Systemic treatment of non-small cell lung cancer brain metastases

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In the systemic treatment of brain metastases from non-small cell lung cancer (BMF-NSCLC) chemo- and targeted therapy are used. Response rates after platinum-based chemotherapy, range from 23% to 45%. Development of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs): gefitinib or erlotinib, was an improvement in treatment of advanced NSCLC patients. EGFR mutations are present in 10–25% of NSCLC (mostly adenocarcinoma), and up to 55% in never-smoking women of East Asian descent. In the non-selected group of patients with BMF-NSCLC, the overall response rates after gefitinib or erlotinib treatment range from 10% to 38%, and the duration of response ranges from 9 to 13.5 months. In the case of present activating EGFR mutation, the response rate after EGRF-TKIs is greater than 50%, and in selected groups (adenocarcinoma, patients of Asian descent, never-smokers, asymptomatic BMF-NSCLC) even 70%. Gefitinib or erlotinib treatment improves survival of BMF-NSCLC patients with EGFR mutation in comparison to cases without the presence of this mutation. There is no data on the activity of the anti-EML4-ALK agent crizotinib. Bevacizumab, recombinant humanised monoclonal antibody anti-VEGF, in the treatment of advanced non-squamous NSCLC patients is a subject of intense research. Data from a clinical trial enrolling patients with pretreated or occult BMF-NSCLC proved that the addition of bevacizumab to various chemotherapy agents or erlotinib is a safe and efficient treatment, associated with a low incidence of CSN haemorrhages. However, the efficacy and safety of bevacizumab used for therapeutic intent, regarding active brain metastases is unknown.

Key words: breast cancer, brain metastases, systemic therapy, targeted therapy.

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Introduction

Between 25% and 30% of non-small cell lung cancer (NSCLC) patients will develop metastatic disease in the brain (brain metastases from non-small cell lung cancer – BMF-NSCLC). Frequently they are the first site of recurrence in early-stage NSCLC patients treated with definitive therapies [1–5]. The prognosis is poor for untreated patients with BMF-NSCLC, with median overall survival (OS) 1–2 months [1, 4, 5]. The combination of neurosurgery with stereotactic radiosurgery (SRS) and/or whole-brain radiotherapy (WBRT) can increase the OS up to 3–6 months, and in selected cases over 12 months [1, 4, 6–10].

Currently, the role of systemic treatment of BMF-NSCLC patients is being widely discussed [3, 4, 10]. Historically, chemotherapy was considered as a poorly effective method of treatment, mainly because of predicted difficulties in penetrating the blood-brain-barrier (BBB). For a long period of time, patients with BMF-NSCLC were excluded from controlled clinical trials for chemotherapy of NSCLC [1, 3, 4, 11, 12]. Nowadays it seems that even if most of the drugs cannot penetrate normal BBB, the integrity of the BBB is significantly altered, e.g. in BMF-NSCLC patients, which can be proved by oedema and increased contrast uptake around the metastatic site [12]. The significant amount of information indicates the possibility of efficient palliative systemic treatment of chosen patients with BMF-NSCLC [2, 3, 10, 11, 13]. The role of targeted therapies, besides chemotherapy, is significantly increasing [1, 4, 10, 13, 14].

The purpose of this work is to review, relying on the literature, the actual knowledge on the methods and results of systemic treatment of brain metastases from non-small cell lung cancer.

Chemotherapy

Recent phase II trials indicate efficacy, however limited, of platinum-based chemotherapy of BMF-NSCLC patients [15–20], which is presented in Table 1.

Phase II trials demonstrating efficacy of first-line BMF-NSCLC chemotherapy.

As outlined in Table 1, the response rates after platinum-based chemotherapy range from 23% to 45%; Chaubet-Houdu and Basse report 23–50%. Literature indicates that temozolomide (TMZ) combined with radiotherapy, in BMF-NSCLC, has a slight influence on survival, but it might increase the toxicity of the treatment [2, 11, 21–23].

Tyrosine kinase inhibitors

Development of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs): gefitinib or erlotinib, has clearly improved the treatment of

Table 1. Efficacy of platinum-based chemotherapy of BMF-NSCLC patients in phase II trials

Authors, publication date, reference no.	Chemotherapy	Number of patients	Overall response rate (%)	Median overall survival (months)
Cotto *et al.* 1996 [15]	cisplatin + fotemustine	31	23	4
Minotti *et al.* 1998 [16]	cisplatin + teniposide	23	35	5
Franciosi *et al.* 1999 [17]	cisplatin + etoposide	43	30	8
Bernardo *et al.* 2002 [18]	carboplatin, navelbine, gemcitabine	22	45	8
Cortes *et al.* 2003 [19]	cisplatin + taxol	26	38	5
Barlesi *et al.* 2011 [20]	cisplatin + pemetrexed	43	42	7

advanced NSCLC patients [3, 4, 9, 10, 13, 24–45]. EGFR mutations are present in 10–25% of NSCLC, with the highest prevalence found in never-smoking women of East Asian descent (up to 55%) [13, 24]. Paez *et al.* and Pao *et al.* found EGFR mutations to be present in 63% and 50% of BMF-NSCLC patients, respectively, which suggests increased risk of developing brain metastases among patients with these mutations [25, 26].

In a non-selected group of patients with BMF-NSCLC the overall response rates after gefitinib range from 10% to 38%, and the duration of response ranges from 9 to 13.5 months [27–30]; erlotinib has similar efficacy [31–35]. It seems that erlotinib achieves higher central nervous system (CNS) concentration in comparison to gefitinib [10, 13]. Gefitinib and erlotinib are both approved as first-line treatment, palliative treatment (second- and third-line), and in combination with radiotherapy (WBRT ± SRS), their efficacy was presented in case reports, case series, and nonrandomised phase II trials [2, 27, 31, 38, 40, 42, 45].

Two phase II trials evaluated the efficacy of TKI in the first-line setting on patients with BMF-NSCLC [38, 40]. Both trials did not include data for EGFR mutations, whereas the studies included never-smokers. Lee *et al.* [40] reported 10 patients; seven demonstrated an objective response to gefitinib, one had a stable disease, and two had a progressive disease after a median 48-week follow-up period. Kim *et al.* [38] presented a group of 23 patients with synchronous BMF-NSCLC with a response rate to gefitinib or erlotinib of 69% and median overall survival of 18.8 months. Heon *et al.* analysed a group of 155 patients with BMF-NSCLC screened for EGFR mutations [41]. The rate of CNS progression was lower among EGRF-mutant patients treated with gefitinib or erlotinib compared with upfront chemotherapy (patients without EGFR mutation) – 33% vs. 48%, respectively, at a median follow-up of 25 months.

Two phase II trials assessed the role of gefitinib in the palliative setting in non-selected patients with BMF-NSCLC [27, 31]. Ceresoli *et al.* [27] reported 41 patients with a 10% response rate and median overall survival of five months, Wu *et al.* [31] reported 40 patients (adenocarcinoma, never-smokers) with a 32% response rate and median overall survival of 15 months. Pesce *et al.* [45] in a randomised study comparing WBRT + gefitinib vs. WBRT + TMZ, failed to show an advantage of gefitinib in a non-selected group of patients with BMF-NSCLC; OS 6.3 months in the gefitinib arm and 4.9 months in the TMZ arm, the difference was statistically irrelevant.

A phase III clinical trial conducted by Sperduto *et al.* [2] showed that TMZ or erlotinib combined with WBRT + SRS in a non-selected group of patients with 1–3 BMP-NSCLC did not improve the OS; however, it increased the toxicity of the treatment.

Welsh *et al.* study [42] evaluated the efficacy of erlotinib in combination with WBRT in 40 patients with BMF-NSCLC. Patients negative for EGFR mutations had a median overall survival of 9.3 months, whereas patients positive for EGFR mutations had 19.1 months. It is also undoubted that either gefitinib or erlotinib can be safely combined with WBRT [43, 44].

Some authors suggest that in selected groups of patients with BMF-NSCLC, commencing treatment with gefitinib or erlotinib, with delayed WBRT, is acceptable. It relates to women with adenocarcinoma, never-smokers, and patients positive for EGFR mutations. Iuchi *et al.* presented good efficacy of gefitinib alone (without radiotherapy) in patients with adenocarcinoma BMF-NSCLC, positive for EGFR mutation – median overall survival 21.9 months in a group of 41 patients [3]. The phase II APRAGE trial, comparing WBRT + gefitinib with gefitinib alone in BMF-NSCLC patients, is ongoing [3, 12].

In conclusion, TKI (gefitinib, erlotinib) overall response rate depends essentially on the presence of EGFR gene activating mutation [10, 12, 13, 36, 37]; if mutation is present, ORR reaches more than 50% [12]. In non-selected groups of patients (adenocarcinoma, Asian descents, never-smokers, asymptomatic BMF-NSCLC) after TKIs therapy, it is possible to reach 70% ORR [13, 38]. TKIs improve survival of BMF-NSCLC patients with EGFR mutations in comparison to patients without these mutations [10, 12, 13, 39].

Crizotinib

In approximately 3–5% of patients with NSCLC, an ALK (anaplastic lymphoma kinase) rearrangement occurs. It results in forming an EML4-ALK fusion gene; it relates to mostly young, male, never-smokers, with adenocarcinoma [10, 12–14, 46]. In this group, administration of crizotinib, an anti-EML4-ALK (echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase) drug, is reasonable and effective [10, 14, 46–48].

Kwak *et al.* [46] reported a 57% response rate, and a randomised phase III trial presented by Shaw *et al.* [47] indicated statistically relevant improvement of progression-free survival of subjects treated with crizotinib, compared to patients treated with a second-line chemotherapy (pemetrexed or docetaxel). Unfortunately, crizotinib has a poor BBB penetration, so its efficacy in BMF-NSCLC patients is doubtful [10, 13, 14, 46, 49–51]. The available literature provides poor corresponding data [12, 49, 50, 52]. Chun *et al.* presented a case of BMF-NSCLC progression during crizotinib treatment, despite regression of the disease outside CNS [49]. Weickhardt *et al.* reported on crizotinib in 38 ALK (+) patients; 28 demonstrated progressive disease, and in 46% the first site of recurrence was BMF-NSCLC. Among patients with isolated recurrence in BMF-NSCLC, treated with radiotherapy (WBRT or SRS) followed by crizotinib, progression-free survival of 7.1 months was obtained [52].

Single cases of BMF-NSCLC responsive to crizotinib were reported by Kaneda *et al.* [53] and Kinoshita *et al.* [48]. Kinoshita suggest that administering ionising radiotherapy before crizotinib treatment may play an important role in both cases [43, 48]. In 2006 Yuan *et al.* indicated in a murine model that CNS radiotherapy increases penetrability of the BBB [54]. Mehra *et al.*, in a phase I trial, demonstrated responses in BMF-NSCLC patients treated with one of the new generation of ALK inhibitors – LDK 378 [55].

Bevacizumab

Bevacizumab is a humanised monoclonal antibody that binds selectively to VEGF – vascular endothelial growth factor. Blocking the VEGF protein should result in impairment of tumour blood vessel growth. Eventually, cancer cells should not develop their own blood supply, causing a lack of oxygen and nutrients, helping to slow down the growth of the tumour. Treatment of advanced NSCLC with bevacizumab remains controversial [1, 12, 13]. Results of two randomised phase III trials, ECOG 4599 and AVAil, reported that bevacizumab combined with chemotherapy improved the response rate and progression-free survival compared to chemotherapy alone in NSCLC. ECOG 4599 also reported a significantly longer OS (12.3 vs. 10.3 months) [56–58]. However, the patient population was restricted to non-squamous histology. Hypertension, massive haemoptysis, disorders in blood coagulation, and BMF-NSCLC were also qualified as exclusion criteria. The restriction of the patient population to non-squamous histology was based on the research of Johnson *et al.*, which indicated the occurrence of life-threatening haemoptysis in this group (4/13 patients) [59]. Exclusion of BMF-NSCLC patients was based on the current opinion that bevacizumab significantly increase the risk of intracranial bleeding in this group [1, 12, 13]. In both trials, the incidence of CNS haemorrhages among patients receiving bevacizumab was similar to the incidence of those reported in patients who did not receive bevacizumab. Based on the results of these trials, bevacizumab is currently licensed for use ase first-line therapy in combination with chemotherapy (carboplatin + paclitaxel) in the USA, or in addition to platinum-based chemotherapy in Europe in patients with advanced non-squamous NSCLC [1]. However, it does not mean it is commonly used; this is because of absent or poor benefit compared to chemotherapy alone, with a slightly increased toxicity [60].

It is obvious that there are no reasons to exclude patients with brain metastases from clinical trials on antiangiogenic agents, as took place in the recent past [1, 13, 56]. Despite antiangiogenic therapy, patients with or without brain metastases have similar risk of intracranial bleeding (90.8–3.3%) [60–64].

Several retro- and prospective clinical trials conducted in the past few years indicate that the combination of bevacizumab with chemotherapy or erlotinib is safe in the treatment of BMF-NSCLC, with a slight risk of intracranial bleeding [60, 62–68].

A prospective phase IV study ARIES evaluated the safety and efficacy of the first-line setting in patients with non-squamous NSCLC treated with bevacizumab combined with chemotherapy. A total of 150 patients with BMF-NSCLC were enrolled, median PFS and OS were 6.0 and 11.7 months, respectively, and no grade 3 to 5 CNS haemorrhage occurred [65].

The phase II study PASSPORT enrolled 115 NSCLC patients with previously treated BMF-NSCLC with WBRT and/or surgery. Patients received as a first-line bevacizumab, with platinum-based doublet chemotherapy or erlotinib, and as a second-line, bevacizumab with single-agent chemotherapy or erlotinib; no grades 1 to 5 CNS haemorrhage, among patients who received bevacizumab-based therapy were reported [62].

The phase III ATLAS study was designed to evaluate the combination of bevacizumab/erlotinib versus bevacizumab/placebo as maintenance therapy after four cycles of induction platinum-containing chemotherapy plus bevacizumab as first-line treatment in advanced NSCLC patients. Among 25 evaluable patients with a history of CNS metastases pretreated with WBRT and/or neurosurgery, one grade 2 CNS bleeding was observed in a patient on post-progression therapy after 14 cycles of bevacizumab [66, 67].

The SAiL study assessed the safety and efficacy of the addition of bevacizumab to first-line chemotherapy. This study proved that bevacizumab-based therapy resulted in median OS of 14.6 months, with a median time to disease progression of 7.8 months. Efficacy was generally similar across chemotherapy regimens. The specific safety of bevacizumab was assessed in patients who either developed BMF-NSCLC during treatment or had occult BMF-NSCLC at

study entry. Of the 281 patients evaluated, five (2%) had CNS bleeding [60].

The phase III BeTaLung study evaluated the addition of bevacizumab to erlotinib for the second-line treatment of advanced NSCLC patients. A total of 636 patients were randomised to receive bevacizumab in combination with either erlotinib or erlotinib alone. The addition of bevacizumab to erlotinib increased PFS compared to erlotinib alone (3.4 vs. 1.7 months, respectively). This trial included patients with BMF-NSCLC, previously treated with WBRT and neurosurgery or WBRT + SRS. Among 68 BMF-NSCLC patients, 37 received erlotinib + bevacizumab and 31 erlotinib alone. No CNS haemorrhage or grade > 3 bleeding was reported in either arm [68].

Besse *et al.* presented an analysis including more than 12,000 advanced/metastatic breast cancer, NSCLC, renal, and colorectal cancer patients, with previously treated CNS metastases, from 13 phase II/III randomised controlled trials, two open-label, single-arm safety studies, and two prospective studies. The rate of cerebral haemorrhage in the bevacizumab-treated group was 3.3%, compared to 1% in the group not treated with bevacizumab. This study suggests that the administration of bevacizumab should no longer be contraindicated based solely on the presence of CNS metastases [63].

Several clinical trials have been launched to determine the safety and efficacy of various other antiangiogenic agents in the treatment of new or progressive brain metastases from solid tumours: sunitinib, cediranib, and vatalanib [1].

In conclusion:

1. Chemotherapy is generally effective in BMF-NSCLC, and platinum-based provides response rates ranging from 23% to 45%.
2. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR – TKIs) – gefitinib and erlotinib – have a definite activity in BMF-NSCLC with activating EGFR mutation, or in selected groups of patients (woman of east Asian descent, never-smokers, those with adenocarcinoma); the response rate ranges from 38% to 70%. Both EGFR-TKIs have been investigated in first-line, palliative, and in combination with radiotherapy. Patients with BMF-NSCLC-EGFR-mutant have improved overall survival compared with EGFR wild-type tumours, when receiving an EGFR inhibitor.
3. There is no data on the activity of the agent ani-EML4-ALK-crizotinib in patients with BMF-NSCLC. Crizotinib has a poor penetration of BBB.
4. Data from a clinical trial enrolling patients with pretreated or occult BMF-NSCLC showed that the addition of bevacizumab to various chemotherapy agents or erlotinib is a safe and efficient treatment, associated with a low incidence of CNS haemorrhage. However, bevacizumab should be used with caution in patients with active BMF-NSCLC.

The authors declare no conflict of interest.

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