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Research Article

Encephalic Radiation Treatment During Tyrosine Kinase Inhibitors (TKIs) in Advanced Non-Small Cell Lung Cancer (NSCLC): Retrospective Real-World Analysis of a Single Centre.

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Abstract

Background: This study aimed to evaluate the outcomes of non-small cell lung cancer (NSCLC) patients with central nervous system (CNS) metastases treated with radiotherapy and targeted tyrosine kinase inhibitors (TKIs); **Methods:** The study reviewed 14 symptomatic NSCLC patients treated with either whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS) while undergoing TKI therapy. **Results:** The median time from TKI initiation to radiotherapy was 16.4 months. No acute toxicity was reported. After a median follow-up of 2.1 months, the intracranial objective response rate (ORR) was 64.3%, with five patients achieving complete cerebral response, four showing partial response, and four having stable disease. Nine patients died due to systemic progression, though they maintained intracranial responses; **Conclusion:** The study suggests that concurrent radiotherapy and TKIs is safe and effective, with survival more influenced by systemic disease progression than intracranial factors.

Keywords: Brain Metastases; Oncogene Addicted Lung Cancer; Targeted Tyrosine Kinase Inhibitors.

Introduction

Brain metastases (BMs) are an area of concern in the management of patients with non-small cell lung cancer (NSCLC). In fact, BMs occur in roughly 40% of individuals with stage IV NSCLC and about 10–20% of cases had BMs at the time of diagnosis [1-4]. The incidence of BMs is higher among patients with oncogene-addicted NSCLC compared to those with wild-type tumors in relation to the longer survival particularly in patients who have ALK and EGFR drivers, whose overall survival (OS) is increased by five years [5,6]

BMs in patients with advanced oncogenic NSCLC by mutation type have higher rates in those with epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), human epidermal growth factor receptor 2 (HER2), Proto-oncogene tyrosine-protein kinase ROS (ROS1), Ret proto-oncogene (RET), and Kirsten rat sarcoma viral oncogene homolog (KRAS), MET exon 14 skipping alterations(METex14). The increased prevalence of cranial magnetic resonance imaging (MRI) screening at the diagnosis of NSCLC has also resulted in increased diagnosis of patients with asymptomatic BMs. [7-10].

Some exceptions (as for KRAS G12C or MET ex14skipping NSCLC), first-line treatment for oncogene-addicted disease is represented by targeted therapies characterized by high penetrability of the blood-brain barrier with effective and prolonged CNS disease response [11].

There are currently no established protocols for BMs treatment of NSCLC oncogene-addicted patients and BMs may be treated with local therapy including surgery or stereotactic radiosurgery (SRS). With a few exceptions, whole brain radiation therapy (WBRT) is becoming decreasingly common [12,13]. For a long time, WBRT has long been used to control brain metastases. The greatest restriction of this therapeutic option is neurocognitive toxicity, despite several studies have been conducted to determine the long-term benefits of hippocampal avoidance without conclusive results [14]. Compared to WBRT, SRS reduces the risk of neurotoxicity by delivering a high dose of radiation to the target tumor while minimizing the dose to normal tissue, either in a single fraction or in multiple fractions. [2-5].

Although SRS has less neurological toxicity, it is often associated with radionecrosis [15]. Data currently available in the literature have shown promising results in the control of BMs. The role of radiotherapy is debated especially with regard to timing. The aim of our study is to review the studies in the literature and to report our experience of irradiation in oncogene-addicted patients with symptomatic BMs.

EGFR

At baseline, the incidence of BMs in EGFR-mutated patients is approximately 23-20%. Over time, this percentage tends to increase. [3,16–19]. During the course of the disease, the percentage of BMs in oncogene-addicted NSCLC can reach up to 70% for the bone marrow and 10% for the spinal cord [17,20–22]. The risk of brain progression during TKIs is also higher in those with BMs at baseline and correlates with a worse prognosis.

In addition, there are conflicting data in the literature as to which subtype is associated with a higher risk of the development of BMs, and there is no evidence that this subtype is associated with a higher risk of the development of BMs.; in fact, some studies report worsening data for the DEL19-mutated variant [21], while others for the L858R-mutated tumors [23,24].

Erlotinib and Gefitinib have been shown to be active in EGFR-mutant BMs patients in retrospective observational and phase II investigations. [25-30] when compared to first-generation TKIs, Osimertinib's ability to cross the blood-brain barrier (BBB) and significantly improve icPFS has revolutionized clinical practice. However, at the 2-year mark, nearly half of the patients experience another recurrence [31].

Numerous Osimertinib resistance pathways have been found, including histologic change, secondary EGFR mutations, and MET proto-oncogene amplification. Patients with BMs upon diagnosis still constitute a challenging-to-treat minority in this situation, which could have an impact on quality of life in the event of local development and result in poorer outcomes [32]. (Figure 1)

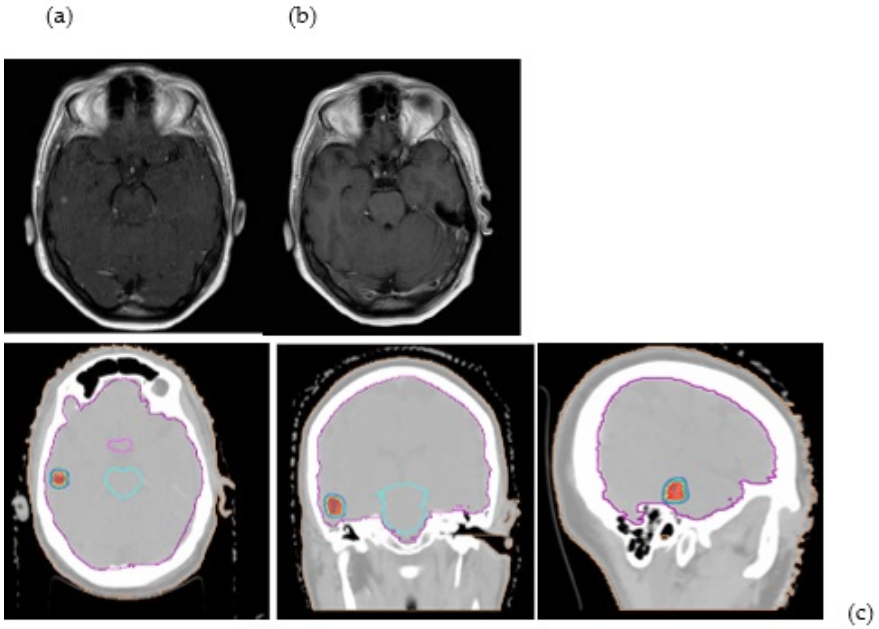

Figure 1: The figure shows an SRS (21 Gy/1fx) of a patient with EGFR t790MUT with a single brain metastasis on pre-RT MRI a) in complete response 45 days post-treatment b) The treatment plan c) shows the dose distribution (95%-130%)

In a recent meta-analysis, Nepote et al. demonstrated a benefit in iPFS and OS in patients with EGFR-mutant NSCLC metastatic to the BM treated with Osimertinib and concurrent brain radiotherapy, showing a significant synergy between the two regimens. Considering this association a first-line treatment option [33].

Anaplastic Lymphoma Kinase

Anaplastic Lymphoma Kinase (ALK) rearrangements result from inversions or translocations on chromosome 2 and are present in 5% of NSCLC tumors. Second- and third-generation TKIs (Lorlatinib,Alectinib, Critinib, Brigatinib, Iruplinalkib) designed to cross the BBB have shown intracranial activity in patients with advanced NSCLC and BMs with ALK rearrangement. This ability to cross the BBB has been found to be superior compared to first-generation TKIs [20,34-42]. The ALTA-1L study, demonstrate that in patients with advanced ALK-positive NSCLC and asymptomatic/stable BMs, naive to TKIs, the median intracranial PFS of patients with baseline BMs was significantly longer with Brigatinib compared to Crizotinib (24.0 vs 5.5 months, P<0.0001) (20).

A 97% reduction in intracranial progression was demonstrate in long-term data from phase 3 CROWN study, which analyzed patients with new or progressive BMs receving Lorlatinib or Crizotinib, a first generation TKI [43]. However, neurocognitive damage is higher in patients treated with lorlatinib compared to Crizotinib (35% vs 11%) [44].

Others

About 1-2% of patients with NSCLC had the ROS1 rearrangement. The risk of brain metastases is higher, even if the percentage of BMs upon diagnosis is lower than that of ALK [45,46]. The RET rearrangement is also present in 1-2% of NSCLC patients [47,48]. It is more common in adenocarcinomas and in non-smoking patients.

The incidence of BMs is 27%, regardless of age, smoking, and type of fusion; this incidence is 49% over the lifetime of patients with NSCL RET rearranged [49]. Activating BRAF mutations occur in approximately 2-4% of patients with NSCLC. The most common BRAF mutation is V600E [50] First-line therapy in V600E-positive patients involves the combination of the BRAF inhibitor (Dabrafenib) and the MEK inhibitor (Trametinib) [51,52].

Although data on intracranial disease control are not available, this combination of TKIs has reported efficacy at the central nervous system level in BRAF V600E-positive melanoma, suggesting the same efficacy in NSCLC [53]. Roughly 13% of NSCLC cases have been found to have the KRASG12C mutation, which changes glycine 12 to cysteine.

The KRAS G12C mutation has recently been identified as a targetable oncogenic mutation. It confers sensitivity to covalent inhibitors. [54,55]. Sotorasib is a selective, irreversible targeted drug that the FDA has approved in second-line treatment for KRAS G12C.

The intracranial efficacy of Sotorasib in KRAS G12C mutated NSCLC patients with BMs previously operated on or undergoing radiotherapy was highlighted in the post-hoc analysis of the phase 1/2 CodeBreaK 100 study [56]. The Real-World data collected by the Italian group has also validated this efficacy [57]. NTRK gene fusions are rare (0.1-1% of cases). Oral TRK inhibitors (Larotrectinib and Entrectinib) are FDA-approved for advanced or metastatic NTRK fusion-positive NSCLC. Entrectinib has shown durable systemic and intracranial activity in 67% of patients in a small number of NTRK fusion-positive NSCLC cases. [58].

The incidence of BMs in patients with MET exon 14 (METex14)–altered at diagnosis is 17% and increases to 36% over a lifetime; Crizotinib can ensure the control of BMs in this setting; however, selective MET inhibitors such as the type Ib inhibitor capmatinib ensure better control of intracranial disease [59]. In (Table 1), we have reported the main studies on the concomitance between RT and molecular-targeted drugs in patients with oncogene-addicted NSCLC that have been published.

	Study tyoe	Mutations	Drugs	n° patients	WBRT	SRS/ SRT	PFS (months)	extracPFS (months)	iPFS	OS
Takeda et al (60)	RS	ALK–rearrangement–positive	Crizotinib	7	4	3	5.5 (2.6-17.2)	4.8 (4.4-7.5)	-	-
Zhao et al (61)	RS	EGFR-mutations	1st gen TKIs	265	36	58*				
			Osimertinib	91	22	24*				
Zhou et al (62)	RS	EGFR-mutations	3rd genTKIs	83	36	47	32.3		37.8	44.5
Zhai et al (63)	RS	EGFR-activating mutations	Osimertinib	21	14+5 (a)	2	9		16.67	29.2
Yu et al (64)	RS	EGFR-mutations	Osimertinib	48			12.9			27.8
Xie et al (65)	RS	EGFR-mutations	Osimertinib	9	-	9	NR			16.2
Tozuka et al (66)	RS	EGFR-mutations	Osimertinib	42	7+1(b)	32+2 (c)	NR	-	.-	NR
Thomas et al (67)	RS	EGFR-mutations	Osimertinib/ Rocilentinib	43	9	34	6.9	NR	20.5	NR
		ALK positive	Alectinib/ Brigantinib/ Lorlatinib/ Ensartinib	20	4	16	13.4	NR	21.8	NR

Gu et al (68)	PS-RS	EGFR-mutations	1st-2nd-3rd gen TKIs	60	ns	ns	12.8(9.3-16.3)	16.3(13.1-19.6)	28.9(13.8-21.2)	42.7
Niu et al (69)	RS	EGFR-mutations	3rd gen TKIs	28	14	14	14(12-21)	-	-	43

RS Retrospective study; PS Prospective study

* upfront stereotactic radiosurgery and/or surgery; gen generation

x HA WBRT, SRS Radiosurgery

(a)WBRT+SIB (b) surgery+WBRT (c) Surgery+SRS

NR not reached

Table 1: Main studies on the interaction of TKIs and encephalic RT

Materials and Methods

We retrospectively identified symptomatic patients treated at our institution who received either WBRT or SRS while undergoing TKIs between January 2021 and June 2024. We evaluated intracranial response and analyzed the interval from initial diagnosis to radiotherapy. All patients had to have undergone systemic staging with CT and brain staging with CT or MRI with contrast. The toxicities were evaluated according to the Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) [60]. All patients were taking full-dose targeted molecular drugs and were re-evaluated systemically and cerebrally after radiotherapy

Results

The analysis included 14 consecutive symptomatic patients on TKIs therapy: 10 with EGFR and 2 with KRAS mutations, 1 with ALK and 1 with RET rearrangement. Eight patients with EGFR mutation were taking Tagrisso, one patient Monocertinib, and one Afatinib. Two KRAS-mutated patients were taking Sotorasib, one RET-rearranged patient was taking Selperbatinib, and one ALK-rearranged patient was undergoing ongoing treatment with Lorlatinib. Nine patients received WBRT (30 Gy in 10 fractions), of which one with integrated simultaneous boost (SIB). Five patients received SRS. Radiotherapy was administered at a median time of 16.4 months from TKIs initiation.

No acute toxicity was reported during treatment.

After a median follow-up of 2.1 months, the intracranial objective response rate (ORR) was 64.3%. Specifically, five patients achieved a complete cerebral response (CR), four showed a partial response (PR), and four demonstrated stability of cerebral disease (SD). One patient had extra-lesional progression (PD) at 45.7 months post-treatment. At the time of analysis, five patients were alive with disease, including two with a complete cerebral response, one with partial response, one with stable disease, and one with exclusively intracranial extra-lesional progression (median follow-up of 21.4 months). Nine patients died due to systemic progression while maintaining intracranial response (median follow-up of 2.8 months after radiotherapy). We have summarized the treatment response characteristics in (Table 2). Radionecrosis has not been recorded.

	CR		PR		SD		PD	
	WBRT	**SRS**	**WBRT**	**SRS**	**WBRT**	**SRS**	**WBRT**	**SRS**
EGFR	2(1+1×)	2*+	4		2			
Ex19, ex21, ex 18	-14.30%	-14.30%	-28.70%		-14.30%			
KRAS					1			1#
					-7.10%			-7.10%
ALK		1 (7.1%)						
RET						1		
						-7.10%		

PD Progression Disease; CR Complete Response; SD Stable Disease

WBRT: 30 Gy in 10 fractions
*SRS: 21Gy in single fraction
+SRS: 30/25/27 Gy in 5/5/3 fractions (3 metastases)
#SRS: 24Gy in 3 fractions-PD in other site
×WBRT+Boost+ Hippocampal avoidance: 30/40 Gy in 10 fractions

Table 2: Brain responses in relation to the molecular driver

Discussion

The role of brain metastases radiotherapy in oncogene addicted NSCLC have shown promising results but the data regarding the association of radiotherapy with TKIs are not strong. Conceptually, brain radiotherapy can disrupt the BBB and increase TKI concentration, improving the local control rate [61]. In the last decade, several studies have demonstrated the effectiveness of radiotherapy combined with EGFR-TKI [62,63]. However, the use of brain radiotherapy combined with EGFR-TKI is still controversial, especially in first-line treatment.

EGFR TKIs combined with brain radiation (both SRS and WBRT) may significantly improve overall survival (46 vs 30vs 25 months, P<0.001), according to an international retrospective study [64]. Another study compared the efficacy of EGFR TKIs + WBRT with EGFR TKIs alone and found that WBRT did not improve intracranial local control or long-term survival in patients with EGFR-sensitive mutations [65]. Another study demonstrated the efficacy of first-generation EGFR-TKI combined with brain radiotherapy as a first-line treatment for patients with EGFR mutations and BMs [29,66]. The introduction of Osimertinib has completely changed clinical practice due to its ability to overcome the BBB, with a significant improvement in iPFS compared to first-generation TKIs. In 2024 the meta-analysis regarding the role of upfront brain RT in patients with BMs from NSCLC undergoing third-generation TKIs was published [33], showing an iPFS and OS benefit.

These considerations should also be extended to NSCLC with ALK rearrangement. ALK inhibitors have improved control of systemic and CNS disease and may have a role in the delay of local therapies in some circumstances. Second- and third-generation ALK inhibitors are now considered first-line therapy for ALK-rearranged NSCLC. However, surgery and RT remain important for the control of large, extensive and symptomatic intracranial disease. Furthermore, ALK inhibitor resistance development will continue to impact progression-free survival.This study has several shortcomings. First main limitation is the mono-institutional and retrospective nature.

The reported experience has some limitations. Firstly, the small number of patients and the retrospective nature of the analysis. However (Table 1) most of the experiences reported in the studies are retrospective and with the exception of studies [67,68] the other experiences are more limited [69-76]. Secondly, this analysis was conducted on a very heterogeneous population both in terms of the present mutation and the radiotherapy treatment performed.

With the exception of four patients who were treated with SRS (1 - 3 fr), the remaining patients performed whole brain treatment (8 patients) and the remaining two patients performed moderate hypofractionated RT. The number of lesions and the total volume dictated the choice of treatment. In all patients, intracranial response was recorded and PFS was dictated by extracranial disease progression. Thus, albeit with the limitation of the short follow-up, dose and fractionation did not influence the control of intracranial disease.

This finding coupled with the systemic progression recorded in the deceased patients suggests a negative selection of patients: firstly, the patients were symptomatic; secondly, they had already developed resistance to the TKI (which they had been taking for 16.4 months). The choice of proposing RT at the onset of BMs would make it possible to prevent neurological symptoms and reduce treatment volumes by favouring synergic action with TKIs, in the face of our experience suggesting that late RT is proposed at a time of resistance to target therapy.

In line with the meta-analysis by Nepote et al [33], radiotherapy could be proposed as an upfront treatment, in light of its synergistic action with TKIs, in order to avoid WBRT treatments by favouring stereotactic radiotherapy. The lack of standardized follow-up, even in relation to the limited monitoring time for death-related events, could have influenced the response rate and the interactions with TKIs concerning toxicities.

This latter point is crucial for defining the appropriate timing. Future prospective studies examining the combination of TKIs will be essential to demonstrate the potential efficacy and safety of this combination.

Conclusions

This single-institution experience suggests that concurrent encephalic radiotherapy and TKIs therapy is safe and effective in NSCLC patients with CNS metastases. Although neurological symptoms are typically associated with poor survival, in this cohort, survival was more strongly influenced by systemic disease progression than by intracranial factors. The high intracranial response rate (64.3%) in contrast with the short overall survival, suggests the potential benefit from an earlier or upfront radiotherapy approach. Considering the retrospective design, limited sample size, and patient heterogeneity, further studies are needed to investigate these findings and to determine optimal timing for encephalic radiotherapy in brain-metastatic NSCLC patients receiving TKIs.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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