Review Article

Combining Whole-Brain Radiotherapy with Gefitinib/Erlotinib for Brain Metastases from Non-Small-Cell Lung Cancer: A Meta-Analysis

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Received 3 July 2015; Accepted 2 December 2015

Academic Editor: Jun Deng

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Background. To comprehensively assess the efficacy and safety of whole-brain radiotherapy (WBRT) combined with gefitinib/erlotinib for treatment of brain metastases (BM) from non-small-cell lung cancer (NSCLC). Methods. Databases including PubMed, EMBASE.com, Web of Science, and Cochrane Library were searched from inception to April 12, 2015. Studies on randomized controlled trials (RCTs) and case-control trials comparing WBRT combined with gefitinib/erlotinib versus WBRT alone for BM from NSCLC were included. Literature selection, data extraction, and quality assessment were performed independently by two trained reviewers. RevMan 5.3 software was used to analyze data. Results. A total of 7 trials involving 622 patients were included. Compared with WBRT alone or WBRT plus chemotherapy, WBRT plus gefitinib/erlotinib could significantly improve response rate (OR = 2.16, 95% CI: 1.35–3.47; P = 0.001), remission rate of central nervous system (OR = 6.06, 95% CI: 2.57–14.29; P < 0.0001), disease control rate (OR = 3.34, 95% CI: 1.84–6.07; P < 0.0001), overall survival (HR = 0.72, 95% CI: 0.58–0.89; P = 0.002), and 1-year survival rate (OR = 2.43, 95% CI: 1.51–3.91; P = 0.0002). In adverse events (III–IV), statistically significant differences were not found, except for rash (OR = 7.96, 95% CI: 2.02–31.34; P = 0.003) and myelosuppression (OR = 0.19, 95% CI: 0.07–0.51; P = 0.001). Conclusions. WBRT plus gefitinib/erlotinib was superior to WBRT alone and well tolerated in patients with BM from NSCLC.

1. Introduction

Brain metastases (BM) are the most frequent intracranial brain tumors, which can be found in approximately 20–40% of all cancer patients. Lung and breast cancers and melanoma are responsible for up to 80% of metastatic brain lesions [1]. Among patients with non-small-cell lung cancer (NSCLC), the proportion that develops brain metastases is as high as 50% [2]. Life expectancy for these patients is poor, and the average survival is 1-2 months without any treatment [3]. A median survival of 3–6 months can be obtained for patients receiving symptomatic therapy with corticosteroids and whole-brain radiotherapy (WBRT) [4].

Recently, several phase II or phase III trials of standard platinum-based chemotherapy regimens for BM from NSCLC have been conducted [5–10], resulting in 23%–68% response rate and 4–12.6-month overall survival. However the effect of combining WBRT with chemotherapy in the management of BM is limited and inconsistent due to the limited ability of most chemotherapeutic drugs to cross the blood brain barrier [11].

In recent years, new targeted therapies are undergoing active development and encouraging results have been obtained so far [12]. A previously published review demonstrated the intracranial efficacy of targeted therapies (EGFR tyrosine kinase inhibitors, ALK inhibitors), which were
globally superior to the efficacy of standard chemotherapy
[13]. However, this review was qualitative and the quality of
evidence was not evaluated. Some retrospective series and
phase II randomized studies have been conducted
currently to compare the efficacy of combining WBRT with
gerfinib/erlotinib versus WBRT alone for patients with BM
from NSCLC.

Our study aims therefore to comprehensively assess the
quality of currently available evidences and to quantitatively
evaluate the efficacy and safety of WBRT combined with
gerfinib/erlotinib for BM from NSCLC.

2. Methods

This study adhered to the Preferred Reporting Items for
Systematic Review and Meta-Analysis (PRISMA) statement
[14]. Ethical approval and patient consent were unnecessary
for the current study as this was a meta-analysis based on
published studies. Literature retrieval, literature selection,
data extraction, and quality assessment were performed inde-
pendently by two trained reviewers; disagreements between
the reviewers were resolved by consulting a third expert
adjudicator.

2.1. Literature Retrieval. Databases retrieved included
PubMed, EMBASE.com, Web of Science (via ISI Web of
Knowledge), and the Cochrane Library from inception to
April 12, 2015, using the terms epidermal growth factor recep-
tor, EGFR, erlotinib, tarceva, erbitinib, iressa, gefitinib, gefti-
atin, brain neoplasm*, brain cancer*, brain carcinoma*,
brain tumor*, metastasis, lung neoplasm*, lung cancer*, lung
carcinoma*, lung tumor*, whole-brain radiotherapy, WBRT,
and other. The references of included studies were tracked
to identify potential relevant studies. The search strategy for
PubMed was as follows: ((((("l lung neoplasm") [Title/Abstract]
OR "lung cancer") [Title/Abstract] OR "lung carcinoma")
[Title/Abstract] OR "lung tumor") [Title/Abstract] OR "Lung
Neoplasms"[Mesh])) AND (("metastasis") [Title/Abstract]) AND
((("brain neoplasm") [Title/Abstract] OR "brain cancer")
[Title/Abstract] OR "brain carcinoma") [Title/Abstract] OR
"brain tumor") [Title/Abstract]) OR "Brain Neoplasms"
[Mesh])) AND (("whole-brain radiotherapy")[Title/Abstract]
OR WBRT)[Title/Abstract] OR "radiation therapy"[Title/Abstract]
OR radiotherapy[Title/Abstract] OR "irradiation
therapy"[Title/Abstract] OR "radiation therapy"[Title/Abstract]
OR "Radiotherapy"[Mesh])) AND ((("epidermal
growth factor receptor") [Title/Abstract] OR EGFR[Title/Abstract]
OR erlotinib[Title/Abstract] OR tarceva[Title/Abstract]
OR erbitinib[Title/Abstract] OR iressa[Title/Abstract]
OR gefitinib[Title/Abstract] OR gefitinib[Title/Abstract]))
OR "Receptor, Epidermal Growth Factor"[Mesh]).

2.2. Inclusion Criteria. Studies meeting the following eligi-
bility criteria were included: (a) type of population: histo-
logically or cytologically confirmed NSCLC and multiple
BM (≥3) documented by MRI or contrast CT scan; aged 18
years of age or older; (b) type of intervention: WBRT plus
erlotinib/gefitinib; (c) type of comparison: WBRT alone or
WBRT plus chemotherapy; (d) type of design: randomized
controlled trials (RCTs) or case-control studies; (e) type of
outcomes: response rate (RR) and overall survival (OS) were
primary endpoints; toxicity, disease control rate (DCR), 1-
year survival rate, and remission rate of central nervous
system (RR-CNS) were secondary endpoints.

2.3. Literature Selection. All records were downloaded and
imported into EndNote X6, which is a reference management
software tool. Duplicates were removed and the title and
abstract of the remaining records were examined indepen-
dently by two reviewers according to inclusion and exclusion
criteria. Then the full texts of potentially relevant studies were
obtained to identify interesting studies. Reasons for exclusion
were documented.

2.4. Data Extraction and Assessment of Risk of Bias. Data
were extracted using a predesigned data extraction sheet
including the first author, year of publications, sample,
median age, intervention regimen, control regimen, study
design, outcomes, median OS, and median PFS. Kaplan-
Meier curve was read by Engauge Digitizer version 4.1 (avail-
able at http://sourceforge.net/) if the adequate data were not
reported in the papers [15], and the formula recommended by
Spruance et al. [16] was used to calculate the corresponding
HR of the missing survival data.

The risk of bias was assessed according to the Cochrane
Handbook version 5.1.0 [17], including method of random
sequence generation (selection bias), allocation concealment
(selection bias), blinding (performance bias and detection
bias), incomplete outcome data (detection bias), and selective
reporting (detection bias). We evaluated methodological
quality as low, high, or unclear risk of bias.

2.5. Data Analysis. The odds ratio (OR) with 95% confidence
interval (95% CI) was calculated regarding to RR, CN-RR,
DCR, 1-year survival rate, and AEs. The Chi-square statistic
was used to assess the heterogeneity between trials with
I² less than 50% and P value greater than 0.10 suggesting
that there was no statistical heterogeneity, and a Mantel-
Haenszel fixed effects model was used for meta-analysis.
A Mantel-Haenszel random effects model was used when
clinical characteristics and methodology were not identified
to have great difference and I² was greater than 50% and P
value was less than 0.10. If the clinical characteristic and/or
methodology across studies were considered to be obviously
different, only qualitative analysis was adopted [18]. Inverse
variance fixed or random effects model was used to pool
the overall hazard ratio (HR) for OS. When heterogeneity was
identified, subgroup analysis and metaregression were
conducted to determine the possible causes of heterogeneity
such as different target agents (erlotinib or gefitinib), different
study designs (randomized or nonrandomized), and sample
size (<100 or ≥100). Sensitivity analysis was performed to
identify influence of the study regarding overall effective size.
In addition, potential publication bias was assessed by using
the Begg and Egger tests [19, 20]. P value less than 0.05 was
considered significant. All data analysis was performed by
using RevMan 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark) and STATA 12.0 software (Stata Corporation, College Station, Texas, USA).

3. Results

3.1. Literature Selection and Characteristics of Included Studies. A total of 426 records were identified from electronic databases and 4 references were tracked. Finally, 7 studies [21–27] involving 622 patients were included. The search results and selection details are shown in Figure 1.

The detailed characteristics of included studies are shown in Table 1. Of the seven studies included, three [22, 24, 26] were randomized controlled trials and four [21, 23, 25, 27] were case-control studies. They were published between 2012 and 2014. The sample sizes ranged from 53 to 161. Three studies could be identified as phase II and four did not report trial phase. Median OS was reported in five studies [22, 24–27], and only two [22, 27] reported median nPFS.

3.2. Assessment of Risk of Bias. The details of this analysis are shown in Figure 2. Four studies were case-control trials; therefore the risk of bias was high regarding adequate sequence generation, adequate allocation concealment, and blinding. Of three RCTs included, all described methods for adequate sequence generation such as center random and minimization method; two RCTs reported using adequate allocation concealment, and one RCT was a double-blinded design study. The overall methodological quality of included studies was poor because only three were RCTs.

4. Results of Meta-Analysis

4.1. Response Rate (RR). Four studies [23–25, 27] reported the overall response rate for patients with BM. The heterogeneity test indicated that a fixed effects model could be used to pool the RR ($I^2 = 17\%$, $P = 0.31$). Compared with WBRT alone, there was a statistically significant improvement in RR for WBRT combined with gefitinib/erlotinib (OR = 2.16, 95% CI: 1.35–3.47; $P = 0.001$) (Figure 3).

Three studies [21, 23, 25] reported the RR-CNS, with 273 patients involved. There was no significant statistical heterogeneity in pooled analysis of all included studies ($I^2 = 22\%$, $P = 0.28$) and thus a fixed effects model was used to perform meta-analysis. Compared with WBRT alone, there was a statistically significant improvement in RR-CNS for WBRT combined with gefitinib/erlotinib (OR = 6.06, 95% CI: 2.57–14.29; $P < 0.0001$) (Figure 3).

4.2. Disease Control Rate (DCR). Four studies [23–25, 27] reported the overall response rate, with 429 patients involved. The heterogeneity test indicated that a fixed effects model could be used ($I^2 = 0\%$, $P = 0.59$). Compared with WBRT alone, there was a statistically significant improvement in DCR for WBRT combined with gefitinib/erlotinib (OR = 3.34, 95% CI: 1.84–6.07; $P < 0.0001$) (Figure 3).

4.3. Overall Survival (OS). Five studies [21, 22, 25–27] reported the overall survival, with 408 patients involved. The heterogeneity test indicated that a fixed effects model could be used ($I^2 = 33\%$, $P = 0.20$). The meta-analysis showed that WBRT combined with gefitinib/erlotinib significantly prolonged OS compared to WBRT alone (HR = 0.72, 95% CI: 0.58–0.89; $P = 0.002$) (Figure 4).

4.4. 1-Year Survival Rate. Four studies [24–27] reported the 1-year survival rate, with 327 patients involved. The heterogeneity test indicated that a fixed effects model could be used ($I^2 = 0\%$, $P = 0.45$). The meta-analysis showed that WBRT combined with gefitinib/erlotinib significantly prolonged 1-year survival rate compared to WBRT alone (OR = 2.43, 95% CI: 1.51–3.91; $P = 0.0002$) (Figure 5).

4.5. Adverse Events (III-IV). The results of the meta-analysis for adverse events are shown in Figure 6. The heterogeneity tests for all adverse events indicated that there were no statistical differences except for myelosuppression (III-IV).
| Studies          | Samples | Median age (years) | Intervention regimens | Control regimens | Design       | Phase | Median OS (months) | Median nPFS (months) |
|------------------|---------|-------------------|-----------------------|------------------|--------------|-------|-------------------|---------------------|
| Zhuang et al., 2013 [21] | 23 31   | 60 (37–76) 63 (43–81) | WBRT 30 Gy/10 f plus erlotinib 150 mg/day | WBRT 30 Gy/10 f  | Case-control | II    | NR                | NR                  |
| Lee et al., 2014 [22]   | 40 40   | 61.3 (48–75) 62.2 (41–73) | WBRT 20 Gy/5 f plus erlotinib 100 mg/day | WBRT 20 Gy/5 f + placebo | Randomized   | II    | 3.4/2.9           | 1.6/1.6             |
| Fu et al., 2012 [23]    | 38 123  | A56 (38–77)       | WBRT 30–40 Gy/2-3 W plus gefitinib 250 mg/day | WBRT 30–40 Gy/2-3 W | Case-control | NR    | NR                | NR                  |
| Wu et al., 2012 [24]    | 35 18   | 18–65             | WBRT 40 Gy/20 f plus gefitinib 250 mg/day | WBRT 40 Gy/20 f  | Randomized   | NR    | 12.1/9.8          | NR                  |
| Zhou et al., 2013 [25]  | 36 22   | 27–75             | WBRT 40 Gy/20 f or 30 Gy/10 f plus gefitinib 250 mg/day or erlotinib 100 mg/day | WBRT 40 Gy/20 f or 30 Gy/10 f plus Taxol 135–175 mg/m² d1 or Alimta 500 mg/m² d1 or DDP 25 mg/m² (d1–3) | Case-control | NR    | 23.2/7.1          | NR                  |
| Pesce et al., 2012 [26] | 16 43   | 57 (46–82) 63 (45–79) | WBRT 30 Gy/10 f plus gefitinib 250 mg/day | WBRT 30 Gy/10 f plus TMZ 75 mg/m²/day | Randomized   | II    | 6.3/4.9           | NR                  |
| Cai et al., 2013 [27]   | 65 92   | 66 (35–81)        | WBRT 29.37–41.24 Gy, 3 Gy/d, 5 times/week plus gefitinib 250 mg/day or erlotinib 100 mg/day | WBRT 29.37–41.24 Gy, 3 Gy/d, 5 times/week | Case-control | NR    | 10.6/7.7          | 6/3.4               |

Notes. W-T: WBRT plus erlotinib/gefitinib; W: WBRT; NR: not reported; OS: overall survival; PFS: progression-free survival.
Table 1: Overview of studies and results

| Study or subgroup | WBRT + gefitinib/erlotinib | WBRT | Weight | Odds ratio M-H, fixed, 95% CI | Odds ratio M-H, fixed, 95% CI |
|-------------------|----------------------------|-------|--------|------------------------------|------------------------------|
| **RR**            |                            |       |        |                              |                              |
| Zhou et al., 2012 | 12                         | 38    | 19     | 123                          | 26.3% 2.53 [0.95, 5.86]       |
| Wu et al., 2012   | 27                         | 35    | 7      | 18                           | 9.0% 5.30 [1.55, 18.20]       |
| Zhu et al., 2013  | 10                         | 36    | 3      | 22                           | 11.5% 2.44 [0.59, 10.07]      |
| Cai et al., 2013  | 50                         | 65    | 65     | 92                           | 53.2% 1.38 [0.67, 2.88]       |
| **Subtotal (95% CI)** | 99                     | 174   | 94     | 255                          | 100.0% 2.16 [1.35, 3.47]      |

Total events: 49

Heterogeneity: $\chi^2 = 3.62, df = 3 (P = 0.31); I^2 = 17%$

Test for overall effect: $Z = 3.19 (P = 0.001)$

| Study or subgroup | WBRT + gefitinib/erlotinib | WBRT | Weight | Odds ratio M-H, fixed, 95% CI | Odds ratio M-H, fixed, 95% CI |
|-------------------|----------------------------|-------|--------|------------------------------|------------------------------|
| **RR-CNS**        |                            |       |        |                              |                              |
| Zhu et al., 2013  | 22                         | 23    | 17     | 31                           | 11.5% 18.12 [2.16, 151.73]    |
| Fu et al., 2012   | 37                         | 38    | 100    | 123                          | 22.8% 8.51 [1.11, 65.27]      |
| Zhou et al., 2013 | 23                         | 36    | 8      | 22                           | 65.7% 3.10 [1.03, 9.33]       |
| **Subtotal (95% CI)** | 97                     | 176   | 100    | 255                          | 100.0% 6.06 [2.37, 14.29]     |

Total events: 82

Heterogeneity: $\chi^2 = 2.55, df = 2 (P = 0.28); I^2 = 22%$

Test for overall effect: $Z = 4.12 (P < 0.0001)$

| Study or subgroup | WBRT + gefitinib/erlotinib | WBRT | Weight | Odds ratio M-H, fixed, 95% CI | Odds ratio M-H, fixed, 95% CI |
|-------------------|----------------------------|-------|--------|------------------------------|------------------------------|
| **DCR**           |                            |       |        |                              |                              |
| Lee et al., 2013  | 0.9163                     | 0.4074| 7.2%   | 0.40 [0.18, 0.89]            |
| Lee et al., 2014  | 0.1165                     | 0.2549| 18.4%  | 0.89 [0.54, 1.47]            |
| Zhou et al., 2013 | 0.6539                     | 0.2806| 15.2%  | 0.52 [0.30, 0.90]            |
| Pesce et al., 2012| 0                          | 0.2439| 20.1%  | 1.00 [0.62, 1.61]            |
| Cai et al., 2013  | 0.3711                     | 0.1746| 39.2%  | 0.69 [0.49, 0.97]            |
| **Subtotal (95% CI)** | 70                     | 100    | 100.0% | 0.72 [0.58, 0.89]            |

Total events: 151

Heterogeneity: $\chi^2 = 1.92, df = 3 (P = 0.59); I^2 = 0%$

Test for overall effect: $Z = 3.96 (P < 0.0001)$

Figure 3: Meta-analysis for RR, RR-CNS, and DCR.

Figure 4: Meta-analysis for OS.

Figure 5: Meta-analysis for 1-year survival rate.
Gene expression tests for interesting outcomes indicated that there
were no statistical differences between studies ($I^2 < 50\%$, $P > 0.10$). Therefore subgroup analysis and meta regression
were not conducted for the current study.

Figure 7 shows the results of sensitivity analysis regarding
OS. We found that excluded studies did not influence the
overall effective size.

4.6. Subgroup Analysis and Sensitivity Analysis. The hetero-
genicity tests for interesting outcomes indicated that there
were no statistical differences between studies ($I^2 < 50\%$, $P > 0.10$). Therefore subgroup analysis and meta regression
were not conducted for the current study.

Figure 7 shows the results of sensitivity analysis regarding
OS. We found that excluded studies did not influence the
overall effective size.

4.7. Publication Bias. For the meta-analyses of RR and OS,
there was no evidence of significant publication bias by
Begg’s test, \( P = 0.142 \). Therefore, urgently needed to systematically assess the quality limited samplesize of Pesce et al.’s study. A meta-analysis was

BM from NSCLC. The discrepancy can be ascribed to the gefitinib could not prolong the survival time for patients with [21]. However, Pesce et al. [26] concluded that WBRT plus gefitinib/erlotinib was well tolerated except for increased risk of rash (III-IV) in the treatment of patients with multiple BM from NSCLC.

Current therapeutic approaches for patients with multiple BM from NSCLC mainly include surgery, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and chemotherapy [28]. However, advances in the understanding of the BM pathobiology and development of molecular targeted agents hold promise for improved prophylaxis and therapy of BM [29]. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), such as erlotinib, have been approved in 2004 by the US Food and Drug Administration for treating locally advanced or metastatic (EGFR) tyrosine kinase inhibitors (TKIs), such as erlotinib, have been approved in 2004 by the US Food and Drug Administration for treating locally advanced or metastatic non-small-cell lung cancer [30]. A mass of studies have demonstrated that the objective response rate is 42.9%–87.5%, and DCR is as high as 87.5%–100.0% for targeted agents combined with radiotherapy in the treatment of patients with multiple BM [31]. A phase II trial also showed that the median overall survival time was 11.8 months for patients with BM from NSCLC [32]. These results are consistent with Zhuang et al. [21]. However, Pesce et al. [26] concluded that WBRT plus gefitinib could not prolong the survival time for patients with BM from NSCLC. The discrepancy can be ascribed to the limited sample size of Pesce et al’s study. A meta-analysis was therefore urgently needed to systematically assess the quality of available evidence and make a scientific conclusion about WBRT plus gefitinib/erlotinib in treating BM from NSCLC.

Regrettably, a subgroup meta-analysis related to EGFR mutation status was not conducted because only one trial was identified. Previous studies showed that targeted therapy was beneficial for patients with BM. The overall response rate was 70%–89% for patients with intracranial lesions, and the overall survival time was 12.9–19.8 months longer [33, 34]. Zhuang et al’s study showed that, compared with EGFR wild-type patients, there was no significant improvement in LPFS, PFS, and OS for mutated EGFR mutation patients [21]. More studies of WBRT plus gefitinib/erlotinib in treatment of BM with EGFR mutations are needed.

The present study had certain limitations. Firstly, the overall methodological quality of included studies was low. Only three RCTs were included to assess the efficacy of the combined treatment. Most of the studies evaluating WBRT plus gefitinib/erlotinib for BM from NSCLC were case series, and only few controlled trials could be identified. Secondly, the small sample size of the included studies might have led to inadequate statistical power. The present conclusions are based on phase II trials, and more phase III randomized controlled trials are needed. Thirdly, subgroup analyses of different pathological subtypes, trial phase, smoking status, median age, and EGFR mutations status were not performed due to inadequate reporting across studies.

Overall, the currently available evidence indicates that RR, RR-CNS, DCR, OS, and 1-year survival rate can be improved by using WBRT combined with gefitinib/erlotinib in patients with BM from NSCLC, and the adverse events (III-IV) are well tolerated. Moreover, the efficacy of other targeted agents for BM from NSCLC should be assessed in future studies.

### Conflict of Interests

The authors declare that they have no conflict of interests.

### Authors’ Contribution

Mao-hua Zheng and Hong-tao Sun contributed equally to this work.

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