. In all patients, NSCLC staging was performed in accordance with the 6th TNM classification system.

Patient selection criteria

The patient selection criteria included the following: (1) pathologically proven primary NSCLC stage IIIB or IV at the time of diagnosis; (2) patients who had received chemotherapy or targeted therapy (including gefitinib,erlotinib,bevacizumab, cetuximab and endostaror) simultaneously, and had experienced failure of second-line therapy; (3) administration of at least one cycle of third-line therapy. Recurrence or progression were evaluated using ultrasound, computed tomography (CT) , bone scan or MRI of the thorax and abdomen. After therapy all patients were followed at our department.

Patients and response to therapy

All patients were evaluated at the time of initial diagnosis. In this study, patients were divided into smokers and nonsmokers. A nonsmoker was defined as a patient who had never smoked or had smoked less than 100 cigarettes during his or her lifetime. A patient who had smoked more than 100 cigarettes was defined as a smoker. The duration of first-, second- and third-line treatment was calculated from the first to the last day of therapy. Response to chemotherapy or targeted therapy was assessed using CT every two cycles or one month, or was evaluated when progression appeared early. Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) [9]. Responses were categorized as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The disease control rate (DCR) was the sum of CR+PR +SD. Toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria, version 3.0 [10]. ECOG PS was systematically assessed and recorded for every patient by inspecting the medical records or regular telephone follow-up contacts.

Statistics

The final date of follow-up used in this study was August 31, 2012. Categorical variables were compared using the x^2 test and continuous variables using the Mann-Whitney non-parametric test. Surviving patients were registered from the first day of therapy to the date of death or the last follow-up visit. PFS encompassed the time from the first cycle of third-line therapy to progression or death. The survival curves were generated using the Kaplan-Meier method and assessed with log rank test. Various prognostic factors regarding influence on survival, including gender, tumor stage and histology, smoking history, surgical history, response to previous treatments, and third-line treatment were evaluated by means of univariate analysis using the log rank test and by multivariate analysis using the Cox proportional hazard model. Values of $p<0.05$ were considered as statistically significant. Statistical analyses were conducted using SPSS, version 17.0 (Chicago, IL, USA).

Results

There were 1780 Chinese patients with NSCLC who received chemotherapy in our hospital from January 2003 to December 2007. Of these, 978 (54.90%) had stage IIIB or IV disease. Second-line or further therapy had been administered to 499 (51.0%) patients; of these, 239 had received second-line treatment only because of tumor progression or deterioration in physical status. The choice to administer third-line treatment was based on patients' and physicians' decision after carefully evaluating potential risks and possible advantages in each single clinical case. A total of 260 (30.4%) patients received third-line treatment in our study (Figure 1). Twenty-seven cases with

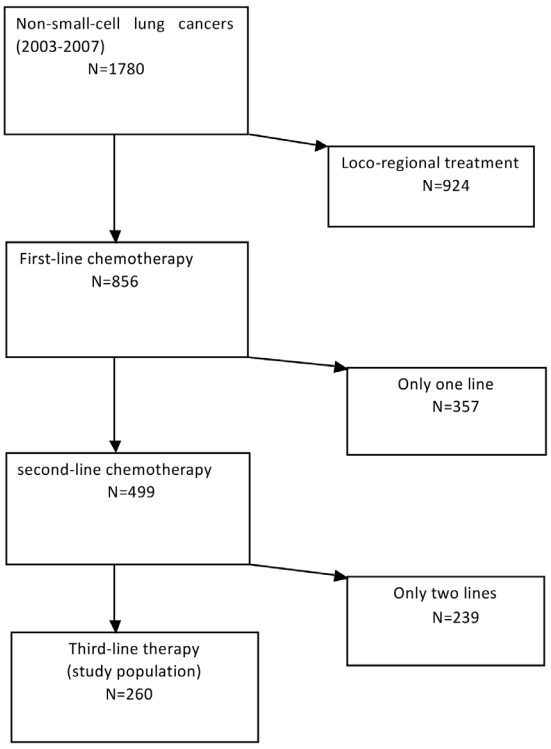

Figure 1. Flow chart illustrating the study population.

Table 1. Clinical characteristics of 233 stage IIIb/IV non small cell lung cancer patients receiving third-line therapy

Characteristics	*N(%)*	*A* *N(%)*	*B* *N(%)*	*C* *N(%)*	*D* *N(%)*	*p-value*
Total	233	61	58	89	25	
Gender						0.706
Male	131 (56.2)	34 (55.7)	32 (54.5)	51 (57.3)	14 (56.0)	
Female	102 (43.8)	27 (44.3)	26 (45.5)	38 (42.7)	11 (44.0)	
ECOG-PS						0.382
0-1	164 (70.4)	47 (76.5)	36 (62.5)	62 (69.7)	19 (76.0)	
≥2	69 (29.6)	14 (23.5)	22 (37.5)	27 (30.3)	6 (24.0)	
Age, years						0.509
≥65	58 (24.8)	20 (32.4)	18 (31.0)	15 (17.3)	5 (20.0)	
<65	175 (75.2)	41 (67.6)	40 (69.0)	74 (82.7)	20 (80.0)	
Smoking status						0.127
Smokers	72 (30.9)	12 (20.5)	19 (32.8)	32 (36.0)	9 (36.0)	
Nonsmokers	161 (69.1)	49 (79.5)	39 (67.2)	57 (64.0)	16 (64.0)	
Histology						0.205
Adenocarcinoma	182 (78.1)	52 (85.2)	51 (87.9)	66 (74.2)	13 (40.6)	
Non-adenocarcinoma	51 (21.9)	9 (14.8)	7 (12.1)	23 (25.8)	12 (59.4)	
Stage						0.708
IV	183 (78.5)	45 (73.8)	47 (81.0)	69 (77.5)	22 (88.0)	
IIIb	50 (21.5)	16 (26.2)	11 (19.0)	20 (22.5)	2 (12.0)	

A: EGFR-TKIs, B: single agent chemotherapy, C: doublet chemotherapy, D: chemo-targeted therapy, PS: performance status

incomplete medical records were excluded, leaving a total of 233 patients for study. Of 233 patients, 15 (13 cases with squamous cell carcinoma and 2 cases with adenocarcinoma) were without EGFR mutation detection. The total EGFR mutation rate was 48.2% (105 cases), and 56.1% (101 cases) in adenocarcinoma.

The patients (N=233) were divided into 4 groups according to the different treatments: 1) The EGFR-TKIs group with 61 patients (26.2%); 2) The single-agent chemotherapy group with 58 patients (24.9%); 3) The two-drug combination chemotherapy group with 89 patients (38.2%); and 4) The chemo-targeted group with 25 patients (10.7%). Patients in the EGFR-TKIs group received erlotinib (N=16) and gefitinib (N=45). Those in the single-agent chemotherapy group received docetaxel (N=31), pemetrexed (N=23), gemcitabine (N=2) and vinorelbine (N=2). In the doublet chemotherapy group 45 patients were administered cisplatin or carboplatin combined with pemetrexed, cisplatin combined with docetaxel (N=31), and 13 patients other non-platinum combinations. In the chemo-targeted group 10 patients were administered double-agent (platinum-based doublet 4 patients, non-platinum-based doublet 6 patients) combined with targeted drug, and 15 single agent (pemetrexed or docetaxel) combined with targeted drug. Targeted drugs included gefitinib, erlotinib, bevacizumab, cetuximab and endostar. The patient clinical features of the 4 groups had no significant differences. Specific clinical characteristics are shown in Table 1. The characteristics of patients that received first-, second- and third-line treatments are listed in Table 2.

All patients were evaluable for treatment efficacy. No CR was noted in the 4 groups. PR was registered in 13.1, 3.4, 9, and 8% in the EGFR-TKIs, single-agent chemotherapy, 2-drug combination and chemo-targeted patients, respectively. DCR was 60.7% (N=37), 41.4% (N=24), 48.3% (N=43) and 52.0% (N=13), respectively, showing no significant differences among groups (p>0.05). The median PFS was 3.83, 2.72, 2.86 and 3.29 months, respectively (p = 0.073, Figure 2), and the median OS was 11.16, 8.24, 8.49 and 9.33 months, respectively (p=0.020, Figure 3). Comparison of OS between the EGFR-TKIs group with the chemo-targeted group (11.16 vs 9.33 months) showed no statistically significant difference (p = 0.105, Figure 4).

Toxicity assessment showed the following: 13 patients (5.6%) refused further therapy due to severe toxicities (3 infection, 4 anemia, 6 leucopenia) and 10 switched from doublet chemotherapy group to single chemotherapy group due to intolerable toxicity (anemia, leucopenia). The overall rate of grade III/IV toxicities was 37.8%. More specifically, it was 16.4, 27.6, 57.3 and 44% in the EGFR-TKIs, single-agent chemotherapy, double-agent chemotherapy and chemo-targeted groups, respectively. The difference between the 4 groups was statistically significant (p <0.001) (Table 3).

At the time of data analysis, only 11 patients were still alive; among them 6 had adenocarci-

Table 2. Characteristics of first-, second- and third-line treatment

Characteristics	*Third-line treatment*		*First-line treatment*		*Second-line treatment*	
	N	%	*N*	%	*N*	%
Total	233	100.0	233	100.0	233	100.0
Patient characteristics on day 1						
ECOG PS						
0-1	164	70.4	175	75.1	170	73.0
≥2	69	29.6	58	24.9	63	27.0
Weight loss since previous line						
No	161	69.2	189	81.1	186	79.8
Yes	72	30.8	44	18.9	47	20.2
Treatment regimen						
Triplet*	0	0	16	6.9	4	1.7
Doublet	89	38.2	168	72.1	96	41.2
Platinum based	76	32.6	164	70.4	88	37.8
Nonplatinum based	13	5.6	4	1.7	8	3.4
Single-agent	58	24.9	4	1.7	45	19.3
Docetaxel	31	13.3	0	0	25	10.7
Pemetrexed	23	9.8	0	0	18	7.7
Gemcitabine	2	0.9	2	0.9	2	0.9
Vinorelbine	2	0.9	2	0.9	0	0
EGFR-TKIs	61	26.2	40	17.2	60	25.8
Chemotherapy plus targeted therapy**	25	10.7	5	2.1	28	12.0
Number of cycles						
1–2	63	27.0	12	5.2	72	30.9
3–4	85	36.5	121	51.9	81	34.7
5–6	20	8.6	52	22.3	20	8.6
>6	4	1.7	8	3.4	0	0
N/A	61	26.2	40	17.2	60	25.8
Acute grade III–IV toxicities						
Hematological	54	23.2	47	20.2	53	22.7
Nausea/vomiting	15	6.4	18	7.7	11	4.7
Hepatic and renal	3	1.3	5	2.1	2	0.9
Rash	6	2.6	10	4.3	11	4.7
Diarrhea	8	3.4	7	3.0	5	2.1
Fever with neutropenia	2	0.9	6	2.6	4	1.7
Tumor control						
Complete response	0	0	8	3.4	0	0
Partial response	20	8.6	100	42.9	32	13.7
Stabilization	97	41.6	92	39.5	84	36.0
Progression	102	43.8	25	10.8	105	45.1
Not reported	14	6.0	8	3.4	12	5.2
RR	20	8.6	108	46.4	32	13.7
DCR	117	50.2	200	85.8	116	49.8
m-OS(months)	9.22		18.53		12.91	

N/A: not applicable; *cisplatin, ifosfamide, vinorelbine or paclitaxel, cisplatin, nimustine or docetaxel, cisplatin, carmustine or docetaxel, oxaliplatin, carmustine or mitomycin, cisplatin, vindesine or adriamycin, cisplatin, vindesine; **gefitinib, erlotinib, bevacizumab, cetuximab, endostar; RR: response rate, DCR: disease control rate, m-OS: median overall survival

Table 3. Toxicity in 233 stage IIIb/IV non small cell lung cancer patients receiving third-line therapy

Toxicity	*A (N=61)*		*B (N=58)*		*C (N=89)*		*D (N=25)*		*p-value*
Grade	*III*	*IV*	*III*	*IV*	*III*	*IV*	*III*	*IV*	
Hematologic	0	0	9	1	23	14	5	2	<0.001
Nausea/vomiting	2	0	4	0	7	0	2	0	0.655
Diarrhea	3	0	1	0	3	0	1	0	0.327
Hepatic and renal	0	0	1	0	2	0	0	0	0.428
Rash	4	1	0	0	0	0	1	0	0.213
Neutropenic fever	0	0	0	0	0	0	0	0	0.182

A: EGFR-TKIs, B: single agent chemotherapy, C: doublet chemotherapy, D: chemo-targeted therapy

Table 4. Prognostic factors regarding overall survival from the initiation of third-line treatment

Prognostic factors	*Univariate analysis*		*Multivariate analysis*		
	Median overall survival (mo)	*p-value*	*Hazard ratio*	*95% CI*	*p-value*
Gender					
Female	12.12	0.233	0.83	0.59-1.42	0.728
Male	6.96		1		
Tumor stage (before first-line)					
IV	8.96	0.325	1.04	0.32-3.40	0.955
IIIB	10.18		1		
Histology					
Non-adenocarcinoma	5.83	0.238	0.44	0.21-0.94	0.034
Adenocarcinoma*	10.17		1		
Smoking history					
Nonsmokers	9.93	<0.001	1.72	1.03-2.88	0.040
Smokers	7.63		1		
Surgical history**					
Yes	10.34	0.085	2.32	0.98-5.51	0.056
No	8.44		1		
Characteristics at initiation of third-line treatment					
Age (years)					
<65	9.71	0.459	1.32	0.42-4.18	0.636
≥65	7.74		1		
ECOG PS					
0-1	10.56	<0.001	3.88	1.34-11.24	0.012
≥2	6.04		1		
Response to previous treatments (first- and/or second-line)					
Disease control	12.50	<0.001	2.72	1.63-3.68	0.031
Progression	7.30		1		
Third-line treatment					
Chemo-targeted	9.33	0.020	0.81	0.57-1.14	0.522
EGFR-TKIs	11.16		1		
Doublet	8.49				
Single-agent	8.24				

*including bronchoalveolar carcinoma, **Surgical removal of the primary tumor or not, mo: months

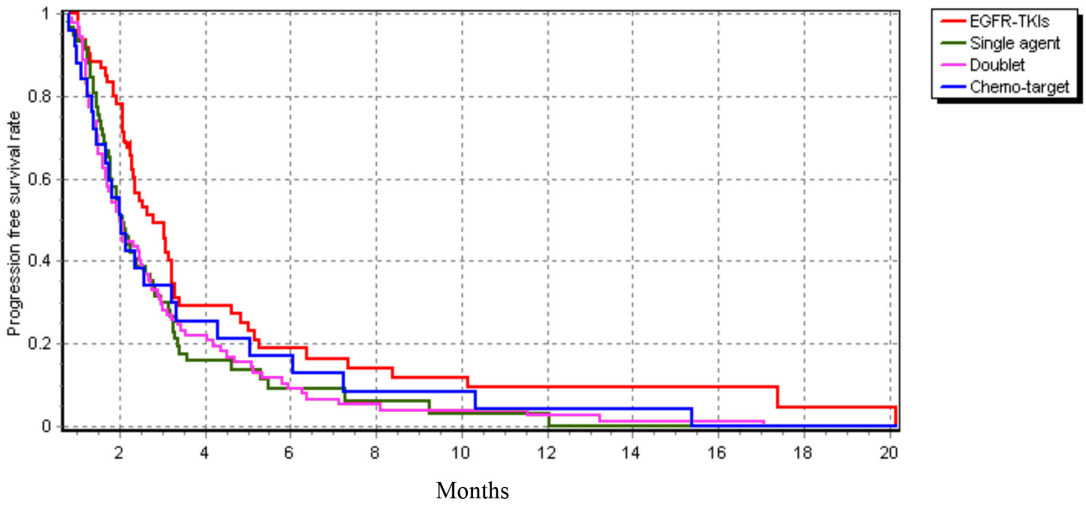

Figure 2. Comparison of progression free survival rate of different treatment options in third-line treatment (3.83 vs 2.72 vs 2.86 vs 3.29, p = 0.073).

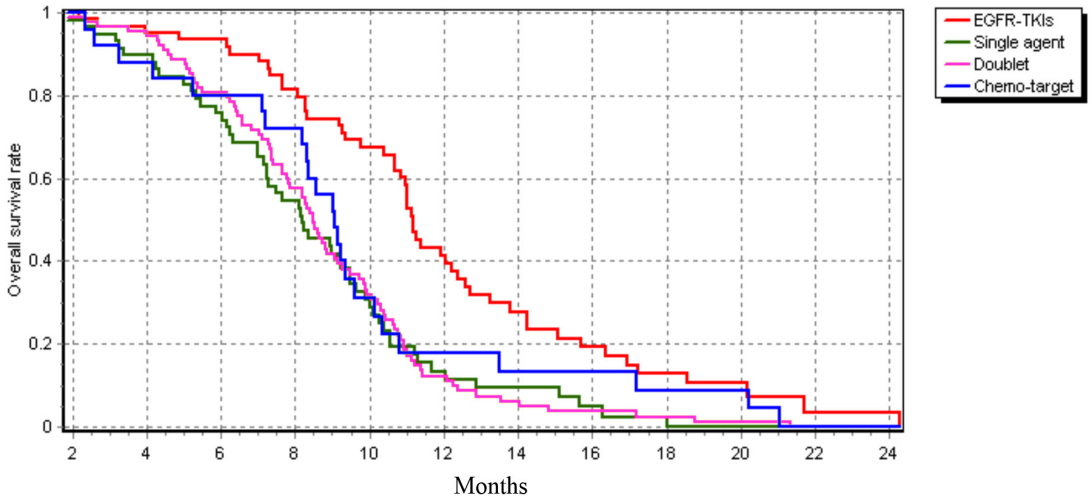

Figure 3. Comparison of overall survival rate of different treatment options in third-line treatment (11.16 vs 8.24 vs 8.49 vs 9.33, p=0.020).

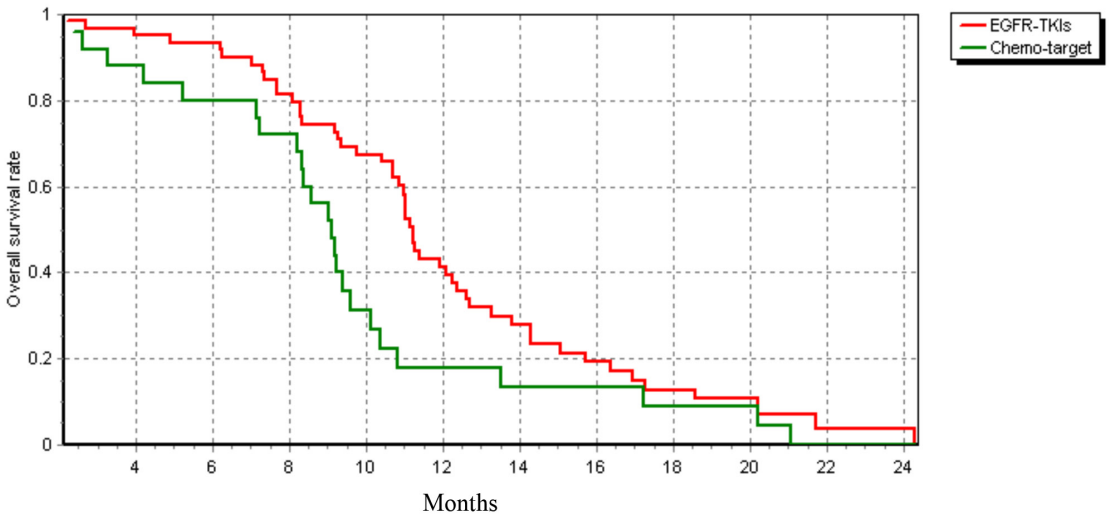

Figure 4. Comparison of overall survival rate of EGFR-TKIs with chemo-targeted group in third-line treatment (11.16 vs 9.33, p=0.105).

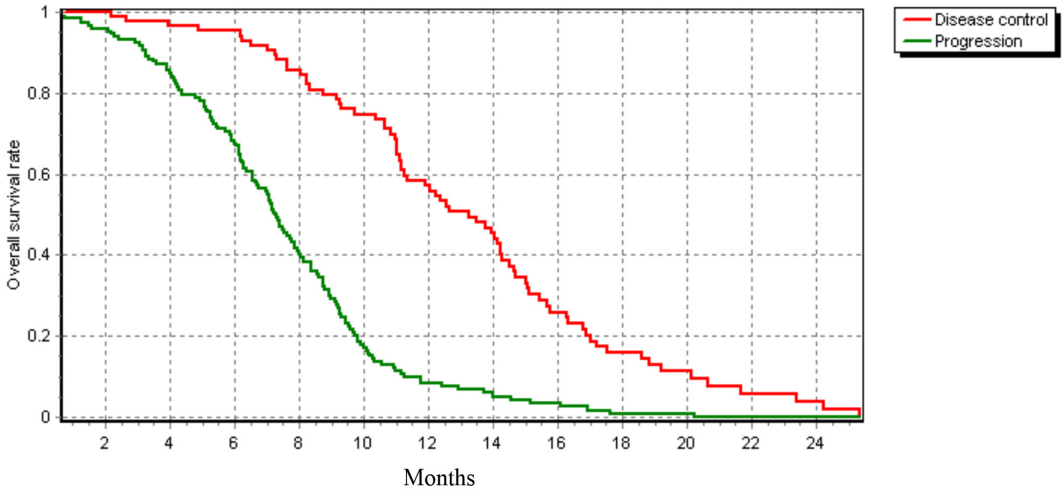

Figure 5. Comparison of overall survival rate in first and/or second-line treatment (12.5 vs 7.3, p<0.001).

noma and 5 had squamous cell carcinoma. The median OS after first-line treatment was 18.53 months. The median survival time after third-line treatment was 9.22 months.

Results from univariate and multivariate analyses are presented in Table 4. With univariate analysis, all of the following factors were found to be predictors of prolonged median OS survival after the initiation of third-line treatment: smoking history (p<0.001), ECOG PS (p<0.001) and response to previous treatments (p<0.001). With multivariate analysis, all of the following factors were found to be predictors of prolonged median OS after the initiation of third-line treatment: histology (p=0.034), smoking history (p=0.040), ECOG PS (p=0.012) and response to previous treatments (p=0.031) (Table 4).

Discussion

New chemotherapeutic and targeted agents, with good efficacy and low toxicity have been successfully developed for first and second-line treatments. However, the implementation of third- and higher line treatments for advanced NSCLC has been considerably slower. In the NCCN Guidelines published in 2012, only erlotinib is currently recommended for third-line treatment of advanced NSCLC. Until now, there have been no relevant studies regarding the application of new third- and higher lines of chemotherapy and targeted therapy for advanced NSCLC.

In the present study, 233 patients treated with third- or higher lines of therapy were enrolled. Analysis indicated that histology, smoking history, PS before third-line therapy, and response to previous treatments were independent prognostic factors for survival; patients with non-adenocarcinoma NSCLC, who had a PS of 2, a history of smoking and had progressed after first- and second-line therapy had a poor prognosis. Kaira et al. retrospectively analysed 124 patients with advanced NSCLC; 10 of these patients survived >5 years. These authors reported that a good PS score and the presence of adenocarcinoma played an important role in the longer survival of these 10 patients [11]. A retrospective study by Girard et al. found that a good PS score (p=0.008) and disease control in patients that had received first and second line therapy (p=0.001) were an independent prognostic factor in identifying candidates for third-line therapy [9]. In another retrospective study, Scartozzi et al. reported that the key predictive factor for OS in patients after third-line therapy was the efficacy of their second-line treatment (p=0.03) [12]. Kawaguchi et al. carried out a retrospective analysis on 26,957 patients with NSCLC; the data were more convincing because the sample size was large. They found that PS score and smoking status were independent prognostic factors for OS [13]. These findings were similar to those of the present study. Fifty-one (21.9%) patients in our study had non-adenocarcinoma NSCLC and 164 patients (70.4%) had a PS score of 0-1, which might also have affected the prognosis of the study population. The median survival time of patients with disease control who received first and second-line treatment was 12.5 months, while for patients with progression who received first and second-line treatment it was 7.3 months; the difference in OS between these two groups of patients after third-line therapy was significant (p <0.001; Figure 5). Similarly, in the current study, the prognosis was better for non-smokers than smokers (9.93 vs 7.63 months p <0.001).

The clinical principle of second-line and higher lines of therapy for NSCLC mainly involves the use of monotherapy. This is because monotherapy has a relatively low toxicity and multiagent therapy may be poorly tolerated by the patients. In a prospective randomized comparative study, Chen et al. found that two-agent chemotherapy may well be a viable option in patients who failed previous chemotherapy, especially if the PS score was 0-1 [14]. Some research has also been carried out regarding chemotherapy administered in combination with targeted therapy. Tham et al. retrospectively analysed 80 patients with advanced NSCLC; 51 patients were given gemcitabine, carboplatin and gefitinib, and 29 were treated with gemcitabine and carboplatin alone. In patients with advanced NSCLC and no previous history of smoking that underwent first-line chemotherapy, it was found that the addition of gefitinib to the chemotherapy regimen improved DFS and OS as compared with chemotherapy alone [15]. Sandler et al. selected 878 patients with advanced NSCLC; 444 of them received paclitaxel plus carboplatin chemotherapy, and the remaining 434 received paclitaxel, carboplatin and bevacizumab. It was reported that in a selected population (patients without squamous cell carcinoma) the use of paclitaxel, carboplatin and bevacizumab significantly improved OS relative to treatment with chemotherapy alone [16]. In the present study, PFS and OS were slightly higher in the double-agent chemotherapy group relative to the single-agent chemotherapy group, but significantly lower than in the EGFR-TKIs and chemo-targeted groups; there was also a significant increase in toxicity in the double-agent chemotherapy group relative to the other groups. Univariate analysis was carried out regarding the median OS for the 4 treatment groups. OS was significantly higher (p=0.020)

in the EGFR-TKIs and chemo-targeted groups than in the single- and double-agent chemotherapy groups. A single factor compararive analysis was conducted regarding the EGFR-TKIs and the chemo-targeted groups, and no significant difference in the OS was found between the groups (p=0.105). The overall incidence of grade III-IV toxicity in the 233 patients treated with third or higher lines of therapy was 37.8% ; in the single-agent chemotherapy group it was 27.6% (16/58), in the double-agent chemotherapy group it was 57.3% (51/89), in the EGFR-TKIs group it was 16.4% (10/61), and in the chemo-targeted group it was 44.0% (11/25). Based on the comparison of the efficacy and toxicity results for the 4 groups it was concluded that chemotherapy and targeted therapy can be used as an alternative treatment option; indeed targeted therapy should be evaluated as a priority for use in third-line therapy.

Finally, our study had the following limitations: first, its design was retrospective; second, it was a single institution and not a multicenter study; third, the sample size was so small that the results may be circumscribed; and fourth, because the study era extended back to 2003, documentation for some cases was incomplete. Accepting that our study had these limitations its findings may still be of help to clinicians in making treatment decisions when dealing with patients with advanced NSCLC and presenting with tumor progression after second-line therapy.

Conclusion

Therapy for advanced NSCLC may be of help to some patient groups. Patients with advanced NSCLC who never smoked, had adenocarcinoma, had good PS scores, and good disease control from the first- and second-line therapies could benefit with third-line treatment. EGFR-TKIs and chemo-targeted therapy showed increased OS compared with single and doublet chemotherapy. Future prospective trials to evaluate third-line treatment strategies for advanced NSCLC are necessary.

Acknowledgments

This study was supported by the Eleventh Five-Military Project Funds, Medical Research Projects (06G106).

Authors' contributions

All authors have contributed substantially to the study. ZZG was responsible for the design of the study, collecting the clinical data, statistical analyses, writing the manuscript and the revision of the manuscript. SCJ contributed to the conception and design of the study, to the critical revision of the manuscript, and to financial support prior to publication. SCL, YL, ZFL, GQZ, LJW were the treating physicians involved with the patients. FQ contributed to statistical analyses.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics 2009. CA Cancer J Clin 2009;59:225–249.
2. Petrelli NJ, Winer EP, Brahmer J et al. Clinical cancer advances 2009:major research advances in cancer treatment, prevention, and screening- reports from the American Society of Clinical Oncology. J Clin Oncol 2009;27:6052–6069.
3. Guan-Zhong Zhang, Shun-Chang Jiao, Zhao-Ting Meng. Pemetrexed plus cisplatin/carboplatin in previously treated locally advanced or metastatic non-small cell lung cancer patients. J Exp Clin Cancer Res 2010;29:38.
4. Thatcher N, Chang A, Parikh P et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer:results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;366(9496):1527-1537.
5. Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-132.
6. Syrigos KN, Saif MW, Karapanagiotou EM, Oikonomopoulos G, De Marinis F. The need for third-line treatment in non-small cell lung cancer:an overview of new options. Anticancer Res 2011;31:649-659.
7. Sun JM, Lee KW, Kim JH et al. Efficacy and toxicity of pemetrexed as a third-line treatment for non-small cell lung cancer. Jpn J Clin Oncol 2009;39:27-32.
8. Girard N, Jacoulet P, Gainet M et al. Third-line chemotherapy in advanced non-small cell lung cancer:identifying the candidates for routine practice. J Thorac Oncol 2009;4:1544–1549.
9. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–216.
10. Trotti A, Colevas AD, Setser A et al. CTCAE v3.0:development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176-181.
11. Kaira K, Takahashi T, Murakami H et al. Long-term

survivors of more than 5 years in advanced non-small cell lung cancer. Lung Cancer 2010 ;67:120-123.

12. Scartozzi M, Mazzanti P, Giampieri R et al . Clinical predictive factors for advanced non-small cell lung cancer (NSCLC) patients receiving third-line therapy:Selecting the unselectable? Lung Cancer 2010;68:433-437.
13. Kawaguchi T, Takada M, Kubo A et al. Performance Status and Smoking Status Are Independent Favorable Prognostic Factors for Survival in Non-small Cell Lung Cancer. A Comprehensive Analysis of 26,957 Patients with NSCLC. J Thorac Oncol 2010;5:620–630.
14. Chen YM, Perng RP, Shih JF, Tsai CM, Whang-Peng J. Salvage therapy for Chinese non-small cell lung cancer patients who failed previous chemotherapy. J Thorac Oncol 2006;1:545-550.
15. Tham CK, Choo SP, Lim WT et al. Gefitinib in Combination with Gemcitabine and Carboplatin in Never Smokers with Non-small Cell Lung Carcinoma. J Thorac Oncol 2009;4:988–993.
16. Sandler A, Gray R, Perry MC et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell-lung cancer. N Engl J Med 2006;355:2542-2550.