Introduction

Lung cancer is the most common malignant tumor worldwide; 85% of which is pathologically diagnosed as non-small-cell lung cancer (NSCLC) [1]. The 5-year survival rate of NSCLC is very low. Approximately, 15–30% of NSCLC patients develop brain metastases [1] with symptoms including headache, vomiting, and visual disturbances. The median survival time of untreated patients with brain metastases is <3–6 months [2]. The incidence of brain metastases has significantly increased because of the use of better diagnostic methods and the improvement of public health awareness. The main treatments for patients with NSCLC are surgery, radiotherapy, and 

Meta-analysis of whole-brain radiotherapy plus temozolomide compared with whole-brain radiotherapy for the treatment of brain metastases from non-small-cell lung cancer

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Keywords
brain metastases, NSCLC, radiotherapy, TMZ

Abstract

The aim of this meta-analysis was to compare the efficiency of whole-brain radiotherapy (WBRT) plus temozolomide (TMZ) with WBRT for the treatment of brain metastases from non-small-cell lung cancer (NSCLC). For dichotomous variables, outcomes were reported as relative risk ratio (RR) and 95% confidence interval (CI) was used to investigate the following outcome measures: overall response rate, headache, gastrointestinal adverse reactions, and hematological adverse reactions. Twelve randomized controlled trials involving 925 participants (480 received WBRT plus TMZ; 445 received WBRT) were included in the meta-analysis. There was a significant difference between the overall response rate (RR = 1.40, 95% CI 1.24–1.57; Z = 5.51; P < 0.00001), gastrointestinal adverse reactions (RR = 1.46, 95% CI 1.05–2.04; Z = 2.27; P = 0.02), and hematological adverse reactions (RR = 1.45, 95% CI 1.04–2.02; Z = 2.21; P = 0.03) of patients treated with WBRT plus TMZ compared with patients treated with WBRT alone. There was no significant difference between headaches (RR = 1.11, 95% CI 0.93–1.02; Z = 1.13; P = 0.26) in patients treated with WBRT plus TMZ compared with patients treated with WBRT alone. In conclusion, the currently available evidence shows that WBRT plus TMZ increases the overall response rate in patients with brain metastases of NSCLC compared with WBRT alone.

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Meta-analysis of WBRT Plus TMZ and WBRT

Materials and Methods

Data sources

We searched the Wanfang Database, PubMed, the Cochrane Library, Medline, and Elton B. Stephens Company (EBSCO) using the keywords “temozolomide OR TMZ” AND “radiotherapy” AND “brain metastases” AND “non-small-cell lung cancer OR NSCLC.” The publication dates were from 1 January 2002 to 1 June 2017 with no restrictions in language.

Study selection

The inclusion criteria for the RCTs were: (i) pathologically confirmed NSCLC and diagnosed brain metastases with computed tomography (CT) or magnetic resonance imaging (MRI); (ii) aged over 18 years; (iii) radiotherapy and chemotherapy tolerated; (iv) expected lifetime of more than 3 months; (v) compared WBRT versus WBRT plus TMZ; and (vi) reported sufficient data on outcomes.

Exclusion criteria were: (i) nonrandomized and nonclinical controlled trials; (ii) trials with missing data; and (iii) duplicate reports, trials of poor methodological quality, and trials with obvious bias.

Quality assessment

The authors used the “Cochrane handbook for systematic reviews of interventions version [8] 5.0.0” to assess the methodological quality of the included RCTs, which assessed: (i) generation of the random allocation scheme (random sequence generation); (ii) allocation concealment; (iii) blinding of participants and personnel; (iv) blinding of outcome assessment; (v) incomplete outcome data; (vi) selective reporting; and (vii) other sources of bias.

Statistical methods

The data were analyzed using Review Manager v.5.3 software (Cochrane Collaboration, Oxford, UK) and SPSS 16.0. For dichotomous variables, outcomes were reported as relative risk ratio (RR) and 95% confidence interval (CI). A P-value of <0.05 was considered statistically significant. The heterogeneity test with inconsistency index ($I^2$) statistic and Q statistic was performed [9]. If the outcomes were found to have good homogeneity ($P > 0.1$; $I^2 \leq 50$%), a fixed effect model was used for secondary

The authors carefully analyzed the methodology of the articles to select the qualified RCTs. With the keywords used, 91 papers (67 in Chinese and 24 in English) were identified. According to the inclusion and exclusion criteria, we independently examined the full text and discussed each article together.

Data extraction and synthesis

The investigators carefully extracted data from the eligible studies. Data included the name of the first author, year of publication, journal name, quality of the study, intervention, number of patients in the study, dosage and duration of the two groups, median survival time, and the number of patients with adverse reactions.

Main outcome(s) and measure(s)

The following outcomes were measured: overall response rate, headache, gastrointestinal adverse reactions, and hematologic adverse reactions. Overall response was defined as complete response and partial response which was measured by brain CT or MRI according to World Health Organization criteria. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. The number of patients with adverse reactions was collected directly from the published papers. Disagreement regarding data extraction was resolved by discussion and consensus among the investigators.

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analysis; if not ($P < 0.1; I^2 > 50\%$), a random-effect model was used [9].

**Results**

As mentioned above, we identified the eligible paper carefully. The literature selection process is presented in the PRISMA flow chart (Fig. 1) according to the PRISMA guidelines. After comprehensive discussion and analysis, 12 RCTs were selected and included for final meta-analysis.

**Included studies**

In total, 925 patients were enrolled in the 12 included RCTs. The patients all had pathologically confirmed NSCLC and brain metastases diagnosed with CT or MRI. Of the 925 patients, 480 received WBRT plus TMZ and 445 received WBRT. Radiation and drug dose varied in different studies. The characteristics of the 12 included RCTs are shown in Table 1. Figure 2 depicts the assessment of the methodological quality of the 12 RCTs. The funnel plot, which was highly symmetrical, was used to analyze the publication bias (Fig. 3).

**Overall response rate**

Eleven RCTs that reported the overall response rate were selected in the analysis. The heterogeneity test for overall response rate was not statistically significant, allowing the data for each outcome to be calculated using the fixed effects model ($I^2 = 14\%; P = 0.31$). The
Table 1. Summary of the characteristics of the 12 trials included in the meta-analysis (1 cycle = 28 days).

| Author             | Groups              | No of patients (WBRT + TMZ/WBRT) | Treatment                                                                 | Gender (Male/Female) | Age (Average age OR Median age) | Pathological type (Squamous cell carcinoma/Adenocarcinoma/Other) | References |
|--------------------|---------------------|----------------------------------|---------------------------------------------------------------------------|----------------------|--------------------------------|------------------------------------------------------------------|------------|
| Chua, et al. (2010)| WBRT + TMZ          | 47                               | WBRT (30 Gy/10 f) + TMZ (75 mg/m² * 21 d or 28 d)                         | 30/7                 | 38–78 (59)                     | -                                                                | [6]        |
| Hassler, et al. (2013)| WBRT + TMZ      | 22                               | WBRT (30 Gy/10 f or 40 Gy/20 f) + TMZ (75 mg/m² * 2 weeks + 100 mg/m² * 14 d * 6 cycles) | 13/9                 | 36–85 (69)                     | -                                                                | [16]       |
| Yong Peng, et al. (2008)| WBRT + TMZ   | 19                               | WBRT (30 Gy/10 f or 40 Gy/20 f) + TMZ (200 mg/m² * 5 * 6 cycles)          | 11/8                 | 35–71 (54)                     | -                                                                | [23]       |
| Shi, et al. (2014) | WBRT + TMZ          | 43                               | WBRT (40 Gy/20 f) + TMZ (75 mg/m² during WBRT)                           | 25/18                | 38–72 (55)                     | 12/29/2                                                          | [21]       |
| Cheng, et al. (2013)| WBRT + TMZ          | 30                               | WBRT (30 Gy/10 f or 40 Gy/20 f) + TMZ (75 mg/m² during WBRT)             | 18/12                | 39–70 (52)                     | -                                                                | [19]       |
| Xie, et al. (2007) | WBRT + TMZ          | 25                               | WBRT (40 Gy/20 f) + TMZ (200 mg/m² * 5 d)                               | 36/14                | 30–70 (56)                     | 20/28/2                                                          | [18]       |
| Fei, et al. (2017) | WBRT + TMZ          | 26                               | WBRT (30 Gy/10 f or 40 Gy/20 f) + TMZ (75 mg/m² during WBRT)             | 16/10                | -                              | 14/9/3                                                          | [24]       |
| Li, et al. (2017)  | WBRT + TMZ          | 39                               | WBRT (40 Gy/20 f) + TMZ (75 mg/m² * 4 weeks + 150 mg/m² * 5 d * 6 cycles) | 19/20                | 21–70 (47.37 ± 4.56)           | -                                                                | [22]       |
| Tian Lu (2015)     | WBRT + TMZ          | 52                               | WBRT (40 Gy/20 f) + TMZ (200 mg/m² * 5 d * 4 cycles)                    | 28/24                | 46–65 (58.9 ± 5.9)             | 47/55/0                                                          | [26]       |
| Doudou, et al. (2015)| WBRT + TMZ      | 18                               | WBRT (40 Gy/20 f) + TMZ (75 mg/m² * 4 weeks + 100 mg/m² * 5 d * 6 cycles) | 23/27                | -                              | 14/8/4                                                          | [7]        |
| Zhao (2016)        | WBRT + TMZ          | 18                               | WBRT (40 Gy/20 f) + TMZ (75 mg/m² * 4 weeks + 150 mg/m² * 5 d * 6 cycles) | 11/7                 | 37–72 (53.5)                   | 38–69                                                           | [13]       |
| Deng (2017)        | WBRT + TMZ          | 129                              | WBRT (30 Gy/10 f) + TMZ (75 mg/m² during WBRT + 100 mg/m² * 5 d * 6 cycles) | 69/60                | 34–85 (60)                     | -227/-                                                          | [25]       |
|                    | WBRT                | 109                              | WBRT (30 Gy/10 f)                                                       | 67/42                |                                |                                                                  |            |

WBRT, whole-brain radiotherapy; TMZ, temozolomide.
Figure 2. Summary diagram of risk of bias percentile chart.
meta-analysis indicated that there was a significant difference in the overall response rate in patients treated with WBRT plus TMZ compared with WBRT alone (RR = 1.40, 95% CI 1.24–1.57; Z = 5.51; P < 0.00001) (Fig. 4).

**Median survival time**

According to SPSS analysis, there was a significant difference about median survival time in patients between the two groups in relevant 10 RCTs (P < 0.05) (Table 2).

And the median survival time of the WBRT plus TMZ was longer than that of the WBRT alone.

**Headache**

Eleven RCTs that reported headache adverse reactions were selected in the analysis. The heterogeneity test for headache was not statistically significant, allowing the data for each outcome to be calculated using fixed effects models (I² = 0%; P = 1.00). The meta-analysis indicated that there was no significant difference in the headache adverse reactions in patients treated with WBRT plus TMZ compared with WBRT alone (RR = 1.11, 95% CI 0.93–1.02; Z = 1.13; P = 0.26) (Fig. 5).

**Gastrointestinal adverse reactions**

Twelve RCTs that reported gastrointestinal adverse reactions were selected in the analysis. The heterogeneity test for gastrointestinal adverse reactions was statistically significant, allowing the data for each outcome to be calculated using random effects models (I² = 70%; P = 0.0001). The meta-analysis indicated that there was a significant difference in the gastrointestinal adverse reactions in patients treated with WBRT plus TMZ compared with WBRT alone (RR = 1.46, 95% CI 1.05–2.04; Z = 2.27; P = 0.02) (Fig. 6).

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Table 2. Median survival time in trials included in the meta-analysis (P < 0.05).

| Study or Subgroup | Events | Total | Weight | RR (95% CI) |
|-------------------|--------|-------|--------|-------------|
| DW + TMZ          | 16     | 18    | 10     | 18          |
| TMZ               | 26     | 16    | 25     | 8.8%        |
| Gung Li (2017)    | 39     | 34    | 24     | 12.9%       |
| Hassler (2013)    | 5      | 22    | 2      | 13.3%       |
| Ji-Yong (2008)    | 19     | 19    | 21     | 10.0%       |
| Jia (2007)        | 25     | 11    | 25     | 5.9%        |
| Le (2014)         | 31     | 43    | 21     | 11.5%       |
| Shi-Jie (2015)    | 30     | 12    | 30     | 6.4%        |
| Tian-Lu (2015)    | 42     | 35    | 50     | 18.1%       |
| Wei (2013)        | 30     | 12    | 26     | 8.9%        |
| Xia (2017)        | 129    | 27    | 109    | 12.8%       |
| Total (95% CI)    | 433    | 397   | 100%   | 1.40 (1.24, 1.57) |

| Study or Subgroup | Events | Total | Weight | RR (95% CI) |
|-------------------|--------|-------|--------|-------------|
| DW + TMZ          | 16     | 18    | 10     | 18          |
| TMZ               | 26     | 16    | 25     | 8.8%        |
| Gung Li (2017)    | 39     | 34    | 24     | 12.9%       |
| Hassler (2013)    | 5      | 22    | 2      | 13.3%       |
| Ji-Yong (2008)    | 19     | 19    | 21     | 10.0%       |
| Jia (2007)        | 25     | 11    | 25     | 5.9%        |
| Le (2014)         | 31     | 43    | 21     | 11.5%       |
| Shi-Jie (2015)    | 30     | 12    | 30     | 6.4%        |
| Tian-Lu (2015)    | 42     | 35    | 50     | 18.1%       |
| Wei (2013)        | 30     | 12    | 26     | 8.9%        |
| Xia (2017)        | 129    | 27    | 109    | 12.8%       |
| Total (95% CI)    | 433    | 397   | 100%   | 1.40 (1.24, 1.57) |

WBRT, whole-brain radiotherapy; TMZ, temozolomide.
Hematologic adverse reactions

Twelve RCTs reporting on hematologic adverse reactions were selected in the analysis. The heterogeneity test for hematologic adverse reactions was statistically significant, allowing the data for each outcome to be calculated using random effects models ($I^2 = 64\%$; $P = 0.001$). The meta-analysis indicated that there was a significant difference in the hematologic adverse reactions in patients treated with WBRT plus TMZ compared with WBRT alone (RR = 1.45, 95% CI 1.04–2.02; $Z = 2.21$; $P = 0.03$) (Fig. 7).

Discussion

In this meta-analysis, we compared WBRT plus TMZ with WBRT for the treatment of brain metastases of NSCLC. The meta-analysis proved that there was a significant difference in the overall response rate in patients between WBRT plus TMZ and WBRT alone. Our findings indicate that the combination therapy can significantly increase the overall response rate, prolong the median survival time, and enhance the antitumor effect.

Approximately, 15–30% of NSCLC patients develop brain metastases [1], which presents a particular challenge. In the past, the standard therapy for brain metastases was WBRT [10], which may provide local disease control, but only has a marginal survival benefit [6]. Unfortunately, owing to the local disease control by WBRT, there is still a high risk in both CNS and systemic progression. The median survival time of patients having WBRT is only 3–4 months after the diagnosis of the brain metastases [6]. Therefore, radiotherapy is often combined with chemotherapy for patients with brain metastases [11, 12].

WBRT can prolong survival, but most patients survive less than half a year after radiation. It is difficult for
many chemotherapeutic agents to reach the focus through the blood–brain barrier, leading to poor efficacy [13]. TMZ is a second-generation, alkylating agent with anti-tumor activity in the brain tumor [14, 15]. The role of chemotherapy for treating brain metastases from NSCLC remains controversial because of its chemical toxicity [16]. Chemotherapy drugs can cross the blood–brain barrier, leading to high concentrations in the CNS. Some past experiments indicate that the efficacy of TMZ is enhanced by radiotherapy [7, 16]. However, the cytotoxic effect of TMZ might be enhanced by its radiosensitization during WBRT in brain metastases. Evidence concerning the efficacy of chemotherapy combined with radiotherapy in patients with brain metastases is accumulating [17]. TMZ can act on various stages of tumor cell division and ultimately promote apoptosis [18, 19].

The important outcome of cancer treatment is overall response rate. According to Figure 4, there was a significant difference in the overall response rate in patients treated with WBRT plus TMZ compared with WBRT alone. However, each RCT reported different radiotherapy doses and TMZ dosages. The overall response rate in the combination therapy group was still 1.4 times greater than that in the WBRT group, which indicates the positive effect of the combination therapy [20]. Another important endpoint in oncology research is survival time. However, as each of the included studies did not provide sufficient data, we could not analyze the median survival time using the hazard ratio (HR). From the published articles, we extracted the relevant data for median survival time of the two comparison groups from 10 RCTs (Table 2). Our findings indicate that the combination therapy prolongs the median survival relative to WBRT alone (Table 1). The mechanism of the antitumor activity may be: (1) Chemotherapy drugs can control the development of the primary lesion and metastatic brain lesions; (2) WBRT disrupts the blood–brain barrier function, rendering it easier for TMZ to cross the blood–brain barrier, thereby improving the curative effect [21, 22]. Although there were more adverse effects in the combined therapy group, they were resolved using medication [23–25]. The patients did not discontinue the treatment because of the TMZ adverse effects. TMZ mainly causes nausea, vomiting, and fatigue, which most patients can tolerate [7]. These results all prove that WBRT combined with TMZ is effective and safe.

The meta-analysis had several limitations. As shown in Table 1, the meta-analysis still analyzed only a limited number of eligible studies and a relatively small number of patients. Of the nine Chinese-language RCTs and the three English-language RCTs, only four demonstrated random allocation methods such as the envelope method and the random number table, while the remaining studies did not specify the method of randomization. In addition, 11 RCTs did not mention the blinding of participants and personnel (Fig. 2). Although the general characteristics of the patients, such as age and Karnofsky performance score (KPS), were roughly the same, the results still involved selection bias. Moreover, as positive results are more likely to be published, publication bias should also be taken into consideration. However, the standard of outcomes including overall response rate, headache, gastrointestinal adverse reactions, and hematologic adverse reactions are objective; therefore, the lack of blinding of observers would not have caused significant bias.

In conclusion, the currently available evidence shows that WBRT plus TMZ can increase the overall response rate in patients with brain metastases of NSCLC, compared with WBRT alone. TMZ can cause some adverse reactions, which are mostly self-limiting and can be controlled.
with drugs. Large, high-quality, double-blind trials are needed to confirm the efficiency of WBRT plus TMZ [26]. The optimal mode and dose of radiotherapy and chemotherapy also needs further research.

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**Conflict of Interest**

The authors declare that they have no competing interests.

**Declaration**

Ethics approval and consent to participate: Not applicable; Consent for publication: Not applicable; Availability of data and material: All data generated or analyzed during this study are included in published article.

**References**

1. Huang, H., J. Liu, Q. Meng, and G. Niu. 2015. Multidrug resistance protein and topoisomerase 2 alpha expression in non-small cell lung cancer are related with brain metastasis postoperatively. Int. J. Clin. Exp. Pathol. 8:11537–11542.

2. Bai, G. R., J. B. An, Y. Chu, X. Y. Wang, S. M. Li, K. J. Yan, et al. 2016. Comparison of the effectiveness of whole-brain radiotherapy plus temozolomide versus whole-brain radiotherapy in treating brain metastases based on a systematic review of randomized controlled trials. Anticancer Drugs 27:1–8.

3. Siena, S., L. Crino, M. Danova, S. Del Prete, S. Casciniu, S. Salvagni, et al. 2010. Dose-dense temozolomide regimen for the treatment of brain metastases from melanoma, breast cancer, or lung cancer not amenable to surgery or radiosurgery: a multicenter phase II study. Ann. Oncol. 21:655–661.

4. Athanassiou, H., M. Synodinou, E. Maragoudakis, M. Paraskevaidis, C. Verigos, D. Misi lilidou, et al. 2005. Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. J. Clin. Oncol. 23:2372–2377.

5. Ostermann, S., C. Csajka, T. Buclin, S. Leyvraz, F. Lejeune, L. A. Decosterd, et al. 2004. Plasma and cerebrospinal fluid population pharmacokinetics of temozolomide in malignant glioma patients. Clin. Cancer Res. 10:3728–3736.

6. Chua, D., M. Krzakowski, C. Chouaid, M. G. Pallotta, J. I. Martinez, M. Gottfried, et al. 2010. Whole-brain radiation therapy plus concomitant temozolomide for the treatment of brain metastases from non-small-cell lung cancer: a randomized, open-label phase II study. Clin. Lung Cancer 11:176–181.

7. Li, Doudou, Zhuohei Bi, Yanhui Jiang, and Yimin Liu. 2015. Effect of whole brain radiotherapy combined with temozolomide in the treatment of brain metastasis of non-small cell lung cancer. Guangdong Med. J. 36:1534–1536.

8. Higgins, J. P. T.S. Green (eds). Cochrane handbook for systematic reviews of interventions version 5.0.0 (updated February 2008) [EB/OL]. [2008-07-7]. http://www.cochranehandbook.

9. Ioannidis, J. P., and N. A. Patsopoulos. 2007. Uncertainty in heterogeneity estimates in meta-analyses. BMJ 335:914–916.

10. Addeo, R., C. De Rosa, V. Faiola, L. Leo, G. Cennamo, L. Montella, et al. 2008. Phase 2 trial of temozolomide using protracted low-dose and whole-brain radiotherapy for nonsmall cell lung cancer and breast cancer patients with brain metastases. Cancer 113:2524–2531.

11. Cortot, A. B., L. Geriniere, G. Robinet, J. L. Breton, R. Corre, L. Falchero, et al. 2006. Phase II trial of temozolomide and cisplatin followed by whole brain radiotherapy in non-small-cell lung cancer patients with brain metastases: a GLOT-GFPC study. Ann. Oncol. 17:1412–1417.

12. Dziadziuszko, R., A. Ardizzoni, P. E. Postmus, E. F. Smit, A. Price, C. Debruyne, et al. 2003. Temozolomide in patients with advanced non-small cell lung cancer with and without brain metastases: a phase II study of the EORTC Lung Cancer Group (08965). Eur. J. Cancer 39:1271–1276.

13. Zhao, S. J. 2016. Clinical efficacy of Temozolomide Combined with whole brain radiotherapy in the treatment of non small cell lung cancer with brain metastasis. Chin J Clin Rational Drug Use 9:102–103.

14. Minniti, G., C. Scaringi, G. Lanzetta, A. Bozzao, A. Romano, V. De Sanctis, et al. 2014. Whole brain reirradiation and concurrent temozolomide in patients with brain metastases. J. Neurooncol. 118:329–334.

15. Kouvavis, J. R., A. Miladou, V. E. Kouloulidas, D. Kolokouris, M. J. Balafouta, X. N. Papacharalampous, et al. 2007. Phase II study of temozolomide and concomitant whole-brain radiotherapy in patients with brain metastases from solid tumors. Onkologie 30:361–366.

16. Hassler, M. R., W. Pfeifer, T. H. Knocke-Abulesz, K. Geissler, G. Altiorjai, K. Dieckmann, et al. 2013. Temozolomide added to whole brain radiotherapy in patients with multiple brain metastases of non-small-cell
17. Zhao, Q., Q. Qin, J. Sun, D. Han, Z. Wang, J. Teng, et al. 2016. Brain radiotherapy plus concurrent temozolomide versus radiotherapy alone for patients with brain metastases: a meta-analysis. PLoS ONE 11:e0150419.

18. Xie, J. Y., D. B. Xiang, G. Wang, Z. Z. Yang, Y. Li, X. Yu, et al. 2007. Temozolomide Combined with whole brain radiotherapy for brain metastases from non-small cell lung cancer clinical research. Chongqing Med. 36:1941–1942.

19. Cheng, W., L. F. Zhang, and N. Xiao. 2013. Efficacy of Temozolomide Combined with radiotherapy for non-small cell lung cancer with brain metastasis. Hebei Med. J. 35:2307–2308.

20. Liao, K., Z. F. Bi, Y. He, and Y. M. Liu. 2012. Whole brain radiation therapy plus temozolomide in the treatment of brain metastases from non small cell lung cancer: a meta-analysis. Zhonghua Yi Xue Za Zhi 92:3199–3203.

21. Shi, L., J. L. Xi, and W. Zeng. 2014. Temozolomide Combined with radiation therapy of non-small cell lung cancer with brain metastases efficacy. Mod. J. Integ. Trad. Chin. Western Med. 23:3002–3003.

22. Li, G. 2017. Comparative analysis of Temozolomide Combined with whole brain radiotherapy in patients with brain metastases from non-small cell lung cancer. Front. Med. 7:153–154.

23. Yong Peng, J., J. L. Zeng, Z. W. Zhu, M. W. Chen, and Z. Q. Zhang. 2008. Oral temozolomide concurrent radiotherapy treatment of non-small cell lung cancer with brain metastasis. Eval. Pract. Clin. Med. 9:37–38.

24. Fei, T., G. Cui, H. Shi, et al. 2017. Clinical observation of radiotherapy combined with temozolomide in the treatment of brain metastasis of non-small cell lung cancer. J. Int. Oncol. 44:271–273.

25. Deng, X., Z. Zheng, B. Lin, H. Su, H. Chen, S. Fei, et al. 2017. The efficacy and roles of combining temozolomide with whole brain radiotherapy in protection neurocognitive function and improvement quality of life of non-small-cell lung cancer patients with brain metastases. BMC Cancer 17:42.

26. Tian-lu, G. 2015. A randomized controlled study of Temozolomide Combined with whole brain radiotherapy for brain metastases from non-small cell lung cancer. Mod. Instrum. Med 21:36–38.