Original article

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Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial

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Background: Brain metastases are a common occurrence in patients with non-small-cell lung cancer (NSCLC). Whole-brain radiotherapy (WBRT) is the standard therapy; more aggressive approaches such as surgery or radiosurgery are indicated in a subset of patients only. The role of systemic treatments remains controversial. Gefitinib is an oral, highly tolerable, specific inhibitor of epidermal growth factor receptor-associated tyrosine kinase, which has shown activity in chemotherapy pretreated NSCLC. The aim of this study was to evaluate the activity and safety of gefitinib in NSCLC patients with brain metastases.

Patients and methods: From January 2001 to May 2003, 41 consecutive NSCLC patients with measurable brain metastases were treated with gefitinib, given orally at daily dose of 250 mg. Thirty-seven patients had received previous chemotherapy and 18 patients had been treated previously with WBRT, completed at least 3 months before entering the trial.

Results: A partial response (PR) was observed in four patients (10%), with stable disease (SD) in seven cases, for an overall disease control (DC) rate (DC = PR+SD) of 27% (95% confidence interval 13% to 40%). Median duration of PR was 13.5 months. Median progression-free survival (PFS) of the whole population was 3 months. DC rate was higher in patients pre-treated with WBRT ($P = 0.05$) and with adenocarcinoma histological type ($P = 0.08$); adenocarcinoma patients had also a longer PFS ($P = 0.04$). Toxicity was mild and consisted of grade 1/2 skin toxicity and diarrhoea, occurring in 24% and 10% of patients, respectively.

Conclusions: Gefitinib can be active on brain disease in NSCLC patients. Since the results of standard therapy for brain metastases in this clinical setting are particularly disappointing, gefitinib appears to be a possible new treatment option.

Key words: brain metastases, gefitinib, non-small-cell lung cancer

Introduction

Brain metastases are the most common type of intra-cranial neoplasm, occurring five to 10 times more frequently than primary tumors of the central nervous system (CNS). Lung cancer is the main source of brain metastases; patients with non-small-cell lung carcinoma (NSCLC) develop CNS metastases in about 20–40% of cases [1]. With the improvement in treatments for extra-cranial disease, both in the early stages and in locally advanced disease, this incidence is likely to rise [2].

Brain metastases are usually associated with poor outcome, and treatment is palliative in most cases. Standard treatment options include symptomatic therapy with corticosteroids and whole-brain radiotherapy (WBRT), which lead to a median survival of 3–6 months [3]. Selected patients with a limited number of small lesions are candidates for surgery [4] or stereotactic radiosurgery [5]. Unfortunately, most patients with NSCLC metastatic to the brain either harbor or develop multiple lesions [1].

Recent trials using platinum-based chemotherapy showed comparable response rates with intra-cranial and extra-cranial disease, suggesting that chemotherapy should be considered for patients with asymptomatic multiple brain metastases [6]. However, the efficacy of chemotherapy for the treatment of brain metastases is limited, and long-term survival remains disappointing [7]. Although this is attributable to several factors, drug delivery to involved tissue is one of the most important issues. Penetration of chemotherapeutic drugs into the central nervous system (CNS) is limited primarily by the blood–brain barrier (BBB) [8].

Gefitinib (Iressa; AstraZeneca, London, UK), is an oral tyrosine kinase (TK) inhibitor of the epidermal growth factor receptor (EGFR). Phase I trials in patients with solid tumors

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refractory to standard chemotherapeutic agents have shown antitumor activity and good tolerability profile, with skin rash and diarrhea as dose-related toxicities [9, 10]. Two large phase II studies conducted in pretreated patients affected by NSCLC achieved a response rate of 18.4% and 11.8%, respectively, and a symptomatic improvement in nearly 40% of cases [11, 12]. In all published trials, no data have been obtained on the activity of gefitinib on brain metastases. On the other hand, preclinical data [13] and some initial case reports showing activity of gefitinib on brain metastases from NSCLC [14–17] seem to suggest a potential role of TK inhibitors in the treatment of NSCLC patients with metastatic CNS disease.

The aim of our study was to evaluate prospectively the activity of gefitinib in a consecutive series of pretreated patients with brain metastases from NSCLC. The drug was provided by AstraZeneca within the expanded access program.

Patients and methods

Patient selection

All patients had to have histologically or citologically diagnosed NSCLC, with measurable brain metastases assessed with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. Two groups of patients were eligible: (i) patients with brain metastases progression after WBRT, provided that it was terminated at least 3 months before starting gefitinib; and (ii) patients not pretreated with WBRT because they were asymptomatic or refused radiotherapy.

Eligibility criteria included age > 18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2, white blood cell count $\geq 3.5 \times 10^9$/l with absolute granulocyte count (AGC) $> 2.0 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, hemoglobin ≥ 9 g/dl, bilirubin < 1.5-fold the upper limit of normal (ULN), prothrombin time or activated partial thromboplastin time < 1.5× control, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 3-fold ULN (could be elevated to 5-fold ULN in patients with known hepatic metastases) and a calculated creatinine clearance rate of > 45 ml/min. Patients with an active infection or other serious concomitant disorders were ineligible.

Written informed consent was obtained from each patient before entering the study. The study was conducted after the approval of the appropriate ethical review boards. Recommendations of the Declaration of Helsinki for biomedical research involving human subjects were also followed.

Study design and treatment

In this study, consecutive NSCLC patients with brain metastases received gefitinib at the daily dose of 250 mg given until disease progression, unacceptable toxicity or refusal. Baseline evaluation included a complete history and physical examination, a complete blood cell count and serum chemistry analysis, urinalysis, and a total-body CT scan. Brain metastases were assessed with contrast-enhanced CT or MRI of the brain. All baseline imaging procedures were performed in the 4 weeks before study entry. After trial inclusion, toxicity and disease-related symptom assessment were performed every 28 days. Toxic effects were assessed according to the National Cancer Institute Common Toxicity Criteria [18]. Symptom assessment was performed by the physician and no questionnaire was used. Side-effects and safety were evaluated clinically and serum creatinine, electrolyte, alkaline phosphatase, bilirubin, AST, ALT, calcium and protein levels were assessed. Patients were evaluated for response according to the RECIST (Response Evaluation Criteria In Solid Tumors) criteria [19]. Patients with a rapid clinical progression before radiologic re-assessment were considered to have progressive disease (PD). Patients in which a complete response (CR), partial response (PR) or stable disease (SD) was measured were considered as having achieved 'disease control' (DC).

Tumor response was assessed by CT scan every 2 months, with a confirmatory evaluation to be repeated in responding patients at least 4 weeks after the initial determination of response. Brain metastases response was assessed at the same time as extra-cranial evaluation (±10 days) using the same diagnostic technique performed in baseline assessment.

Statistical considerations

Forty patients were to be enrolled onto the study, as calculated according to the method described by Gehan [20]. This was to ensure that if the drug had a < 20% DC rate, the study could be terminated with a maximal error of 5% in estimation of the true response rate. Response to treatment was evaluated according to the intention-to-treat principle. Confidence limits (95% CI) of response rates were estimated. Progression-free survival (PFS) was defined as the period from the first day of treatment to the date of first evidence of disease progression or last follow-up. Overall survival (OS) was calculated from the first day of therapy until death or last follow-up. Actuarial survival curves were generated using the method of Kaplan and Meier.

Response rates were analyzed according to the following variables: age (less than median value versus greater than median value), gender, ECOG PS (0 versus 1 versus 2), histology (adenocarcinoma including bronchiolar-alveolar carcinoma (BAC) versus non-adenocarcinoma), number of metastatic sites apart from CNS (0–1 versus > 1), previous systemic treatment (none/one versus more than one lines of chemotherapy), previous platinum-based chemotherapy (yes versus no) and previous WBRT (yes versus no). All parameters were analyzed as categorical variables. Spearman's test was used to compare percentages in subsets of patients through univariate analysis. Multivariate analysis was performed using a logistic regression model. The impact of these variables on PFS and OS was evaluated by univariate analysis using the log-rank test. The independent value of variables was assessed in multivariate analysis using the Cox proportional hazard regression model with an estimate of hazard ratios (HR). All probability values were two-sided.

Results

Patient characteristics

Between January 2001 and May 2003, 41 consecutive patients entered the study at the two participating institutions (24 at the Department of Oncology, Bellaria Hospital, Bologna, and 17 at the Department of Oncology, Scientific Institute San Raffaele, Milan). Patient characteristics are summarized in Table 1.

The majority of patients were male (71%) with a median age of 62 years (range 42–78). Most patients had a good PS (0–1 ECOG), even though 60% of them had two or more extracranial sites of disease. Adenocarcinoma was the most frequently observed histologic subtype (66% including BAC). All patients except four had been pretreated with chemotherapy, mostly with platinum-based regimens. In four patients, gefitinib was administered as first-line treatment due to poor PS and comorbidities precluding chemotherapy administration. Eighteen patients (44% of the study population) had received previous WBRT. Median time from the end of radiotherapy and the beginning of gefitinib administration was 213 days.

Table 1. Patient characteristics ($n = 41$)

	n	%
Gender		
Male	29	71
Female	12	29
Age (years)		
Median	62	
Range	42–78	
Histology		
Adenocarcinoma	23	56
Bronchiolar-alveolar carcinoma	4	10
Squamous cell carcinoma	2	5
NSCLC (not otherwise specified)	8	20
Large cell carcinoma	3	7
Carcinoma with sarcomatoid elements	1	2
Number of extracranial disease sites		
0 (brain only)	3	7
1	14	33
2	8	20
≥ 3	16	40
Symptoms at study entry		
All symptoms	29	70
Neurological symptoms	9	22
ECOG performance status		
0	15	37
1	17	41
2	9	22
Previous chemotherapy lines		
0 (gefitinib as first line)	4	10
1	21	51
2	11	27
3+	5	12
Pretreated with platinum	33	80
Previous WBRT		
Yes	18	44
No	23	56

NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; WBRT, whole-brain radiotherapy.

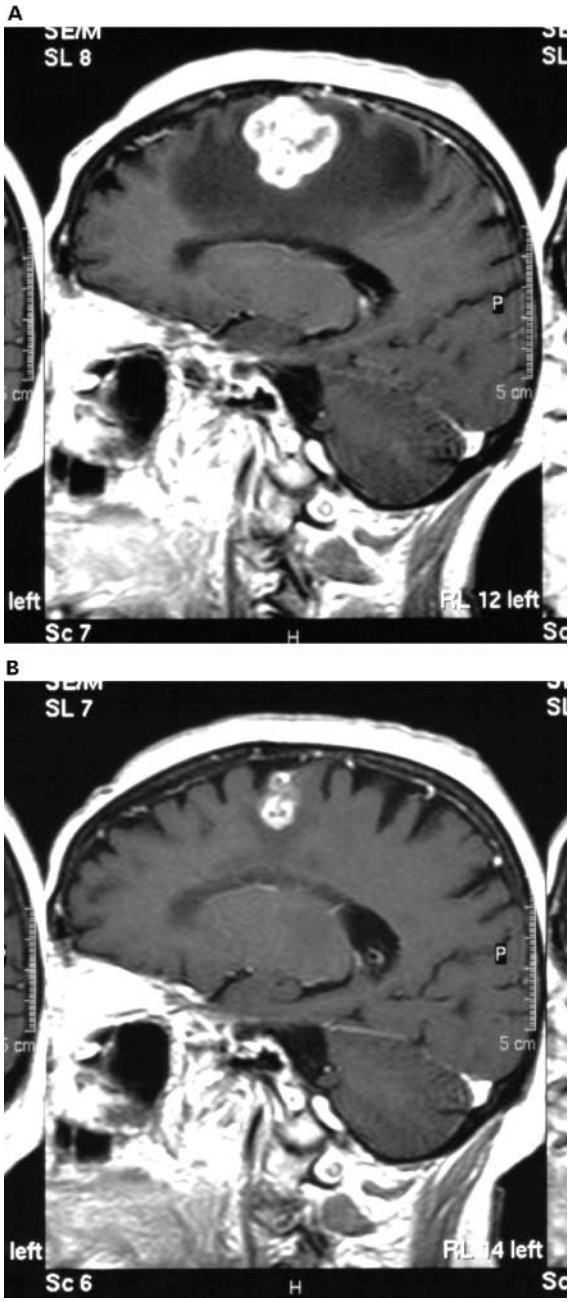

Figure 1. Sagittal sections of a T1-weighted magnetic resonance imaging study of the brain. (**A**) Baseline study showed a large brain metastasis with surrounding edema. (**B**) The study was repeated after 4 weeks of gefitinib therapy, showing a major decrease in the size of the lesion. The patient was a 78-year-old female, not pretreated with whole-brain radiotherapy. Gefitinib was administered as first-line treatment.

Activity and efficacy measures

All patients were evaluated for response, both in brain and extracranial disease sites. No case of mixed response (i.e. CNS response and extracranial progression, or vice versa) was observed. Among the 41 patients enrolled, we registered four PRs (10%) (Figure 1). Median duration of response was 13.5 months (range 3–15). Seven patients had SD (17%) with a median duration of 4 months (range 3–11), for an overall DC rate of 27% (95% CI 13% to 40%). Two patients were not evaluable for response. In one case a PR was observed at extracranial sites (lung and pleura) with symptom improvement, but brain metastases were not evaluated due to sudden death as a result of pulmonary embolism at 4 months. This patient was considered as having disease progression according to the intention-to-treat principle. The other patient refused any further radiological assessment after baseline evaluation; he is alive and well at 13 months, and still on treatment. In statistical analysis, this patient was not considered a responder, but was included in the group of patients achieving DC. Including this patient,

the DC rate was 29% (95% CI 15% to 43%). Overall, disease-related symptoms improved in 32%, remained stable in 32% and worsened in 36% of patients. Nine patients had neurological symptoms at trial inclusion, despite the administration of steroids; an improvement occurred in four cases. All responding patients showed rapid tumor regression, which was evidenced at first post-baseline assessment. In particular, one radio-naïve patient showed an impressive response after 4 weeks of treatment (Figure 1); tumor regression was confirmed at 2 and 4 months.

No patient- or treatment-related variable was related to PR in univariate analysis; histology was of borderline significance ($P = 0.13$), with four of 27 PRs (15%) in patients with adenocarcinoma (one BAC) compared with none of 14 in patients with other histologies. A multivariate test for PR confirmed this trend, but the difference was not significant ($P = 0.08$; HR 1.3; 95% CI 0.9–1.9). Previous WBRT ($P = 0.0006$) showed a significant prognostic value in univariate analysis for DC; DC was achieved in 10 of 18 previously irradiated patients (56%) compared with two of 23 radio-naïve cases (9%). Histology was of borderline significance ($P = 0.13$) in favor of adenocarcinoma, with 10 of 27 (37%) cases with adenocarcinoma achieving a DC compared with two of 14 (14%) with non-adenocarcinoma tumors. Multivariate analysis confirmed the correlation of DC with previous WBRT ($P = 0.02$; HR 1.4; 95% CI 1.0–1.9); histology was nearly significant ($P = 0.10$; HR 1.3; 95% CI 0.9–1.8).

At a median follow-up of 11 months, 11 patients are still alive and five patients are free of disease progression and still on treatment (at >3, >3, >8, >13 and >14 months, respectively). One patient died at 4 months, while in PR at extracranial sites, due to massive pulmonary embolism. Figure 2A and B shows the actuarial survival curves for the entire population. Median PFS was 3 months (range 0 to >14). PFS was significantly related to adenocarcinoma histology in multivariate analysis ($P = 0.04$; HR 2.3; 95% CI 1.0–5.1), and age <62 years had borderline significance ($P = 0.09$; HR 2.0; 95% CI 0.9–4.7). PFS was longer in patients previously submitted to WBRT (4 months compared with 2 months in non-irradiated patients), but this difference was not significant ($P = 0.17$; HR 1.9; 95% CI 0.8–4.6). Median OS was 5 months (range 0 to >24) and was related to PS ($P = 0.01$; HR 2.2; 95% CI 1.2–4.0). Patients with PS 0 had a median OS of 8 months, compared with 4 months and 1 month for patients with PS 1 and 2, respectively. Furthermore, patients with less than two sites of metastatic disease, apart from CNS, survived significantly longer in comparison with patients with an higher metastatic burden (7.5 compared with 2 months, respectively) ($P = 0.03$; HR 3.0; 95% CI 1.1–8.0).

Toxicity

Side-effects were generally mild and consisted mainly of diarrhea and skin toxicity. Grade 1–2 diarrhea occurred in six patients (15%), while grade 1–2 skin disorders, including rash, pruritus, dry skin and acne, were observed in 10 patients (24%). Grade 1 nausea was registered in two patients and a mild, transient conjunctivitis was observed in one case. In all cases toxicity resolved while on treatment, without dose reduction or drug withdrawal. No patient experienced interstitial lung disease-type events during the study.

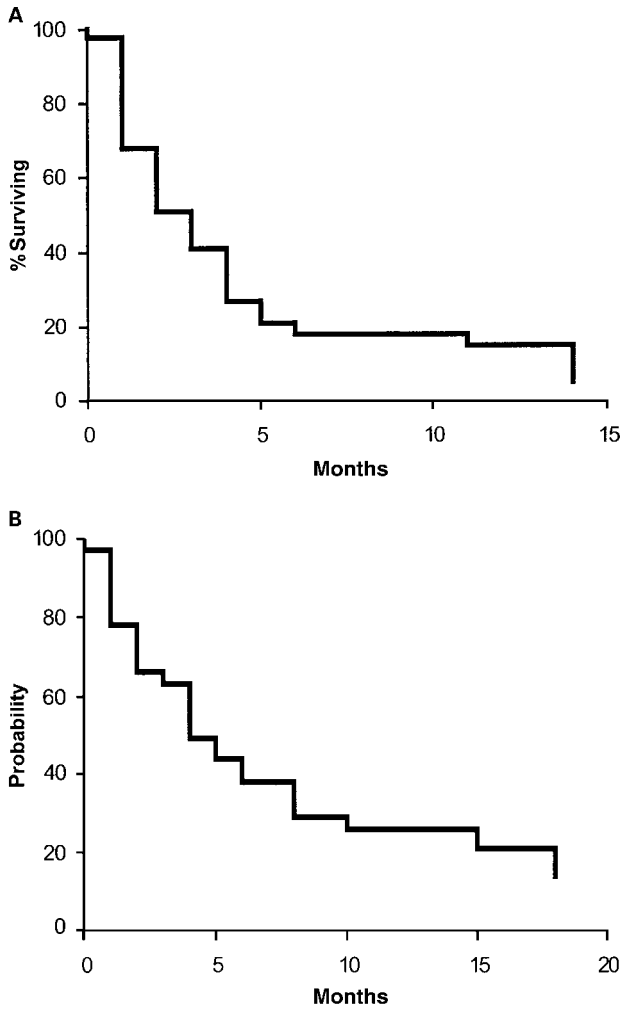

Figure 2. Actuarial progression-free survival (**A**) and overall survival (**B**) curves for the entire population.

Discussion

Patients with advanced NSCLC relapsing after chemotherapy generally have a poor prognosis, particularly in the case of brain metastases. Standard treatment for brain metastases is WBRT; more aggressive treatment with surgery or stereotactic radiotherapy is possible only in a subset of patients. The role of systemic treatment in this setting remains controversial. Data from large series of patients treated with gefitinib are lacking because the presence of CNS disease has mostly been considered among exclusion criteria, and in any case data on brain metastases have not been analyzed separately [11, 12].

In our series of 41 consecutive cases, we registered an interesting activity of gefitinib in this heavily pretreated group of patients. Four major responses in brain metastases (10%) were observed, both in previously irradiated and non-irradiated

patients; overall, nearly 30% of patients appeared to achieve DC as a result of the treatment. All responding patients showed rapid tumor regression that was evidenced at the first post-baseline assessment. Neurological status improvement was also observed in four of nine symptomatic patients. These findings confirm previous case reports of activity of gefitinib on brain metastases from NSCLC [14–17]. The efficacy of single-agent or combination chemotherapy in disseminated NSCLC with brain metastases remains unsatisfactory [7, 21]; this is commonly attributed to the presence of the BBB, which allows only relatively low concentrations of most cytotoxic agents in the normal CNS. However, the protective role of the BBB is limited to normal brain and micro-metastatic disease, while in overt metastatic disease it may already be disrupted by the presence of brain metastases and/or previous radiotherapy [7, 8]. In fact, in experimental models, BBB functions begin to fail with metastatic lesions of a few millimeters [22]. Gefitinib has low molecular weight and excellent cell penetration [23]; however, preclinical data showed only a low distribution of ^{14}C-radiolabeled drug to the CNS, as assessed by quantitative whole-body autoradiography 2 h after oral dosing during peak concentrations in non-tumor-bearing rats (data on file at AstraZeneca). Recently, a study in mice has shown therapeutic activity of gefitinib in intracranial tumors overexpressing EGFR; oral administration of high-dose gefitinib (50–100 mg/kg/day during weekdays for 3 weeks) had marked efficacy, resulting in increased survival and nearly complete inhibition of receptor phosphorylation with minimal systemic and neurological toxicity [13]. No pharmacokinetic and clinical data on the ability of gefitinib to cross the BBB in patients have been published so far, and no conclusion can be drawn about this issue in humans.

In our study, gefitinib proved effective both in WBRT-pretreated and WBRT-naïve subjects, with three PRs and 10 cases of DC in patients pretreated with radiotherapy, and one PR and two cases of DC in patients not previously brain-irradiated. DC was significantly higher in irradiated patients in univariate and multivariate analyses. Moreover, we observed in these patients a trend towards better PFS. Whether these observations could be due to changes in BBB permeability induced by WBRT or simply to a selection bias of patients with a more indolent disease course is difficult to ascertain. Median time from the end of WBRT to gefitinib administration was ~7 months. Data on duration of BBB disruption after radiotherapy are extremely heterogeneous in clinical studies and experimental models [8], varying from hours to years. On the other hand, several authors have suggested that the DC achieved with gefitinib could be a function of an intrinsically more indolent tumor biology (e.g. in adenocarcinoma or in BAC) [11, 12]. Furthermore, preclinical data on erlotinib, another orally active EGFR TK- inhibitor, suggest that exposure to multiple chemotherapeutic agents may result in some cell lines becoming more dependent on the EGFR signaling pathway and thus more sensitive to EGFR inhibitors [24]. This could be also the case in WBRT-pretreated patients, in which radio-resistant clones could have developed increased sensitivity to gefitinib. Interestingly, cellular resistance to ionizing radiation has been shown to be casually associated with functional expression of EGFR in experimental models [25].

Adenocarcinoma was found to be a favorable prognostic factor for response in the IDEAL 1 and IDEAL 2 trials [11, 12]; our series confirmed these data, but were lacking statistical significance, probably due to the small sample size of the study population. Nevertheless, we observed a longer PFS in adenocarcinoma cases. The higher activity of gefitinib in this histotype could be of importance in NSCLC patients with brain metastases, as adenocarcinoma is highly represented in this subset of patients [3].

Treatment was well tolerated, with mild diarrhea and skin toxicity, confirming the favorable adverse event profile of gefitinib in heavily pretreated NSCLC patients.

In conclusion, our observations suggest that gefitinib, at the standard dose of 250 mg/day, can be active on brain disease in NSCLC patients. Since the results of standard therapy for brain metastases in this clinical setting are particularly disappointing, gefitinib appears to be a possible new treatment option. To assess the role of this compound better, we have planned a new trial in asymptomatic radio-naïve patients with brain metastases from NSCLC who have relapsed following previous chemotherapy.

References

1. Wen PY, McLaren Black P, Loeffler JS. Metastatic brain cancer. In De Vita VT Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology, 6th edition. Philadelphia, PA: Lippincott Williams and Wilkins 1999; 2655–2670.
2. Ceresoli GL, Reni M, Chiesa G et al. Brain metastases in locally advanced non-small cell lung cancer after multimodality treatment: risk factors analysis. Cancer 2002; 95: 605–612.
3. Lagerwaard FJ, Levendag PC, Nowak PJCM et al. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. Int J Radiat Oncol Biol Phys 1999; 43: 795–803.
4. Shahidi H, Kvale PA. Long-term survival following surgical treatment of solitary brain metastasis in non-small cell lung cancer. Chest 1996; 109: 271–276.
5. Sheenan JP, Sun MH, Kondziolka D et al. Radiosurgery for non-small cell lung carcinoma metastatic to the brain: long-term outcomes and prognostic factors influencing patient survival time and local tumor control. J Neurosurg 2002; 97: 1276–1281.
6. Crinò L, Scagliotti GV, Ricci S et al. Gemcitabine and cisplatin versus mitomycin, ifosfamide, and cisplatin in advanced non-small cell lung cancer: a randomized phase III study of the Italian Lung Cancer Project. J Clin Oncol 1999; 17: 3522–3530.
7. Postmus PE, Smit EF. Chemotherapy for brain metastases of lung cancer: a review. Ann Oncol 1999; 10: 753–759.
8. Van Vulpen M, Kal HB, Taphoorn MJB, El Sharouni S. Changes in blood–brain barrier permeability induced by radiotherapy: implications for timing of chemotherapy? Oncol Rep 2002; 9: 683–688.
9. Baselga J, Rischin D, Ranson M et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. J Clin Oncol 2002; 20: 4292–4302.

10. Herbst RS, Maddox AM, Rothenberg ML et al. Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small cell lung cancer and other solid tumors: results of a phase I trial. J Clin Oncol 2002; 20: 3815–3825.
11. Fukuoka M, Yano S, Giaccone G et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small cell lung cancer. J Clin Oncol 2003; 21: 2237–2246.
12. Kris MG, Natale RB, Herbst RS et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer. A randomized trial. JAMA 2003; 290: 2149–2158.
13. Heimberger AB, Learn CA, Archer GE et al. Brain tumors in mice are susceptible to blockade of epidermal growth factor receptor (EGFR) with the oral, specific, EGFR-tyrosine kinase inhibitor ZD1839 (Iressa). Clin Cancer Res 2002; 8: 3496–3502.
14. Cappuzzo F, Ardizzoni A, Soto-Parra H et al. Epidermal growth factor receptor targeted therapy by ZD1839 (Iressa) in patients with brain metastases from non-small cell lung cancer (NSCLC). Lung Cancer 2003; 41: 227–231.
15. Fujiwara K, Kiura K, Ueoka H et al. Dramatic effect of ZD1839 (Iressa) in a patient with advanced non-small cell lung cancer and poor performance status. Lung Cancer 2003; 40: 73–76.
16. Villano JL, Mauer AM, Vokes EE. A case study documenting the anticancer activity of ZD1839 (Iressa) in the brain. Ann Oncol 2003; 14: 656–658.
17. Takahashi H, Ohrui T, Ebihara S et al. Effect of gefitinib (ZD1839) on metastatic brain tumour. Lung Cancer 2004; 43: 371–372.
18. National Institutes of Health. Common Toxicity Criteria. Bethseda, MD: National Institutes of Health, Cancer Therapy Evaluation Program, Division of Cancer Treatment, 1993.
19. Therasse P. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92: 205–216.
20. Gehan EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. J Chronic Dis 1961; 13: 346–353.
21. Dziadziuszko R, Ardizzoni A, Postmus PE et al. 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 2003; 39: 1271–1276.
22. Lesser GJ. Chemotherapy of cerebral metastases from solid tumors. Neurosurg Clin N Am 1996; 7: 527–536.
23. Barker AJ, Gibson KH, Grundy W et al. Studies leading to the identification of ZD1839 (IRESSA): an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor targeted to the treatment of cancer. Bioorg Med Chem Lett 2001; 11: 1911–1914.
24. Perez-Soler R, Dai Q, Ling YH et al. Molecular mechanisms of sensitivity and resistance to the HER1/EGFR-tyrosine kinase inhibitor erlotinib (Tarceva™). Lung Cancer 2003; 41(Suppl 2): S72 (Abstr 247).
25. Liang K, Ang KK, Milas L et al. The epidermal growth factor receptor mediates radioresistance. Int J Radiat Oncol Biol Phys 2003; 57: 246–254.