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Effect of pemetrexed on brain metastases from nonsmall cell lung cancer with wild-type and unknown EGFR status

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Abstract

We aimed to evaluate the effectiveness of pemetrexed-based chemotherapy in wild-type nonsmall-cell lung cancer (NSCLC) patients with brain metastases (BM). Brain metastases are a common cause of mortality in NSCLC patients. For epidermal growth factor receptor (EGFR) wild-type patients, therapeutic options for BM are even limited. Pemetrexed-based therapy is a standard care for patients with EGFR-negative, nonsquamous NSCLC. Besides local therapy, pemetrexed is the preferred chemotherapy for wild-type BM patients, but the efficacy is uncertain.

We retrospectively studied 138 NSCLC patients with BM whose EGFR status were unknown or wild-type. All patients received first-line pemetrexed-based chemotherapy from 2010 to 2015. Forty-six of 89 patients with unknown EGFR status were treated with EGFR TKIs after progression.

Among the 138 patients, 49 (35.5%) were EGFR wild-type and 89 (64.5%) were unknown EGFR status. The median overall survival (OS), and the median intracranial progression-free survival (iPFS) was 21.0 months, 9.5 months, respectively. Patients who received more than 4 cycles of chemotherapy had significantly longer OS than those who received 3 to 4 cycles (Mantel-Byar X-squared = 6.65, $P = .001$). In the EGFR wild-type group, the median OS, and the median iPFS was 17.7 months, 7.6 months, respectively. And patients treated with pemetrexed plus platinum tended to have a longer OS than those who were treated with pemetrexed alone ($P = .078$). In the subgroup with unknown EGFR status, we noted a statistically significant improvement in OS for the patients who received EGFR tyrosine kinase inhibitors (TKIs) after progression of 29 months compared to 20.3 months of the EGFR TKIs naïve arm ($P = .027$).

Pemetrexed shows an ideal effectiveness in EGFR wild-type and unknown status NSCLC patients with BM, and has a favorable control on brain localizations. EGFR wild-type patients can significantly benefit from pemetrexed continuation maintenance.

Abbreviations: ALK = anaplastic lymphoma kinase, ARMS = amplification refractory mutation system analysis, BBB = blood–brain barrier, BM = brain metastases, CR = complete response PR = partial response, EGFR = epidermal growth factor receptor, GPA = graded prognostic assessment, iPFS = intracranial progression-free survival, KPS = Karnofsky Performance Scale, MRI = magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, NSCLC = nonsmall-cell lung cancer, ORR= objective response rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, RT = radiation therapy, RTOG = radiation therapy oncology group, SD = stable disease, SRS = stereotactic radiosurgery, TKIs = tyrosine kinase inhibitors, WBRT = whole-brain radiotherapy.

Keywords: brain metastases, epidermal growth factor receptor, nonsmall-cell lung cancer, pemetrexed

1. Introduction

Brain metastasis (BM) is a common cause of mortality in patients with nonsmall-cell lung cancer (NSCLC), developing in approximately 25% to 40% of patients with advanced adenocarcinomas and the incidence of BMs is still increasing.[1,2] Traditionally, treatment approaches include surgical resection, radiation therapy, and palliative chemotherapy directed toward symptom palliation. Recent years, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) have already reshaped the treatment approaches toward EGFR mutant NSCLC patients with BM, with reported response rate of around 70% and median progression-free survival (PFS) of approximately 1 year.[3,4] However, for patients with EGFR wild-type, the choice is even limited. Chemotherapy is an indispensable treatment approach for EGFR wild-type patients. Pemetrexed is a multitarget antifolate agent, inhibits thymidylate synthase and other folate-dependent enzymes involved in the metabolism and synthesis of DNA precursors.[5,6] Previously, some retrospective studies with small sample size had indicated that the use of combined cisplatin and pemetrexed therapy showed a good

tolerability and efficiency in managing nonsquamous NSCLC patients with inoperable BMs.[7–9] However, systematic studies are still lacking in this field so far. Especially for EGFR wild-type and anaplastic lymphoma kinase (ALK) negative patients with BMs, there has been no report on the efficacy of pemetrexed therapy. Thus, we evaluated the efficacy of pemetrexed-based chemotherapy on BM patients with EGFR wild-type and unknown EGFR status, and further analyzed the prognostic factors.

2. Patients and methods

2.1. Patients

We retrospectively studied 138 EGFR wild-type and unknown status patients with BM from 2010 to 2015. Due to the limitation of the medical insurance, icotinib was not covered by Zhejiang Medicare until June 2016, gefitinib and erlotinib were not covered until September 2017. And earlier version of drug instructions recommended that EGFR TKIs were suitable for locally advanced or metastatic NSCLC after the failure of first-line chemotherapy, regardless of gene status. Therefore, all patients received first-line pemetrexed-based chemotherapy in our study. Other eligibility criteria included the following: aged 18 years or older and have been treated with pemetrexed-based therapy consecutively. Exclusion criteria included the following: Karnofsky Performance Scale (KPS) <50, diagnosed with BM during the treatment of pemetrexed, lost to follow-up. Thirty patients received pemetrexed maintenance therapy after 4 cycles of chemotherapy until disease progression. And 59 (46 were unknown EGFR status) patients were treated with EGFR TKIs after progression. Patient follow-up by telephone was done until October 2017. Treatment response was evaluated and survival data were collected and analyzed. The informed consent was waived and this investigation was approved by the Zhejiang Center Hospital Ethics Committee.

2.2. Assessment

EGFR wild-type patients were confirmed by the amplification refractory mutation system analysis (ARMS). BMs in these patients were confirmed by magnetic resonance imaging (MRI). The objective tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

2.3. Study design

Using patient hospital records, follow-up registration records, and follow-up phone records, we collected clinical and survival information for the patients. The following data were collected and recorded: age, sex, smoking status, KPS at the time of BM, number of BMs and extracranial metastases, primary tumor histological type, EGFR status, therapy for brain metastasis, radiation therapy (RT) types, and interval between RT and diagnosis. Patients were categorized by age (<65 years, ≥65 years), sex (male, female), smoking status (never, ≤20 packyear, ≥20 packyear), KPS (≥70, <70), extracranial metastases (yes or no), number of brain metastases (1 tumor, 2–3 tumors, more than 3 tumors), primary tumor histology (adenocarcinoma, others), EGFR status (EGFR wild-type, unknown status), ALK status, chemotherapy (single agent, dual agents), cycles of chemotherapy (≤4, 5–6 cycles, >6 cycles), and RT types (without, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) or combination). Finally, a graded prognostic assessment (GPA)

was calculated for each patient to determine whether the cohorts shared similar prognostic features.

Subgroup analysis was performed based on EGFR status, patients were divided into 2 groups: EGFR wild-type (n=49) and unknown EGFR status (n=89). Within the EGFR wild-type group, 36 patients received RT, and 13 were not treated with any local treatment. In the unknown EGFR status group, 46 patients received EGFR TKIs after the first-line chemotherapy progression. The major focus of the study was overall survival, defined as the duration of time from the diagnosis of brain metastases until death or the most recent follow-up.

2.4. Statistical analysis

Patient OS was assessed using the Kaplan–Meier method. Log-rank tests were used to determine statistically significant differences between the survival curves for each group. The effect of chemotherapy on survival was tested using the Mantel-Byar method for comparisons of patients treated with different cycles of chemotherapy. Finally, the Cox proportional hazard regression model (forward Wald method) was used for multivariate analysis of the groups to study the effect of prognostic factors from the Kaplan–Meier single variant test (age, KPS, number of intracranial lesions, extracranial metastasis) and clinical factors (pemetrexed-based chemotherapy, cycles of chemotherapy), and to evaluate which factors were associated with patient survival as well as to analyze differences in the survival curves for each subgroup. Statistical analyses were conducted with R (R Foundation for Statistical Computing, Vienna, Austria) and SPSS software, version 20.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Patients characteristics

A total of 138 nonsquamous NSCLC patients diagnosed with BMs were retrospectively studied in the study, 80 (58.0%) were male. The median age was 57 years (range 29–78 years), and 20 patients (14.5%) had a KPS score <70. Sixty-seven patients (48.5%) were smokers and 46 patients (33.3%) had heavy smoking histories (>20 packyear). These cases included 118 (85.5%) adenocarcinomas and 20 nonadenocarcinoma cases, which were identified as poorly differentiated carcinoma. Regarding EGFR mutation status, 49 (35.5%) were EGFR wild-type, and 89 (64.5%) were unknown EGFR status. One hundred eight (78.3%) patients received 3 to 4 cycles, 30 (21.7%) patients continued on to maintenance therapy. Ninety-eight (71%) patients received dual agents, and 40 (29%) were treated with pemetrexed alone. A total of 59 (42.8%) patients received EGFR TKIs after progression, among which 46 (78.0%) of them did not test the EGFR status and 13 (22%) were EGFR wild-type. And 109 (79%) patients had received RT, including 80 (58.0%) patients received WBRT, 19 (13.8%) patients received SRS/surgery, only 10 (7.2%) were treated with WBRT plus SRS/surgery. Other demographic and clinical characteristics of the patients are shown in Table 1. Thirty-five patients were alive at the time of this analysis, and the overall median clinical follow-up duration was 24 months (range, 2.7–77.5 months).

3.2. Survival outcomes

The median OS from diagnosis of BM was 21.0 months for the whole cohort (95% CI, 17.2–24.8 months). The Kaplan–Meier

Table 1

Patient characteristics at baseline.

Characteristic	Whole group, n=138 (100%)	EGFR wild-type group, n=49 (35.5)	Unknown EGFR status group, n=89 (64.5)
Median age, y (range)	57 (29–78)	53 (29–78)	62 (38–78)
Gender			
Male	80 (58.0)	33 (67.3)	47 (52.8)
Female	58 (42.0)	16 (32.7)	42 (47.2)
KPS			
<70	20 (14.5)	4 (8.2)	16 (18.0)
≥70	118 (85.5)	45 (91.8)	73 (82.0)
Smoking status			
Never	71 (51.5)	19 (38.8)	52 (58.4)
Slight (≤20 package)	21 (15.2)	8 (16.3)	13 (14.6)
Heavy (>20 package)	46 (33.3)	22 (44.9)	24 (27.0)
Histology			
Adenocarcinomas	118 (85.5)	43 (87.8)	75 (84.3)
Nonadenocarcinomas	20 (14.5)	6 (12.2)	14 (15.7)
RTOG GPA			
0–2.5	108 (78.2)	41 (83.7)	82 (92.1)
3–4	30 (21.7)	8 (16.3)	7 (7.9)
Number of BM			
1	50 (36.2)	19 (38.8)	31 (34.8)
2–3	42 (30.4)	16 (32.6)	26 (29.2)
>3	46 (33.3)	14 (28.6)	32 (36.0)
Extracranial metastasis			
No	32 (23.2)	16 (32.7)	16 (18.0)
Yes	106 (76.8)	33 (67.3)	73 (82.0)
Chemotherapy			
Single agent	40 (29.0)	11 (22.4)	29 (32.6)
Dual agents	98 (71.0)	38 (77.6)	60 (67.4)
Cycles of chemotherapy			
3–4 cycles	108 (78.3)	35 (71.4)	73 (82.0)
>4 cycles	30 (21.7)	14 (28.6)	16 (18.0)
RT			
Without	29 (21)	13 (26.6)	16 (18.0)
WBRT	80 (58.0)	22 (44.9)	58 (65.2)
SRS	19 (13.8)	9 (18.3)	10 (11.2)
Combination	10 (7.2)	5 (10.2)	5 (5.6)

Values are presented as number (%).

EGFR = epidermal growth factor receptor, GPA = graded prognostic assessment, KPS = Karnofsky Performance Scale, RT = radiation therapies, RTOG = radiation therapy oncology group, SRS = stereotactic radiosurgery, TKIs = tyrosine kinase inhibitors, WBRT = whole brain radiation therapy.

curve for OS is shown in Fig. 1A. The patients with unknown EGFR status showed a longer OS (median time, 24.0 months) than the patients with EGFR wild-type (median time, 17.7 months), but the difference was not statistically significant (P = .24) (Fig. 2A). The patients who received more than 4 cycles of chemotherapy have a significantly longer OS than these who
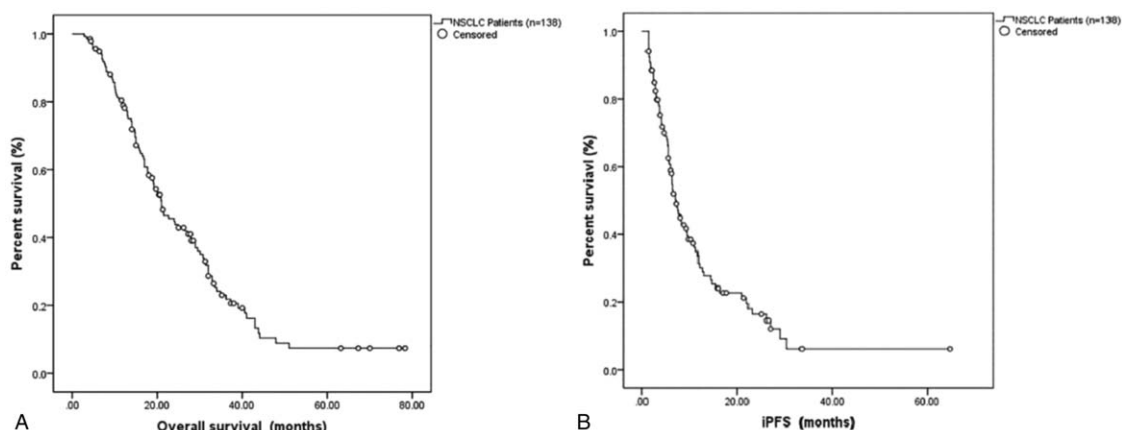

Figure 1. (A) Kaplan–Meier curve illustrating OS of all NSCLC patients. (B) Kaplan–Meier curve illustrating iPFS of all NSCLC patients. iPFS = intracranial progression-free survival, NSCLC = nonsmall cell lung cancer.
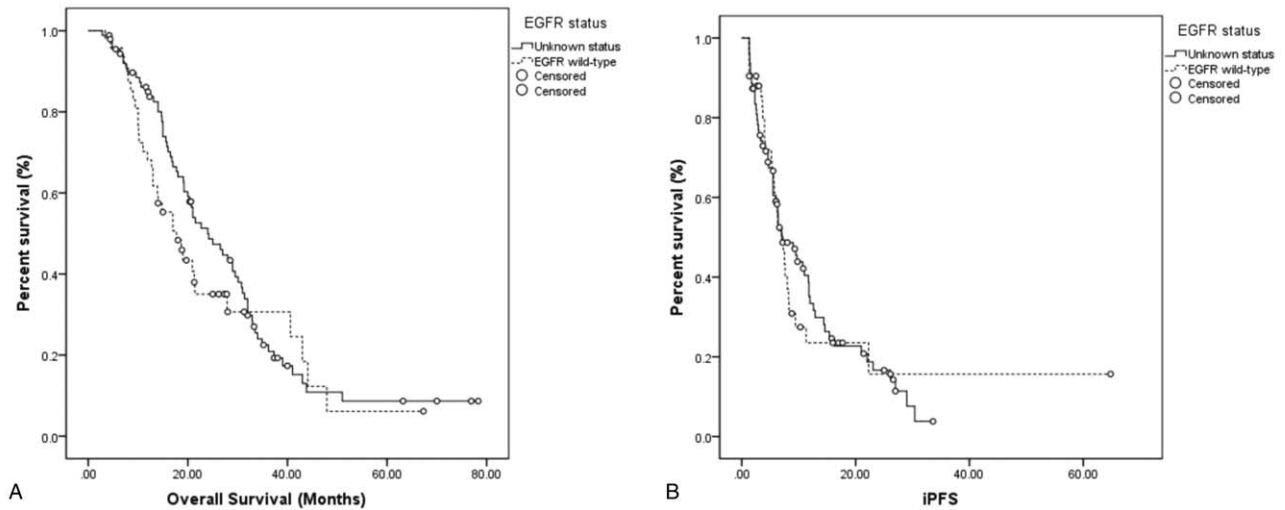
Figure 2. (A) Kaplan–Meier curve illustrating OS of EGFR wild-type and unknown status patients. (B) Kaplan–Meier curve illustrating iPFS of EGFR wild-type and unknown status patients.

received 3 to 4 cycles (Mantel-Byar X-squared = 6.65, P = .001) (Fig. 3A). There was no difference in OS between the patients with combination of pemetrexed chemotherapy and with single agent of pemetrexed (P = .90).

3.3. Intracranial control analysis

The intracranial PFS (iPFS) of patients treated with pemetrexed was 9.5 months (95% CI, 6.6–12.4 months) (Fig. 1B). Those patients who received more than 4 cycles of chemotherapy tend to have longer iPFS than those patients who received 3 to 4 cycles (Mantel-

Byar X-squared = 1.67, P = .19) (Fig. 3B). The patients with combination therapy of pemetrexed and platinum showed better iPFS than those with single agent of pemetrexed (10.7 months vs 7.2 months), but without statistical significance (P = .270). Similar results were also found in unknown EGFR status patients and EGFR wild-type patients (11.7 months vs 7.6 months, P = .23) (Fig. 2B). A total of 29 (21.0%) patients have received pemetrexed-based chemotherapy without CNS radiation, 3 patients had complete response (CR), 11 patients had partial response (PR), 14 patients had stable disease (SD), and 1 patient had progressive disease (PD). The objective response rate (ORR) was 48.3%.
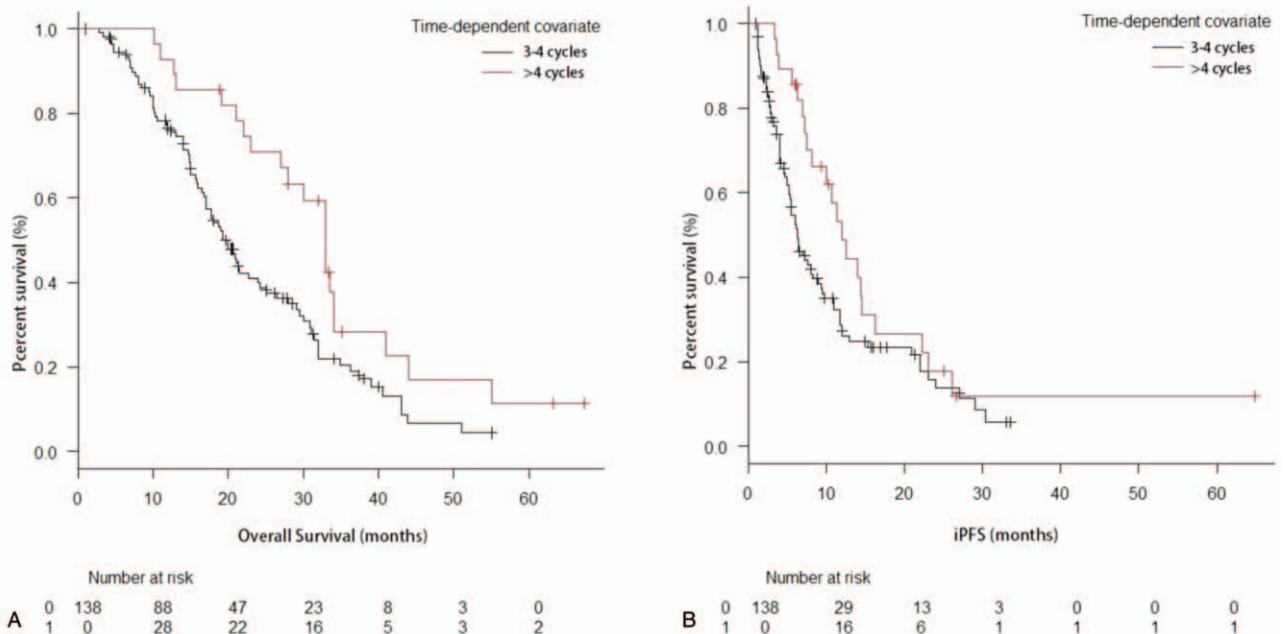

Figure 3. (A) Mantel-Byar analysis of patient OS stratified by cycles of chemotherapy (3–4 cycles vs >4 cycles); (B) Mantel-Byar analysis of patient iPFS stratified by cycles of chemotherapy (3–4 cycles vs >4 cycles).
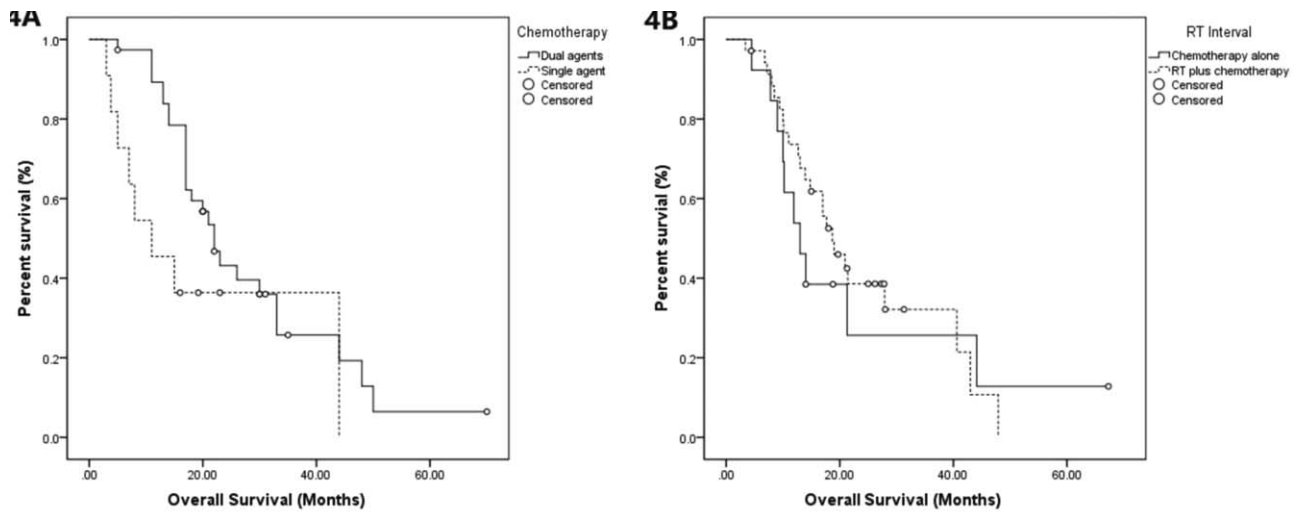
Figure 4. (A) Kaplan–Meier curve analyses of OS on EGFR wild-type patient stratified by agent of chemotherapy (single agent vs dual agents). (B) Kaplan–Meier curve analyses of OS on EGFR wild-type patient stratified by RT interval (chemotherapy alone vs RT plus chemotherapy).

3.4. Efficiency of pemetrexed in EGFR wild-type patients

In the EGFR wild-type subgroup, the median OS was 17.7 months (95% CI, 12.6–22.8 months) (Fig. 2A) and the iPFS was 7.6 months (95% CI, 5.4–8.6 months) (Fig. 2B). Patients treated with dual agents showed a longer OS than those who were treated with pemetrexed alone (17.7 months vs 11.0 months), but the difference was not statistically significant ($P=.078$) (Fig. 4A). Patients who received more than 4 cycles of chemotherapy tended to have longer OS than those who received 3 to 4 cycles (Mantel-Byar X-squared=0.86, $P=.35$), and longer iPFS than 3 to 4 cycles patients (Mantel-Byar X-squared=0.13, $P=.72$). The median OS was similar between the RT plus chemotherapy group and the chemotherapy alone group (18.7 months vs 13.0 months, $P=.677$) (Fig. 4B). No survival difference was found based on the interval time of RT ($P=.820$).

3.5. TKIs for unknown EGFR status patients after progression

Due to the limitation of the medical insurance, the costs of gene detection were not covered and EGFR TKIs were only covered in

locally advanced or metastatic NSCLC patients after the failure of first-line chemotherapy till June 2016 in Zhejiang. It is regrettable that there were number of patients with unknown EGFR status. In subgroup analyses of unknown EGFR status patients, the median OS was 24.0 months (95% CI, 18.2–29.8 months) and the iPFS was 11.7 months (95% CI, 7.6–15.2 months). We noted a statistically significant improvement in median OS for the patients who received EGFR TKIs after progression (46/89) compared to those who did not (43/89). The median OS was 29.0 months in the EGFR TKIs group and 20.3 months in the EGFR TKIs naïve group ($P=.027$).

3.6. The utility of the GPA index model

To assess the utility of the GPA to predict survival of the whole group, the patients were analyzed according to radiation therapy oncology group (RTOG) GPA score, and the median survival was calculated for each group. There was no difference in the OS ($P=.13$) of the group with a GPA score of 0 to 2.5 and those with a GPA score of 3 to 4 (20.0 months vs 22.7 months) (Fig. 5A). Further, in the EGFR wild-type subgroup, we found the OS of
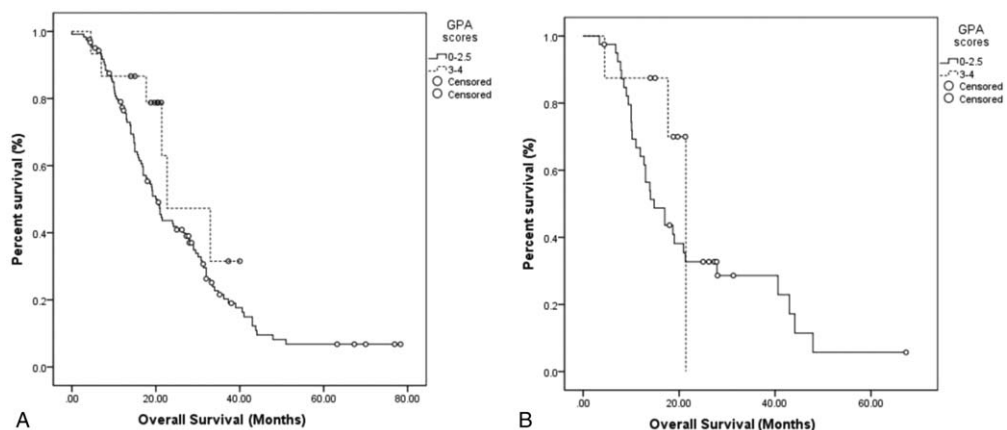

Figure 5. (A) Kaplan–Meier curve analyses of OS patient stratified by GPA scores (0–2.5 vs 3–4). (B) Kaplan–Meier curve analyses of OS on EGFR wild-type patient stratified by GPA scores (0–2.5 vs 3–4).

patients with a GPA score of 0 to 2.5 tended to be worse than those with a GPA score of 3 to 4 (14.8 months vs 21.4 months), but also the difference was not statistically significant (P = .22) (Fig. 5B). This result suggested that the GPA could probably predict survival for this patient population.

3.7. Multivariate analysis

In the multivariate analysis, gender, age, smoking history, KPS, number of intracranial lesions, extracranial metastasis, EGFR status, local treatment of intracranial lesions, cycles of pemetrexed chemotherapy were not found to significantly influence the prognosis. Although it is showed that EGFR status tend to influence the OS, it was not statistically significant (P = .081).

In the EGFR wild-type subgroup, we found age (P = .01), KPS (P = .00), and cycles of pemetrexed chemotherapy (P = .03) were significantly associated with OS, but the number of intracranial lesions, extracranial metastasis were not independent predictors.

4. Discussion

The majority of patients with newly diagnosed EGFR wild-type of NSCLC present with inoperable disease, and platinum-based doublets are recommended as front-line treatment for these patients. Cytotoxic agents clinically tested in combination with cisplatin or carboplatin include pemetrexed, gemcitabine, vinorelbine, irinotecan, and taxanes. Pemetrexed has showed activity in nonsquamous carcinomas with good tolerability, but little is known about its efficacy on brain metastases.

The role of chemotherapy for the treatment of BM has been limited by poor efficacy and high toxicity. Most chemotherapy drugs could not cross the blood–brain barrier (BBB) and would therefore not be active against metastatic disease. However, it is known that the BBB is disrupted when brain metastases develop.[10,11] It is reported that pemetrexed could be detected in cerebrospinal fluid and that pemetrexed combined with platinum achieved a good intracranial response in brain metastases of NSCLC.[8,12,13]

In our study, the median OS was 21.0 months for the whole cohort. The PFS was 8.3 months (95% CI, 6.9–9.7 months) and iPFS was 9.5 months. Our results have verified the ideal efficiency of pemetrexed in the management of NSCLC with BM. Previously a phase II study by Zhang et al[14] had shown that pemetrexed/cisplatin treatment provided comparable overall survival outcomes and was better tolerated than gemcitabine/cisplatin in Chinese patients with advanced NSCLC. And a case report indicated that pemetrexed/cisplatin could achieve excellent efficacy in the primary lesion of the lungs and BM lesion.[15] The improvement of efficacy and tolerance reached in nonsquamous advanced NSCLC patients supported the role of pemetrexed in systematic therapy.

We found patients who received more than 4 cycles of chemotherapy had better survival and intercranial control than those received 3 to 4 cycles (Mantel-Byar X-squared = 0.77, P = .001). According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines version 2.2018 in Oncology for NSCLC, systematic therapy for patients with the PS score of 0 to 2 are usually administered for 4 to 6 cycles in total. For patients with stable disease or response after four cycles, it is recommended of continuation maintenance or switch maintenance.[16] A phase III study (PARAMOUNT) had demonstrated that pemetrexed continuation maintenance therapy resulted in improved OS and PFS versus placebo in nonsquamous

NSCLC.[6,17] In our study, most patients received 4 cycles chemotherapy at most, only 3 patients obtained pemetrexed maintenance treatment. All patients we studied were NSCLC with BM, concerning to the performance status and poor tolerance of chemotherapy, most patients did not get 6 cycles as borderline. We assume that, in some degree, the more cycles of pemetrexed were given, the better survival patients would receive.

The results of our study indicated that the combination of pemetrexed and platinum had the tendency to improve the iPFS and OS when comparing to the single-agent of pemetrexed in EGFR wild-type patients. It is known that cisplatin has formed the backbone of most chemotherapy regimens for NSCLC.[18] One possible reason for our results that did not reach the statistical significance was the limit of small sample size. In clinical practice, we used to adopt platinum-based doublet chemotherapy regiments to achieve a greater disease control.

There was no improvement in the OS of patients who received RT plus chemotherapy compared with these received chemotherapy alone in our study (18.7 months vs 13.0 months, P = .667), which varies from previous studies. It is reported by Cagney et al[19] patients receiving pemetrexed after brain-directed stereotactic radiation appear to benefit from improved intracranial disease control. Our results could be because most patients in the EGFR wild-type group received RT, and only 3 patients did not receive any local treatment. We assume that our conclusion may be due to the small sample size and the nonrandomized study. We are supposed to consider the optimal timing of RT interval according to the BM symptoms. And further randomized controlled trials are needed to examine the correlation between the timing of RT interval and OS.

It is regrettable that the number of patients with unknown status was large because genetic testing was not widely used in earlier years. Due to previous limitations gene detection costs were not covered by basic medical insurance. In subgroup analyses of unknown EGFR status patients, we found a statistically significant improvement in OS of 29.0 months for these who received EGFR TKIs after progression, comparing with only 20.3 months in the EGFR TKIs naïve group (P = .027). As we all know, there are about 40% to 50% of EGFR mutant patients in Asian NSCLC patients. We assume in our study, there could be undetected EGFR mutant patients in these who did not test the EGFR status before. For this part of people, they could markedly benefit from EGFR TKIs and have better survivals. Although China is still a developing country, it is highly recommended for patients to have EGFR gene tested to provide more options for treatment.

There are many limitations in the present study. First, we used a retrospective design, and due to the variety of exclusion factors, there may have been bias in choosing patients. Therefore, the results reported here are not entirely representative of a large sample population. Second, based on the baseline clinical characteristics of the patients, the treatment groups were not homogeneous. Third, the choice for treatment was not random because it was determined by the willingness of both the physicians and the patients, which may have led to deviations between the 2 treatment groups. Finally, follow-up data on toxicities, cognitive impairment and quality of life were lacking, and we were therefore unable to analyze these factors.

5. Conclusion

Pemetrexed shows an ideal effectiveness on EGFR wild-type and unknown EGFR status patients with brain metastases from

advanced NSCLC, and have a good control of activity on brain localizations. EGFR wild-type patients can significantly benefit from pemetrexed continuation maintenance. And the combination of pemetrexed and platinum have the tendency to prolong survival. Although these encouraging results may not be representative of the overall population of patients with advanced lung cancer and brain metastases, they also suggest that the administration of pemetrexed may partially contribute to the differences in response rates, warranting further careful evaluation in prospective randomized studies.

Author contributions

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Resources: Yun Fan.
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