RESEARCH COMMUNICATION

Gefitinib Alone or with Concomitant Whole Brain Radiotherapy for Patients with Brain Metastasis from Non-small-cell Lung Cancer: A Retrospective Study

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Abstract

Background: Gefitinib, a tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR), is used both as a single drug and concurrently with whole brain radiotherapy (WBRT) the standard treatment for brain metastases (BM), and is reported to be effective in a few small studies of patients with BM from non-small-cell lung cancer (NSCLC). However, no study has compared the two treatment modalities. This retrospective analysis was conducted to compare the efficacy of gefitinib alone with gefitinib plus concomitant WBRT in treatment of BM from NSCLC. Methods: We retrospectively reviewed 90 patients with BM from NSCLC who received gefitinib alone (250mg/day, gefitinib group) or with concomitant WBRT (40Gy/20f/4w, gefitinib-WBRT group) between September 2005 and September 2009 at Sun Yat-Sen University Cancer Center. Forty-five patients were in each group. Results: The objective response rate of BM was significantly higher in gefitinib-WBRT group (64.4%) compared with gefitinib group (26.7%, P<0.001). The disease control rate of BM was 71.1% in gefitinib-WBRT group and 42.2% in gefitinib group (P=0.006). The median time to progression of BM was 10.6 months in gefitinib-WBRT group and 6.57 months in gefitinib group (P<0.001). The median overall survival(OS) of gefitinib-WBRT and gefitinib alone group was 23.40 months and 14.83 months, respectively (HR, 0.432, P=0.002). Conclusion: Gefitinib plus concomitant WBRT had higher response rate of BM and significant improvement in OS compared with gefitinib alone in treatment of BM from NSCLC.

Keywords: Non-small-cell lung cancer - gefitinib - whole brain radiotherapy - brain metastasis

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Introduction

Brain metastases (BM) are found in approximately 20-40% of all patients with non-small-cell lung cancer (NSCLC), especially in adenocarcinoma (Olak 1999; Yawn et al., 2003). The outcomes of BM from NSCLC are very poor with few effective treatment options. The median overall survival time (OS) of patients without treatment is less than 3 months (Nussbaum et al., 1996). Whole brain radiotherapy (WBRT) as a standard therapy for patients with BM from NSCLC had been commonly used with median OS ranging from 3 to 6 months. Chemotherapy leads to a median survival of 3-6 months for patients with BM from NSCLC. Few pilot studies reported that patients with BM from NSCLC treated with chemotherapy concurrently with WBRT had a median OS of 7.6-8 months (Furuse et al., 1997; Quantin et al., 1999; Moscetti et al., 2007).

Gefitinib, a tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR), was reported to be effective and brought the median OS of 9-13.5 months to patients with BM from NSCLC (Heimberger et al., 2002; Ceresoli et al., 2004; Hotta, 2004; Namba et al., 2004; Takahashi et al., 2004; Shimato et al., 2006; Kim et al., 2009). With the concept of the disruption of blood brain barrier (BBB) by BM and radiation therapy, gefitinib with small molecular weight may have the ability to penetrate the BBB (Fidler et al., 2002; Van et al., 2002; Jackman et al., 2006). Furthermore, gefitinib might enhance radiosensitivity (Bianco et al., 2002; Huang et al., 2002; Bonner et al., 2006; Shimato et al., 2006; Das et al., 2007; Park et al., 2010). Until now, only few outcome data from retrospective studies and phase II studies are available to report the treatment of gefitinib plus concomitant WBRT in BM from NSCLC. Ceresoli et al reported that among patients with BM treated with gefitinib, disease control rate (DCR) was significantly higher in patients pretreated with WBRT (P=0.05) (Ceresoli et al., 2004). In a phase II prospective study of gefitinib plus concurrent WBRT for BM from NSCLC, Ma S et al reported that the median

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overall survival, the response rate (RR) and DCR of BM were 13 months, 81% and 95%, respectively (Ma et al., 2009).

Up to present, there are no trials comparing gefitinib alone and gefitinib plus concomitant WBRT. Therefore, we have retrospectively reviewed 90 patients with BM from NSCLC treated at Sun Yat-Sen University Cancer Center, and focused on comparing the efficacy and toxicities of gefitinib alone with gefitinib plus concomitant WBRT in patients with BM from NSCLC.

Materials and Methods

Patients and evaluation of the response and toxicity

Between September 2005 and September 2009, patients with BM from NSCLC treated with gefitinib alone or with concomitant WBRT were enrolled into this retrospective study conducted at Sun Yat-Sen University Cancer Center. They were followed up until April 2011, and the median follow-up time was 23 months (range:1-60 months). The eligible patients were historically diagnosed with adenocarcinoma of lung cancer and had confirmed brain metastases by magnetic resonance imaging (MRI). All patients should have at least one measurable BM with diameter larger than 10 mm. Patients pretreated for BM with surgery, radiosurgery, EGFR-TKI or WBRT were excluded. All patients had complete medical records. The study was reviewed and approved by the Institutional Review Board of Sun Yat-Sen University Cancer Center. Tumor response was assessed by clinical evaluation, CT and MRI. Baseline assessment was performed within 2 weeks before gefitinib treatment. Chest CT scan and brain MRI were performed within 2 weeks before gefitinib administration, every 2 or 3 months thereafter until disease progression. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, including complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). The responders were the combination of CR and PR, and the disease control includes CR, PR and SD. Toxicity evaluations were based on the National Cancer Institute Common Toxicity Criteria (NCICTC) version 2.0. and assessed every 1 month.

Treatment

Patients were treated with 250 mg/day gefitinib until the radiological confirmed PD, the symptomatic deterioration or unacceptable toxicity. The dose of concomitant WBRT was 40Gy in 20 fractions. In the gefitinib-WBRT group, the median interval between the administrations of gefitinib to the beginning of WBRT was 15 days (0-34days).

Statistical methods

Descriptive analyses were performed on two defined groups: gefitinib group and gefitinib-WBRT group. Time to progression (TTP) of CNS lesions was defined as the time from first gefitinib intake until the first documented progression of CNS lesions. Progression-free survival (PFS) was calculated from the date of the administration of gefitinib until disease progression or until death from any cause. OS was calculated from the time of the administration of gefitinib until death from any cause.

The Pearson chi-square test or the Fisher exact test was used to compare treatment groups with patients' characteristics and response rates. The Kaplan–Meier method was used to generate the survival curves and analyze the distribution of time-to-event variables. Univariate and multivariate analyses were performed for analyzing overall survival outcome. The impact of the potential variables affecting PFS and OS was assessed by univariate analysis with the log-rank test. Multivariate analysis was evaluated using a logistic regression model to predict the clinical response to the treatment regimen. In a multivariate analysis, the following variables were included, gender, age, performance status (PS), smoking history, the addition of WBRT, number and size of brain metastases, EGFR mutations status, and the extracranial metastases. The Cox regression method was used to identify the most important independent prognostic factors and estimate the hazard ratio (HR). All tests and confidence intervals (CIs) were two sided and a significance level was 0.05. Statistical analyses were performed using SPSS software, Version 13.0.

Results

Baseline characteristics

A total of 90 patients were selected. Forty-five patients treated with gefitinib with concomitant WBRT was entitled into gefitinib-WBRT group, and 45 patients treated with gefitinib alone were in gefitinib group. Patients' demographic and clinical characteristics were listed in Table 1. Baseline characteristics were well balanced between gefitinib group and gefitinib-WBRT group. Forty-four patients (48.9%) had BM at initial diagnosis, with 21 in gefitinib group and 23 in gefitinib-WBRT group. Sixty-five patients (72.2%) had gefitinib as the initial therapy of BM while twenty-five patients (27.8%) had received previous chemotherapy after diagnosis of BM, mostly with platinum-based regimens. Twenty patients (22.2%) underwent EGFR testing, and 12 patients had mutations in EGFR including 8 exon 19 deletions and 4 exon 21 L858R point mutations. Ninety patients were available for the evaluation of response and toxicities.

Response and survival

For 90 patients, taking into account of both CNS and

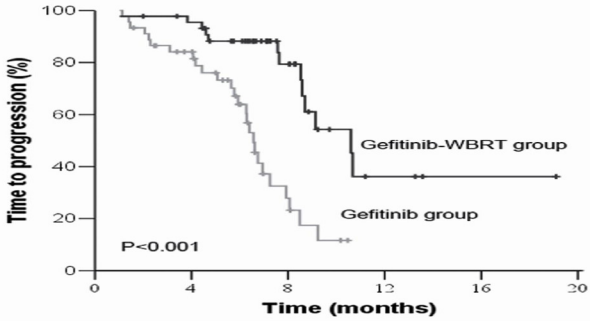

Figure 1. Kaplan-Meier Estimates of Time to Progression of Brain Metastases among All Patients in Gefitinib or Gefitinib-WBRT Group

Table 1. Characteristic of Patients

Characteristics	Gefitinib (n=45)	Gefitinib-WBRT (n=45)	P value
Gender, n (%)			0.67
Male	19(42.2)	21(46.7)	
Female	26(57.8)	24(53.3)	
Age (yr)			0.29
≤65	39(86.7)	42(93.3)	
>65	6(13.3)	3(6.7)	
Median (yr)	56	52	
Range (yr)	24-81	30-74	
Performance status			0.634
0-2	32(71.1)	34(75.6)	
3-4	13(28.9)	11(24.4)	
Smoking			0.81
Never or light smoker	34(75.6)	33(73.3)	
Heavy smoker	11(24.4)	12(26.7)	
No. brain metastases			0.29
≤5	20(44.4)	25(55.6)	
>5	25(55.6)	20(44.4)	
Size of brain metastases (mm)		0.07	
≤20	42(93.3)	35(77.8)	
>20	3(6.7)	10(22.2)	
EGFR mutations			0.71
Negative	5(11.1)	3(6.7)	
Positive	5(11.1)	7(15.6)	
Unknown	35(77.8)	35(77.8)	
No. organs with extracranial metastases			0.33
0	11(24.4)	8(17.8)	
1	16(35.6)	23(51.1)	
≥2	18(40)	14(31.1)	
No. prior chemotherapy			0.23
0	19(42.2)	27(600	
1	16(35.6)	12(26.7)	
≥2	10(22.2)	6(13.3)	
Prior thoracic irradiation			1
Yes	6(13.3)	6(13.3)	
No	39(86.7)	39(86.7)	

Never-smokers were defined as those who had smoked less than 100 cigarettes during their lifetime; Light smokers were defined as those who had smoked less than 10 packs a year; EGFR, epidermal growth factor receptor

extracranial lesions, the overall RR and DCR were 31.1% (1CR+27PR) and 40% (1CR+20PR+15SD), respectively. The median PFS was 6.1 months (95%CI, 5.19-7.01 months). The median OS was 18.16 months (95%CI, 14.41-21.92 months). Efficacy and survival analysis regarding the gefitinib group and gefitinib-WBRT group were listed in Table 2. The RR and DCR of CNS lesions were statistically higher in gefitinib-WBRT group. The TTP of CNS disease (Figure 1) and primary lesions were longer in gefitinib-WBRT group than the gefitinib group. The PFS and the OS were in favor of the gefitinib-WBRT group. The median PFS for gefitinib-WBRT group and gefitinib group were 7.12 months (95%CI, 5.72-8.52 months) and 4.17 months (95%CI, 3.03-5.30 months), respectively (P=0.001). The median OS was 23.4 months (95%CI, 17.15-29.65 months) in gefitinib-WBRT group versus 14.83 months (95%CI, 9.84-19.83 months) in gefitinib group (P=0.002, Figure 2). There was an 18.4% reduction in the risk of two-year death in gefitinib-WBRT group, compared with gefitinib group. The Kaplan-Meier curves for both PFS and OS had a sustaining separation,

Table 2. Treatment Response and Survival for 90 Patients

	Gefitinib (n=45)	Gefitinib-WBRT (n=45)	P value
Brain metastases			
RR (%)	12 (26.7)	29 (64.4)	<0.001
DCR (%)	19 (42.2)	32 (71.1)	0.006
TTP (months)	6.57	10.6	<0.001
Primary thoracic lesions			
RR (%)	12 (26.7)	14 (31.1)	0.642
DCR (%)	17 (37.8)	18 (40)	0.829
Median TTP (months)	5.33	7.91	0.001
Median PFS (months)	4.17	7.12	0.001
Median OS (months)	14.83	23.4	0.002
Rate at 1-yr (%)	58	81	
Rate at 2-yr (%)	27	45.4	

RR, response rate; DCR, disease control rate; TTP, time to progression; PFS, progression-free survival; OS, overall survival; WBRT, whole brain radiation therapy

Table 3. Treatment response according to EGFR mutation status

Response	Gefitinib group		Gefitinib-WBRT group	
	EGFR wild-type (n=5)	EGFR mutant (n=5)	EGFR wild-type (n=3)	EGFR mutant (n=7)
Brain metastases				
RR (%)	0	2 (40)	0	5 (71.4)
DCR (%)	1 (20)	4 (80)	1 (33.3)	6 (85.7)
Primary thoracic lesions				
RR (%)	1 (20)	3 (60)	1 (33.3)	5 (71.4)
DCR (%)	1 (20)	4 (80)	1 (33.3)	6 (85.7)
Overall				
RR (%)	1 (20)	3 (60)	1 (33.3)	5 (71.4)
DCR (%)	1 (20)	4 (80)	1 (33.3)	6 (85.7)

RR, response rate; DCR, disease control rate; WBRT, whole brain radiation therapy; EGFR, epidermal growth factor receptor

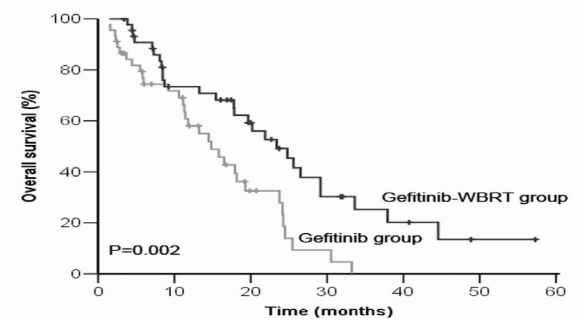

Figure 2. Kaplan-Meier Estimates of Overall Survival among All Patients in Gefitinib or Gefitinib-WBRT Group

which indicated the survival advantage lasted for at least several months.

Treatment response according to EGFR mutation status was listed in Table 3. In our study, it showed that in gefitinib group, gefitinib was more effective in patients with EGFR mutations than in patients with EGFR wild-type status in both primary lesions and BM. The similar result could be seen in gefitinib-WBRT group.

Out of 90 patients, 72 patients (80%) progressed. Sixty patients (83.3%) experienced disease progression in primary tumor, and 43 patients (59.7%) in BM. Ten

patients (22.2%) in gefitinib-WBRT group compared with 19 patients (42.2%) in gefitinib group were evaluated to have the CNS lesions as the first site of treatment failure (P=0.042). In the patients who suffered from progressive disease, about half of the patients received one or more regimens of chemotherapy in subsequent treatments. 16 patients received erlotinib, and other patients did not receive further treatment, due to refusal of chemotherapy or poor performance status. Seventy-three (81.1%) patients died at the last follow-up.

Univariate and Cox analysis

In univariate analysis, performance status (P<0.001), EGFR mutation status (P=0.019), and the addition of WBRT (P=0.003) were significant prognostic factors for overall survival. In multivariate analysis, PS (P=0.009, HR, 2.03, 95%CI: 1.19-3.48), EGFR mutations (P=0.032, HR, 0.092, 95%CI, 0.01-0.816) and the addition of concurrent WBRT (P=0.01, HR, 0.48, 95%CI, 0.277-0.836) were independently associated with overall survival.

Toxicity and safety

All 90 patients were included in the toxicity analysis. Most of toxicities were mild to moderate in both groups. Skin toxicity came out to be the most common toxicity, which was 44.4% (20/45) in gefitinib group and 46.7% (21/45) in gefitinib-WBRT group (P = 0.832). The diarrhea was 37.8% (17/45) in gefitinib group and 42.2% (19/45) in gefitinib-WBRT group (P=0.667), respectively. Alopecia was significantly higher in gefitinib-WBRT group 73.3% (33/45) compared with gefitinib group 4.4% (2/45, P=0.001). Headache (9 vs. 6), and vomiting (10 vs. 8), and hypomnesia (11 vs. 5) were more common in gefitinib-WBRT group compared with gefitinib group, but no significant difference was found. None of 90 patients experienced gefitinib-related lung toxicity and hepatic dysfunction. Nausea and fatigue were rarely observed. There was no significant difference in PS between the two groups of patients before or after the treatment.

Discussion

BM were associated with poor prognosis without effective treatment options. Therapeutic modalities to BM include WBRT, stereotactic radiosurgery (SRS), surgery, and chemotherapy. For many years, WBRT had been standard treatment for BM from NSCLC with OS ranging from 3 to 6 months. The addition of systematic chemotherapy to WBRT was shown to improve outcome for patients with BM from lung cancer, and the median OS was 7.6-8 months (Furuse et al., 1997; Quantin et al., 1999; Moscetti et al., 2007). Gefitinib, as a novel target therapeutic drug, has been commonly used for treating NSCLC in recent years. Some retrospective analyses showed that gefitinib were also effective in patients with BM from NSCLC and brought the median OS of 9-13.5 months to patients (Heimberger AB et al., 2002; Ceresoli et al., 2004; Hotta, 2004; Namba et al., 2004; Takahashi et al., 2004; Shimato et al., 2006; Kim et al., 2009). A phase II study by Ma et al. (2009) reported that the median overall survival of patients with BM under the treatment of gefitinib with concomitant WBRT was 13 months. To our knowledge, there are no studies comparing gefitinib with gefitinib with concomitant WBRT in patients with BM from NSCLC.

Only minimal published data are available regarding the clinical outcome of patients with BM from NSCLC treated with gefitinib and WBRT. Ceresoli et al. (2004) reported that in patients with BM from NSCLC treated with gefitinib, the DCR was significantly higher in WBRT pretreated patients. In a phase II prospective study of gefitinib plus WBRT treatment, the RR and DCR of BM were 81% and 95%, and the median PFS and OS were 10 months and 13 months, respectively (Ma et al., 2009). In our study, the addition of concomitant WBRT to gefitinib significantly increased the RR and DCR of CNS lesions. Our results indicated that WBRT was a necessary method to achieve better tumor control in the brain, and WBRT was still fundamental therapy in the treatment of BM from NSCLC. Patients treated with gefitinib with concomitant WBRT had superior TTP of BM compared with gefitinib alone group (10.6 vs. 6.57 months, P<0.001). Our study showed significant survival benefit of gefitinib with concomitant WBRT compared with gefitinib alone (23.4 vs. 14.83 months, P=0.002). We hypothesized that the long duration of disease control of CNS lesions contributed to the survival advantage. Gefitinib with concomitant WBRT was superior choice for patients with BM from NSCLC treated with EGFR-TKI. We noted that the overall survival in our study was much longer than that of previously reported studies for BM patients receiving gefitinib (Ceresoli et al., 2004; Hotta et al., 2004; Namba et al., 2004; Takahashi et al., 2004; Shimato et al., 2006), which was probably due to the high proportion of patients received fully post-progression treatments after gefitinib regimen.

The attribution of the enhanced effectiveness might be synergistic effects of gefitinib and WBRT. Some studies reported that gefitinib might enhance radiosensitivity. Gefitinib might sensitize cells to the effects of radiation in the A549 cell line of lung cancer (Bianco et al., 2002; Park et al., 2010). Huang et al. reported that the combined treatment with radiation and gefitinib produced a synergistic tumor growth inhibition in SCC-1 xenografts (Huang et al., 2002). van VM et al reported that the radiation therapy might disrupt the BBB (van et al., 2002). We assumed that the addition of WBRT might increase the concentration of gefitinib in the CNS.

EGFR mutation, females, never or light smokers, adenocarcinoma, and East Asian origin were regarded as favorable clinical predictors to gefitinib in clinical studies. Two retrospective studies reported that the EGFR mutations and the administration of EGFR TKI during WBRT were independently associated with clinical response to WBRT and the highest responsive rate of 84.6% (11 of 13) was noted in patients with EGFR mutations and receiving EGFR TKI during WBRT (Das et al., 2007; Gow et al., 2008). In our study, for the 20 patients with EGFR mutation status available, the RR and DCR of BM were higher in EGFR mutation positive patients compared with EGFR mutation negative patients

both in gefitinib group and gefitinib-WBRT group. EGFR mutations are associated with the increased incidence rates of response both in primary tumors and BM (Mok et al., 2009), and they might be predictive for response of BM if EGFR mutations are present in CNS lesions. Das et al. (2007) showed that NSCLC cell lines harboring EGFR mutations exhibited significant delays in the repair of ionizing radiation-induced DNA double-strand breaks and had increases in apoptosis. Another in-vitro study discovered that the survival of lung cancer cell lines with EGFR mutations in response to ionizing radiation was reduced 500-fold to 1,000-fold compared with those of the wild type (Das et al., 2006). We guessed that patients with EGFR mutations could benefit more from the combined regimen of gefitinib with concomitant WBRT. However, the low proportion of the detection of EGFR mutations led to unsound proof to show the relationship between the EGFR mutations and the radiosensitivity.

However, it remains unknown about the optimal time to add WBRT to gefitinib treatment. Shukuya et al reported that continuous EGFR-TKI administration following WBRT for NSCLC patients with isolated CNS failure remained to be effective, and the RR, the DCR of CNS lesions were 41% and 76%, respectively (Shukuya et al., 2011). To our knowledge, there are no clinical trials to compare concomitant and sequential therapy of gefitinib and WBRT. Future trials should investigate the optimal regimen of gefitinib and WBRT combination therapy.

In conclusion, gefitinib and concomitant WBRT showed an advantage over gefitinib alone in terms of PFS, OS and TTP of CNS lesions. More prospective studies should be carried out to compare the efficacy of gefitinib plus concomitant WBRT with gefitinib or WBRT alone in patients with BM from NSCLC with undefined EGFR status. More studies should be performed to find whether gefitinib is better than radiotherapy in EGFR mutated patients with BM. Future studies should issue the problem of whether gefitinib plus concomitant WBRT is superior to chemotherapy plus concomitant WBRT in BM patients with EGFR mutations. Furthermore, well-designed studies are needed to find the optimal time to give WBRT during the gefitinib treatment.

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The author(s) declare that they have no competing interests.

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