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Review

Optimal management of brain metastases in oncogenic-driven non-small cell lung cancer (NSCLC)

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ABSTRACT

Brain metastases are common events in the natural course of many advanced solid cancers like breast, lung and renal cancer or melanoma with a cumulative risk of 10–30% in adults [1–3]. Non-small cell lung cancer (NSCLC) is associated with an increased risk for the development of brain metastases and the prognosis until recently has been poor except for some patients' subgroups and depending on the disease-specific GPA prognostic factors [4].

For patients receiving only best supportive care, average survival is about 3 months and it is assumed that through additional whole brain radiotherapy average survival may be improved up to 6–9 months in selected patients [5].

In recent years, complex treatment strategies for different solid tumors have been developed and this has impacted on the general management of brain metastases. Most of the studies on brain metastases have included different histological subtypes and therefore have made tumor- specific recommendations difficult. In this review, we discuss the current evidence on management of brain metastases and incorporate specific recent data on oncogenic-driven NSCLC in order to suggest recommendations on the optimal management of brain metastases in this subgroup of NSCLC where formal level I evidence is lacking.

1. General management of brain metastases

1.1. Incidence of brain metastases from NSCLC

Lung cancer is the leading cause of cancer-related mortality in both men and women. Non-small cell lung cancer (NSCLC) accounts for 85–90% of all lung cancer incidence [6] and also represents the most common cause of cerebral metastasis either at diagnosis or at relapse/progression [7]. Approximately 10–20% of NSCLC patients will have brain metastasis at initial presentation [8,9]. Another 25–50% will develop brain metastases during the course of their disease [10]. Among NSCLC histological subtypes, non-squamous carcinomas carry a greater risk for extra-thoracic metastasis compared to squamous cell histologies [11]. The relative frequency of central nervous system (CNS) metastasis is also higher patients with lung adenocarcinoma (54% and 58.6%) compared to non-adenocarcinoma subtypes (large cell carcinoma: 17.7% and squamous cell carcinoma: 9.9%) [12–14].

Development of CNS metastases leads to significant morbidity from neurocognitive and functional deficits. Consecutive loss of autonomy adversely impacts quality of life [15]. Often symptomatic palliative treatment with steroids and anti-epileptic drugs is indicated. Presence of brain metastasis is associated with poor prognosis, with median overall survival (OS) of 4–6 months [16,17].

1.2. The role of local therapies

For patients with up to 4 brain metastases (BMs), surgical resection or radiosurgery without whole brain radiotherapy (WBRT) has evolved as the preferred treatment option [18–20]. In the EORTC trial 22952–26001 (all primaries, 53% NSCLC and 12% melanoma patients) [18], SRS alone (n = 100) resulted in local control rates of ~70% at 1 year. Similar figures have been reported in other randomized studies [20–22] with no detrimental effects on survival compared with SRS plus WBRT. SRS alone also results in less frequent cognitive decline

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compared to SRS combined with WBRT. Brown et al. evaluated cognitive decline among 213 patients with 1–3 brain metastases who were randomized to receive SRS alone or SRS combined with WBRT [20]. At 6 months, for patients having cognitive evaluations, cognitive deterioration was less frequent in the SRS arm (52% vs. 85% p = 0.00031) reaching statistical significance for immediate memory (p = 0.00062), delayed memory (p = 0.00054), processing speed (p = 0.023), and executive function (p = 0.015). The role of WBRT has been updated in 2015 ASTRO guidelines which state there is no evidence that the addition of WBRT impacts on OS (http://www.choosingwisely.org/astro-releases-second-list/), however it may reduce the development of new BMs. These recommendations should be discussed with the patient, particularly with respect to the rationale for surveillance MRI imaging following SRS alone [23].

Surgical resection may be necessary to control symptomatic BMs or to obtain tissue for histological or molecular diagnosis. Postoperative radiotherapy is indicated to reduce the risk of local recurrence from ~60% to 30% [18,24]. SRS to the resection cavity should be adopted as the new standard of care in these patients [22,25] after two prospective trials demonstrated equivalent OS of postoperative WBRT and radiosurgery to the resection cavity only.

1.3. Recent developments of local therapies for brain metastases

Recently, the “dogma” of SRS for up to 4 BMs has been challenged with a reported series of 1194 patients (75% NSCLC) being treated for up to 10 metastases with SRS. [26,27]. Of the 208 patients treated for 5–10 metastases, the median OS was 10.8 months, similar to patients (n = 531) with 2–4 metastases. Feasibility and toxicity of such an approach has been subsequently evaluated in a prospective phase II study investigating hypo-fractionated radiosurgery in 5 fractions for up to 10 BMs [28]. One-year local control was 83%. Toxicity was dependent on the location of the treated lesions. Grade 3–5 toxicity was reported in 1.9% non-deep lesions compared to 25% for deep lesions, resulting in a 10% crude per patient rate of grade 3–5 toxicity.

With an SRS only approach, a higher risk of distant CNS failure has been observed. In the setting of newly occurring BMs after initial SRS treatment, a standard of care has not been established by prospective trials and WBRT remains the predominantly used treatment option. The application of multiple courses of SRS represents an emerging concept in order to defer or even avoid WBRT. At present, only retrospective data on the safety of this approach exists including a retrospective analysis of 95 patients treated with SRS. This series showed that newly diagnosed BMs could be treated safely and effectively with additional courses of SRS [29] with only 20% within this study received eventually WBRT as salvage treatment.

Nevertheless, WBRT still represents an effective treatment to prevent distant CNS relapse [18–20]. If disseminated intracranial spread not suitable for SRS has developed, it may be recommended in good performance patients with reasonable prognosis. On the basis of The QUARTZ study, WBRT should not be recommended for poor prognosis patients [30]. Although not yet formally proven in a randomized fashion, hippocampal-avoidance WBRT could be considered to preserve neurocognitive function without increasing the risk of peri-hippocampal recurrence [31,32]. The single arm phase II RTOG 0933 study allowed a relevant volume of normal brain to receive more than 34 Gy in ten fractions (maximum 40 Gy) to achieve the dose gradient to the hippocampus. The long-term consequences of such an approach are not known yet. We recommend to apply optimized automated treatment approach to homogenize and reduce dose within the normal brain [33].

1.4. The role of systemic cytotoxic therapy

Although brain metastases can be treated effectively by SRS and WBRT, OS was only impacted in favorable prognosis patients with CNS-predominant distant metastases, as systemic therapy for effective treatment of extracranial disease was lacking [34]. The use of systemic therapy in patients with BM has been challenging because of resistance to conventional chemotherapies in often heavily pre-treated patient population and the paucity of well-conducted randomized trials in a heterogeneous patient population. Today, newer agents in the field of immunotherapy and targeted therapies are playing an important role in the up-front management of brain metastases, highlighting the importance of a multidisciplinary approach.

1.5. Prognostic scores and patient selection

Prognostic scores such as the Recursive Portioning Analysis (RPA) or the Graded Prognostic Assessment (GPA) have been validated in several studies. [4,35,36] The RPA was generated using data from 1200 patients in 3 clinical trials performed by the Radiation Therapy Oncology Group (RTOG). The RPA considers patient’s age, Karnofsky Performance Status (KPS), control of primary tumor and extracranial metastases and defines 3 categories of disease with median OS ranging from 2.3 to 7.1 months. The GPA estimates survival for patients with BMS with a score (0, 0.5 and 1.0) for four parameters including age, Karnofsky Performance Status (KPS), presence of extracranial metastases and number of BMs.

Several studies applying GPA showed a wide variation in survival prediction by diagnosis [37]. Hence the original GPA score has been extended and a disease-specific GPA was designed using retrospective data from a database of 3940 patients treated for brain metastases by examining individual tumor types as an independent prognostic factor [36]. For lung cancer patients with BMs, the prognostic factors significantly associated with overall survival were age, KPS, extracranial metastases and the number of brain metastases. Four prognostic strata were defined, with median survival ranging from 3.0 to 14.8 months.

In summary, it is important to emphasize that high quality level I data exists for local treatment including surgery of up to four BMs and SRS should be the preferred treatment option in asymptomatic patients, unless new practice changing level I evidence appears (e.g. for systemic treatment in tumors with driver mutations). Nevertheless, all prospective evidence is based on trials including different histologies and is not focused on single disease entities.

2. Driver mutations in NSCLC – A paradigm shift in patients with brain metastases

2.1. Incidence and prognosis of patients with brain metastases from driver mutated NSCLC

Approximately 10% of Caucasian patients and up to 30% of East Asian patients with lung adenocarcinoma harbor an epidermal growth factor receptor (EGFR) activating mutation [38]. The EGFR is a tyrosine kinase (TK) receptor belonging to the ErbB family of receptors. EGF and other growth factors trigger through the EGFR signaling pathway several downstream pathways for different cellular processes such as DNA-synthesis and cell proliferation. Somatic activating mutations, predominantly in exons 18–21 result in continuous activation of EGFR and subsequent uncontrolled cell division [39,40]. Most EGFR mutations referred to a deletion of exon 19 and to a point mutation in exon 21 accounting for more than 90% of all known activating EGFR mutations [41,42]. A further 3–7% of patients will have a translocation of the anaplastic lymphoma kinase (ALK) gene [9,43,44]. The most common translocation in NSCLC is the EML4-ALK fusion gene, resulting in autophosphorylation and constitutive activity of ALK and activating downstream pathways like RAS and PI3K signaling cascades [45]. Other reported molecular aberrations are KRAS mutations, Met amplification and ROS1, RET or NTRK gene fusions [46].

The incidence of BMs at presentation is higher in the oncogenic-driven population (25%) compared to unselected NSCLC patients (10%) [9] possibly indicating a tropism for the brain [47–49]. Furthermore

the increasing incidence of brain metastases in this patient cohort may also be a consequence of improved survival after the introduction of targeted therapies. The CNS is also common site of relapse in patients treated with tyrosine kinase inhibitors with BMs incidence ranging from 30 to 60% in EGFR-mutant and 40–70% in ALK-positive NSCLC. [9,45,47]. Nevertheless, patients with EGFR or ALK driven NSCLC and BMs have a markedly longer OS compared to patients without molecular aberrations [50–52]. To reflect this difference the disease specific GPA has been further refined by incorporating the molecular status of the primary tumor into the model (EGFR and ALK alterations): the so-called Lung-molGPA is able to accurately differentiate the different prognostic groups and mutational status plays an integral part in predicting prognosis of these patients [50,53].

2.2. Efficacy of targeted therapy on brain metastasis

After discovery of multiple molecular abnormalities in the last decade several drugs were developed for the treatment of oncogenic-driven NSCLC. Patients with BMs were excluded from earlier clinical studies due to the anticipated poor prognosis of this patient group with the CNS was considered a pharmacological sanctuary site due to blood-brain-barrier efflux pumps restricting transit of pharmacological agents by reducing intra-cerebral drug levels. [54,55]

Retrospective studies have reported high intracranial response rates in EGFR and ALK positive lung cancer treated with TKIs, questioning the role of the BBB and the brain as a separate compartment. [56,57] More recent prospective data that included patients with brain metastasis in analysis better inform on the efficacy of TKI therapy on BMs [58–64].

2.2.1. EGFR

First-generation EGFR-TKIs such gefitinib and erlotinib have been established as effective first-line therapy in NSCLC patients harboring an activating EGFR mutation in exon 19 or 21. [46,65,66] Lower CNS response rates are reported compared to extra-cranial disease with first-generation EGFR-TKIs. A pooled analysis of 16 trials (n = 464 pts) reported intracranial response rate of 51.8% and an intracranial disease control rate of 75.7% in patients with BMs in the overall patient population [58]. This may be due to reduced CNS concentration of gefitinib and erlotinib and suggesting limited blood-brain-barrier penetration [67–69]. To overcome reduced BBB penetration, dose drug administration alterations such as weekly intermittent “pulsatile” therapy, has been suggested as an effective alternative strategy to increase concentration in the CSF, however this has not been adopted in routine practice or guidelines. [59,70].

Second-generation irreversible EGFR-TKI afatinib was compared to standard platinum doublet therapy for previously untreated EGFR-mutant stage IIIB/IV adenocarcinoma patients in two randomized open-label, phase III clinical trials; LUX-Lung 3 and LUX-Lung 6. Afatinib significantly improved PFS, ORR and patient reported outcomes compared to chemotherapy. In patients with asymptomatic brain metastasis at baseline, a combined analysis of LUX-Lung 3 and 6 showed longer PFS with afatinib versus chemotherapy (8.2 versus 5.4 months; ORR 70–75% vs. 20–27%; HR = 0.50; p = 0.0297), although no difference in OS was observed [71].

Osimertinib, a third generation EGFR TKI has also demonstrated CNS activity [72]. Osimertinib potently and selectively inhibits both EGFR and T790 M resistance mutations. In the BLOOM study, Osimertinib was evaluated in patients progressing on prior EGFR-targeted TKI with leptomeningeal metastases and brain metastases from EGFR-mutant NSCLC. In 10 out of 32 patients radiological improvement was observed and 13 patients showed stable disease [73]. The phase III AURA3 study compared Osimertinib to platinium-based chemotherapy in T790M-positive advanced NSCLC patients who had progressed on or after prior first-line EGFR-TKI therapy. Patients with stable, asymptomatic CNS metastases were eligible for inclusion. In a subgroup analysis, two patient-sets were examined: the CNS evaluable for response set (cEFR) included only patients with ≥ 1 measurable CNS metastases and the CNS full analysis set (cFAS) included patients with ≥ 1 measurable and/or non-measurable CNS metastases. In the cEFR (n = 46), CNS ORR was 70% with osimertinib and 31% with chemotherapy (p = 0.015). In the cFAS, CNS ORR was 40% vs 17% (p = 0.014) for osimertinib and chemotherapy, respectively. In both the cEFR and cFAS groups, median CNS duration of response was 8.9 vs 5.7 months for osimertinib and chemotherapy, resepctively. Median CNS PFS in the cFAS group was significantly longer with osimertinib than with chemotherapy (11.7 vs 5.6 m; HR 0.32; 95% CI 0.15, 0.69; p = 0.004) [60]. The safety profile of osimertinib was consistent with what reported previously with worse adverse events in the platinum-based chemotherapy group.

Osimertinib in the first-line setting demonstrates longer PFS (18.9 vs 10.2 months) and CNS control than gefitinib or erlotinib in the recently published FLAURA trial. Improved median PFS (18.9 months compared to 10.2 months) and overall survival interim data analysis favoured osimertinib. Improvements were seen in all prespecified subgroups, including patients with brain metastases suggesting a significant CNS penetration [74]. In this trial brain imaging was mandatory in patients with known or suspected CNS metastases and follow-up imaging was only conducted in patients with confirmed brain metastases.

2.2.2. ALK

A number of agents have been FDA approved for the treatment of ALK-rearranged NSCLC including first- (crizotinib), second- (ceritinib) and next-generation (alectinib, lorlatinib, brigatinib) agents. The European Medicines Agency (EMA) has also approved crizotinib, certinib and alectinib with approval pending for brigatinib.

Crizotinib was the first ALK inhibitor approved for treatment of ALK-rearranged NSCLC and also shows marked antitumor activity in advanced ROS1-rearranged NSCLC [75].

Crizotinib showed a significantly longer PFS compared to platinum-pemetrexed chemotherapy in ALK-rearranged NSCLC patients [76] and also higher intracranial disease control rate at 12 weeks (85% v 45%, p < 0.001) and 24 weeks (56% versus 25%, p = 0.006) in 23% of patients with treated BMs, compared to chemotherapy alone. Intracranial time to progression was not significantly improved.

Among patients with BMs, PFS was significantly improved (BM present: HR, 0.40; P < .001; median, 9 versus 4 months) and remained significant in the intent-to-treat population (HR, 0.45; P < .001; median, 10.9 versus 7.0 months) in the crizotinib arm [77]. In a retrospective pooled analysis of PROFILE 1005 and PROFILE 1007 trials, patients treated with Crizotinib beyond disease progression had significantly longer OS [78]. In previously untreated patients with BMs, the intracranial response rate was only 18%, while intracranial disease control rate was 56% at 12 weeks [78]. Reduced CNS penetration and acquired drug resistance limited the efficacy of crizotinib on CNS metastases, [79,80]. In crizotinib treated patients, CNS is the most common site of progression [81] with up to 70% of patients developing of new intracranial lesions or progression of BMs, suggesting CNS-specific acquired resistance to crizotinib [62,82].

Subsequently, novel ALK inhibitors have been developed to overcome crizotinib-resistant mutations and to improve CNS disease control. Ceritinib has a 20-fold greater inhibitory potency than crizotinib with better CNS penetration while also retaining activity against the most common crizotinib-resistance mutation, such as the gatekeeper ALK L1196 M mutation [83–85]. ASCEND-4, an open-label randomized multicenter phase III trial showed a statistically significant and clinically meaningful improvement in PFS for first-line ceritinib versus chemotherapy in patients with advanced ALK-rearranged NSCLC [86]. Overall intracranial response rate in patients with measurable BMs at baseline and at least one post-baseline assessment was 72.7% (95% CI = 49.8–89.3; n = 22) vs 27.3% (95% CI = 10.7–50.2; n = 22) for ceritinib and chemotherapy, resepectively. Among patients with BMs at

presentation, median PFS was 10.7 vs 6.7 months (HR = 0.70; 95% CI = 0.44–1.12) for the ceritinib group and the chemotherapy group, respectively. Consistent with these data, in two previous single-arm studies of ceritinib in crizotinib-naive patients (ASCEND-1 and ASCEND-3) median PFS was similarly prolonged and intracranial efficacy was also reported [87,88].

Next generation ALK inhibitor alectinib has shown impressive and durable response rates within CNS. Data from two phase III studies demonstrated significant decrease in CNS progression for patients with ALK rearranged NSCLC in the first-line and second-line setting. The ALUR trial compared third-line alectinib versus chemotherapy in ALK-positive NSCLC previously treated with platinum-based doublet CT and crizotinib. Median PFS was significantly longer in the alectinib group compared to the chemotherapy group (9.6 vs 1.4 months (hazard ratio [HR] = 0.15, 95% confidence interval [CI] = 0.08–0.29; P < .001). Alectinib demonstrated a higher CNS ORR compared to chemotherapy, (54.2% vs 0%, p < 0.001) among patients who had measurable CNS disease at baseline. In untreated ALK-positive NSCLC, the ALEX and J-ALEX trials confirmed improved PFS and toxicity profile with alectinib compared to crizotinib. [89]. In the phase III ALEX study 43 patients had measurable CNS lesions at baseline. Alectinib resulted in higher CNS ORR (81% vs 51%) compared to crizotinib, including n = 8 (38%) patients in the alectinib group achieving complete CNS response. Durable CNS responses were also observed with a median duration of IC response of 17.3 vs 5.5 months in the alectinib group and crizotinib group, respectively [89]. Within the intention-to-treat population, alectinib resulted also in superior control of existing CNS metastasis compared to crizotinib (CNS progression rate: 12 vs 45%) also significantly prolonging time to CNS progression (HR 0.16, p < 0.001). Of note, baseline brain imaging and regular follow-up brain imaging was mandatory. This is of considerable relevance as different brain imaging management strategies may influence the available data on brain metastases, e.g. no specific management versus reduced brain follow-up e.g. in the FLAURA trial.

The phase II ALTA clinical trial evaluated brigatinib in crizotinib-pretreated patients with locally advanced or metastatic ALK-positive NSCLC. The trial was designed to investigate the efficacy and safety of brigatinib at two dosing regimens and patients were randomized to brigatinib either at the dose of 90 mg once daily (arm A) or 180 mg once daily following a 7-day lead-in of 90 mg once daily (arm B). Significant CNS efficacy was shown patients with brain metastases. About two-thirds of the patients in the high-dose regimen with measurable brain metastases had an intracranial response with a median intracranial duration of response of 16.6 months [90]. Brigantinib was also assessed against crizotinib in a phase 3 trial in 275 patients with advanced ALK-positive NSCLC who had no previously received an ALK-inhibitor. In this cohort 90 patients had brain metastases at baseline and 39 had measurable brain metastases with a diameter > 10 mm. The intracranial response rate among patients with measurable brain metastases was 78% with brigatinib and 29% with crizotinib demonstrating a clear predominance favouring brigantinib. 9% (12 of 137 patients) in the brigantinig group vs. 19% (26 of 138 patients) in the crizotinib group had intracranial disease progression. Consindering the 12-month intracranial disease progression free survival in patients with baseline brain metastases, the survival rate was higher among patients in the brigantinib group (67% vs 21%) [91].

Lorlatinib is a ALK-TKI designed to overcome resistance to other ALK inhibitors and to penetrate the blood-brain barrier. [92] Intracranial response rates of 44% for target and non-target lesions and 60% for target lesions respectively have been reported. [93].

In summary, later generation ALK TKIs demonstrate superior CNS penetration and efficacy leading to comparable intra- and extra-cranial response duration [63,64,94]. With the caveat of data extracted from subgroup analysis, the efficacy of these newer TKIs in patients with brain metastases, intracranial response rates and intracranial disease control rates of 30–67% and 75–90% have been observed. Nevertheless, the issue of best treatment sequence is not yet solved and will have to be the topic of further investigations [95].

2.3. Redefining the role of local therapies in the era of effective systemic therapies

2.3.1. EGFR mutant NSCLC

A large body of preclinical data exists investigating the EGF receptor and its role in modulating radio-sensitivity in vitro. Interestingly, this largely affects the situation of EGFR-wild type overexpression, which confers a more radio-resistant phenotype. In regards to radiation, one of the relevant mechanisms is radiation-induced nuclear translocation of the receptor. This activates a relevant repair mechanism involved in radiation-induced double strand break repair, namely non-homologous end-joining repair. Inactivating down-stream effects of EGFR-overexpression by EGFR-directed inhibition, e.g. TKIs or mAB, abrogated this effect and increased radio-sensitivity in vitro and in vivo.

In contrast, mutant EGFR cell lines were shown to have greater radio-sensitivity than their wild-type counterparts and as such, combination therapies of RT and TKI may further increase this effect in an additive fashion. The combination of EGFR-directed TKI agents and radiotherapy has been prospectively explored in a number of studies, although in an unselected EGFR-mt population. An unselected population of NSCLC patients with multiple BMs were assigned to receive whole brain radiotherapy with or without erlotinib [96]. No difference in CNS PFS or OS was observed and it was noted that the majority of patients were EGFR-wild type. The RTOG 0329 trial further expanded on the concept and introduced SRS as a local dose intensification to WBRT and erlotinib or temozolomide in NSCLC with one to three brain metastases [97]. In a phase II study, NSCLC patients with BM, regardless of EGFR status, received WBRT plus erlotinib [98]. A ORR of 86% was observed but attributed to a considerable portion of EGFR mutated tumors which then translated also into a very favorable OS of 19.1 months (EGFR-mut) compared to 9.3 months (EGFR-wt). Results from these prospective studies were quite disappointing but likely reflect the non-selective use of EGFR directed therapy. A systematic review investigating the role of radiotherapy in EGFR-mutant NSCLC compared to TKI only showed that integrating radiotherapy into TKI treatment may translate into an overall survival benefit at 2 years, although probably at the expense of slightly higher CNS toxicity [99]. At present, there is no prospective data on combination of EGFR-TKIs and SRS in EGFR mutant patients.

2.3.2. ALK positive NSCLC

In preclinical studies, simultaneous radiotherapy and ALK-TKIs may synergistically affect tumor growth and microvascular density, [100,101] therefore providing a rationale for potential role combination in increasing local control. Unfortunately, neither prospective nor compelling retrospective clinical data confirms this hypothesis.

This may partly be explained by the clinical detectable response rates of ALK-TKI that may lead to impressive response rates and even radiologic disappearance of brain metastases. CNS penetration and efficacy is even higher with drugs such as ceritinib, alectinib and brigantinib [63,64,94]. Therefore, in case of limited CNS progression, with extracranial disease control, switching to next-generation TKI without brain radiotherapy is considered a viable option, as it may translate into further CNS response.

Clinical data on combination of ALK directed TKI and radiotherapy is scarce. Available retrospective analyses allow cautious conclusions to be drawn. The retrospective analysis of the PROFILE 1005/1007 studies evaluated the effect of crizotinib in patients with stable BMs with or without prior local brain radiotherapy [62]. Intra- and extracranial response rates were similar and intracranial progression rate with or without prior radiotherapy was similar (70% and 72%, respectively). A striking difference was seen in the ORR (33%) and time to intracranial progression (median 13.2 months) in the patients having received prior

radiotherapy compared to the patients without radiotherapy with 18% and 7 months, respectively, emphasizing the role of local therapy for effective and sustained response of BMs. A retrospective multi-institutional review of 90 patients with brain metastases from NSCLC with ALK-rearrangement revealed an OS of 49.5 months for TKI treatment and combined brain-directed radiotherapy [102]. The effect of either treatment alone is difficult to assess, as 86 out of 90 patients had received some form of radiotherapy for newly diagnosed or progressing metastases. Repeated courses of radiotherapy, mainly in the form of SRS, were administered and up to 23% had received at least three courses of radiotherapy indicating that local radiotherapy played an important role in intracranial disease control after cranial progression while on TKI treatment.

Although next-generation ALK inhibitors (ceritinib, alectinib, brigantinib, lorlatinib) exhibit more pronounced CNS activity, resistance may develop as early as within the first year, with CNS progression as a significant morbidity and mortality factor [103]. As the optimal sequencing and combination of ALK-TKI treatment has not been defined in this situation, local therapies to target brain progression will need to be taken into account.

2.4. Optimal timing of radiotherapy in newly diagnosed brain metastases

In the light of the aforementioned treatment results with TKI therapy alone, the value of local therapy, especially radiotherapy, has been challenged. Although with formal level I evidence lacking, upfront TKI treatment in EGFR or ALK positive NSCLC patients with brain metastases is a potential option which is widely accepted in clinical practice [104].

Notably, 3 prospective randomized studies addressing the question of optimal timing of radiotherapy did not show an OS benefit for upfront radiotherapy, either as WBRT or SRS, compared to a salvage approach [105–107]. As these studies were initiated before the discovery of driver mutations, these results are of limited value in this particular patient population. Nevertheless, it reflects the necessity to address the issue of optimal timing of local therapies in the era of CNS-effective systemic agents.

Although patients with driver mutations exhibit a very favorable survival following TKI treatment, even with BMs, it is important to bear in mind that these studies 1) did not specifically focus on brain metastases, 2) allowed subgroup analysis with few patients with brain metastases, 3) only reported response rate and duration, and not local control of individual lesions, 4) allowed radiotherapy to be given irrespective of timing.

The largest retrospective series reported so far, a pooled multicenter analyses of NSCLC patients with EGFR mutation and brain metastases, showed a significant OS benefit in patients with newly diagnosed BMs receiving upfront radiotherapy plus EGFR-TKI treatment [108]. This study has several limitations that need to be taken into account when interpreting results. Firstly, over 70% of patients did not have extracranial metastases at the time of BMs. Secondly, patients treated with up-front TKI and up-front WBRT were more likely to be stage IV at diagnosis therefore conferring a worse prognosis. In addition, patients who received up-front EGFR-TKI were more likely to have asymptomatic BMs (88% EGFR-TKI v 49% WBRT, 51% SRS; $P < .001$). In addition, the study excluded patients who failed to receive EGFR-TKI after WBRT or SRS and those who failed to receive RT after intracranial progression whilst on a EGFR-TKI. Together with that, there is no data on follow-up details, including extracranial metastases, subsequent systemic therapies, and neuro-cognitive assessments. This could affect implications for clinical practice on the basis of the study conclusion, especially for up-front WBRT.

In another retrospective study analyzing the outcome of ALK translocated NSCLC patients with brain metastases, a very favorable outcome has been reported following ALK targeted treatment [102]. Still, most of these patients had received repeated radiotherapy interventions, making it difficult to discern the effect of TKI and radiotherapy treatment on the outcome of their brain metastases and assess the optimal timing of radiotherapy.

Although next generation TKIs exhibit a significantly better CNS penetration and therefore response rate/ duration of response; intracranial progression after single agent targeted treatment still poses a significant problem after a median response duration of 9–12 months [109,110] and requires local intervention for effective CNS disease control.

Although effective CNS-directed TKI treatment is available, retrospective data suggests a role for early integration of radiotherapy intervention, although the optimal timing has not yet been defined [52,99,108,111].

2.5. Toxicity considerations when combining TKI with radiotherapy

EGFR–TKIs have been administered simultaneously with WBRT in phase I/II studies in NSCLC without a significant increase in (neuro-) toxicity [98,112]. Caution should be applied when radiosurgery is given in addition to WBRT and EGFR-TKI, as this has been associated with increased toxicity [97]. No comparable prospective experience exists for ALK targeting agents.

Three recent systematic reviews concluded that no significantly increased risk of toxicity of targeted therapy in combination with radiotherapy except for erlotinib or VEGF targeted therapy is to be expected, although data on ALK targeted treatment is still very limited [113–115].

In particular, prospective data on the feasibility and safety of TKI treatment and simultaneous sole SRS treatment is still lacking.

Therefore, if there are concerns regarding tumour flare following the interruption of TKIs, even if for only a few days, radiotherapy may be given while the patient remains on the TKI. Otherwise, a drug holiday of up to one week (3 days before and after SRS) is considered safe per expert consensus [116].

3. Defining the optimal management of brain metastasis in oncogenic driven NSCLC

With the detection of EGFR-mutations and ALK-translocations in NSCLC adenocarcinoma and the respective targeted argents, the general management and OS of NSCLC exhibiting driver mutations has considerably changed, especially in patients harboring brain metastases, and the role of local therapies in combination with systemic therapies is not precisely defined [58,102,108,111,117,118].

The most recent EANO guidelines on diagnosis and treatment of BMs comprehensively summarizes the current evidence however do not derive clear consensus recommendations in this specific patient population [119].

In the following we attempt to combine the current knowledge existing for brain metastases treatment in solid tumors with the latest evidence in patients with brain metastases from oncogenic-driven NSCLC to derive a proposed algorithm of individual patient management in the absence of unequivocal prospective evidence.

3.1. Screening and follow-up

Currently, screening for BMs is not routinely recommended in asymptomatic NSCLC patients. However, according to a recent EORTC-led survey, this is already performed by 85% of the physicians [116]. Most often physicians screened patients with a driver mutation (51%), stage III (63%), and only in 43% with stage IV disease. As screening procedures should only be implemented if the diagnostic result has a therapeutic impact, it appears reasonable to adopt a pragmatic approach and perform a baseline brain scan before initiation of TKI treatment or switch to next line TKI. This ensures a) that in the presence of brain metastases, the CNS efficacy of the TKI can be monitored and

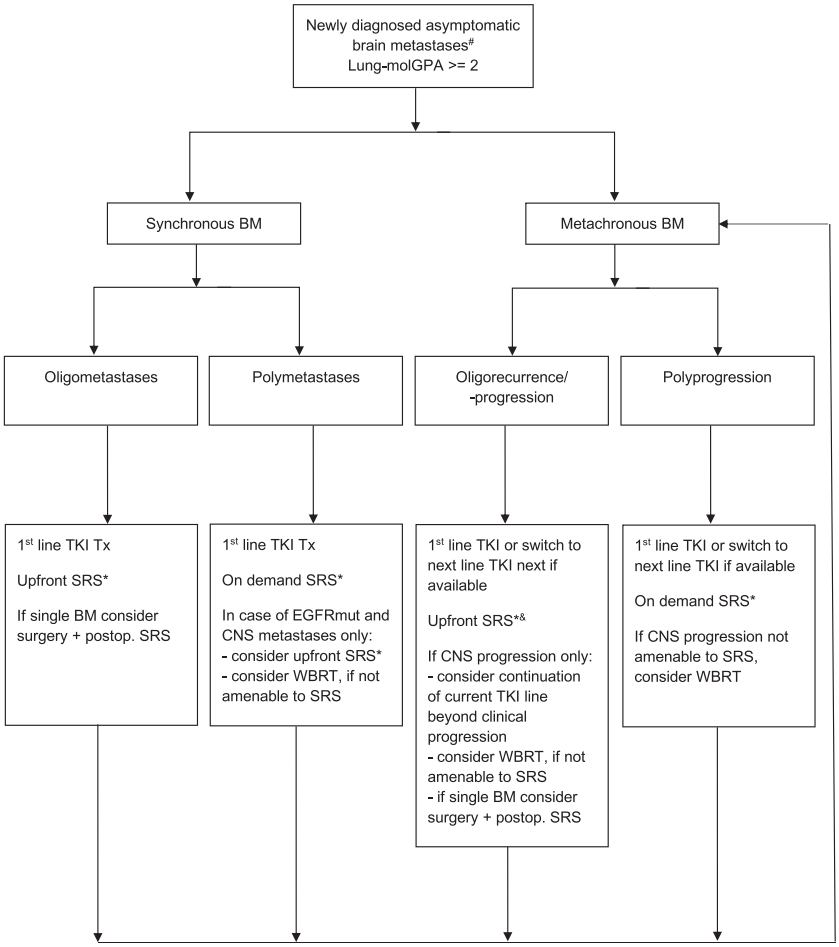

Fig. 1. Proposed treatment algorithm for management of asymptomatic brain metastases from driver mutated NSLC.

local treatment options be evaluated and b) that in the absence of brain metastases at baseline and CNS progression/relapse only, TKI continuation and local brain-directed therapy may be the choice of treatment.

Routine brain scans at pre-specified time points cannot be recommended. NCCN guidelines suggest imaging follow up every 2–3 months for patients with BMs who have received CNS-directed therapy (https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf). Thin sliced MRI brain with contrast is preferred to detect small lesions and to guide treatment selection, but CT is still performed in up to 48% of patients according to local or national policies [116].

3.2. Prognostic scores for decision making

Several validated scores (RPA, GPS, dsGPA) are available to estimate prognosis of patients with brain metastases. The recently published Lung-molGPA is the most specific to this patient cohort, as it also incorporates mutational status into the prognostic tool [50]. Together with age, performance status, number of brain metastases (1–4 v > 4), presence/absence of extra-cranial disease, this tool also incorporates tumor's mutational status. The scoring system is able to clearly define patient groups with clinically-relevant different prognosis. For example, patients with GPA ≥ 2.5 exhibit a median survival of at least 12 months (non-adenocarcinoma histology) and 26.5 months (adenocarcinoma histology) thus justifying the incorporation of local treatment options into combined modality treatment. Unfortunately, the use of this prognostic score is only slowly adopted, as witnessed by a recent European survey [116].

3.3. Decision making according to the pattern of brain metastases occurrence

In newly diagnosed asymptomatic brain metastases, the proposed algorithm (Fig. 1) is based on the assumption that specific CNS directed therapy (systemic +/- local therapy) should be implemented if the Lung-molGPA score is greater than 2.5 leading to a projected ≥12 months OS. The next decision point is then whether BMs have been detected synchronous or metachronous to the diagnosis and therapy of the primary disease. This allows separation of true oligometastatic disease suitable for intensive combined modality treatment in curative intent from metachronous oligorecurrence/-progression or more widespread metastatic disease, as a different biological behavior is assumed. Of note, in the case of oligometastases or oligorecurrence/-progression, to 4 brain metastases are being considered in this context. This reflects the current level I evidence for SRS/surgery in the treatment of brain metastases from solid tumors and the inclusion of this number in the Lung-molGPA as a separate prognostic parameter.

Current guidelines recommend appropriate TKI treatment as standard of care for stage IV oncogenic-driven NSCLC [116,117]. In the light of the summarized data on brain efficacy of different TKIs, first line recommendation for newly diagnosed brain metastases may change in the near future. Due to the advent of these newer generations of TKIs the optimal sequence of TKI treatment needs to be defined as well as the role of continuing TKI treatment beyond clinical progression before switching to next line of systemic treatment [109,110].

For synchronous oligometastatic CNS disease, a potentially curative approach should be followed incorporating early integration of local therapies. If simultaneous extracranial disease progression occurs in the

case of oligorecurrence or oligoprogression, it is a clinical decision based on the current treatment to initiate or continue on TKI treatment beyond clinical progression and incorporate local ablative therapies or to switch to next available line of TKI and reserve local therapies for further oligoprogression. Both approaches are suitable and possible scenarios within the currently recruiting HALT trial investigating the role of SBRT for oncogene addicted oligoprogressive NSCLC, as only extracranial progression is considered as long as newly appearing brain metastases are suitable for SRS (https://clinicaltrials.gov/ct2/show/NCT03256981).

CNS relapse or progression only represents a specific situation in which local CNS-directed therapy plays a major role. In case of limited (≤ 4) brain metastases, upfront SRS should be considered as evaluated by the respective prospective phase III trials. For multiple BMs not suitable for SRS, whole brain radiotherapy may be considered in particular for EGFR mutated NSCLC patients.

With regard to systemic treatment, the respective TKI treatment should be initiated or continuation of current TKI treatment "beyond clinical progression" should be considered, as the extracranial activity in these patients is still preserved.

For widespread metastatic disease, systemic treatment is the treatment of choice irrespective of the number of brain metastases and local CNS-directed therapy should be reserved "on demand" for the aforementioned situation of oligoprogression or to prevent progressive metastases to become symptomatic. In the case of CNS multiple BMs in EGFR mutated NSCLC, an upfront approach with local therapies may be considered but also starting with an EGFR-TKI is a viable option.

As indicated in the flow chart, if further progression occurs this algorithm is generally applicable in an iterative way by re-evaluation of the Lung-molGPA and re-entering at the metachronous decision point.

4. Conclusion

This review summarizes the current data and evidence for the management of brain metastases for driver mutated NSCLC and proposes a treatment algorithm in the setting of limited prospective evidence. As optimal management of asymptomatic brain metastases in NSCLC patients with driver mutations is not yet well defined and a matter of debate, prospective evaluation with a clinically meaningful endpoint is urgently needed.

Ideal world goals for optimal management have been critically formulated:

1 Prevent pre-mature death in the time period before multi-organ disease compromises vital functions
2 Preserve age-matched cognitive and neurological function as if brain metastasis would not have developed
3 Achieve these goals without unnecessary resource utilization treating patients rather than scans
4 Bear in mind that radiotherapy results are better if the total intracranial tumor volume is lower

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