ORIGINAL RESEARCH ARTICLE

# Supportive Care Costs Associated with Second-Line Chemotherapy in Chinese Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer: A Retrospective Cohort Study

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## Abstract

*Purpose* To compare supportive care costs associated with second-line chemotherapy for advanced non-squamous non-small cell lung cancer (advNS-NSCLC) in Chinese patients.

*Methods* This retrospective cohort study included patients receiving pemetrexed or docetaxel-based second-line chemotherapy for advNS-NSCLC in four Chinese hospitals from 2007 to 2012. The best matched pairs between pemetrexed and other regimens were identified using propensity score methods for head-to-head comparisons of supportive care costs per treatment cycle. Linear regression analyses were performed to rank log10 scale of supportive care costs per treatment cycle associated with chemotherapy by tumor response and hematologic toxicity.

*Results* 384 patients were included to create propensity score-matched treatment groups for pemetrexed singlet versus docetaxel singlet, platinum/pemetrexed, and platinum/docetaxel, respectively. Pemetrexed singlet was associated with significantly less supportive care costs per treatment cycle than the two doublets (platinum/pemetrexed: median difference −RMB 9,877, $p = 0.003$; platinum/docetaxel: median difference −RMB 8,370, $p = 0.009$; 1 RMB = 0.16 USD) but not docetaxel singlet in matched patients. Of the four studied chemotherapy regimens, pemetrexed singlet was associated with the lowest log10 scale of supportive care costs per treatment cycle in patients with tumor control (coefficient relative to docetaxel singlet −1.049, $p < 0.001$) or leukopenia (coefficient relative to docetaxel singlet −0.991, $p = 0.034$).

*Conclusion* Pemetrexed singlet cost significantly less for supportive care than pemetrexed or docetaxel-based doublets when treating Chinese patients with AdvNS-NSCLC in the second-line setting. Pemetrexed singlet was also

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associated with significantly less supportive care costs per treatment cycle than docetaxel singlet in patients with tumor control or leukopenia.

## Key Points

Pemetrexed singlet was likely to be more cost-effective than platinum/pemetrexed, having comparable tumor response but significantly less overall hospital costs in the second-line setting for advanced non-squamous non-small cell lung cancer (advNS-NSCLC).

Pemetrexed singlet could save enough supportive care costs to completely offset the high drug acquisition cost of pemetrexed when compared with platinum/docetaxel doublet in the second-line setting for advNS-NSCLC.

Pemetrexed singlet significantly saved supportive care costs likely through reducing the severity of hematologic toxicity when compared with docetaxel singlet in the second-line setting for advNS-NSCLC.

## Introduction

Following decades of industrialization in China, the annual incidence and mortality rates of lung cancer in the country have soared up to 53.6 and 45.6 % per 100,000 persons, respectively, and lung cancer has replaced liver cancer as the top cause of cancer-related death in China [1–3]. Due to the challenges of early tumor detection [4–6], over half of Chinese patients with lung cancer are diagnosed at advanced stages [7]. Since non-small cell lung cancer (NSCLC) accounts for over 80 % of all lung cancer cases [8], systemic chemotherapy is the primary therapeutic option for extending survival and control disease symptoms in Chinese lung cancer patients [9].

Second-line chemotherapy was established a decade ago after docetaxel was proven clinically efficacious in previously treated patients with advanced NSCLC [10]. More recent clinical evidence suggested that the use of pemetrexed, the second cytotoxic agent introduced into the second-line setting in 2005 [11], likely resulted in better disease response and less toxicity in patients with advanced non-squamous NSCLC (advNS-NSCLC) [12, 13]. A recent survey of physicians across 12 large cities in China suggested that treatment with a platinum-based doublet with pemetrexed or docetaxel was also frequently used in the second-line setting for advanced NSCLC [9]. Even though

platinum-based doublets increase tumor response by 5–10 %, they cause significantly greater toxicity than singlet-agent treatment [14]. This significant increase in toxicity associated with doublet treatments is likely to result in increased consumption of healthcare resources. Thus, the main purpose of our study was to investigate the impact of singlet and doublet treatments on hospital costs for supportive care and thus clarify the appropriateness of using platinum-based doublets in the second-line setting for advNS-NSCLC from a perspective of resource use in hospitals where chemotherapy is usually delivered to Chinese patients.

## Patients and Methods

Chemotherapy care in China is usually delivered in tertiary-care hospital settings in order to manage the clinical toxicity of chemotherapy and improve patient tolerance [15]. Thus, we were able to use reliable hospital data to conduct this retrospective cohort study to assess supportive care costs associated with singlet or platinum-based doublet treatment with pemetrexed or docetaxel in the second-line setting for advNS-NSCLC in Chinese patients. The four selected hospital settings included one tumor-specialized hospital and one general hospital in Beijing [Chinese Academy of Medical Sciences Tumor Hospital (CAMSTH), Xuanwu Hospital (XWH)] and in Changsha [Hunan Provincial Tumor Hospital (HNPTH), Xiangya Hospital (XYH)], respectively, in order to represent current referral patterns and socioeconomic distribution in Chinese patients with advNS-NSCLC [16]. This study was approved by the ethics committees of the selected four hospitals.

### Patient Identification

Hospital admission registry databases in the four hospitals were searched using the key words "lung cancer", "NSCLC", "non-squamous NSCLC", "adenocarcinoma lung cancer", or "large-cell lung cancer" to identify patients hospitalized due to lung cancer. Because our study was designed to identify eligible patients and retrospectively collect data through electronic hospital information systems, we defined our search period according to the launch year of the electronic hospital information systems in the four participating hospitals. The search periods therefore differed according to hospital: 3 years for XYH (1 January 2010 to 31 December 2012), 4 years for CAMSTH (1 January 2009 to 31 December 2012), and 6 years for XWH and HNPTH (1 January 2007 to 31 December 2012). The identified patients were further linked with their hospital records to review their tumor

stage, histologic type, and history of chemotherapy for further eligibility assessment. Our study included patients with stage IIIb or IV biopsy-confirmed non-squamous NSCLC who received singlet or platinum-based doublet treatment (pemetrexed has been approved to treat advanced NSCLC with cisplatin only in the second-line setting) containing pemetrexed (given with supplementation of folic acid and vitamin B12) or docetaxel as second-line chemotherapy, which was defined as subsequent chemotherapy after the failure of either first-line chemotherapy or maintenance therapy. Our study excluded patients who had no tumor histology information or had mixed squamous and non-squamous histology. In order to control possible confounding effects associated with target treatment for epidermal growth factor receptor (EGFR) on the treatment effects of chemotherapy, our study further excluded patients receiving EGFR tyrosine kinase inhibitor or EGFR monoclonal antibodies in the first-line setting or as combination treatment in the second-line setting.

Data Extraction

For data extraction, the follow-up time was defined as the period from the admission date of the first hospitalization to the discharge date of the last hospitalization associated with second-line chemotherapy, which ended upon treatment discontinuation due to progressive disease or for other reasons. Our study reviewed medical records associated with the first hospitalization to extract patient baseline characteristics including demographics, smoking status, physical condition (assessed by Eastern Cooperative Oncology Group, ECOG, performance status), marrow function, tumor stage, tumor histologic subtype, and metastatic status. Medical records associated with each hospitalization during the follow-up were reviewed to extract admission and discharge date, dose and administration schedule of chemotherapy, tumor response [assessed according to the response evaluation criteria in solid tumors (RECIST) [17]], and recorded adverse events (AEs) related to chemotherapy (assessed by the Common Terminology Criteria for Adverse Events with modification on anemia [18]). Laboratory blood testing records associated with each hospitalization were reviewed to confirm hematologic AEs recorded in clinical notes. Hospital costs were extracted through review of billing summaries at hospital discharge.

Outcome Measures

The primary outcome measures in our study were hospital costs. Because hospital costs were classified differently in the four hospitals, the hospital costs were re-classified as chemotherapy drug costs (acquisition costs for chemotherapeutic agents), non-chemotherapy drug costs (acquisition costs for supportive medications treating adverse events associated with chemotherapy, symptoms related to advNS-NSCLC, or underlying co-morbidities), and non-drug care costs (total hospital costs excluding acquisition costs of all medications). Hospital supportive care costs were defined as the combination of non-chemotherapy drug costs and non-drug care costs. Since tumor response and hematologic AEs likely had substantial impact on hospital resource utilization, our study also measured the best tumor response [classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the definition of RECIST] and the occurrences of hematologic AEs, including neutropenia, leukopenia, anemia, and thrombocytopenia during chemotherapy, in order to explore their relationship with hospital costs. In addition, our study counted treatment cycles which were needed for calculating hospital costs per treatment cycle (HCTC).

Data Analyses

HCTC was calculated for each included patient by dividing the aggregated hospital costs by the number of completed treatment cycles. HCTC was presented in Renmingbi (RMB), the Chinese currency with an exchange rate against the US dollar of 1 RMM = US$0.16 in 2012. Propensity score methods were used to create 1:1 matched treatment groups for singlet treatment with pemetrexed versus docetaxel, platinum/pemetrexed, and platinum/docetaxel, respectively, for adjusted head-to-head comparisons on best tumor response, hematologic AEs, and allocation of HCTC. The matching condition was defined as a propensity score difference of less than 0.01 between matched pairs. The paired $t$ test and McNemar's test were used to assess differences in continuous and dichotomous outcomes between propensity score-matched treatment groups. Because cost data are often skewed and it is not appropriate to use means to describe the centre of cost data, the Wilcoxon rank sign test was used to compare median cost outcomes between propensity score-matched treatment groups. Because conventional linear regression analysis is typically not recommended to directly analyze skewed hospital costs [19], the log10 scale of HCTC for supportive care, which included non-chemotherapy drugs and non-drug care, was used as the dependent variable in multiple conventional linear regression analyses to rank the impact of the studied chemotherapy regimens on supportive care costs in patients stratified by their best tumor response and hematologic AEs, respectively. Docetaxel singlet was used as reference regiment in this linear regression analysis because it is the first well established second-line chemotherapy for NSCLC. SAS 9.2 was used to perform the

data analysis, and statistical significance was defined as $p < 0.05$.

## Results

According to the inclusion and exclusion criteria, 9,270 patients with a primary diagnosis of lung cancer were identified and 8,886 patients were excluded (134 had no pathological information, 181 with small cell lung cancer, 458 with squamous NSCLC, 314 with mixed with squamous cell histology, 279 with tumor stage less than IIIB, 7,018 with no second-line chemotherapy, 287 with TKI or EGFR monoclonal antibodies in the first- or second-line settings, and 215 with treatment regimens not containing pemetrexed or docetaxel). The final study cohort included 384 eligible patients, 46 receiving pemetrexed, 61 receiving docetaxel, 161 receiving platinum/pemetrexed (73 using cisplatin, 42 using nedaplatin, 37 using carboplatin, five using lobaplatin, and four using oxaliplatin) and 116 receiving platinum/docetaxel (51 using cisplatin, 31 using nedaplatin, 26 using carboplatin, four using lobaplatin, and four using oxaliplatin). The patient identification processes in the four hospitals are illustrated in Fig. 1.

Creating Propensity Score Matched Treatment Groups

The four study treatment groups had similar patient baseline characteristics with a few exceptions. Patients receiving pemetrexed were significantly older than those receiving platinum/pemetrexed (57.8 vs. 53.9 years, $p = 0.021$) or platinum/docetaxel (57.8 vs. 53.4 years, $p = 0.019$). Patients in the pemetrexed singlet treatment group also had significantly higher neutrophilic granulocyte counts ($5.2 \times 10^9$/L) than the docetaxel singlet treatment group ($4.1 \times 10^9$/L, $p = 0.017$) or platinum/docetaxel doublet ($4.0 \times 10^9$/L, $p = 0.003$) and significantly higher white blood cell count (WBC) ($7.8 \times 10^9$/L) than patients in the other three chemotherapy regimens, respectively (docetaxel singlet: $6.4 \times 10^9$/L, $p = 0.008$; platinum/pemetrexed doublet: $6.8 \times 10^9$/L, $p = 0.026$; platinum/docetaxel doublet: $6.4 \times 10^9$/L, $p = 0.001$). By adjusting for these unbalanced patient baseline characteristics, propensity score methods created matched treatment groups for pemetrexed versus docetaxel singlet (17 pairs, propensity score: $0.3969 \pm 0.2126$ vs. $0.3966 \pm 0.2125$, $p = 0.830$), platinum/pemetrexed (33 pairs, propensity score: $0.2480 \pm 0.1274$ vs. $0.2472 \pm 0.1260$, $p = 0.246$), and platinum/docetaxel (29 pairs, propensity score: $0.2850 \pm 0.1379$ vs. $0.2855 \pm 0.1370$, $p = 0.4933$), respectively. The balance of baseline characteristics between pemetrexed singlet and platinum/pemetrexed doublet were significantly improved

with propensity score matching as the mean of the $p$ values associated with baseline characteristics increased by 81.8 % from 0.391 to 0.711 (Fig. 2a). However, the balance of baseline characteristics for pemetrexed versus docetaxel singlet (Fig. 2b) and platinum/docetaxel (Fig. 2c) showed only slight improvement.

Adjusted Comparisons on Best Tumor Response and Hematologic Adverse Events

The number of treatment cycles associated with pemetrexed singlet was similar to that for the two platinum-based doublets but 2.4 cycles more than docetaxel singlet (3.9 vs. 1.5 cycles, $p = 0.193$) in propensity score-matched patients. Our study did not identify any cases of CR associated with the four studied chemotherapy regimens in the propensity score-matched patients. Further, adjusted head-to-head comparisons did not show any significant differences in best tumor response [relative risk (RR) for PD ranged from 1.000, $p = 1.000$ when compared with docetaxel to 2.335, $p = 0.157$ when compared with platinum/docetaxel] or unknown tumor response (RR ranged from 0.818, $p = 0.480$ when compared with platinum/docetaxel to 0.842, $p = 0.467$ when compared to platinum/pemetrexed) between pemetrexed and the other three chemotherapy regimens. However, tumor response information was lacking in 50 % or more of the matched patients due to early treatment discontinuation (less than two completed treatment cycles). When examining AEs, pemetrexed singlet was associated with significantly lower rates of neutropenia (6.1 vs. 30.3 %, RR 0.201, $p = 0.021$) and anemia (39.4 vs. 69.7 %, RR 0.565, $p = 0.004$) compared to platinum/pemetrexed and significantly lower rates of neutropenia (3.5 vs. 24.1 %, RR 0.143, $p = 0.034$) and leukopenia (3.5 vs. 34.5 %, RR 0.100, $p = 0.007$) compared to platinum/docetaxel. The rate of any hematologic AE was also significantly lower in the matched pemetrexed group compared to the matched platinum/pemetrexed group (42.4 vs. 75.8 %, RR 0.559, $p = 0.005$). Significant differences in the occurrence of hematologic AEs were not observed in the adjusted comparisons of pemetrexed and docetaxel singlet treatments. The comparisons of best treatment response and haematologic AEs between pemetrexed singlet and the other three chemotherapy regimens in propensity score-matched patients are summarized in Table 1.

Adjusted Comparisons on the Allocation of Hospital Costs per Treatment Cycle (HCTC)

Adjusted comparisons showed significantly higher median HCTC for chemotherapy drugs with pemetrexed singlet treatment compared to docetaxel (median difference RMB
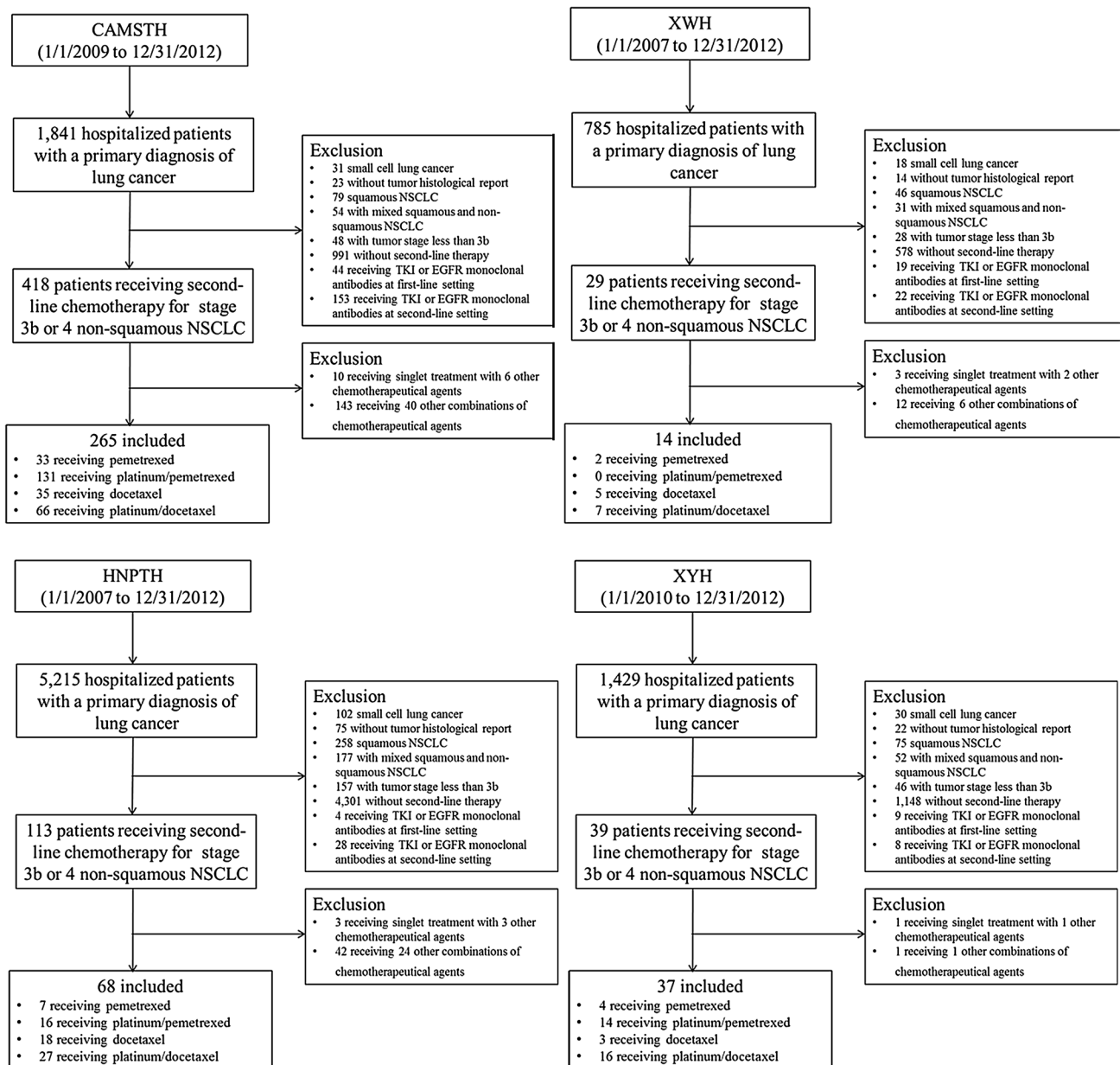
**Fig. 1** Flowchart identifying eligible patients receiving second-line chemotherapy for AdvNS-NSCLC in the four participating tertiary care hospitals. *AdvNS-NSCLC* advanced non-squamous non-small cell lung cancer, *TKI* tyrosine-kinase inhibitor, *EGFR* epidermal growth factor receptor, *CAMSTH* Chinese Academy of Medical Sciences Tumor Hospital, *XWH* Xuanwu Hospital, *HNPTH* Hunan Province Tumor Hospital, *XYH* Xiangya Hospital

6,762, $p < 0.001$) or platinum/docetaxel (median difference RMB 5,063, $p < 0.001$). However, non-chemotherapy drug costs (median difference −RMB 5,963, $p = 0.015$) and non-drug care costs (median difference −RMB 1,189, $p = 0.022$) were lower with pemetrexed singlet than with platinum/docetaxel, which offset the increased HCTC for chemotherapy drugs (median difference for total HCTC: −RMB 3,213, $p = 0.620$). Pemetrexed singlet was associated with cost savings for total HCTC (median difference −RMB 11,351, $p < 0.001$) in the adjusted comparison with

platinum/pemetrexed; pemetrexed singlet cost less for chemotherapy drugs (median difference −RMB 5,819, $p = 0.124$) and also cost significantly less for both non-chemotherapy drugs (median difference −RMB 6,406, $p = 0.004$) and non-drug care (median difference −RMB 1,798, $p = 0.015$). If taking non-chemotherapy drug costs and non-drug care costs together as supportive care costs, pemetrexed significantly saved HCTC for supportive care when compared to platinum/pemetrexed (median difference −RMB 9,877, $p = 0.003$) or platinum/docetaxel

**(a)**

| Variable | Unadjusted Comparison for Pemetrexed (n=46) vs. Platinum/pemetrexed (n=161) | | | Adjusted Comparison for Pemetrexed vs.Platinum/pemetrexed (33 pairs) | |
|---|---|---|---|---|---|
| | Mean/% | P-value | | Mean/% | P-value |
| **Demography** | | | | | |
| Age (years) | 57.8 vs. 53.9 | **0.021** | | 55.5 vs. 56.6 | 0.654 |
| Male (%) | 60.9 vs. 62.1 | 0.865 | | 60.6 vs. 63.6 | 0.808 |
| BMI | 23.9 vs. 23.6 | 0.681 | | 24.4 vs. 23.3 | 0.279 |
| Non-smoker (%) | 39.1 vs. 41.0 | 0.866 | | 39.4 vs. 45.5 | 0.564 |
| **Public health insurance type (%)** | | | | | |
| Urban residents | 58.7 vs. 55.3 | 0.738 | | 54.5 vs. 51.5 | 0.808 |
| Rural residents | 17.4 vs. 14.3 | 0.641 | | 15.2 vs. 15.2 | 1.000 |
| **ECOG performance status (%)** | | | | | |
| 0 | 37.0 vs. 51.6 | 0.095 | | 45.5 vs. 36.4 | 0.467 |
| 1 | 54.4 vs. 44.7 | 0.315 | | 48.5 vs. 57.6 | 0.439 |
| **Baseline marrow function** | | | | | |
| Hemoglobin (g/l) | 118.6 vs. 124.6 | 0.065 | | 120.8 vs. 118.5 | 0.625 |
| Neutrophilic granulocyte count ($\times10^9$/l) | 5.2 vs. 4.5 | 0.084 | | 4.7 vs. 4.2 | 0.332 |
| White cell count ($\times10^9$/l) | 7.8 vs. 6.8 | **0.026** | | 7.2 vs. 6.9 | 0.517 |
| Platelet count ($\times10^{10}$/l) | 24.8 vs. 23.5 | 0.355 | | 24.9 vs. 24.8 | 0.989 |
| **Disease stage and histology (%)** | | | | | |
| Stage 4 | 91.3 vs. 95.7 | 0.267 | | 93.9 vs. 93.9 | 1.000 |
| Adenocarcinoma type | 95.7 vs. 98.1 | 0.308 | | 100.0 vs. 100.0 | 1.000 |
| Large-cell type | 4.4 vs. 1.2 | 0.215 | | 0.0 vs. 0.0 | 1.000 |
| **Number of metastasis site (%)** | | | | | |
| 1 | 21.7 vs. 31.7 | 0.206 | | 30.3 vs. 33.3 | 0.706 |
| 2 | 28.3 vs. 21.7 | 0.428 | | 21.2 vs. 21.2 | 1.000 |
| 3 or above | 28.3 vs. 30.4 | 0.856 | | 30.3 vs. 27.3 | 0.782 |
| **Site of metastasis (%)** | | | | | |
| Brain | 15.2 vs. 25.5 | 0.169 | | 18.2 vs. 15.2 | 0.739 |
| Bone | 50.0 vs. 46.0 | 0.738 | | 51.5 vs. 48.5 | 0.808 |
| Liver | 6.5 vs. 14.3 | 0.211 | | 9.1 vs. 12.1 | 0.655 |
| Pleural | 32.6 vs. 26.7 | 0.459 | | 30.3 vs. 39.4 | 0.467 |
| **Group mean for P-value** | 0.391+/-0.292 | | | 0.711 +/-0.232 **(p<0.001)** | |

1 0.8 0.6 0.4 0.2  0  0.2 0.4 0.6 0.8  1
P value before matching    P value after matching

**(b)**

| Variable | Unadjusted Comparison for Pemetrexed (n=46) vs. Docetaxel (n=61) | | | Adjusted Comparison for Pemetrexed vs.Docetaxel (17 pairs) | |
|---|---|---|---|---|---|
| | Mean/% | P-value | | Mean/% | P-value |
| **Demography** | | | | | |
| Age (years) | 57.8 vs. 57.9 | 0.985 | | 55.2 vs. 55.9 | 0.812 |
| Male (%) | 60.9 vs. 60.7 | 1.000 | | 52.9 vs. 58.8 | 0.739 |
| BMI | 23.9 vs. 23.4 | 0.560 | | 23.9 vs. 24.4 | 0.765 |
| Non-smoker (%) | 39.1 vs. 36.1 | 0.841 | | 47.1 vs. 47.1 | 1.000 |
| **Public health insurance type (%)** | | | | | |
| Urban residents | 58.7 vs. 65.6 | 0.546 | | 76.5 vs. 76.5 | 1.000 |
| Rural residents | 17.4 vs. 14.8 | 0.792 | | 11.8 vs. 17.6 | 0.564 |
| **ECOG performance status (%)** | | | | | |
| 0 | 37.0 vs. 29.5 | 0.533 | | 29.4 vs. 41.2 | 0.527 |
| 1 | 54.4 vs. 67.2 | 0.229 | | 70.6 vs. 52.9 | 0.366 |
| **Baseline marrow function** | | | | | |
| Hemoglobin (g/l) | 118.6 vs. 118.7 | 0.980 | | 112.5 vs. 118.2 | 0.441 |
| Neutrophilic granulocyte count ($\times10^9$/l) | 5.2 vs. 4.1 | **0.017** | | 3.9 vs. 4.0 | 0.822 |
| White cell count ($\times10^9$/l) | 7.8 vs. 6.4 | **0.008** | | 6.1 vs. 6.1 | 0.923 |
| Platelet count ($\times10^{10}$/l) | 24.8 vs. 24.4 | 0.828 | | 22.1 vs. 22.9 | 0.794 |
| **Disease stage and histology (%)** | | | | | |
| Stage 4 | 91.3 vs. 91.8 | 1.000 | | 88.2 vs. 94.1 | 0.564 |
| Adenocarcinoma type | 95.7 vs. 96.7 | 1.000 | | 94.1 vs. 100.0 | 1.000 |
| Large-cell type | 4.4 vs. 1.6 | 0.576 | | 5.9 vs. 0.0 | 1.000 |
| **Number of metastasis site (%)** | | | | | |
| 1 | 21.7 vs. 34.4 | 0.198 | | 35.3 vs. 47.1 | 0.317 |
| 2 | 28.3 vs. 34.4 | 0.536 | | 11.8 vs. 23.5 | 0.157 |
| 3 or above | 28.3 vs. 23.0 | 0.654 | | 35.3 vs. 17.6 | 0.180 |
| **Site of metastasis (%)** | | | | | |
| Brain | 15.2 vs. 24.6 | 0.334 | | 17.6 vs. 17.6 | 1.000 |
| Bone | 50.0 vs. 54.1 | 0.700 | | 52.9 vs. 47.1 | 0.706 |
| Liver | 6.5 vs. 6.6 | 1.000 | | 5.9 vs. 0.0 | 1.000 |
| Pleural | 32.6 vs. 44.3 | 0.238 | | 41.2 vs. 23.5 | 0.317 |
| **Group mean for P-value** | 0.616+/-0.330 | | | 0.682 +/-0.287 **(p=0.449)** | |

P value prior to propensity score matching   1 0.8 0.6 0.4 0.2  0  0.2 0.4 0.6 0.8  1   P value after propensity score matching
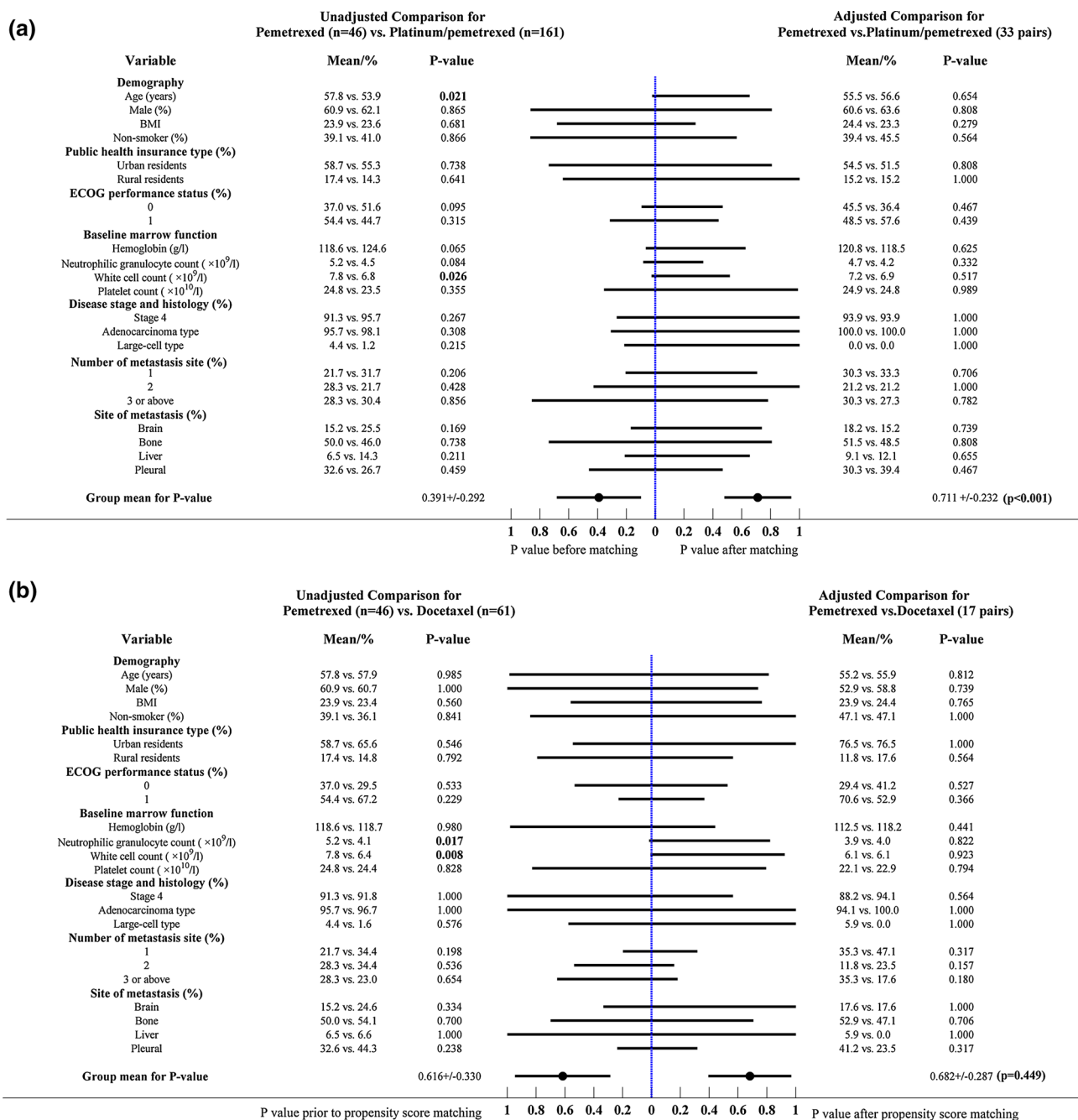
**Fig. 2** Comparison of baseline patient characteristics between pemetrexed singlet and the other three studied chemotherapy regimens prior to and after propensity score matching. **a** Pemetrexed vs. platinum/pemetrexed. **b** Pemetrexed vs. docetaxel. **c** Pemetrexed vs. platinum/docetaxel. *BMI* body mass index, *ECOG* Eastern Cooperative Oncology Group

(median difference −RMB 8,370, *p* = 0.009), respectively, while supportive care costs did not differ between pemetrexed and docetaxel singlet treatment. Comparisons of the allocation of HCTC and supportive care costs per treatment cycle between pemetrexed singlet and the other three studied chemotherapy regimens in the propensity score-matched patients are summarized in Table 2.

## Impact of Chemotherapy Regimens on HCTC for Supportive Care

Docetaxel was used as the reference regimen in order to rank the impact of the four studied regimens on the log10 scale of HCTC for supportive care in multiple linear regression analyses. Pemetrexed singlet was associated with
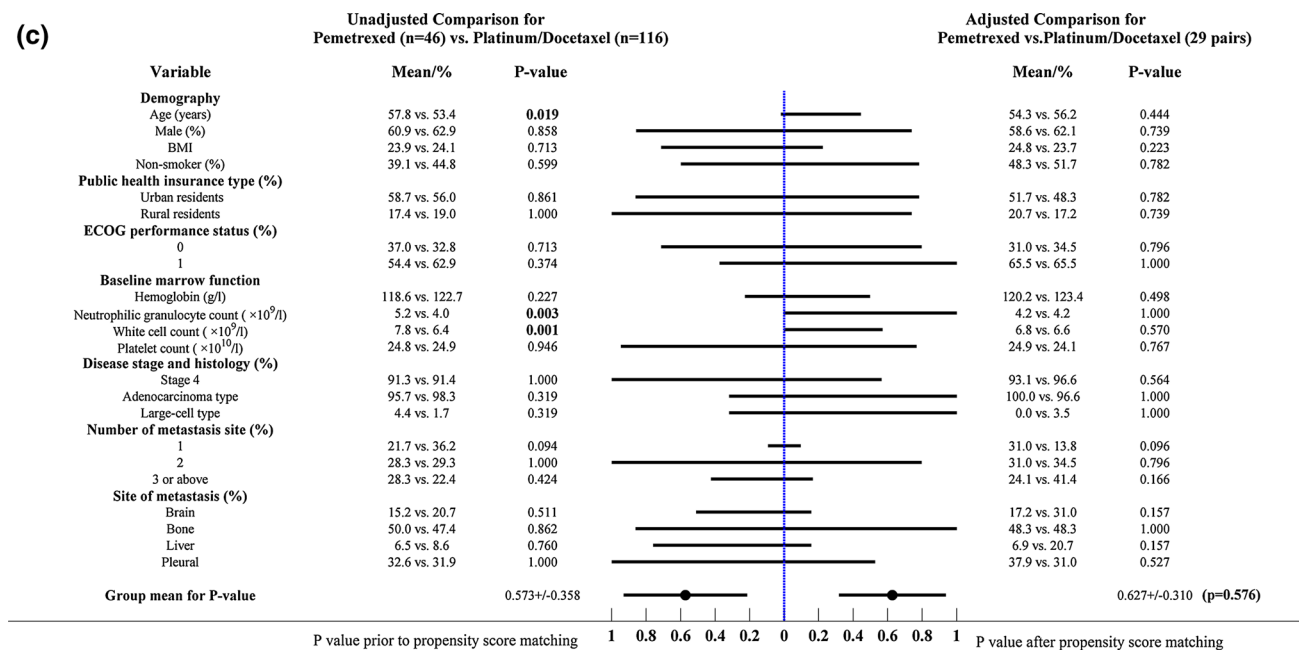
**(c)**

| Variable | Unadjusted Comparison for Pemetrexed (n=46) vs. Platinum/Docetaxel (n=116) | | | Adjusted Comparison for Pemetrexed vs. Platinum/Docetaxel (29 pairs) | |
|---|---|---|---|---|---|
| | Mean/% | P-value | | Mean/% | P-value |
| **Demography** | | | | | |
| Age (years) | 57.8 vs. 53.4 | **0.019** | | 54.3 vs. 56.2 | 0.444 |
| Male (%) | 60.9 vs. 62.9 | 0.858 | | 58.6 vs. 62.1 | 0.739 |
| BMI | 23.9 vs. 24.1 | 0.713 | | 24.8 vs. 23.7 | 0.223 |
| Non-smoker (%) | 39.1 vs. 44.8 | 0.599 | | 48.3 vs. 51.7 | 0.782 |
| **Public health insurance type (%)** | | | | | |
| Urban residents | 58.7 vs. 56.0 | 0.861 | | 51.7 vs. 48.3 | 0.782 |
| Rural residents | 17.4 vs. 19.0 | 1.000 | | 20.7 vs. 17.2 | 0.739 |
| **ECOG performance status (%)** | | | | | |
| 0 | 37.0 vs. 32.8 | 0.713 | | 31.0 vs. 34.5 | 0.796 |
| 1 | 54.4 vs. 62.9 | 0.374 | | 65.5 vs. 65.5 | 1.000 |
| **Baseline marrow function** | | | | | |
| Hemoglobin (g/l) | 118.6 vs. 122.7 | 0.227 | | 120.2 vs. 123.4 | 0.498 |
| Neutrophilic granulocyte count ($\times 10^9$/l) | 5.2 vs. 4.0 | **0.003** | | 4.2 vs. 4.2 | 1.000 |
| White cell count ($\times 10^9$/l) | 7.8 vs. 6.4 | **0.001** | | 6.8 vs. 6.6 | 0.570 |
| Platelet count ($\times 10^{10}$/l) | 24.8 vs. 24.9 | 0.946 | | 24.9 vs. 24.1 | 0.767 |
| **Disease stage and histology (%)** | | | | | |
| Stage 4 | 91.3 vs. 91.4 | 1.000 | | 93.1 vs. 96.6 | 0.564 |
| Adenocarcinoma type | 95.7 vs. 98.3 | 0.319 | | 100.0 vs. 96.6 | 1.000 |
| Large-cell type | 4.4 vs. 1.7 | 0.319 | | 0.0 vs. 3.5 | 1.000 |
| **Number of metastasis site (%)** | | | | | |
| 1 | 21.7 vs. 36.2 | 0.094 | | 31.0 vs. 13.8 | 0.096 |
| 2 | 28.3 vs. 29.3 | 1.000 | | 31.0 vs. 34.5 | 0.796 |
| 3 or above | 28.3 vs. 22.4 | 0.424 | | 24.1 vs. 41.4 | 0.166 |
| **Site of metastasis (%)** | | | | | |
| Brain | 15.2 vs. 20.7 | 0.511 | | 17.2 vs. 31.0 | 0.157 |
| Bone | 50.0 vs. 47.4 | 0.862 | | 48.3 vs. 48.3 | 1.000 |
| Liver | 6.5 vs. 8.6 | 0.760 | | 6.9 vs. 20.7 | 0.157 |
| Pleural | 32.6 vs. 31.9 | 1.000 | | 37.9 vs. 31.0 | 0.527 |
| **Group mean for P-value** | | 0.573+/-0.358 | | | 0.627+/-0.310 (p=0.576) |

P value prior to propensity score matching   1  0.8  0.6  0.4  0.2  0  0.2  0.4  0.6  0.8  1   P value after propensity score matching

**Fig. 2** continued

the lowest log10 scale of HCTC for supportive care in 108 patients with tumor control (PR or SD) (coefficient −1.049, $p < 0.001$) (Fig. 3a), 88 patients experiencing leukopenia (coefficient −0.991, $p = 0.034$) (Fig. 3b), and 202 patients with any hematologic AEs (coefficient −0.467, $p = 0.034$) (Fig. 3c). Non-significant trends also showed that pemetrexed singlet was associated with the lowest common logarithm of HCTC for supportive care in 160 patients without any hematologic AEs (coefficient −0.407, $p = 0.079$), 79 patients with neutropenia (coefficient −0.973, $p = 0.064$), and 80 patients with thrombocytopenia (coefficient −0.638, $p = 0.090$).

## Discussion

Our study is the first real-world study demonstrating that platinum-based doublet treatment did not have a superior tumor response but caused more toxicity and cost more when compared with singlet treatment in the second-line setting for advNS-NSCLC patients in China. Since tumor response did not differ among the regimens, the substantial hospital cost savings for supportive care associated with pemetrexed compared to the platinum-doublets were perhaps the result of the lower rates of occurrence of neutropenia or leukopenia. Pemetrexed singlet also significantly saved supportive care costs when compared to docetaxel singlet in patients experiencing hematologic AEs. This finding may suggest that the hematologic AEs

associated with pemetrexed singlet could be less severe and require less hospital care for management.

Use of pemetrexed singlet resulted in fewer occurrences of neutropenia and leukopenia and had lower associated supportive care hospital costs, likely due to less use of expensive granulocyte colony stimulating factor (G-CSF) and antibiotics for treatment of these AEs and reduced length of hospital stay for AE management [20]. For example, we observed that the occurrence rates of neutropenia associated with the two platinum-based doublets were five to six times the neutropenia rate associated with pemetrexed singlet in the propensity score-matched patients (6.1 vs. 30.3 % for pemetrexed vs. platinum/pemetrexed; 3.5 vs. 24.1 % for pemetrexed vs. platinum/docetaxel). Thus, our results indicated substantial hospital cost savings mainly with non-chemotherapy drugs associated with pemetrexed singlet when compared to the two platinum-based doublets. In addition, patients receiving chemotherapy regimens associated with a higher risk of neutropenia or leukopenia are often given prophylactic treatment and may be treated more aggressively to improve treatment tolerance and prevent life-threatening infection [21, 22]. Thus, the effects associated with prophylactic treatment and aggressive AE management would be accounted for in hospital costs of supportive care, which included both medications and non-drug care for prevention and management of hematologic AEs. Significantly reduced supportive care costs associated with pemetrexed singlet in patients experiencing leukopenia suggest that AE

**Table 1** Head-to-head comparisons of best tumor response and occurrences of hematologicl adverse events (AEs) between pemetrexed and the other three studied chemotherapy regimens in propensity score-matched patients

| Treatment | Pemetrexed vs. platinum/pemetrexed | | | | Pemetrexed vs. docetaxel | | | | Pemetrexed vs. platinum/docetaxel | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Matched pairs | 33 | | | | 17 | | | | 29 | | | |
| Outcome | % | % | RR | $p$ value | % | % | RR | $p$ value | % | % | RR | $p$ value |
| Best tumor response | | | | | | | | | | | | |
| PR | 12.1 | 12.1 | 1.000 | 1.000 | 11.8 | 5.9 | 2.000 | 0.564 | 13.8 | 10.4 | 1.322 | 0.706 |
| SD | 12.1 | 12.1 | 1.000 | 1.000 | 11.8 | 5.9 | 1.998 | 0.564 | 10.3 | 17.2 | 0.600 | 0.480 |
| PD | 27.3 | 18.2 | 1.500 | 0.439 | 23.5 | 23.5 | 1.000 | 1.000 | 24.1 | 10.3 | 2.335 | 0.157 |
| Unknown | 48.5 | 57.6 | 0.842 | 0.467 | 52.9 | 64.7 | 0.818 | 0.480 | 51.7 | 62.1 | 0.833 | 0.366 |
| Hematologic AEs | | | | | | | | | | | | |
| Neutropenia | 6.1 | 30.3 | 0.201 | **0.021** | 11.8 | 23.5 | 0.500 | 0.414 | 3.5 | 24.1 | 0.143 | **0.034** |
| Leukopenia | 9.1 | 21.2 | 0.429 | 0.103 | 11.8 | 23.5 | 0.500 | 0.414 | 3.5 | 34.5 | 0.100 | **0.007** |
| Thrombocytopenia | 15.2 | 21.2 | 0.717 | 0.480 | 23.5 | 5.9 | 4.000 | 0.180 | 20.7 | 27.6 | 0.750 | 0.564 |
| Anemia | 39.4 | 69.7 | 0.565 | **0.004** | 35.3 | 29.4 | 1.200 | 0.541 | 37.9 | 44.8 | 0.846 | 0.637 |
| Any hematologic AE | 42.4 | 75.8 | 0.559 | **0.005** | 47.1 | 52.9 | 0.889 | 0.416 | 44.8 | 69.0 | 0.650 | 0.071 |

Bold values represent $p < 0.05$

*PR* partial response, *SD* stable disease, *PD* progressive disease, *RR* rate ratio

**Table 2** Head-to-head comparisons of the allocation of hospital costs per treatment cycle (HCTC) between pemetrexed and the other three studied chemotherapy regimens in propensity score-matched patients (1 RMB ¥ = US$0.16)

| Allocation of HCTC | Median | Median | Median difference | $p$ value |
|---|---|---|---|---|
| Comparison | Pemetrexed vs. platinum/pemetrexed | | | |
| Matched pairs | 33 pairs | | | |
| Chemotherapy drug | ¥11,034 | ¥16,853 | −¥5,819 | 0.124 |
| Non-chemotherapy drug | ¥3,094 | ¥9,500 | −¥6,406 | **0.004** |
| Non-drug care | ¥2,991 | ¥4,788 | −¥1,798 | **0.015** |
| Total HCTC | ¥20,247 | ¥31,597 | −¥11,351 | **0.005** |
| HCTC for supportive care | ¥5,054 | ¥14,931 | −¥9,877 | **0.003** |
| Comparison | Pemetrexed vs. docetaxel | | | |
| Matched pairs | 17 pairs | | | |
| Chemotherapy drug | ¥11,034 | ¥4,272 | ¥6,762 | **<0.001** |
| Non-chemotherapy drug | ¥2,475 | ¥6,546 | −¥4,071 | 0.225 |
| Non-drug care | ¥2,991 | ¥4,022 | −¥1,032 | 0.378 |
| Total HCTC | ¥21,548 | ¥14,754 | ¥6,793 | 0.487 |
| HCTC for supportive care | ¥5,054 | ¥10,482 | −¥5,428 | 0.225 |
| Comparison | Pemetrexed vs. platinum/docetaxel | | | |
| Matched pairs | 29 pairs | | | |
| Chemotherapy drug | ¥10,880 | ¥5,817 | ¥5,063 | **<0.001** |
| Non-chemotherapy drug | ¥2,793 | ¥8,756 | −¥5,963 | **0.015** |
| Non-drug care | ¥2,991 | ¥4,179 | −¥1,189 | **0.022** |
| Total HCTC | ¥17,381 | ¥20,594 | −¥3,213 | 0.620 |
| HCTC for supportive care | ¥5,321 | ¥13,691 | −¥8,370 | **0.009** |

Bold values represent $p < 0.05$

severity may have differed between pemetrexed and docetaxel. The doubled median supportive care costs associated with docetaxel compared with pemetrexed, coupled with similar rates of leukopenia occurrence, might suggest the need for more aggressive treatments for leukopenia associated with docetaxel. We speculate that use of more aggressive treatments for leukopenia associated with docetaxel treatment might have offset previously
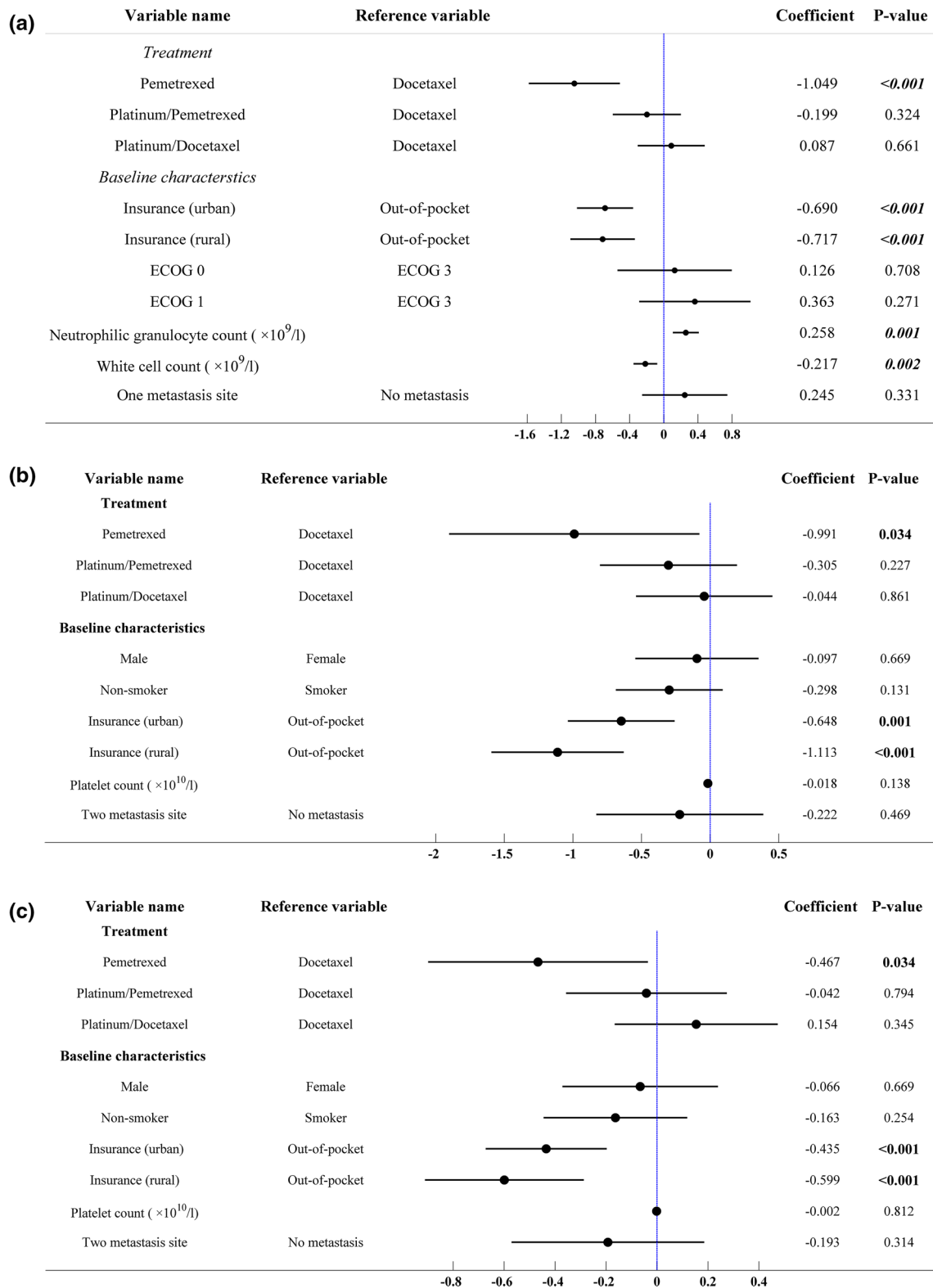
**Fig. 3** Impact of the four studied chemotherapy regimens (docetaxel as reference) on the log10 scale of hospital costs per treatment cycle for supportive care in patients with tumor control, leukopenia, or any hematologic AEs during treatment. **a** Patients with tumor control (PR or SD) ($n = 108$). **b** Patients with leukopenia ($n = 88$). **c** Patients with any hematologic AEs ($n = 202$). *AE* adverse event, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ECOG* Eastern Cooperative Oncology Group

reported significant differences in the occurrence of grade 3 or 4 leukopenia between the two singlet treatments in the clinical trial setting [11]. Our study also demonstrated that supportive care costs associated with pemetrexed were significantly reduced when compared with docetaxel in patients who had PR or SD for their best tumor responses. This finding may suggest that patients treated with docetaxel singlet consumed more health resources for AE management because supportive care costs for disease-related symptoms should be much reduced in those patients who responded to the two singlet treatments. Thus, this finding further supports the earlier hypothesis of the confounding effects associated with AE management in our study, and future cohort studies should make full adjustment for AE management when assessing clinical toxicity associated with chemotherapy in real-world clinical settings.

Our study findings have significant implications for clinical practices, health-policy making, and future research. Our study has confirmed that supportive care costs are highly sensitive to hematologic toxicity associated with chemotherapy [15]. If we consider tumor response and less clinical toxicity as health benefits, pemetrexed singlet would likely be cost-effective compared to the two platinum-based doublets by having comparable clinical effectiveness while costing less for hospital care. Future cost-effectiveness analysis is needed to confirm our speculation on the inappropriateness of treating advNS-NSCLC patients with platinum-based doublets in the second-line setting [14]. As the first real-world study estimating hospital costs associated with second-line chemotherapy for advNS-NSCLC patients in China, our study provides reliable cost data sources for future cost-effectiveness analysis and budget impact analysis, which are increasingly used to support reimbursement decision making in China. Our study also suggests that supportive care costs could be used as an indicator for the intensity of AE management that could indirectly reflect the differences in toxicity profile between chemotherapy regimens. Because real-world studies are usually associated with uncontrolled confounders due to missing data, health resource utilization associated with treatments should be used as a supplementary outcome measure to confirm or explain the observed clinical outcome differences in future real-world studies.

Several limitations should be considered when interpreting the results of this study. Small sample size was a major limitation in our study. Our study was only able to create 17 propensity score-matched pairs for pemetrexed versus docetaxel. With such a small sample size, our study was unable to detect any significant differences in tumor response, treatment toxicity, and supportive care costs between the two singlet treatments. Even though referral patterns and geographic location were taken into account

for hospital selection to control for possible selection bias associated with practices and social economic status, the use of pemetrexed treatment was not evenly distributed in the four hospitals, and the hospital settings were not adjusted in our data analyses due to the small sample size. Since the cost of pemetrexed per treatment cycle was twofold higher than docetaxel, patients receiving pemetrexed treatments likely had a higher socioeconomic status, which may cause overuse of health resources as richer patients are likely to pursue more expensive care. Thus, hospital costs associated with pemetrexed could be overestimated. Missing information was another major limitation in our study. Tumor response assessment was lacking in nearly half the included patients and our study was unable to collect information on AEs and medical care that occurred outside of the study hospital settings. With relatively small numbers of matched pairs, the missing information might explain why our study was unable to observe previously reported statistical differences in treatment effectiveness and hematologic toxicity between pemetrexed singlet and docetaxel singlet in the second-line setting for advNS-NSCLC. Our study findings might have limited generalizability as chemotherapy care could also be delivered in outpatient settings in other countries. However, the chemotherapy care settings are unlikely to significantly affect the trend of our findings because AE management, the essential component of chemotherapy care, should not be affected by care settings. Finally, our study did not follow up patients for overall survival and health resource utilization after second-line chemotherapy and future cost-effectiveness analyses are still needed to further confirm our study findings.

In summary, platinum/pemetrexed did not have superior tumor response but increased hospital costs when compared to pemetrexed singlet treatment in the second-line setting for adv-NS NSCLC in Chinese patients. Pemetrexed singlet treatment was able to save enough supportive care costs to offset the high chemotherapy drug costs when compared to platinum/docetaxel doublet. Pemetrexed singlet treatment also cost significantly less for supportive care than docetaxel singlet treatment in patients with tumor control or leukopenia. The numerically lower occurrences and lower severity of hematologic AEs in patients receiving pemetrexed singlet likely contributed to the saved supportive care costs. Future cost-effectiveness analyses taking into account overall survival benefits and health resource utilization after second-line chemotherapy are needed to confirm our study findings.

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