

Role of Epidermal Growth Factor Receptor (EGFR) Inhibitors and Radiation in the Management of Brain Metastases from EGFR Mutant Lung Cancers

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Brain metastases • Lung cancer • Epidermal growth factor receptor mutation • Radiation therapy • Targeted therapy

ABSTRACT

The growth of genotype-directed targeted therapies, such as inhibitors of the epidermal growth factor receptor (EGFR), has revolutionized treatment for some patients with oncogene-addicted lung cancer. However, as systemic control for these patients has improved, brain metastases remain an important source of morbidity and mortality. Traditional treatment for brain metastases has been radiotherapy, either whole-brain radiation or stereotactic radiosurgery. The growing availability of drugs that can cross the blood-brain barrier and have activity in the central nervous system (CNS) has led to many studies

investigating whether targeted therapy can be used in combination with or in lieu of radiation. In this review, we summarize the key literature about the incidence and nature of EGFR-mutant brain metastases (EGFR BMs), the data about the activity of EGFR inhibitors in the CNS, and whether they can be used as front-line therapy for brain metastases. Although initial use of tyrosine kinase inhibitors for EGFR BMs can often be an effective treatment strategy, multidisciplinary evaluation is critical, and prospective studies are needed to clarify which patients may benefit from early radiotherapy. *The Oncologist* 2018;23:1054–1062

Implications for Practice: Management of brain metastases in epidermal growth factor receptor (EGFR) mutant lung cancer is a common clinical problem. The question of whether to start initial therapy with an EGFR inhibitor or radiotherapy (either whole-brain radiotherapy or stereotactic radiosurgery) is controversial. The development of novel EGFR inhibitors with enhanced central nervous system (CNS) penetration is an important advance in the treatment of CNS disease. Multidisciplinary evaluation and evaluation of extracranial disease status are critical to choosing the best treatment option for each patient.

INTRODUCTION

Identification of activating mutations in the epidermal growth factor receptor (EGFR) in lung cancer was a monumental advance in our understanding of the molecular basis of carcinogenesis [1, 2]. The activity of EGFR-specific tyrosine kinase inhibitors (TKIs) against such cancers ushered in an era of genotype-directed targeted therapy that fundamentally changed the overall approach to lung cancer. Despite these advances, the central nervous system (CNS) remains a common site of metastatic spread and morbidity for patients with EGFR-mutant lung cancer.

Management of EGFR-mutant brain metastases (EGFR BMs) presents multiple challenges. Radiotherapy (RT), either with whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS), has been the mainstay of treatment for brain metastases due to the poor blood-brain barrier penetration of most systemic therapies. However, there has recently been increasing concern

about the potential long-term impact of cranial RT, especially WBRT, upon neurocognitive function and quality of life [3]. Given the prolonged survival of patients with EGFR BMs [4], the late toxicities of cranial RT have become a growing concern. Furthermore, EGFR inhibitors have consistently shown some degree of activity in the brain even without RT [5–10]. In this context, there has been interest in omitting or delaying cranial radiation for EGFR BMs by using TKIs. In this review, we will summarize the literature about the characteristics of EGFR BMs as well as describe the CNS activity of various EGFR inhibitors. We will also review the key literature about the sequencing of TKIs and RT for EGFR-mutant patients with newly diagnosed brain metastases.

MATERIALS AND METHODS

We conducted a computerized literature search in PubMed to identify publications relevant to the topic of EGFR, EGFR

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inhibitors, lung cancer, and brain metastases. We included only full text publications written in English and selected the studies based on methodological design and sample sizes. We prioritized prospective studies or large retrospective studies. We did not include publications in abstract form if the data included were of exceptional relevance to this review and were not published in a full-length format. We also examined the references of selected studies to identify additional references that did not appear in our original searches. The following data were extracted from the published articles, as available: characteristics of the study population, length of follow-up, incidence of extracranial disease, rates of salvage therapy, CNS overall response rate (CNS ORR), CNS progression-free survival (CNS PFS), and overall survival (OS).

RESULTS

Characteristics of Patients with EGFR Brain Metastases

Many studies have shown that patients with EGFR driver mutations appear to have a similar incidence of brain metastases when compared with the overall lung cancer population. In a review of 93 patients with lung adenocarcinoma brain metastases treated at our institution from 2004 to 2008, 44% carried an EGFR mutation and 56% did not [11]. Similarly, in a genotyped cohort of 209 patients from Colorado, there was a similar distribution of brain metastases among patients with EGFR, KRAS, ALK, and wild-type lung cancers [12]. A retrospective case control study from The Netherlands [13] identified 62 patients with stage IV EGFR mutant lung cancer and paired them with consecutive patients with KRAS mutant and wild-type lung cancer. A similar incidence of brain metastases was identified in each group.

However, several studies, mostly from Asia, have suggested an increased risk of BMs in EGFR mutant lung cancer. In a cohort of 314 lung adenocarcinoma patients from Korea [14], 51 patients had brain metastases. In a multivariable model, EGFR mutation was associated with an increased risk of brain metastasis (adjusted OR 3.83, $p = .001$) but no increased risk of extracranial metastasis. A study from the People's Republic of China [15] showed that among 234 patients with lung adenocarcinoma, 108 carried EGFR mutations. Seventy-six of these patients developed brain metastasis, which was significantly higher than the rate among those without EGFR mutation. There was no difference seen in the rate of extracranial metastatic disease. On multivariable analysis, EGFR mutation was associated with an independent increased risk of brain metastases (OR 2.52, $p = .022$).

There are some data that EGFR mutation may impact the clinical presentation of BMs. The Chinese study suggested that patients with EGFR mutation had larger and more numerous BMs compared with Wild Type patients [15]. Another study of 57 patients with lung adenocarcinoma with synchronous brain metastasis [16] reported that EGFR exon 19 deletion was associated with more numerous brain metastases compared with wild-type cancers, although that was not true of cases with EGFR exon 21 mutations. In addition, the median size of the tumors in patients with exon 19 deletion was smaller compared with wild-type cancers, as was the associated peri-tumoral edema. Radiographic analysis of 200 patients with brain metastases treated in Japan [17] demonstrated that EGFR L858R was

associated with more superficial lesions, preferentially located in the caudate, cerebellum, and temporal lobes compared with exon 19 patients. These data, while still preliminary, suggest that different EGFR mutations may result in somewhat different patterns of CNS metastasis. Analysis of patterns of EGFR BMs remains a nascent area of investigation, and hopefully future studies will shed more light on the differences in presentation among different genotypes.

One important point to emphasize is that patients with EGFR BMs can have a prolonged survival. The Graded Prognostic Assessment for Lung Cancer (dsGPA), a system used to define prognosis of brain metastases from lung cancer, was recently updated to include presence of mutations in EGFR or ALK, along with the traditional risk factors of age, Karnofsky performance status, extracranial metastases, and number of brain metastases. The investigators found that patients in the best prognosis group, which includes patients with targetable mutations, had a median survival of 46.8 months [18]. These data emphasize that therapeutic considerations for patients with EGFR BMs must consider the short-term and long-term risks of treatment.

In summary, EGFR BMs are a common problem, although it remains unclear whether there is truly an increased incidence compared with other genotypically defined lung cancer groups. However, as more EGFR inhibitors enter clinical practice, the resultant increased survival of patients with EGFR-mutant lung cancer will translate into a longer time in which brain metastases may develop. Thus, identifying the optimal strategy for CNS control of EGFR BMs remains an important area of study.

The Activity of TKIs in the CNS

The early availability and widespread use of the first-generation EGFR inhibitors, erlotinib and gefitinib, led many to investigate whether these drugs had any activity in the CNS. These data, summarized in Table 1, generally demonstrate a high overall CNS response rate to first-generation EGFR TKIs. For example, a retrospective study from Spain [8] examined 69 patients with brain metastases who were treated with erlotinib on prospective trials, including 17 with EGFR mutations. Half of the patients with EGFR mutation did not receive brain radiation prior to starting erlotinib. Among these patients, erlotinib yielded an 82% objective response rate (ORR) including a 47% complete response (CR) rate. A larger study from the People's Republic of China [23] of 43 patients with confirmed EGFR BMs treated with erlotinib or gefitinib showed a 57% ORR in the CNS compared with 91% for extracranial disease (ECD). None of the patients had received CNS RT prior to treatment. Although this ORR is lower than that in many of the other studies, this study did include patients receiving TKI as second-line therapy. Additionally, the disease control rate was 91% for the CNS versus 95% for ECD, suggesting many patients had at least stable disease in the CNS. The median progression free survival (PFS) was 9.7 months for intracranial disease versus 13.7 months for extracranial disease, indicating that CNS progression occurred earlier than systemic progression. Consistent with these clinical data, pharmacologic studies have shown that both gefitinib and erlotinib are present in the CNS with a cerebrospinal fluid (CSF) penetration rate of 1.13% and 2.77%, respectively [29]. Although this degree of CNS penetration is low, the extreme sensitivity of EGFR-addicted cancers to EGFR

Table 1. List of selected studies examining the efficacy of EGFR TKIs for patients with EGFR brain metastases

Study [reference]	Design	TKI	Patients, <i>n</i>	EGFR mutation, %	Median FU, mo.	CNS ORR, %	OS, mo.	CNS PFS, mo.	Rate of salvage RT, %	TTS, mo.
Porta et al. [8]	Retro	Erlotinib	69	25	NA	82 ^a	12.9 ^a	11.7 ^a	NA	NA
Namba et al. [19]	Retro	Gefitinib	15	NA	8.3	82	8.3	8.7	NA	NA
Ceresoli et al. [20]	Pro	Gefitinib	41	NA	11	10	5	NA	NA	NA
Wu et al. [21]	Pro	Gefitinib	40	NA	12	38	15	NA	NA	NA
Iuchi et al. [22]	Pro	Gefitinib	41	100	NA	88	21.9	14.5	49	17.9
Zhang et al. [23]	Retro	Erlotinib	13	100	NA	57	23.6	9.7	42	NA
		Gefitinib	30							
Kim et al. [6]	Pro	Erlotinib	7	100	21.8	70	18.8	7.1	48	19.3
		Gefitinib	16							
Park et al. [10]	Pro	Erlotinib	6	100	17.5	NA	15.9	NA	50	12.6
		Gefitinib	22							
Heon et al. [9]	Retro	Gefitinib/ Erlotinib	24	100	30	NA	31	56	NA	NA
Wu et al. [24]	Pro	Erlotinib	48	17	NA	NA	18.9	10.1	35	NA
Katayama et al. [5]	Retro	Erlotinib	7	86	NA	50	2.9	3	NA	NA
Hoffknecht et al. [25]	Retro	Afatinib	100	100	NA	35	9.8	NA	NA	NA
Schuler et al. [25]	Pro	Afatinib	81	100	NA	NA	22.4	15.2	NA	NA
Mok et al. [27]	Pro	Osimertinib	93	100	8.3	70	NR	11.7	NA	NA
Yang et al. [28]	Pro	Osimertinib	25	100	13.8	64	NR	NA	NA	NA

^aFor those with EGFR mutations.

Abbreviations: CNS, central nervous system; CNS ORR, objective response rate in the CNS; CNS PFS, intracranial progression-free survival; EGFR, epidermal growth factor receptor; FU, follow-up; mo., months; NA, not available; NR, not reached; OS, overall survival; RT, radiotherapy; TKI, tyrosine kinase inhibitor; TTS, time to salvage radiation.

inhibitors allows responses to occur even with a low concentration of drug in the CNS; in addition, the presence of CNS metastases themselves can disrupt the blood-brain barrier more than predicted by pharmacologic studies [30].

Afatinib, an irreversible second-generation EGFR TKI, was evaluated for activity in the CNS of patients who received it under a compassionate access program [25]. Of 541 patients receiving the drug, 100 patients had either parenchymal brain metastases or leptomeningeal disease, with 74% having documented EGFR mutation. In the 31 patients evaluated for CNS response, the CNS ORR was 35%. This was an impressive result given these patients had been previously treated with chemotherapy and at least one other TKI. The disease control duration was approximately 4 months. CSF analysis of one patient showed a CSF penetration rate of 0.7% and a concentration of 1 nM, which is in the range of K_i of the drug. Retrospective analysis of patients with EGFR BMs in the LUX-Lung 3 and LUX-Lung 6 randomized trials of afatinib compared with front-line chemotherapy (cisplatin and pemetrexed or gemcitabine) [26] showed that, as in the overall study population, the PFS was longer for EGFR BM patients on afatinib compared with chemotherapy (8.2 months and 5.4 months for afatinib and chemotherapy, respectively; hazard ratio [HR] 0.50, 95% confidence interval [CI]: 0.27–0.95, $p = .0297$). Interestingly, the PFS benefit of afatinib was higher in those who received prior WBRT ($n = 24$) than those who did not ($n = 57$). Although CNS ORR was not reported, the overall ORR was 82% for those with exon

19 deletion and 60% for those with L858R mutations. In patients with common EGFR mutations, the afatinib group had a longer median time to CNS progression (LUX-Lung3: 15.2 months vs. 5.7 months; LUX-Lung 6: 15.2 months vs. 7.3 months).

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The third-generation EGFR TKI osimertinib is specifically designed to overcome the common T790M resistance mutation, and emerging data suggest that it is very effective against EGFR BMs, including those that developed on another EGFR TKI. Our group published a case series of patients with dramatic response to osimertinib after progression on rociletinib, an experimental third-generation EGFR TKI, including three patients who developed new BM on rociletinib, which subsequently responded to osimertinib [31]. Pharmacokinetic data from a patient in the Aura phase II extension cohort [32] found a CSF concentration of 3.44 nM, higher than analogous data for earlier TKIs and comparable to the predicted plasma free

circulating concentration. More recent direct measurements suggest osimertinib has a CSF/free plasma ratio of ~16% [33]. Analysis of 25 patients with asymptomatic EGFR BMs from this cohort [28] showed a CNS ORR of 64% (4 CR, 12 partial response [PR]), with 2 patients having lesion growth. In the AURA3 randomized trial of osimertinib versus chemotherapy for T790M-positive patients progressing on first-line EGFR TKIs [34], 144 of the 490 patients had CNS metastatic disease. Among these patients, osimertinib was associated with an improved PFS compared with chemotherapy (8.5 months for osimertinib and 4.2 months for chemotherapy; HR 0.32, 95% CI 0.21–0.49). It remains to be seen whether other T790M-specific EGFR inhibitors currently in development will match osimertinib's CNS activity.

There are a few newer EGFR TKIs being specifically designed for enhanced CNS penetration. For example, AZD3759, a novel first-generation-like EGFR TKI, has been shown to accumulate in pharmacologic doses in the CSF and have activity in preclinical models. In two patients treated on the phase I BLOOM trial [35], the concentration of drug in the CSF was approximately equal to that in the serum, with some evidence of CNS response. In addition, tesavatnib may have enhanced CNS penetration, although limited clinical data are available at this time [36].

Synthesizing the data, it appears that the response rates of EGFR BMs to CNS-penetrant TKIs are in the range of 60%–80%, which is similar to that of WBRT. The duration of intracranial response is more variable, with a range of 3–14.5 months, likely depending in part on the extent of prior treatment of the patients in each study. Approximately 25%–50% [10, 22, 37] of patients receive salvage RT. Thus, a significant proportion of patients who are treated with initial TKI with documented EGFR BMs never go on to receive cranial RT. It remains unclear whether RT is not given in these cases due to long-term control in the brain, extensive intracranial recurrence (e.g., leptomeningeal dissemination), or lack of sufficient follow-up in these small reports.

Combining EGFR TKIs and radiotherapy

With the promising results of EGFR TKIs in EGFR BMs, there has been a lot of interest in combining EGFR TKIs with brain RT. A prospective U.S.-based phase II trial tested the combination of erlotinib and WBRT in 40 patients with brain metastases from lung adenocarcinoma [38]. The combination was well tolerated without an increase in CNS or skin toxicity. Only nine of the patients were confirmed to carry an EGFR mutation, and the CNS ORR was 89% for those with EGFR mutations compared with 63% for those known to lack EGFR mutations. These data were supported by a U.K. study [39] that randomized patients with non-small cell lung cancer and BMs to erlotinib or placebo concurrently with WBRT. Only one patient had a documented EGFR mutation. There was no difference between the groups in terms of response, PFS, or OS, nor was there a difference in toxicity, other than lower levels of fatigue in the group receiving erlotinib/WBRT. These two prospective studies show that combining EGFR TKIs with WBRT is reasonably well tolerated and is an option for those with EGFR mutations, but the low number of patients with documented EGFR mutations in these trials negates the ability to perform efficacy analyses. Furthermore, it should be noted that the majority of these patients did not have EGFR mutations, and the survival was poor. Thus, very few

data regarding potential late neurocognitive toxicity of EGFR inhibitors combined with WBRT are available.

Retrospective studies specific to EGFR BMs also suggest that combining brain RT and EGFR TKIs is tolerable but have yielded conflicting data on efficacy. For example, a series of 230 patients with EGFR BMs from Shanghai had 116 patients who received TKI alone, whereas 51 patients received both TKI and WBRT [40]. The patients receiving WBRT were more likely to be symptomatic from their BMs but were otherwise well matched. The CNS ORR was equal in both groups at 53%, and the CNS PFS was also similar (6.9 months for TKI alone and 7.4 months for TKI/WBRT). However, overall survival was worse in the group receiving TKI/WBRT (21.6 months vs. 26.4 months, $p = .049$). There was no analysis of causes of death, but this observation raises the question as to whether excess toxicity secondary to WBRT may have played a role in the worse outcome in this group.

In contrast, a cohort of 132 patients with EGFR BMs from Wuhan included 79 patients treated with TKI alone and 43 treated with TKI/WBRT [41]. Again, the TKI/WBRT patients were more likely to be symptomatic but were otherwise similar. The CNS ORR for TKI alone was 39% versus 68% for TKI/WBRT ($p = .001$). The median CNS time-to-progression was 18.2 months for TKI and 24.7 months for TKI/WBRT ($p = .004$). Neurocognitive assessment showed that at 6 months, there was significant impairment in memory and learning with TKI/WBRT compared with the TKI alone group, although these differences lessened at the 2-year follow-up. Similarly, another cohort of 133 patients from Zhengzhou [42] also showed a longer CNS PFS (16 months vs. 11.5 months) among the 67 patients who received TKI/WBRT compared with the 66 patients who got TKI alone, although this was seen mostly in patients with L858R mutations.

Combining EGFR TKIs and SRS is generally thought to be safe and well tolerated. Given the limited schedule of SRS and the small volume involved, there are few reports of increased toxicity with EGFR inhibitors. For example, a series from the Cleveland Clinic showed no increase in radiation necrosis among lung adenocarcinoma patients receiving SRS with EGFR TKI compared with those receiving SRS alone (10.3% vs. 7.9%) [43].

Can TKIs Be Used Instead of RT?

With the excellent response rates seen with TKIs in the CNS and the potential for neurotoxicity with WBRT [3, 44], investigators have asked whether patients with EGFR BMs can be treated with TKIs upfront, delaying or perhaps eliminating the need for cranial radiotherapy. A number of retrospective studies have addressed this question, with varying results (Table 2). For example, a study from Korea reviewed 121 patients with EGFR BMs at diagnosis [45]. Of these 121 patients, 59 received RT upfront (32 SRS, 26 WBRT, 1 both) and 62 were treated with initial TKI (primarily gefitinib). The patients who received initial RT were more likely to be symptomatic, whereas the group receiving TKIs had more patients with >5 metastases and were more likely to have extracranial disease. The intracranial disease control rate (CR, PR, or stable disease) was higher with brain RT (80% vs. 60%, $p = .019$), but there was no difference in median CNS PFS (16.6 months for RT and 21.0 months for the TKI group). There was no difference in 3-year landmark survival, with the RT group achieving 72% 3-year OS and the TKI group

Table 2. Listing of studies comparing initial TKI therapy with RT

Study	Arms	Patients, <i>n</i>	Median FU, mo.	CNS ORR, %	OS, mo.	CNS PFS, mo.	ECD, %
Jiang et al. [40]	TKI	116	NA	53	26.4 ^a	6.9	59
	TKI + WBRT	51		53	21.6	7.4	61
Zhu et al. [42]	TKI	66	18	NA	15	11.5	65
	TKI + WBRT	67		NA	22 ^a	16 ^a	66
Chen et al. [41]	TKI	79	36.2	39	41.1	18.2	NA
	TKI + WBRT	53		68 ^a	48	24.7 ^a	NA
Liu et al. [37]	TKI	57	26	NA	~21	~18	63.5
	RT	39		NA	~21	~18	
Byeon et al. [45]	TKI	62	18.4	NA	NR	21	93
	RT (WBRT/SRS)	59		NA	NR	16.6	68
Gerber et al. [46]	TKI	63	20	NA	26	16	NA
	WBRT	32			35	24 ^a	NA
	SRS	15			64 ^a	NA	NA
Magnuson et al. [47]	TKI	17	20.6	76	19.4	10.6	53
	WBRT	17		88	29.9	37.9 ^a	54
	SRS	16			58.4 ^a		
Magnuson et al. [48]	TKI	131	22	NA	25	17	22
	WBRT	120			30 ^a	24	22
	SRS	100			46 ^a	23	28
Doherty et al. [49]	TKI	26	NA	67	18.5	16.2	97 ^b
	WBRT	103		80	19.9	NR ^a	97 ^b
	SRS	34		76	23.9	12	100 ^b
Fan et al. [50]	TKI	41	28.5	78	27.9	13.9	90
	RT (WBRT/SRS)	56		86	31.9	22.4 ^a	61
Yang et al. [51]	TKI	85	16.5	65 ^a	18.0	10 ^a	22
	WBRT ± CTX	91		37	20.5	4.8	27

^a*p* < .05.^bIncludes 21 patients with ALK rearrangement.

Abbreviations: ALK, anaplastic lymphoma kinase; CNS, central nervous system; CNS ORR, objective response rate in the CNS; CNS PFS, intracranial progression-free survival; CTX, chemotherapy; ECD, extracranial disease; FU, follow-up; mo., months; NA, not available; NR, not reached; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy.

68%. Again, only 24% of patients in the TKI alone group required salvage RT. These data suggest that initial TKI in lieu of radiotherapy is a reasonable approach for selected groups of patients.

Recently, a randomized trial from the People's Republic of China evaluated 176 patients who were assigned to receive icotinib (a first-generation EGFR inhibitor) or WBRT with or without chemotherapy [51]. The primary endpoint of CNS PFS was significantly longer for the icotinib group compared with WBRT (10.0 months vs. 4.8 months, *p* = .014). The CNS ORR was significantly higher for icotinib (65%) compared with WBRT (37%). This low ORR for WBRT is unusual and may have contributed to the inferior outcomes in this study. Additionally, 20% of the patients in the WBRT group dropped out, lessening the power of the study and likely affecting the efficacy of randomization. Furthermore, the WBRT arm received chemotherapy rather than TKI, and thus the study cannot directly address whether initial TKI is a better choice than initial RT followed by TKI. However, this is one of the only randomized trials that have attempted to shed light on the optimal management of EGFR BMs.

Several studies have argued that omitting RT from upfront treatment may be associated with inferior outcomes. A systematic review and meta-analysis from 2015 examined 12 studies including 363 patients with EGFR BMs who received TKI, WBRT, SRS, or some combination [52]. There was no significant difference in CNS ORR between TKI monotherapy upfront or concurrent/sequential RT/TKI. There was a small but significant improvement in CNS PFS at 4 months with WBRT upfront compared with TKI monotherapy (relative risk [RR] 1.05, 95% CI 0.98–1.12, *p* = .03). The OS rate at 2 years was higher with sequential upfront WBRT (RR 1.33, *p* = .05) or SRS (RR 2.08) compared with TKI alone. There were more neurological adverse events in arms receiving RT [52]. One concern about this study is how the apparently small improvement in intracranial disease control at 4 months translates to a larger benefit in overall survival at 2 years. However, this meta-analysis suggests that there may be some advantage to pursuing upfront RT in select groups of patients.

Multiple recent single institutional series have tried to clarify whether there is a benefit to initial RT. The majority of studies (summarized in Table 2) demonstrate that initial brain RT

results in improved intracranial control, but this may not necessarily translate to improved survival. For example, a study of 110 patients with EGFR BMs from Memorial Sloan Kettering Cancer Center included 63 patients treated initially with erlotinib and 47 who had initial RT (32 WBRT, 15 SRS) [46]. The patients receiving RT were more likely to be symptomatic. The SRS group tended to have fewer tumors and a higher dsGPA score [53]. In this cohort, there was no difference in survival between the erlotinib group and the WBRT group. However, the WBRT group did have a longer time to intracranial progression (24 months vs. 16 months, $p = .04$). The SRS group demonstrated improved survival compared with the erlotinib group, which is not unexpected given the higher dsGPA score in this group. In the cohort who received initial erlotinib, 38% of patients ultimately received brain RT at a median of 17 months after the diagnosis of brain metastasis. Thus, the majority of patients receiving initial TKI never went on to receive RT.

Another recent retrospective cohort study from Yale provocatively suggested that patients with EGFR BMs may derive a survival benefit from early cranial radiotherapy [47]. A total of 50 patients who were TKI-naïve and received different therapies were examined; 17 had initial TKI, 17 had WBRT then TKI, and 16 had SRS then TKI. These groups were similar in terms of dsGPA score, but the patients receiving RT first were more likely to be symptomatic from their CNS disease. These groups had similar rates of extracranial disease as well as similar performance status. The CNS ORR was similar for both groups (88% and 76% for RT and TKI, respectively), akin to other studies discussed above. OS was significantly longer in the initial RT group compared with the initial erlotinib group (34.1 months vs. 19.4 months, $p = .01$). When separating by type of RT, those treated with initial SRS had the best survival (median 58.4 months), and the initial WBRT group was intermediate (29.9 months). On multivariable analysis, initial RT and fewer than two organs with metastatic disease were significantly associated with overall survival. Interestingly, of 24 patients for whom a cause of death was identified, only 5 died of intracranial disease, whereas 15 died of extracranial disease. However, four of the five patients who died of intracranial disease were treated with initial erlotinib. Of the 15 patients in the RT group who died, only 1 died of intracranial disease. Although the numbers are small, these data raise the possibility that at least some of the patients receiving initial TKI may succumb to intracranial disease, which may have been prevented with initial radiotherapy.

Expanding on this finding, an updated analysis including data from several institutions demonstrated similar results [48]. They analyzed 351 patients with TKI-naïve EGFR BMs, easily the largest cohort of patients with EGFR BMs analyzed to date. The patients were evenly divided, as 37% received initial TKI, 34% received WBRT followed by TKI, and 29% received SRS followed by TKI. Again, patients receiving initial TKI were less likely to be symptomatic and had smaller brain metastases. More patients with a poor prognosis (dsGPA 0–1.5) received initial WBRT. The SRS patients had a better dsGPA, had fewer brain metastases, and were more likely to have been early stage at initial diagnosis of disease. There was no difference in performance status or presence of extracranial disease among the three groups. As might be expected based on dsGPA, the best overall survival

Key Take-Home Points

- Patients with EGFR BMs can have a long survival
- EGFR TKIs have activity in the CNS, especially newer agents like osimertinib
- Multidisciplinary evaluation is essential to select an optimal strategy tailored for the patient
- Selected patients with small/asymptomatic lesions may delay or avoid radiation with TKI upfront and close surveillance
- There may be a benefit to early radiotherapy in some patients, especially those with limited extracranial disease, but avoiding the toxicity of conventional WBRT is important

was in the SRS group (46 months). The WBRT group had a longer OS (36 months) compared with the group that received initial TKI (25 months). Furthermore, restricting the analysis to the most favorable group (dsGPA 2–4), the WBRT group again had a longer OS (52 months) compared with the TKI group (32 months). Interestingly, only 52% of patients receiving initial TKI received RT at some point in their course (43% WBRT, 43% SRS, 14% both). It is unclear whether the OS of the group that received salvage RT was similar to those who received RT upfront. It would be very interesting to know if close surveillance and early salvage for the TKI patients would result in similar outcomes to using RT upfront. There was no difference in the use of second-line systemic therapy among the groups. Initial radiotherapy (WBRT and SRS) remained significantly associated with improved survival in multivariable analysis. One notable difference in this study from many of the others was the relatively low burden of extracranial disease in this cohort. Only 24% of patients had extracranial metastases, compared with 50%–100% of patients in the other studies. It seems plausible that for patients with limited or no extracranial disease, improved intracranial control takes on additional importance and might translate into better overall survival.

One possible explanation for the worsened survival in the TKI upfront group would be that patients may progress in such a way that renders them unfit for salvage therapy. From the Yale study, it appears that patients receiving TKI upfront are more likely to have the CNS as an isolated site of first failure (46% vs. 15%, $p = .01$). As noted above, this failure was associated with an increased risk of death from intracranial disease. The most likely concern would be the development of leptomeningeal disease, which is associated with a very poor prognosis. However, the study of 110 EGFR BM patients treated at Memorial Sloan Kettering found that 16% of patients developed leptomeningeal disease at a median of 15 months from diagnosis. There was no difference in incidence between the erlotinib, whole brain, and SRS groups. Thus, the data are mixed on whether using a TKI upfront may result in potentially unsalvageable intracranial progression.

DISCUSSION

Brain metastases in lung cancer remain a vexing problem for clinicians. In patients with EGFR mutations, where systemic therapy has resulted in prolonged survival, treatment of

intracranial disease has become an especially challenging problem. The desire to balance long-term CNS control with potential detrimental neurocognitive effects of early cranial RT makes the initial management of these patients controversial. As described above, many of the EGFR TKIs have activity in the CNS that is comparable to WBRT. Both erlotinib and gefitinib are present in the CSF, although at lower levels than in plasma. Exciting new data regarding novel third-generation TKIs, particularly osimertinib, suggest that such drugs may have an even greater efficacy for EGFR BMs. Furthermore, newer agents still in early phase studies have the potential for further improvements in CSF penetrance and CNS activity.

Review of the literature regarding the choice of initial therapy for EGFR BMs demonstrates significant heterogeneity and potential for selection bias, but it appears that the majority of studies show an improvement in intracranial control with upfront brain RT compared with TKI alone, without a difference in overall survival. Perhaps this is not entirely surprising, as multiple studies of brain metastases from many cancer types have shown that RT-mediated improvement in intracranial control does not necessarily translate into improved overall survival [3, 54, 55].

Most of the studies discussed above show a similar intracranial response rate for either EGFR TKIs or radiotherapy, which raises the question of why there may be a difference in outcome in some subsets of patients. Most of the deaths reported were due to extracranial disease, which was unlikely to be influenced by the choice of initial RT. However, one possibility is that a subset of patients with EGFR BMs progress in the CNS after initial response to TKIs in a way that makes subsequent salvage WBRT much less effective (e.g., leptomeningeal dissemination). However, the data supporting this idea are limited. Another possibility is that initial brain RT may result in increased efficacy of TKIs in the CNS due to disruption of the blood-brain barrier or some other mechanism. These studies suffer from their retrospective nature, as the choice between TKI and RT is likely driven by multiple factors, not all of which can be accounted for by propensity score, multivariable regression, or other correction techniques.

CONCLUSION

Moving forward, the choice of initial therapy for EGFR BMs must integrate these data along with the potential toxicity of WBRT, which was not adequately addressed in most of these studies. The preliminary data regarding the efficacy of newer TKIs against EGFR BMs (especially osimertinib) suggest that these drugs may be better initial therapies than erlotinib and gefitinib and thus may obviate the prior data comparing initial TKI versus RT. This is especially pertinent because standards of care are currently transitioning to upfront osimertinib. The FLAURA trial, a phase III randomized comparison of osimertinib versus either erlotinib or gefitinib, recently showed a significant PFS benefit for osimertinib, including among patients with CNS metastases [56]. A prospective randomized study in patients presenting with EGFR BMs comparing, for example, osimertinib followed by RT at progression to RT followed by osimertinib and examining key outcomes including intracranial control, quality of life, and neurocognitive measures would be the best way to address this question. Retrospectively, a more detailed

analysis of patterns of CNS failure in patients treated with TKI as well as an analysis of causes of death would also help shed light on these questions.

In the absence of that data, we favor a multidisciplinary evaluation with consideration of initial TKI or SRS for those with limited intracranial disease. We favor initial TKI for lesions that are small, with minimal edema, and in areas where tumor growth is unlikely to result in neurologic symptoms. For patients with more diffuse disease, we generally recommend WBRT for those who are symptomatic or have larger lesions or significant vasogenic edema. We also consider investigational cognitive sparing strategies including hippocampal avoidance WBRT [57], as well as the use of memantine [58] to attempt to mitigate the long-term adverse toxicity associated with WBRT. In selected patients, we use upfront SRS (single dose or occasionally fractionated) to individual lesions that are located in areas likely to produce symptoms upon progression, or those approaching 1 cm or greater. In these patients, we might consider treating only those most concerning lesions and rely on TKI to control the remainder of the lesions in an attempt to avoid the toxicity of WBRT. In some patients, the need for achieving extracranial control is the driving factor to start TKI therapy before radiation. In patients on TKI with diffuse CNS progression, we typically hold TKI for the duration of WBRT. If patients need SRS, the TKI can be continued, or held for a day or so surrounding SRS depending on the preference of the treatment team. Patients who are started on initial TKI therapy must be closely monitored to ensure that there is no symptomatic progression and to ensure that if there is intracranial progression it is caught at a time when salvage radiotherapy can still be entertained.

The preliminary data regarding the efficacy of newer TKIs against EGFR BMs (especially osimertinib) suggest that these drugs may be better initial therapies than erlotinib and gefitinib and thus may obviate the prior data comparing initial TKI versus RT. This is especially pertinent because standards of care are currently transitioning to upfront osimertinib.

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DISCLOSURES

Zofia Piotrowska: AstraZeneca, Ariad/Takeda, Novartis, Guardant Health, AbbVie, Boehringer-Ingelheim (C/A), Novartis (to institution) (RF); **Lecia V. Sequist:** AstraZeneca, Pfizer, Novartis, Boehringer-Ingelheim, Merrimack (C/A), AstraZeneca, Pfizer, Novartis, Boehringer-Ingelheim, Merrimack, Incyte (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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For Further Reading:

Maikel Verduin, Jaap D. Zindler, Hanneke M.A. Martinussen et al. Use of Systemic Therapy Concurrent With Cranial Radiotherapy for Cerebral Metastases of Solid Tumors. *The Oncologist* 2017;22:222-235.

Implications for Practice:

The treatment of symptomatic brain metastases diagnosed while patients are receiving systemic therapy continues to pose a dilemma to clinicians. Will concurrent treatment with cranial radiotherapy and systemic therapy (chemotherapeutics, molecular targeted agents, and monoclonal antibodies), used to control intra- and extracranial tumor load, increase the risk for neurotoxicity? This review addresses this clinically relevant question and evaluates the toxicity of combining systemic therapies with cranial radiotherapy, based on currently available literature, in order to determine the need to and interval to interrupt systemic treatment.