The diagnosis and treatment of brain metastases in EGFR mutant lung cancer

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Practice Points

- EGF receptor (EGFR) mutant lung cancer brain metastases are characterized by widespread, small volume metastases over both hemispheres of the brain.
- Treatment of oligometastatic brain metastases in EGFR mutant lung cancer, as with EGFR wild-type tumors, may include radiosurgery or surgery in selected individuals.
- EGFR tyrosine kinase inhibitors (TKIs) show activity in management of brain metastases from EGFR mutant lung cancer.
- The most effective order of delivery of treatment modalities (whole brain radiotherapy, chemotherapy, EGFR TKIs) has yet to be determined.
- EGFR TKIs have been shown to be feasible in combination with whole brain radiotherapy and possibly act as radiosensitizers.
- Withdrawal of EGFR TKI can result in sudden symptomatic deterioration of the disease, including brain metastases.
- On progression of brain metastases in patients already on EGFR TKIs, and depending upon what other treatments have already been given, treatment modalities include local therapies, WBRT, chemotherapy and next-generation EGFR TKIs. Clinical trials are needed to define the role of reintroduction of previous EGFR TKI.

SUMMARY The epidemiology of non-small-cell lung cancer (NSCLC) has changed with a new pattern of disease emerging – a form of adenocarcinoma in mostly younger female patients, who are never or light smokers and more frequently in East Asian populations. Description of EGF receptor (EGFR) mutations has allowed new management strategies to evolve. Oral targeted therapies have broadened the treatment options in the advanced setting with the potential for periods of long term response. The brain is a common site of metastases with EGFR mutated lung cancer typically displaying asymptomatic, small volume, multiple lesions that respond to treatment. We explore the role of local and system therapies for brain metastases in this disease including the role of EGFR inhibitors.

EGFR mutations in lung cancer

EGF receptor (EGFR) is a cell surface protein, a member of the *ErbB* group of receptors. Mutations in the EGFR gene confer a higher response to EGFR targeting tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib [1]. Over 90% of activating EGFR mutations consist of small in-frame deletions within exon 19 and a point mutation (L858R) in exon 21 [2]. A further 5% of EGFR mutations are due to a point mutation (G719) in exon 18 [3]. A secondary mutation of exon 20 (T790M) has been linked with acquired resistance to EGFR TKIs [4, 5]. Patients with lung cancer harboring an EGFR mutation are typically female, never smokers and have predominantly an adenocarcinoma histology. They represent approximately 10% of all Western NSCLC patients but the frequency in East Asian NSCLC patients can be as high as 40% [6]. The patients are younger and generally fitter than the

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typical lung cancer population. The link between EGFR mutational status and prognosis is clearly established in a number of tumor types. The link is less clear in lung cancer, although meta-analysis has shown a worse prognosis (hazard ratio 1.13) for EGFR mutations [7].

The typical presentation of a patient with advanced NSCLC has changed from that of a long-term smoker with acceptance of a smoking related disease to a young patient, bewildered at being diagnosed in the absence of obvious risk factors. Debate continues as to whether EGFR mutant positive lung cancer is increasing in frequency in recent years or whether the perceived increase is an effect of the declining population of smokers as smoking becomes less prevalent. Certain series looking at temporal changes in lung cancer in never smokers report an increase in incidence since the 1930s [8, 9]. A Swedish study reported an increase from 1.5 per 100 000 in 1976–1980 to 5.4 per 100 000 in 1991–1995 [10]. However, a large analysis of populations in the USA found no increase in incidence of lung cancer in never smokers from 1959 to 2004 [11].

EGFR tyrosine kinase inhibitors in lung cancer

There is clear evidence behind the use of the EGFR TKIs erlotinib and gefitinib in advanced NSCLC with improved survival observed for lung cancers with an EGFR mutation in both the first and second-line settings [12–14]. In the Mok *et al.* pivotal Phase III trial (IPASS) never-smokers or light smokers were randomized to gefitinib or carboplatin in the first-line setting. A total of 261 patients had EGFR-mutations. In these patients progression-free survival was significantly better with gefitinib than carboplatin-paclitaxel (hazard ratio for progression or death of 0.48; 95% Confidence Interval [CI] 0.36–0.64; $p < 0.001$). In the subgroup of 176 patients without EGFR mutation, progression-free survival was significantly improved with carboplatin-paclitaxel (hazard ratio for progression or death 2.85; 95% CI 2.05–3.98; $p < 0.001$) [12]. The development of second generation EGFR TKIs such as afatinib have further broadened treatment options [15]. A Phase III randomized controlled trial of afatinib versus pemetrexed and carboplatin chemotherapy demonstrated a 11.1 versus 6.9 months improvement in progression-free survival with a hazard ratio of 0.58 (95% CI 0.43–0.78; $p = 0.0004$).

This progression-free survival benefit is similar in magnitude to that seen in the result of trials comparing gefitinib or erlotinib with chemotherapy in patients with EGFR mutated disease [12,13]. The investigation of first-line erlotinib in a European population of patients with EGFR mutant lung cancer revealed similar results to these Asian population trials [16]. In addition, chemotherapy, radiotherapy and surgery remain available and useful at different points in a patient's treatment journey.

In the setting of early stage, radically treatable NSCLC with an EGFR mutation, TKIs are as yet, of unproven benefit. Gefitinib has been studied in a recent randomized controlled trial of patients with completely resected stage IB, II or IIIA NSCLC [17]. The trial closed early, but with a median follow-up of 4.7 years there was no difference in overall survival seen with a hazard ratio of 1.24 (95% CI 0.94–1.64; $p = 0.14$). Of the 503 patients enrolled, only 15 had EGFR mutated tumors but these also had no survival benefit with a hazard ratio of 3.16 (95% CI 0.61–16.45; $p = 0.15$). A trial of adjuvant gefitinib in 243 patients unselected for EGFR status following concurrent chemoradiotherapy with cisplatin and etoposide and consolidation docetaxel demonstrated no survival benefit (median overall survival 23 months for gefitinib versus 35 months for placebo, $p = 0.13$). However, there was increased toxicity in the gefitinib arm with a toxic death rate of 2% versus 0% [18]. The results of the first adjuvant trial of erlotinib versus placebo after curative surgery (RADIANT trial) will be presented later this year.

Brain metastases in EGFR mutated lung cancer

In advanced EGFR mutated NSCLC the sites of metastatic disease differ from that of EGFR wild-type disease. Typically there is a polka dot appearance of widespread small lesions both in the lung and in the brain. The lesions are bigger than the classic 'miliary' appearance of tuberculosis [19]. The true incidence of brain metastases in EGFR mutant NSCLC is unknown as retrospective series only report cases where a diagnosis has been made – an unknown number of patients have undiagnosed, asymptomatic brain metastases. Clinical trials frequently exclude patients with brain metastases and, in general, select patients with good performance status. Also, unless specified as an endpoint, rates of

brain metastases as a site of relapse may not be recorded. Nevertheless, the development of metastasis in the brain is a frequent occurrence in NSCLC affecting up to half of patients at some time during their disease, resulting in significant morbidity and mortality. A recent review from Korea describes 314 patients who presented with lung cancer, were tested for an EGFR mutation and had an MRI of the brain. Brain metastases were found in 51 patients, 161 had local disease, and 102 extracranial metastases). As expected in an East Asian population the incidence of EGFR mutation positivity was 44%, but the patients with brain metastases had a high EGFR rate of 65%. Surgery was undertaken in 133 patients. Relapse in the brain as a subsequent event was more common in the patients with an EGFR mutation than in the wild type population [20].

We have no reliable figures for the incidence of metastatic brain disease from EGFR lung cancer, however consideration of the above data allows us to estimate the incidence of EGFR mutated brain metastases in the general population. In 2012 there were 42,026 cases on lung cancer diagnosed in the UK, 87% of which were NSCLC. If we estimate that approximately 10% of these will have an EGFR mutation and 40% of these will develop brain metastases then we will have approximately 1400 patients per year presenting with new brain metastases [21]. This highlights the importance of developing evidence-based, effective treatments for this patient population.

Treatment of brain metastases

Treatment of brain metastases depends on multiple factors including number and site of the metastatic intracranial disease, whether the patient is symptomatic from the metastases and their fitness. Steroids and, if required, anticonvulsants play a role in the immediate management at the time of diagnosis. In general, patients with a single site of disease can be considered for local interventions such as surgery or radiosurgery. If the intracranial disease is more widespread, then whole brain radiotherapy (WBRT) should be considered, especially in symptomatic patients. Systemic treatments with chemotherapy or, in the case of EGFR mutated NSCLC, EGFR TKIs, can be used in combination with WBRT or alone. The timings of WBRT and systemic treatments are another consideration, largely governed by the severity of symptoms of the brain metastases.

WBRT

WBRT is widely available and is the standard therapy for patients with multiple brain metastases. NSCLC is an intrinsically radioresistant malignancy. As such the doses achievable in treating the brain of a NSCLC patient are unlikely to achieve full disease control. WBRT often provides an improvement in symptoms and enables patients to stop steroid treatment, though side effects can include memory loss, fatigue and dementia in the older datasets [22]. However, the most recent data in small cell lung cancer suggest that as long as dose is kept standard, sequelae are not so frequent and are reversible [23]. Trial data comparing WBRT to best supportive care alone is limited. The ongoing QUARTZ study randomizes patients with brain metastases from NSCLC to best supportive care alone versus best supportive care and WBRT thus aiming to provide evidence in this area [24]. In addition, the optimum order of administration of WBRT and systemic treatments (such as chemotherapy and EGFR TKIs) has yet to be determined. In practice, in the symptomatic patient, a rapid response to treatment is required so local therapies are usually favored but a head to head comparison of speed to response is not available. When WBRT is used alone it has been historically associated with an increase in median survival from 4 to 6 months [25]. A recent Cochrane systemic analysis included 39 trials with 10,835 patients. The review concluded that altered WBRT dose-fractionations compared to the standard of 3000 cGy in 10 fractions or 2000 cGy in 4 or 5 fractions did not provide extra benefit. A radiosurgical boost may benefit selected patients but is of unproved benefit in those with multiple brain metastases. The addition of WBRT to radiosurgery conferred no benefit in terms of overall survival but improved local control [26].

There is preclinical evidence that lung cancer cells harboring an EGFR mutation are more radiosensitive than those with wild type EGFR. EGFR plays a role in the cellular response to ionizing radiation, translocating to the nucleus and binding to enzymes involved in non-homologous end-joining. In EGFR mutated cell lines cells are defective in repairing ionizing-radiation induced DNA damage [27]. It is not known whether this translates into EGFR mutations predicting a higher response to WBRT. Most retrospective clinical studies are confounded by concurrent or sequential administration of EGFR-targeted

drug therapy and often the number of patients with a documented EGFR mutation is very small: in the largest series to date, only 17 of the 69 patients analysed had an EGFR mutation [28]. A retrospective review of 123 patients with locally advanced NSCLC treated with radiotherapy observed that overall survival was higher in the 25% of patients with EGFR mutant tumours with a 2-year estimated survival of 92.6% versus 69.0% ($p = 0.04$). The 2-year locoregional recurrence rate was lower in EGFR mutant than in wild-type EGFR tumors (17.8% versus 41.7%, $p = 0.005$). Most patients did not receive a TKI at any point. The authors conclude that these results may support the hypothesis that the presence of an EGFR mutation confers sensitivity to radiotherapy or chemotherapy [29].

EGFR tyrosine kinase inhibitors

Treatment of brain metastases in advanced solid tumors is problematic as systemic treatment may not have full penetration of the blood–brain barrier, the endothelial lining of the CNS vessels restricting transit from the systemic circulation to the cerebrospinal fluid (CSF). The passage of drugs relies on receptor-mediated mechanisms and transporters such as P-glycoprotein (Pgp) actively transporting drugs back into the systemic circulation. It is thought that the presence of brain metastases allows disruption of the blood–brain barrier allowing drugs to concentrate in the brain. In animal models it has been shown that brain metastases vary in their blood–tumor-barrier permeability and the blood–tumor-barrier permeability varies even between different areas of the same tumor [30]. Clearly some degree of passage into the brain is seen with EGFR TKIs in lung cancer as responses have been seen with gefitinib, erlotinib and, more recently, afatinib. In general, while there is probably little difference in efficacy between erlotinib and gefitinib, the biological effectiveness of the standard dose of erlotinib may be higher than the current recommended dose of gefitinib. When CSF concentrations of gefitinib and erlotinib were directly compared in a series of 15 Japanese patients, the mean steady state CSF concentration and penetration rate of gefitinib 250 mg daily were lower than with erlotinib 150 mg daily [31]. In leptomeningeal disease, erlotinib shows greater activity in terms of cytological clearance of CSF compared with gefitinib. In a retrospective review of patients receiving EGFR TKIs for leptomeningeal disease

by Lee *et al.*, gefitinib and erlotinib were administered to 11 and 14 patients, respectively. Patients treated with erlotinib showed better cytologic conversion rate (defined as absence of malignant cells in the CSF) than those with gefitinib (64.3% [9/14] in the erlotinib arm versus 9.1% [1/11] in the gefitinib arm; $p = 0.012$) [32].

An additional potential problem with EGFR TKIs in this setting is that of potential tumor EGFR mutation heterogeneity with certain clones retaining EGFR wild-type. EGFR mutation intra-tumoral heterogeneity has been reported to correlate with response to gefitinib [33]. However, others reported uniform distributions of EGFR mutations intra-tumorally and have suggested that it is variations in the copy number of intra-tumoral EGFR that gives the appearance of heterogeneity [34].

Currently the clinical evidence for the effectiveness of EGFR TKIs in treating active brain metastases is largely in the form of case reports or case series and indeed, at this point in time most practitioners in lung cancer have seen such cases for themselves. Cases reports have appeared for erlotinib since 2006. In a case–control study of 69 Spanish NSCLC patients with brain metastases treated with erlotinib, an EGFR-mutant population (17 patients) was compared with a population with unknown or wild-type EGFR (52 patients). As in other reports, the patients with EGFR-mutated tumors responded to treatment and lived longer than the EGFR wild type group, who effectively were not receiving any active treatment [28]. The use of WBRT in both arms was confounding. Overall survival was better in the mutated group (12.9 months; 95% CI 6.2–19.7 months) compared with the wild type group (3.1 months; 95% CI 2.5–3.9 months) ($p < 0.001$). The figure of 3.1 months is comparable with other datasets for outcome in NSCLC patients with brain metastases. A recently reported Phase II trial in 48 patients from a Chinese population has assessed the efficacy of erlotinib as second-line therapy for NSCLC brain metastases [35]. Inclusion criteria included adenocarcinoma or confirmed activating EGFR mutation NSCLC and asymptomatic brain metastases without extra-cranial progressive disease after first-line platinum-based chemotherapy. Erlotinib 150 mg daily was associated with a 4.4 month median progression free survival (95% CI 0.0–11.6), extending to 15.2 months (95% CI 8.3–22.2) for those with EGFR mutant disease ($p = 0.02$). Median overall survival was 18.9 months for both

patients with EGFR mutant and EGFR wild-type disease (95% CI 14.4–23.4).

There are individual case reports of response to afatinib in NSCLC patients with brain metastases. In a Phase I trial of afatinib in 53 patients, a patient with an EGFR mutation showed response in brain and thoracic disease [36]. The patient was a 55 year old ex-smoker. She achieved a partial response to afatinib 10 mg but after 14 months relapsed with brain metastases. She was treated with a higher dose of 40 mg and achieved a partial response in her brain disease that lasted a further 10 months.

EGFR TKIs in combination with WBRT

The combination of erlotinib with WBRT has been studied with caution. Radical thoracic irradiation has been associated with high toxicity when given concurrently with erlotinib, though the antiangiogenic agent bevacuzimab was also involved in this combination [37]. The SWOG 00279 trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer showed no improvement in median overall survival, although the patient cohort was not selected for EGFR status [18]. The numbers of patients with EGFR mutations in reported studies to date are either small or unknown. The results of the Phase II TACTIC trial were presented at the World lung cancer conference 2013. This randomized controlled trial of WBRT plus erlotinib versus WBRT plus placebo included patients with NSCLC with newly diagnosed brain metastases. Patients were randomized to standard WBRT or WBRT plus erlotinib 100 mg daily. A total of 80 patients were randomized. Toxicity was similar between the two arms, with grade 3 or 4 rash more common in the erlotinib arm (20 versus 5%). There was no improvement in neurological progression free survival (median neurological progression free survival 1.6 months in both arms, hazard ratio 0.95, 95% CI 0.59–1.54, $p = 0.84$) or overall survival (median overall survival 2.9 months in the placebo arm versus 3.4 in the erlotinib arm, 95% CI 0.58–1.55, $p = 0.83$). Only 3% of the patients had an EGFR mutation which may explain this lack of efficacy. Interestingly, the median overall survival was similar to historical reports for this group of patients; this was a patient group unselected for better outcome and the authors suggest that better prognostic indices are needed to guide these treatment decisions [38].

There is an association of higher grade skin toxicity and sensitivity to lower doses of TKIs in patients with EGFR mutations so it maybe that hypersensitivity to radiotherapy occurs in these patients and therefore a lower dose TKI maybe required when combined with WBRT [39]. As yet, this has not been clinically investigated.

Chemotherapy

Primary chemotherapy for advanced NSCLC has long been a recognized treatment strategy and responses in all subgroups including the EGFR mutated subgroup are observed. Pemetrexed is particularly active in adenocarcinoma and gives responses in brain metastases with one small trial of 39 patients showing a clinical benefit in 69% of patients [40]. A retrospective review of two randomized controlled trials of pemetrexed in NSCLC with a combined total of 2296 patients showed an odds ratio for brain metastases associated with exposure to pemetrexed of 0.49 (95% CI 0.32–0.76, $p = 0.001$) [41].

Second-line treatment of brain metastases

In clinical practice, TKIs can control brain metastases for long periods of time, but in general relapse occurs at some point. There is no consensus on the most appropriate treatment at this point. The following strategies can be employed:

- **Addition of whole brain radiotherapy**

In patients who have not already received WBRT, WBRT can be instigated. We have no randomized data to support this approach.

- **Continuation of EGFR TKI post-progression**

An important question is that of continuing EGFR TKI after cranial disease development or progression occurs whilst on the drug. It has been postulated that continuous EGFR blockade would help to maintain control of neurological disease, slowing the rate of disease progression and stopping a ‘tumor flare’ phenomena. It is often clinical practice for patients to continue to receive a TKI on-study if there is evidence of extra-cranial control of disease. Early erlotinib trials also allowed this practice within their protocols [14] and this strategy is employed in other tumor types with specific targeted therapies; for example, anti-HER-2 therapies in metastatic breast cancer and imatinib in gastro-intestinal stromal tumors. Though we have no randomized data

to support this approach in EGFR mutant lung cancer, individual case reports do describe patients for whom a degree of disease control seems to be achieved though on-going EGFR inhibition [36]. It has been observed that EGFR mutant tumors can progress rapidly on cessation of erlotinib or gefitinib. This has been termed 'tumor flare' or 'disease flare'. In an analysis of 61 patients enrolled on clinical trials it was judged that 14 patients had disease flare, defined as hospitalization or death in the wash-out period from the EGFR TKI [42]. Within our clinical practice we have seen cases of prolonged response of brain metastases to EGFR TKIs and used continued EGFR inhibition to avoid tumor flare. One such patient (an unpublished case report) was of a 53 year old who was diagnosed with metastatic adenocarcinoma of the lung of unknown EGFR mutational status with brain metastases. He was treated initially with WBRT followed by four cycles of cisplatin and pemetrexed with progressive disease noted at the completion of treatment. He was then commenced on erlotinib to which he obtained a partial response in his thoracic disease and his cerebral disease. The thoracic and brain disease progressed after 12 months of erlotinib treatment and the erlotinib was stopped. This was followed by a sudden decrease in functioning with confusion and lethargy. Erlotinib was recommenced via a nasogastric feeding tube. This was followed by prompt resolution of his symptoms and a return to his previous level of functioning. He continued the erlotinib and on a weaning dose of steroids with only minimal radiological disease progression, until he entered the afatinib expanded access program 8 months later. After 2 months on afatinib he was admitted to hospital with pneumonia and some signs of brain disease progression with dilatation of the cerebral ventricles and died.

• Dose increase of EGFR TKI

Trial data on the use of EGFR TKIs in NSCLC remains restricted to use either first-line or second-line after failure of standard chemotherapy. Anecdotal active strategies in patients who have developed brain metastases on TKI include increasing the dose of TKI within the recommended therapeutic window if it has been reduced because of toxicity, switch to a next generation TKI or standard chemotherapy. Within most of these cases WBRT is also used at some point in time. It is therefore difficult to know

which modality produces the observed patient responses. At present a dose escalation policy should not be undertaken outside a clinical trial and even within a clinical trial some measure of drug level must be incorporated – whether pharmacokinetics or a measure of CNS penetration [43]. The largest series to date is that of 11 patients with EGFR-mutant lung cancer and brain or lepto-meningeal metastasis treated with 'pulsatile' once weekly erlotinib at a median weekly dose of 1500 mg after progression on conventional daily erlotinib or gefitinib [44]. Kuiper *et al.*'s attempts to treat with erlotinib within a trial setting led to the trial being discontinued after 11 patients as the trial met the predefined stopping criteria. The disease control rate was 36.4% and median progression-free survival 1.6 months (95% CI 1.3–2.0 months) [KUIPERJ, PERS. COMM.].

• Rechallenge with an EGFR TKI

In practice, as described in our case study above, if EGFR TKIs are available through funding routes then rechallenge is often attempted. It might be expected that afatinib would have a role after erlotinib or gefitinib failure as it is irreversible, rather than a reversible, second-generation EGFR TKI. There have been efforts to investigate the role of EGFR TKIs following failure of a first EGFR TKI. Miller *et al.*'s Phase IIb/III trial of afatinib versus placebo following failure of erlotinib, gefitinib or both in patients with advanced NSCLC. The trial reported no benefit in terms of overall survival though a progression-free survival benefit was seen with a median progression-free survival of 3.3 months in the afatinib group (95% CI 2.79–4.40) and 1.1 months in the placebo group (65% CI 0.95–1.68) with a hazard ratio of 0.38, 95% CI 0.31–0.48, $p < 0.0001$. The lack of survival benefit may due to subsequent cancer treatments given after the trial drugs (68% of patients in the afatinib group and 79% in the placebo group received other cancer treatments) [45].

There is great interest in ways of overcoming EGFR TKI resistance. Preclinical work into methods of EGFR resistance has identified potential mechanisms including the development of secondary mutations of EGFR (such as T790M), MET amplification, HER-2 up-regulation, KRAS activation and histological transformation to another histological subtype such as small cell [46]. At present targeting of

these pathways is largely still at the preclinical, or very early phase clinical trial stage.

Treatment of solitary brain metastasis & oligometastatic brain metastases

Though, as discussed, the typical presentation of patients with EGFR-mutated lung cancer is with multiple small brain metastases patients can present with a single site of metastasis or oligometastatic disease. As with the EGFR wild-type lung cancer radiosurgery (stereotactic surgery) or surgical resection can be considered. Such approaches require careful patient selection with a reasonable degree of patient fitness and lack of rapidly progressing disease extracranially required. In a study of patients with advanced malignancies those with a single site of metastatic disease in the brain benefitted from the addition of radiosurgery to WBRT with an improvement in overall survival from 4.9 to 6.5 months ($p = 0.0393$). In those with oligometastatic brain disease a survival advantage was not seen [47]. When comparing WBRT and neurosurgery to WBRT alone a survival advantage is also seen in those with a single site of disease [48, 49].

Asymptomatic brain metastases

Patients with asymptomatic brain metastases are often diagnosed on staging imaging prior to planned curative surgery or radical radiotherapy. Asymptomatic as distinct from symptomatic, or 'active' brain metastases do not have an evidenced based treatment pathway. However there are some reports of retrospective series available. These suggest that upfront chemotherapy may be as effective as WBRT in NSCLC (unselected for EGFR status) [50, 51]. We do not know what the natural history is of asymptomatic brain metastases as in general a local or systemic treatment is offered on the basis that asymptomatic patients would be thought to do better than symptomatic patients. Subsequent treatment decisions are guided, as in symptomatic brain metastases, by patient choice, patient fitness and co-morbidities. Options include chemotherapy alone and EGFR TKIs. Unanswered questions include the need to consolidate the local response with WBRT immediately or whether this should be delayed.

Prophylaxis of brain metastases

Use of EGFR TKIs delays progression of metastatic NSCLC but it is not clear if they specifically delay the development of brain metastases.

The RADIANT trial is ongoing and may further clarify this question.

Prophylactic cranial irradiation (PCI) is cranial irradiation given to high-risk patients with no evidence of intracranial disease with the aim of reducing the development of brain metastases. It is standard practice in small cell lung cancer. PCI has been shown to reduce the risk of developing brain metastasis in high-risk NSCLC, but this does not translate into an improved disease-free or overall survival [52, 53]. There is an ongoing study in The Netherlands looking at this strategy in a similar design to the Gore *et al.* study, which hopefully will recruit well [54]. PCI has not been studied in the sub-set of patient with EGFR mutations.

Conclusion & future perspective

Patients with EGFR mutation driven lung cancer represent a new phenotype of lung cancer and brain metastases affects a large proportion of these patients. The clinical characteristics and response to non-TKI treatments are similar to those observed in patients with brain metastases from EGFR wild-type cancers. Though the EGFR TKIs have activity in the treatment of brain metastases and possibly as radiosensitisers with WBRT, robust Phase III clinical trial data is required. The most effective combination and order of delivery of available treatment modalities has yet to be defined. At disease progression, dose escalation of TKI or 'pulsatile' administration has been attempted but is not proven or a standard therapy. In the setting of a single site of brain metastasis neurosurgery and radiosurgery can be considered.

Over the next years, as prognosis for patients improves, there will hopefully be the opportunity for larger randomized trials to answer some of the questions posed in this summary. There is a need for data derived from EGFR mutant only groups given that much of the data we have currently are derived from EGFR mutant and wild-type populations. The role of the second-generation EGFR TKI afatinib is yet to be defined within the treatment paradigm of brain metastases from EGFR mutant lung cancer. This, and other next-generation EGFR TKIs, may provide further incremental improvements in patient outcomes. Further investigation into methods of EGFR resistance will hopefully lead to the development of new novel agents or new combinations of agents to combat EGFR resistance.

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