Treatment Outcome of Elderly Patients with Advanced Non-Small Cell Lung Cancer Treated with Supportive Care and Supportive Care plus Chemotherapy or Targeted Therapy

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Abstract

Objective: To determine whether supportive care plus chemotherapy or targeted therapy improved survival benefit, compared with supportive care alone, in the elderly patients with advanced non-small cell lung cancer.

Methods: The authors conducted a retrospective cohort study of the elderly patients (age 65 years or older) with advanced non-small cell lung cancer who had visited the oncology clinic at Vajira hospital between 2010 and 2012. Progression free survival (PFS) and overall survival (OS) were compared between groups by using the log-rank test. Demographic and clinical treatment variables were examined for association with survival outcome using Cox proportional hazards regression models.

Results: Three hundred and thirty-one patients were included. Two hundred eight patients (63%) received supportive care plus chemotherapy or targeted therapy and 123 patients (37%) received supportive care alone. Median PFS times were 6.63 months among patients receiving chemotherapy or targeted therapy versus 3.93 months among those receiving supportive care alone ($p = 0.013$). Median OS times were 9.97 months versus 4.43 months, respectively ($p < 0.001$). With univariate analyses, the Eastern Cooperative Oncology Group performance status and brain metastasis were significantlyassociated with survival outcome.

Conclusion: Our results found the statistically significant improved PFS and OS in patients who were treated with supportive care plus chemotherapy or targeted therapy compared with supportive care alone.

Keywords: Treatment, elderly patient, lung cancer

ผลการรักษามะเร็งปอดชนิดเซลล์ไม่เล็กระยะลุกลามในผู้สูงอายุที่ได้รับการรักษาตามอาการและการรักษาตามอาการร่วมกับยาเคมีบำบัดหรือยาออกฤทธิ์พุ่งเป้า

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาผลการรักษาตามอาการร่วมกับยาเคมีบำบัดหรือยาออกฤทธิ์พุ่งเป้าเทียบกับการรักษาตามอาการเพียงอย่างเดียว ในกลุ่มผู้ป่วยสูงอายุที่ได้รับการวินิจฉัยเป็นมะเร็งปอดชนิดเซลล์ไม่เล็กระยะลุกลาม

วิธีดำเนินการวิจัย: ทำการเก็บข้อมูลย้อนหลังของกลุ่มศึกษาคือ ผู้ป่วยที่อายุมากกว่าหรือเท่ากับ 65 ปี ที่ได้รับการวินิจฉัยเป็นมะเร็งปอดชนิดเซลล์ไม่เล็กระยะลุกลามและเข้ารับการตรวจรักษาที่ห้องตรวจเคมีบำบัด โรงพยาบาลวชิรพยาบาลในช่วงระหว่างปี พ.ศ. 2553 ถึง พ.ศ. 2555 โดยศึกษาเปรียบเทียบค่าระยะปลอดโรคกำเริบและค่าการรอดชีวิตระหว่างกลุ่มผู้ป่วยที่รักษาตามอาการร่วมกับยาเคมีบำบัดหรือยาออกฤทธิ์พุ่งเป้าเทียบกับกลุ่มที่รักษาตามอาการเพียงอย่างเดียวและวิเคราะห์ปัจจัยที่มีความสัมพันธ์ต่ออัตราการรอดชีวิต

ผลการวิจัย: ผู้ป่วยทั้งหมด 331 รายได้รับการรักษาตามอาการร่วมกับยาเคมีบำบัดหรือยาออกฤทธิ์พุ่งเป้า 208 ราย (ร้อยละ 63) ได้รับการรักษาตามอาการเพียงอย่างเดียว 123 ราย (ร้อยละ 37) ค่ามัธยฐานระยะปลอดโรคกำเริบของกลุ่มที่ได้รับยาเคมีบำบัดหรือยาออกฤทธิ์พุ่งเป้าร่วมด้วย คือ 6.63 เดือน สูงกว่ากลุ่มที่ไม่ได้รับ คือ 3.93 เดือน ($p = 0.013$) ค่ามัธยฐานระยะการรอดชีวิตของกลุ่มที่ได้รับยาเคมีบำบัดหรือยาออกฤทธิ์พุ่งเป้าร่วมด้วยคือ 9.97 เดือน สูงกว่ากลุ่มที่รักษาตามอาการเพียงอย่างเดียวที่มีค่ามัธยฐานการรอดชีวิตคือ 4.43 เดือน ($p < 0.001$) ปัจจัยด้านสภาพร่างกายตามเกณฑ์ประเมินของEastern Cooperative Oncology Group และการแพร่กระจายของมะเร็งไปที่สมอง เป็นปัจจัยที่สัมพันธ์ต่ออัตราการรอดชีวิตอย่างมีนัยทางสถิติ

สรุป: ในกลุ่มผู้ป่วยสูงอายุที่ได้รับการวินิจฉัยเป็นมะเร็งปอดชนิดเซลล์ไม่เล็กระยะลุกลาม การรักษาตามอาการร่วมกับยาเคมีบำบัดหรือยาออกฤทธิ์พุ่งเป้า มีค่าระยะการปลอดโรคและค่าการรอดชีวิตที่ยาวนานกว่าเมื่อเทียบกับการรักษาตามอาการเพียงอย่างเดียว

Introduction

Lung cancer remains a major cause of death related to cancer around the world.[1] In Thailand it is the second commonest cancer among men and the third commonest cancer among women, with approximately 15,000 new cases diagnosed per year.[2]

For patients with advanced stage non-small cell lung cancer (NSCLC), supportive treatment plus palliative chemotherapy or targeted therapy improve survival outcome and quality of life in previous studies.[3-5] However, many side effects have also occurred during systemic therapy. According to national comprehensive network guideline of non-small cell lung cancer version 2.2013[6], the treatment options for patients with advanced stage depend on many factors, e.g., numbers and sites of metastatic lesion, status of epidermal growth factor receptor (EGFR) mutation, patient's age and performance status. Older patients that have physiologic changes associated with agingmay decrease tolerability to systemic treatment.

In the past, there were few studies in elderly patients with advanced lung cancer and rare randomized controlled phase III studies. Gridelli, et al. had established a phase III trial and reported that patients who were treated with vinorelbine plus supportive care had a significantly longer median duration of survival than patients receiving supportive care alone.[7] However, the targeted therapy such as EGFR tyrosine kinase inhibitor (EGFR TKI), had no phase III study in elderly patients with lung cancer.Subgroup analysis of the BR.21 trial revealed that older patients experienced greater toxicity whereas survival and quality of life benefits were similar for both erlotinib and placebo group.[8]

Although the standard treatment of elderly patients with advanced non-small cell lung cancer was supportive care, the addition of systemic treatments,e.g., chemotherapy or targeted therapy still had a few studies. So this study was conducted to determine whether supportive care plus chemotherapy or targeted therapy improved survival benefit, compared with supportive care alone, in Thai elderly patients with advanced NSCLC.

Patients and methods

The study had been approved by the institutional review board of Faculty of Medicine Vajira hospital. The hospital medical databasewas search to identify patients with the diagnosis of advanced stage lung cancer between 2010 and 2012. Eligible patients included patients age65 years or older, receiving treatment at the oncology clinic and had histologically proven non-small cell carcinoma. Patients with a history of other malignancies were excluded.

Data collection

Data of performance status according to the Eastern Cooperative Oncology Group (ECOG), underlying diseases, histological subtype, metastatic sites, treatments, side effects, disease progression and death were collected from medical record.Modalities of treatments were categorized into two groups: (1) supportive care alone and (2) supportive care plus chemotherapy or targeted therapy. Determination of progressive disease status was established using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.The adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

The primary trial end point was progression free survival (PFS). PFS was defined as the time from start of treatment to disease progression or death from any cause. Secondary end point wasoverall survival (OS), defined as time from start of treatment to death from any cause. Patients with no event at the time of analysis were censored at the date of the last follow-up. To detect a hazard ratio of 0.3 for PFS in the supportive care plus chemotherapy or targeted therapy arm relative to the supportive care alone

arm, approximately 331 patients were required.[9]

The chi-squared test was used to determine significant differences in patient characteristics. PFS and OS curves were calculated using the Kaplan-Meier method. The log-rank test was used to compare PFS and OS between groups. Demographic and clinical treatment variables were examined for association with survival outcome using univariateand multivariate Cox proportional hazards regression models. The analysis was performed using the statistical software SPSS for Windows version 13. The p-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

From January 2010 through December 2012, 331 patients were enrolled. Two hundred eight patients (63%) received supportive care plus chemotherapy or targeted therapy and 123 patients (37%) received supportive care alone. Patient demographics and clinical characteristics were shown in Table 1. As expected, the supportive care plus chemotherapy or targeted therapy arm had more patients with ECOG performance status (PS) 0-2. The percentage of patients with ECOG PS 0, 1 and 2 were 9.1% vs 1.6%, 41.4% vs 4.1% and 21.6% vs 13%, respectively (p<0.001).While we found a higher percentage of patients with brain metastasis in the supportive care alone arm (17.9% vs 7.2%;p=0.016), there was no statistically significant difference in other metastatic sites, e.g., lung, liver, bone, pleura, adrenal gland and non-regional lymph nodes.We also found significantly higher percentage of patients with hypertension and heart disease in the supportive care alone arm (39% vs 26.9%; p = 0.022 and 16.3% vs 5.7%; p = 0.002, respectively). Regarding to the histological subtype of NSCLC, nearly half of patients in the supportive care alone arm (44.7%) and about one-third of patients in the other arm (35.1%) had unknown subtype.

Table 1:

Patient demographics and clinical characteristics

Characteristics	Supportive care alone (n=123)	Supportive care plus CMT or targeted therapy (n=208)	p-value
Gender			
Male	52 (42.2)	119 (57.2)	
Female	71 (57.8)	89 (42.8)	0.009*
ECOG PS			
0	2 (1.6)	19 (9.1)	
1	5 (4.1)	86 (41.4)	
2	16 (13)	45 (21.6)	
3	37 (30.1)	8 (3.8)	
4	3 (2.4)	0 (0)	
NA	60 (48.8)	50 (24.1)	<0.001*

Table 1:

Patient demographics and clinical characteristics

Characteristics	Supportive care alone (n=123)	Supportive care plus CMT or targeted therapy (n=208)	p-value
Underlying disease			
Diabetic mellitus	14 (11.4)	38 (18.2)	0.214
Hypertension	48 (39)	56 (26.9)	0.022*
Chronic kidney disease	4 (3.3)	6 (2.9)	0.85
Dyslipidemia	7 (5.7)	14 (6.7)	0.708
Heart disease	20 (16.3)	12 (5.7)	0.002*
Stroke	5 (4.1)	5 (2.4)	0.394
COPD	12 (9.8)	14 (6.7)	0.323
Histological subtype			
Squamous	19 (15.5)	17 (8.2)	
Adenocarcinoma	48 (39)	117 (56.2)	
Large	1 (0.8)	1 (0.5)	
Unknown	55(44.7)	73 (35.1)	0.016*
Numbers of metastatic site			
1	74 (60.2)	121 (58.2)	
2	35 (28.4)	76 (36.5)	
3	12 (9.8)	9 (4.3)	
>3	2 (1.6)	2 (1)	0.143
Sites of metastasis			
Lung	68 (55.3)	106 (51)	0.447
Liver	13 (10.6)	18 (8.7)	0.563
Bone	37 (30.1)	66 (31.7)	0.733
Brain	22 (17.9)	15 (7.2)	0.003*
Pleura/pleural effusion	43 (35)	86 (41.3)	0.25
Adrenal gland	1 (0.8)	5 (2.4)	0.294
Non-regional lymph nodes	5 (4.1)	12 (5.7)	0.497

Abbreviations: CMT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not available; COPD, chronic obstructivepulmonary disease. * Statistical significant value

Treatment administration

The regimens of chemotherapy and targeted therapy were shown in Table 2. Of 208 patients in supportive care plus systemic treatment group, the majority (81.7%) received the platinum-doublet chemotherapy regimen. Most common regimens were carboplatin plus gemcitabine (31.3%) and carboplatin plus paclitaxel (29.3%).Thirty patients (14.4%) received single agent chemotherapy, e.g., gemcitabine (9.6%), vinorelbine (3.8%) and docetaxel (1%). Only 9 (4.3%) received targeted therapy e.g. erlotinib and gefitinib. No patient received the combination of chemotherapy and targeted therapy.

Efficacy

At data cutoff (January 2014), all patients had progressive disease. Among patients who receiving supportive care plus chemotherapy or targeted therapy, median PFS time was 6.63 months versus 3.93 months for those receiving supportive care alone (p = 0.013; Figure 1). At the time of this analysis, 90% in the supportive care plus chemotherapy or targeted therapy arm and 96% in the supportive care alone arm had died, median OS times were 9.97 months versus 4.43 months, respectively (p <0.001; Figure 2). The1-year OS werealso significantly higher in patients receiving supportive care plus chemotherapy or targeted therapy than in those receiving supportive care alone, 32.7% versus 17.9%, respectively.

Prognostic factors

On the basis of a Cox regression analysis, sex, any underlying diseases, and numbers of metastatic site were not statistically significant factors associated with outcome. However, with univariate analyses, we found the ECOG PS and brain metastasis as the factors associated with survival outcome. The relative risks for death were

Table 2:

The regimens of chemotherapy and targeted therapy administered.

Regimens	No. of patients (n=208)	%
Doublet agent chemotherapy		
Carboplatin plus gemcitabine	65	31.3
Carboplatin plus paclitaxel	61	29.3
Carboplatin plus docetaxel	5	2.4
Carboplatin plus pemetrexed	14	6.7
Carboplatin/cisplatin plus etoposide	24	11.5
Single agent chemotherapy		
Gemcitabine	20	9.6
Vinorelbine	8	3.8
Docetaxel	2	1
Targeted therapy		
Erlotinib	8	3.8
Gefitinib	1	0.5

12.7 times (90%CI, 4.4 to 36.6 times) higher for patients with ECOG PS 4 than those with ECOG PS 0 and 3.1 times (90%CI, 1.9 to 5 times) higher for patients with ECOG PS 3 than those with ECOG PS 0. The relative risk of death was 1.8 times (90% CI, 1.3 to 2.4 times) higher for patients with brain metastasis than for those with no brain metastasis.

Safety

The common hematologic adverse events (AEs) typically associated with doublet-agent chemotherapy, including anemia, thrombocytopenia, neutropenia and febrile neutropenia, were grade 1 and 2 events.There were no grade 4 events except for one grade 4 case of thrombocytopenia in patient receiving the combination of carboplatin and etoposide.Other common AEs, such as nausea, vomiting, rash, pruritus, were also reported in the doublet-agent chemotherapy groupmore than another groups. Peripheral sensory neuropathywere associated with paclitaxel. Almost of non-hematologic AEs were grade 1 and 2. Only one patient who was receiving the combination of carboplatin and paclitaxel developed grade 3.No deaths resulting from anyAEs were reported.

Discussion

Among patients with NSCLC, the elderly hasbeen reported in an increasing frequency. The aim of treatment in advanced stage are not only to prolonged survival but importantly to maintain the quality of life. A review of the SEER Medicare data

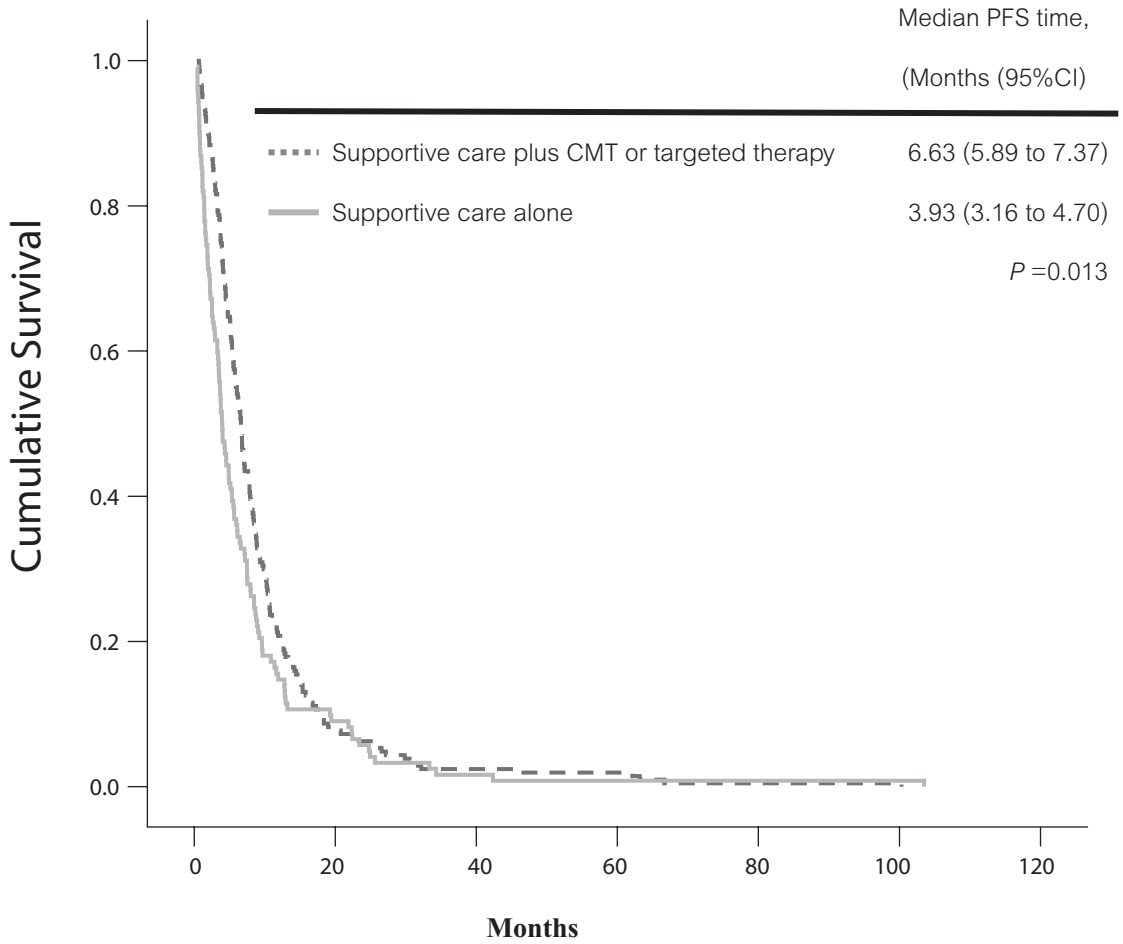

Figure 1: Kaplan-Meier estimates of progression free survival (PFS) among patients receiving supportive care plus chemotherapy (CMT) or targeted therapy and supportive care alone.

from 1994to 1999 found that a much lower rate of chemotherapy use in the elderly than expected in the overall population.[10] The comorbidities and tolerability of treatments are obstacles to decide the systemic treatment in the elderly. Therefore, we have established this retrospective study to evaluate the efficacy and safety of supportive care plus chemotherapy or targeted therapy compared with supportive care alone in the elderly patients with advanced NSCLC.

As expected, our results found the statistically significant improved survival and acceptable toxicities in patients who were treated with chemotherapy or targeted therapy. This finding is in support to result from the ELVIS study (Elderly Lung Cancer Vinorelbine Italian Study), which previously reported that vinorelbine plus best supportive care (BSC) was superior to BSC alone in elderly patients with ECOG PS 0-2, in term of both survival and quality of life.6In the ELVIS study, the median OS times were 7 months versus 5.25 months, respectively. While as, the median OS times in this study were 9.97 months versus 4.43 months, respectively. Notably, this study had some population of ECOG PS 3-4, especially in the supportive care alone arm. This may be a possible reason for a lower median survival time among those receiving only supportive care. Furthermore, the other difference between the studies was that the ELVIS study only included patients receiving vinorelbine, whereas our study enrolled all kinds of systemic treatment (e.g. doublet-agent

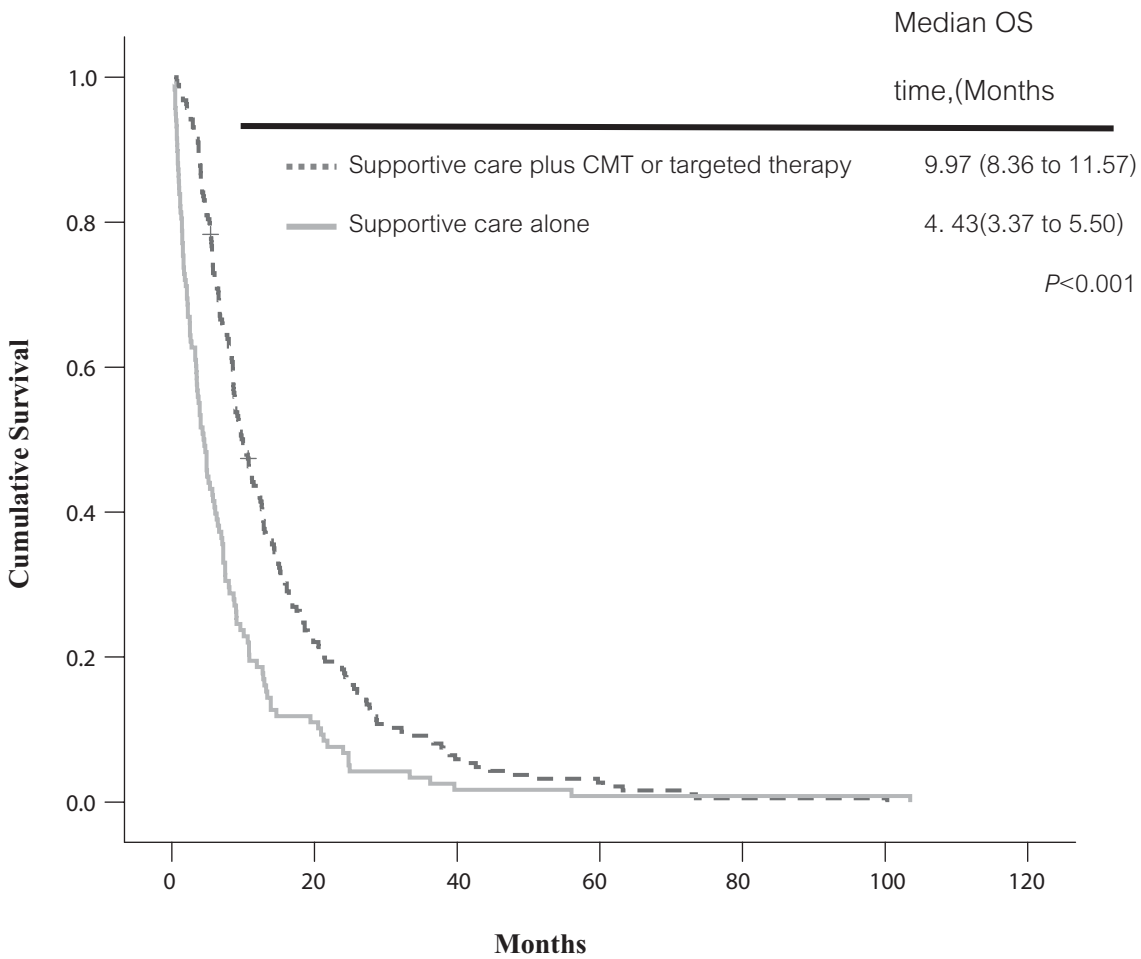

Figure 2: Kaplan-Meier estimates of overall survival (OS) among patients receiving supportive care plus chemotherapy (CMT) or targeted therapy and supportive care alone.

chemotherapy, single-agent chemotherapy and targeted therapy). The platinum-doublet chemotherapy was the major drug agent. This may explain for a longer median survival time among those receivingsupportive care plus chemotherapy or targeted therapy than result in the ELVIS study among those receivingvinorelbine.

According to the benefit of combination chemotherapy regimen compared with single-agent chemotherapyin the elderly patients with advanced NSCLC, there were few studies and conflicting results, e.g.,Gridelli et al. reported that combination of vinorelbine and gemcitabine compared with single gemcitabinewas no difference in survival outcome.[11] Contradictly, Frasci, et al. found that combination of vinorelbine and gemcitabine was associated with a better survival than vinorelbine alone.[12] Quoix, et al. found that combination of carboplatin and paclitaxel was associated with a significantly longer survival than single agent therapy with vinorelbine or gemcitabine.[13] However, our study had quite small numbers of patient in single-agent chemotherapy group and targeted therapy group, so we did not analyze in subgroupaccording to the regimens of systemic treatment. More research is needed in the future.

Conclusion

In summary, we found elderly patients with advanced NSCLC treated with supportive care plus chemotherapy or targeted therapy have significantly increased survival outcome compared with those treated with supportive care alone. With regard to toxicity, no new safety concern was observed in this study.

Potential conflicts of interest

None.

Acknowledgement

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