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Leptomeningeal carcinomatosis in non-small cell lung cancer patients: A continuing challenge in the personalized treatment era

J. Remon [a,1], E. Le Rhun [b,2], B. Besse [a,c,*]

[a] Gustave Roussy, Medical Oncology Department, Villejuif, France
[b] Neurology, Oscar Lambert Center Lille, Neuro-Oncology Department, Lille University Hospital and Lille University, INSERM U-1192, France
[c] Paris Sud University, France

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ABSTRACT

Leptomeningeal metastasis is a fatal manifestation seen in advanced cancer patients. Its incidence is increasing, reaching 3.8% in molecularly unselected non-small cell lung cancer patients and up to 5% and 9% in *ALK*-rearranged and *EGFR*-mutant lung cancer patients, respectively. The prognosis remains poor despite systemic treatment, intrathecal chemotherapy, radiation therapy and personalized treatments in molecularly selected patients. However, new therapies with improved cerebral-spinal fluid penetration have been developed for subgroups of molecular selected patients indicating they could be promising therapeutic options for managing leptomeningeal disease. Systemic chemotherapy, which may be combined with intrathecal chemotherapy, remains standard treatment for lung cancer patients with leptomeningeal disease and a good-risk profile. We summarize evidence reported in the literature for managing this complication in lung cancer patients. Based on this, we have selected potential therapeutic strategies that could be used in daily clinical practice.

Introduction

Leptomeningeal metastases (LM) are the multifocal seeding of the leptomeninges by malignant carcinomatous cells [1]. Malignant cells can reach the meninges by several different pathways: haematogenous spread via arterial or venous circulation, perivascular lymphatic spread, endoneural and perineural spread, direct spread from metastases located in the brain or bone in proximity to the subarachnoid or ventricular spaces, and spread from choroid plexus and subependymal metastases. Two types of leptomeningeal tumor spread can be distinguished: the first with free-floating non-adherent cancer cells (diffuse type); and the second characterized by contrast-enhanced leptomeningeal nodules (nodular type). LM are found in approximately 5% of patients with malignant tumours [1], and most arise from lung, breast carcinoma and melanoma [2]. In autopsy series, LM incidence may be 20% or more for many solid tumours [3], suggesting that they are clinically underdiagnosed and likely occur at a late stage of the disease. Clinical features vary according to the CNS region involved. Classically, three domains of neurological functions are used to characterize the clinical features: the cerebral hemisphere, cranial nerve, and spinal cord and exiting nerve roots [4].

LM are becoming increasingly common due to availability of improved treatments, leading ultimately to prolonged patient survival, and as neuroimaging methods improve. However, prognosis of LM remain poor, with patient performance status (PS) being the main prognostic factor [2]. Up to one-third of patients are treated with best supportive care alone [5]. Despite the lack of standard treatment, active treatment has been associated independently with longer overall survival (OS) [5] .

Among non-small cell lung cancer (NSCLC) patients, the incidence of LM is 3.8%, being more frequent in adenocarcinoma subtype. One-third of patients have concomitant brain metastases [6]. Median OS of NSCLC patients with LM ranges from 3.6 to 11 months [6,7], mostly as a consequence of using modern systemic therapies, which decrease the risk of death (hazard ratio [HR], 0.24; $P = 0.007$) [8]. In the modern treatment era, LM is a devastating complication for oncologic patients, including molecularly selected patients, and the optimal therapeutic approach remains a challenge. This review explores the present cutting edge options for diagnosis, systemic treatment and immunotherapy for LM

* Corresponding author at: University Paris-Sud and Gustave Roussy Cancer Campus, 114 Rue Edouard Vaillant, 94805 Villejuif, France. Fax: +33 (0)1 42 11 52 19.
E-mail addresses: JORDI.REMON-MASIP@gustaveroussy.fr (J. Remon), Emilie.lerhun@chru-lille.fr (E. Le Rhun), Benjamin.BESSE@gustaveroussy.fr (B. Besse).
[1] Gustave Roussy Cancer Campus, 114 Rue Edouard Vaillant, 94805 Villejuif, France. Fax: +33 (0)1 42 11 52 19.
[2] Neuro-oncology, Neurosurgery Department, Salengro Hospital, Rue Emile Laine, 59037 Lille cedex, France. Fax: +33 (0)3 20 44 68 08.

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among NSCLC patients, examining the efficacy of personalized treatments in molecularly-selected lung cancer patients with LM. Based on our literature review we have selected some therapeutic recommendations, which could be used in daily clinical practice (Table 1).

Diagnostic

Diagnosis of LM is based on three assessments types: clinical, imaging and cerebral-spinal fluid (CSF) cytological examinations. Initial clinical manifestations can be subtle and may include cauda equine symptoms or signs, cranial nerve deficits, headaches and back pain, visual disturbances, diplopia, hearing loss and neurocognitive syndromes. In advanced stages, symptoms related to elevated intracranial pressure could occur [9,10]. In current trials, it is based on the identification of malignant cells in the CSF, or in absence of its identification based on suggestive clinical and imaging findings. Brain and spine MRI represent the gold standard for the imaging evaluation of LM. LM brain involvement is observed in 40–75% and spine involvement in 15–25% of cases. The sensitivity of MRI in LM from solid tumors is estimated at 70–87% and the specificity at 75–94% [11]. Gadolinium-enhanced MRI could increase sensitivity specially for LM manifest primarily or solely as cranial nerve involvement [12]. Any irritation of the leptomeninges including neurosurgery or lumbar punctures can induce contrast enhancement, thus MRI should be obtained prior to such procedures whenever feasible. Of note, a normal MRI does not rule out LM [10], and it can occur in up to 20% of cases [5]. Standard CSF evaluations are abnormal in more than 90% of cases [11] with elevated protein levels or hypoglucorachia in CSF [13]. CSF cytological analysis remains the gold standard for identification of LM with a sensitivity of the first CSF examination varying from 45% to 50%. Usually two successive CSF samples are required to adequately assess cytology [10]. However, in up to 30% of LM the CSF cytological analysis is negative and MRI suggests the diagnosis [5]. Several procedures can increase the sensitivity of the cytological analysis, such as the tumor marker-immunostaining fluorescence *in situ* hybridization (TM-iFISH) in lung cancer patients [14]. Likewise, CSF analysis using CellSearch™, an epithelial-cell adhesion molecule (EpCAM)-based method involving immunomagnetic enrichment followed by flow cytometry, which was designed for peripheral blood studies, has been reported by different teams and appears promising [4,15]. Direct DNA sequencing of LM in CSF of NSCLC patients allows identification of sensitizing and resistance *EGFR* mutations, even in the absence of malignant cell in the CSF, reporting equivalent *EGFR* mutation subtypes in the CSF and in the primary tumor [16,17].

Treatment

Treatment objectives for LM are to improve neurologic symptoms, quality of life, and survival, while maintaining marginal toxicity. Standard treatment is yet to be established due to the lack of randomized clinical trials with definitive conclusions. This situation is explained by low incidence rates, the rapidly progressing nature of the disease, and the heterogeneous LM population. As such, most treatment recommendations are based on clinical experience or patient cohorts and experts' experience, all with low levels of evidence. Parameters defining poor-risk and good-risk patients categories (Table 2) have been defined in an attempt to distinguish patients in whom only supportive care is appropriated. One major problem for evaluating the efficacy of treatments for LM is the lack of standardization with respect to response criteria (clinical, neuroimaging, and CSF analysis) in clinical trials [10]. Recently, the Response Assessment in Neuro-Oncology (RANO) LM working group critically re-evaluated the endpoints and response criteria across published randomized studies [10]. Based on this preliminary work, the group has proposed three basic elements in assessing response in LM: a standardized neurological examination, CSF cytology or flow cytometry, and radiologic evaluation. However, this instrument will require prospective validation [116]. However, we can already establish that among NSCLC patients with LM, survival could be considered the most important indicator of response evaluation.

Intrathecal chemotherapy

Intrathecal chemotherapy (ITC) in combination with systemic treatment is the mainstay of treatment for non-nodular types of LM, although its superiority compared with systemic treatment alone has not been established in randomized trials [18–23]. Recently, some retrospective data have reported its efficacy among NSCLC patients [24,25]. A recent pooled analysis, evaluated 589 NSCLC patients receiving ITC, with 37 patients receiving ITC only, while 552 patients received multiple interventions, such as ITC, whole-brain radiotherapy (WBRT), epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), systemic chemotherapy or best supportive care. The study reported a re-evaluated cytological, clinical and radiographic rates of 55% (53–60%; $n = 49$), 64% (53–79%; $n = 58$), and 53% ($n = 32$), respectively, and median OS of 6.0 months. The median survival time of patients who received ITC only (7.5 months) was much longer than that of patients who received multiple interventions (3.0–5.0 months) [26]. However, given the limited number of patients, the heterogeneity in the ITC treatment and other confounding factors it is difficult to draw robust conclusions about the efficacy of ITC in NSCLC patients and clinical trials are needed.

In another study in NSCLC patients, cytological response after ITC was reported to be a prognostic factor (median survival of 5.5 months for cytological responders versus 1.4 months for non-responders, $p = 0.075$). PS and clinical improvement after ITC were also significant prognostic factors [25]. However, predictive value of cytological conversion remains controversial.

Intact blood–brain and blood-CSF barriers limit penetration into the CSF of most anticancer drugs, giving CSF exposure of usually less than 5% of the plasma concentration [4]. Three drugs are routinely used for intrathecal application: methotrexate, Ara-C (liposomal cytarabine), and thiotepa (Table 3). Methotrexate is the drug with the broadest experience in treating LM, however the precise schedule of administration and the duration of treatment has not been established. The most common doses of methotrexate are 10–15 mg twice weekly for 4–6 weeks as treatment induction. If negative cytology is achieved after induction, induction therapy once weekly is continued for another month before switching to monthly maintenance ITC [9,13] (Table 3). However, the RANO group reported that CSF response definitions vary widely across trials [10]. It has been suggested that at each ITC, CSF should be taken and analyzed to monitor the disease response in parallel with the patient's clinical course. In patients without cytology clearance and clinically stable or improved outcomes, it may be advisable to continue the induction ITC for 1 month before switching to maintenance ITC. Termination of ITC may be indicated in cases of clinical or CSF cytology deterioration [9,13], however the duration of the maintenance treatment is not consensual. A leukoencephalopathy after methotrexate may occur, especially if methotrexate is administered after rather than before radiotherapy. Thus in combined treatments, methotrexate ITC should be administered 2 or 3 weeks before WBRT [9]. Also, in 10–50% of cases reversible chemical aseptic meningitis may occur after IT liposomal cytarabine that can be overcome with oral steroids.

Table 1
Recommendations for diagnostic and treatment of leptomeningeal carcinomatosis in non-small cell lung cancer patients. LC: leptomeningeal metastases. ITC: intrathecal chemotherapy.

Diagnostic
- Diagnosis of LM is based on three assessments types: clinical, imaging and cerebral-spinal fluid cytological examinations.
- Oncogenic driver mutations can be detected in the CSF.

Treatment
- Good-prognostic risk patients: intensive treatment is recommended
- Low-prognostic risk patients: best supportive care is appropriate

Intrathecal chemotherapy
- Intrathecal chemotherapy might have an impact in the outcome of NSCLC patients with LM, specially among those with cytological response.
- There is no standard regimen of ITC chemotherapy.
- Intrathecal chemotherapy is not appropriate for the treatment of nodular type of LM or bulky disease.
- Is not well established for molecular selected patients whether TKI should be administered or not concomitantly with ITC, however, it seems that concomitant treatment could have a positive impact in the outcome of these patients, except for *ALK*-rearranged patients treated with third-generation ALK TKIs.

Systemic chemotherapy
- Systemic chemotherapy after LC diagnosis in NSCLC patients is a prognostic factor.
- There is no standard systemic treatment, and the choice should be based on histologic subtype and molecular profile.
- Pemetrexed in non-squamous histology subtype has been reported as an effective treatment in patients with brain and leptomeningeal metastases.
- Patients with good PS and patients with LM at the time of initial NSCLC diagnosis are the most favourable subpopulation.
- The efficacy of bevacizumab in LC remains unknown.

Radiotherapy
- Focal radiotherapy could be applied for those patients with nodular type leptomeningeal disease or in symptomatic sites.
- The efficacy of whole brain radiotherapy in NSCLC patients with LM remains unclear with contradictory results in survival efficacy.
- Concomitant strategies with ITC are not recommended based on the risk of increased toxicity.

EGFR-mutant patients
- Based on the retrospective data and small sample size of the cohorts, firm conclusions cannot be drawn about the best therapeutic strategy in *EGFR*-mutant patient.
- Erlotinib could be more effective than gefitinib, and high doses of EGFR-TKI may be an appropriate strategy. However, the optimal dose and schedule remains unclear.
- High doses of EGFR TKI have no clear impact in survival but can achieve neurological symptoms improvement.
- Erlotinib 300 mg maybe a plausible option.
- Concomitant ITC should be recommended.
- Osimertinib 160 mg might be effective, but is still being evaluated.

ALK-rearranged patients
- The optimal approach for *ALK*-positive patients with LM is not yet defined.
- First-generation ALK TKIs has poor blood brain barrier penetration.
- Third-generation ALK TKIs may provide more efficacy into the CNS.
- In case of LM, if there are no option for second- or third-generation ALK TKI treatment, crizotinib and concomitant ITC could be recommended.

Other molecular alterations
- The majority of oncogenic driver mutations in NSCLC patients are treated with TKI, with low CSF penetration.
- No standard treatment exists for *HER2*- or *BRAF*-mutant NSCLC patients with LM.
- Systemic chemotherapy plus ITC is appropriate for these subgroups of lung cancer patients.
- In HER2-positive breast cancer patients with LC, intrathecal trastuzumab has reported some efficacy, and it may be an option in the lung cancer setting. The optimal dose, the schedule and the convenience of combining with ITC are not yet consensual. Efficacy among *HER2*-mutant NSCLC patients is unknown.

Immunotherapy
- Intracranial activity of immunotherapy has been reported (especially in cases of brain metastases), but not predictive factors are currently available and the efficacy in molecularly-selected NSCLC patients is unknown.

Table 2
Risk group stratification for leptomeningeal metastases patients (Adapted from NCCN guidelines 1.2016).

Poor risk group	Good risk group
Low performance status (<60%)	High performance status (⩾60%)
Multiple, serious, or major neurological deficits	No major neurological deficits
Extensive systemic disease with few treatment options	Minimal systemic disease
Bulky central nervous system disease	Reasonable systemic treatment options, if needed
Encephalopathy	

Renal impairment may increase the risk of methotrexate toxicity [9].

Systemic chemotherapy

Most patients suffering from LM have active systemic disease that requires systemic treatment, the latter possibly also being active on LM [4]. Median OS after LM diagnosis in NSCLC patients is 4.3 months. Systemic chemotherapy after diagnosis of LM in NSCLC patients is a prognostic factor (OS: 11.5 months versus 1.4 months for patients without systemic treatment, $p < 0.0001$) [25]. Patients with good PS and patients with LM at the time of initial NSCLC diagnosis are the most favourable subpopulation [25].

Table 3
Principal agents and schedules used for intrathecal chemotherapyCSF: cerebrospinal fluid.

Agent	Half life in CSF	Protocol
Methotrexate	4,5–8 h	*Standard* 10–15 mg twice weekly during 4 weeks followed by 10–15 mg once weekly during 4 weeks, followed by 10–15 mg monthly *High dose* 15 mg/day from day 1 to 5 every 2 weeks Maxim dose: 150 mg
Liposomal cytarabine	14–21 days	50 mg every 2 weeks (total, 8 weeks) followed by 50 mg once monthly
Thiotepa	3–4 h	10 mg twice par week (total, 4 weeks), followed by 10 mg once par weeks (total, 4 weeks), followed by 10 mg once monthly

No standard systemic treatment has been defined, and the choice should be based on histologic subtype and the molecular

profile of NSCLC patients. Pemetrexed combined with a platinum may be considered as the first-line treatment option for advanced NSCLC patients, especially those with non-squamous histology [27]. Although measured pemetrexed CSF concentrations in patients with an intact blood–brain barrier appear to be too low to be effective against CSF disease [28], patients without brain metastases receiving maintenance pemetrexed developed fewer brain metastases than patients on the other regimens [29].

Several studies have reported that vascular endothelial growth factor (VEGF) levels in the CSF of patients with LM were at least 14-fold higher than those in patients with other neurological disorders, and it was a negative prognostic factor [30,31]. Moreover, in a preclinical model, bevacizumab, a monoclonal anti-VEGF. A antibody prevents brain metastasis formation in lung adenocarcinoma [32], but its efficacy in LM remains unknown. Among breast cancer patients with LM, the combination bevacizumab, etoposide cisplatin exhibited promising efficacy [33]. It is unknown whether the combination bevacizumab-pemetrexed can eliminate or delay the LM onset in NSCLC patients.

Radiotherapy

Radiotherapy is manly given for symptoms alleviation, CSF flow correction or for debulking to facilitate chemotherapy [13]. It is appropriate for patients with nodular type leptomeningeal disease. WBRT is typically used in cases of concurrent brain metastases or major meningeal cerebral involvement. Focal radiotherapy is used for meningeal nodular spinal or cerebral lesions or in symptomatic areas (fossa posterior or cauda equine) even in the absence of imaging abnormalities [9]. However, use of WBRT in NSCLC patients with LM needs to be better defined in clinical trials given its impact on patients' quality of life. In a retrospective cohort of NSCLC patients with LM ($n = 212$), the median OS for patients who underwent WBRT for LM was longer than in those patients who did not (10.9 months versus 2.4 months, $p = 0.002$) [6]. On the other hand, a recent study showed no difference in OS between patients treated with WBRT ($n = 46$) and those who were not ($n = 59$, $p = 0.84$), with a median OS for the whole cohort of 3 months [24]. Another retrospective study reported limited efficacy of WBRT alone as palliative treatment (median OS of 2 months) in 27 breast and lung cancer patients unsuitable for chemotherapy. The absence of cranial nerve dysfunction was the only significant prognostic factor for OS for with WBRT (median 3.7 *vs.* 19.4 weeks, $p < 0.001$) [34].

In a recent phase II trial with 59 patients with LM from solid tumors (including 32 NSCLC patients) and adverse prognostic factors, a combination of intensive treatment of concurrent radiotherapy (whole brain and/or spinal canal radiotherapy, 40 Gy/20f) and intrathecal methotrexate reported a median survival of 6 months and 1-year OS of 21.3%. Among NSCLC patients, clinical response rate was 87.5%, which correlated with OS (median OS 6.7 months), however, the toxicity of the combination treatment (20% severe toxicity including 15% grade 3 encephalopathy) argues against this strategy in daily clinical practice [35]. Prognostic factors should be taken into consideration to identify patients who are likely to benefit from WBRT. Concomitant strategies with ITC should be balanced against toxicity risks and are not considered as standard due to the toxicity profile.

Molecularly-selected lung cancer patients

Approximately 20–25% of advanced NSCLC tumours, especially the adenocarcinoma subtype, have an actionable oncogenic driver mutations [36] allowing personalized treatment. In Caucasian patients, the most frequent genetic alterations in advanced NSCLC are the *KRAS* mutation in ~29% of patients, the *EGFR* mutations in ~11%, *ALK* rearrangements in ~5% [37], and *MET* mutations (exon 14) in 4% [38]. Other less frequent mutations include *BRAF* and PIK3CA mutations in ~2%, each, *HER2* mutations in 1% of tumours [37], and *ROS1* rearrangements in 1% [39]. These oncogenic drivers are almost always mutually exclusive in this patient population [40].

Personalized treatment with targeted therapies that match oncogenic drivers mutations has a clinical benefit for the patients [36,40]. However, the efficacy of personalized therapies with TKIs or monoclonal antibodies among molecularly-selected advanced NSCLC patients and LM is unknown because this population is excluded from clinical trials. Thus, the majority of data comes from retrospective analyses or from clinical cohorts. Recently among *EGFR*-mutant patients with brain metastases, upfront EGFR TKI (icotinib) improve outcome compared to initial WBRT [41], but remains unknown if this strategy is effective as monotherapy or in combination with WBRT among LM population. However, based on preliminary efficacy of third-generation TKI radiotherapy may be delayed if clinical improvement occurs after personalised treatment initiation.

EGFR-mutant NSCLC patients

EGFR mutations predict sensitivity to first- and second-generation EGFR TKIs such as erlotinib, gefitinib or afatinib. Response rate, progression-free survival and quality of life with EGFR TKIs are superior to standard first-line platinum doublet chemotherapy, making them the standard of care [42].

It has been suggested that *EGFR* mutations appear early during multistep carcinogenesis and may even be associated with a metastatic tropism to the brain [43]. A review of 1,127 NSCLC patients found that those with *EGFR*-mutations were more likely to develop brain metastases (31.4% versus 19.7%, odds ratio, 1.86, 95% CI 1.39–2.49; $p < 0.001$), and leptomeningeal dissemination (30.8% versus 12.7%; odds ratio 3.04, 95% CI 1.64–5.78; $p < 0.001$) than those with wild-type *EGFR* tumours [44]. In another retrospective cohort ($n = 5387$), LM was also significantly more frequent in *EGFR*-mutant tumors than EGFR-wild-type NSCLC patients (9.4% *vs.* 1.7%, $p < 0.001$) [45].

Globally the incidence of LM among *EGFR*-mutant NSCLC patients is ~9% [6,45,46]., with a median survival of 3.1 months, similar to that of unselected NSCLC patients. Although median OS in this group is poor, 44% of patients have prolonged survival of more than 6 months, suggesting a trend toward better prognosis for this subgroup of lung cancer patients with LM. PS is the most important prognostic factor [46], and EGFR TKI therapy after diagnosis of LM remains an independent predictive factor of extended survival (median OS 10.0 *vs.* 3.3 months, $p < 0.001$) [6,7,45], with different prognoses according to the *EGFR*-mutation subtype [7]. In other retrospective series, the use of EGFR TKIs improved OS which reached a median of 19 months [24,25]. No other patient- or treatment-related characteristics, including as age and treatment with high-dose EGFR TKI, influenced survival after LM diagnosis [46]. Also, a combination of WBRT and TKIs did not add any survival benefit beyond that in patients receiving only TKIs [45].

In *EGFR*-mutant NSCLC patients the median time-elapsed between diagnosis of advanced NSCLC and LM is 13.6 months [46]. However, the use of EGFR TKIs does not affect the incidence or timing of LM development, and this risk increases over the time [47]. This may well be explained by the inability of currently available first-generation EGFR TKIs to cross the intact blood–brain barrier at recommended doses [48–51], making alternative strategies essential.

One strategy to achieve therapeutic dosing concentrations with EGFR TKIs in CSF is to increase the EGFR TKI dose [52–55]. In a phase I study, high-dose gefitinib (750 or 1000 mg daily) resulted in neurologic symptom improvements in 57% of NSCLC patients who had shown prior response to an EGFR TKI, with modest benefit in outcome with a median OS 3.5 of months [56]. In a retrospective analysis of 35 *EGFR*-mutant NSCLC patients with acquired resistance to conventional doses of erlotinib and LM, high-dose erlotinib (200 mg on alternate days, 300 mg on alternate days, 300 mg every 3 days, 450 mg every 3 days, or 600 mg every 4 days) gave 30% of radiological response, 50% of neurological symptoms improvement and a median survival from LM diagnosis of 6.2 months, along with grade 3–4 toxicities. Unfortunately, no significant OS difference was observed between high-dose erlotinib and those without [54]. This lack of survival improvement with high-doses EGFR TKIs compared with standard doses has been also reported in a recent retrospective cohort (2.4 months versus 3.1 months, $p = 0.863$) [46]. However, despite no improvement in OS, this strategy can clearly be used to palliate LM-related neurological symptoms. Intermittent (pulsatile) high dose administration of erlotinib (1500 mg/week) achieves a higher CSF concentration than standard dosing, and it also successfully controlled LM with a median survival of 12 months [55,57].

Both gefitinib and erlotinib showed efficacy in LM. However, compared to gefitinib, erlotinib showed higher CSF concentrations (28.7 versus 3.7 ng/mL, $p = 0.0008$) and penetration levels (2.77 versus 1.13%, $p < 0.0001$) [58]. In addition, a retrospective study reported, higher cytologic conversion rates have been reported with erlotinib compared to gefitinib (64.3% versus 9.1%, $p = 0.012$) [59]. Also, erlotinib could overcome LM appearing during gefitinib therapy [60]. Finally, in another retrospective cohort, erlotinib as treatment for LM developed during gefitinib treatment among *EGFR*-mutant patients ($n = 34$) achieved a response rate of 65% and median survival of 9.5 months, suggesting that treatment with another EGFR TKI is an option when LM are diagnosed [6].

Afatinib, a second-generation EGFR TKI, is also effective for managing brain metastases and LM. In a combined pre-specified subset analysis of two randomized phase III trials, the progression-free survival was significantly improved with afatinib versus with chemotherapy in patients with asymptomatic brain metastases (8.2 versus 5.4 months; HR, 0.50; $p = 0.0297$). Approximately 30% of patients with brain metastases had previously received radiotherapy [61]. Also in a cohort of pretreated NSCLC patients with brain metastasis or leptomeningeal disease, median time to afatinib failure for patients with CNS metastasis (metastases or LM) was 3.6 months, which did not differ from a matched group of patients without CNS metastases. In addition, a 35% rate of cerebral responses were reported, providing overall support for afatinib activity in intracranial disease [62]. Recently it has been reported that the median CSF penetration rate of afatinib was 1.65% with higher efficacy of afatinib in patients harbouring uncommon EGFR-mutations such as exon 18 mutations [63].

In *EGFR*-mutant NSCLC patients with LM, the limited number of patients, the use of ITC and WBRT prescribed in some patients are confounding factors. Given the absence of head-to-head comparisons among gefitinib, erlotinib, and afatinib, the optimal dose and schedule of EGFR TKIs remains unclear, and there are no clear predictive-factors for high-dose EGFR TKI. It is likely that doubling doses of erlotinib will impact outcome in these patients. An observational study is underway to identify predictive biomarkers for LM in *EGFR*-mutant NSCLC patients and establish the most appropriate EGFR TKI treatment among this population (NCT02803619). It is not clear whether ITC should be applied to *EGFR*-mutant NSCLC patients with LM as standard treatment concomitant to EGFR TKI. However, based on the recent data, ITC should be discussed as a potential therapeutic strategy in *EGFR*-mutant patients.

The substitution of threonine to methionine at amino acid position 790 (*T790M*) in exon 20 of the *EGFR* gene is the most frequent mechanism of acquired resistance in *EGFR*-mutant NSCLC patients treated with EGFR TKIs, accounting for 49–63% of cases depending on the detection method. [64–66].

Osimertinib (AZD9291) is a third-generation oral EGFR TKIs [67], recently approved by both the FDA and the EMA at 80 mg daily in patients with acquired EGFR *T790M* mutations. Preclinical data demonstrated greater penetration and brain exposure with osimertinib than with gefitinib, rociletinib or afatinib [68], suggesting that it may be an effective treatment for LM [69].

Preliminary results from the phase I BLOOM trial have reported long-lasting clinical and radiological activity of osimertinib at 160 mg among 21 EGFR TKI pre-treated *EGFR*-mutant NSCLC patients with LM (confirmed by CSF cytology) and controlled extra cranial disease [70]. The ongoing phase II BLOOM study (NCT02228369) is enrolling *T790M* positive (tested in plasma or tissue) NSCLC patients and LM. However, *T790M* status in an individual patient can be spatiotemporally heterogeneous because of selective pressure from EGFR-TKIs. In a recent study, among 12 thoracic *T790M*-positive tumours with CNS progression including LM, 10 were CNS-*T790M*-negative [71]. This could be explained by the fact that intact blood-brain-barrier inhibits penetration of EGFR TKI into the CNS, and *T790M*–mutation resistance could not be detected in the tumor cells from the CSF.

Today, it is unknown whether development of LM in *T790M*-positve NSCLC patients receiving osimertinib at 80 mg daily could be overcome by doubling the osimertinib dose. This strategy of isolated CNS progression (not LM) on osimertinib 80 mg daily is being investigated in an ongoing phase II clinical trial (NCT02736513).

Three phase II trials have reported improved outcome with the combination erlotinib-bevacizumab [72,73] and gefitinib-bevacizumab [74] as first-line treatment in the Asian and Caucasian population. Based on the increased VEGF levels in CSF of patients with LM [30,31] the combination of osimertinib and bevacizumab may delay or overcome neurological progression in *EGFR*-mutant NSCLC patients. This strategy is being tested in an ongoing clinical trial (NCT02803203).

While effective treatment is lacking due to limited blood-brain-barrier penetration of currently available EGFR TKIs, new compounds are expected. The unbound brain-to-plasma ratio, termed $K_{p,uu}$ is a measurement of brain penetration potential. When $K_{p,uu}$ is near to 1, the compound is at distribution equilibrium between the plasma and the brain compartments. When $K_{p,uu}$ is less than 1, a compound is a substrate for an efflux transporter and / or brain penetration is limited by low passive permeability across the blood-brain-barrier [75]. AZD3759 is a new EGFR TKI against sensitizing *EGFR* mutations but not the resistant *T790M* mutation, with significantly higher penetration across the blood-brain-barrier ($K_{p,uu,brain} = 0.86$) compared with other available EGFR TKI ($K_{p,uu,brain} < 0.2$ for erlotinib and gefitinib, and $K_{p,uu,brain} \sim 0.39$ for osimertinib) [76]. In a recent phase I trial (NCT02228369), AZD3759 (200 mg twice daily) demonstrated encouraging efficacy among 29 pretreated *EGFR*-mutant NSCLC patients with CNS progression including LM confirmed by CSF positive cytology [77].

Preliminary results with osimertinib 160 mg and AZD3759 for LM suggest efficacy of these treatments, however, it is unknown which of these treatments is better and whether sequential treatment could be appropriate according to the *T790M*-status in CSF.

ALK rearrangement

ALK rearrangements result from inversions or translocations on chromosome 2 and occurs in approximately 5% of advanced adenocarcinoma lung cancer patients independently of ethnicity [78]. The incidence of LM among *ALK*-positive NSCLC patients is

5% and the interval from NSCLC diagnosis to development of LM is relatively long (approximately 9 months), suggesting that LM is a late complication [79].

Crizotinib is a TKI that targeting *ALK*, *ROS* and *MET* based on two randomized phase III trials and is the standard first-line [80] and second-line treatment [81] in *ALK*-positive NSCLC patients.

ALK-positive NSCLC patients are associated with a relevant incidence of CNS metastases, affecting approximately 35–50% of patients [82,83]. Currently is not clear whether this increased risk is an expression of the natural disease course independent of the therapy received, or as in *EGFR*-mutant NSCLC patients, is related to low CSF penetrance of ALK TKIs. Crizotinib has poor CNS penetration, with a CSF-to-plasma ratio of 0.026 [84]. Although the efficacy of crizotinib for the CNS lesions remains controversial, a recent retrospective investigation of *ALK*-positive NSCLC patients with brain metastasis enrolled in the PROFILE 1005 and PROFILE 1007 studies [85] as well as the PROFILE 1014 [86], demonstrated that crizotinib is associated with a high disease control rate for brain metastasis. However, brain metastasis comprises the most common site of progressive disease with crizotinib in patients with or without baseline brain metastasis. Two cases reports noted the efficacy of crizotinib with or without intrathecal methotrexate for treating LM in *ALK*-positive NSCLC patients [8,87]. However, the relative contribution of crizotinib versus methotrexate on treatment effects is unclear. Taken together, these results support the need for more potent ALK TKIs, with improved CNS penetration, are awaited.

Ceritinib is a second-generation ALK inhibitor that is 20 times as potent as crizotinib and is effective in ALK-positive patients who progress while on crizotinib, including patients with brain metastasis [88]. The efficacy of ceritinib in the CNS in crizotinib-pretreated patients has been confirmed in the phase II ASCEND-2 trial [89]. Based on this efficacy in brain metastatic patients, an international prospective phase II open-label study specifically evaluating the antitumor activity of ceritinib in patients with *ALK*-positive NSCLC that is metastatic to the brain or leptomeninges is ongoing (ASCEND-7, NCT02336451).

Alectinib a highly selective ALK inhibitor has demonstrated activity in crizotinib-resistant patients with brain metastasis in a phase I/II trial [90] and in a recent phase III study, alectinib significantly improved progression-free survival over crizotinib as first-line treatment in *ALK*-positive Japanese NSCLC patients, and even in patients with brain metastasis ($n = 43$, $HR = 0.08$; [0.01–0.61]) [91], suggesting it could be a new standard treatment in this population. Specifically, alectinib demonstrated clinical activity in four *ALK*-positive and LM NSCLC patients previously treated with crizotinib and ceritinib. This activity is feasible on the basis of animal models, in which alectinib shows high brain-to-plasma ratios (0.63–0.94) and activity in intracranial tumor implantation models. In contrast to crizotinib and ceritinib, preclinical studies also suggest that alectinib is not a substrate of P-glycoprotein, a key drug efflux pump typically expressed in the brain-blood-barrier, suggesting that alectinib may have greater CNS activity than other ALK TKIs [92]. This is being addressed in the ongoing phase III AXEL trial (NCT02075840) evaluating first-line crizotinib versus alectinib in treatment-naive, *ALK*-positive NSCLC patients, enrolling patients with asymptomatic brain or leptomeningeal metastases. Moreover, time to CNS progression is a key secondary endpoint of the study, which may in turn provide important prospective data on the CNS antitumor activity of both agents.

Dose intensification of alectinib (900 mg twice daily) overcomes incomplete ALK inhibition in the CNS at conventional doses (600 mg twice daily) and prolongs the durability of responses in patients with CNS metastases, particularly those with leptomeningeal carcinomatosis [92], suggesting that dose intensification may be appropriated for *ALK*-positive patients with LM. However, this evidence is rather limited and should not be considered as standard.

Brigatinib (AP26113), an ALK-TKI, has shown a 67% of intracranial response and median PFS of 18.4 months in patients with active brain metastases [93,94] but its efficacy in LM is still unknown. However, the ALTA-1L trial (NCT02737501), which compares brigatinib versus crizotinib as first-line treatment in ALK-positive patients, may help to answer this question because LM is not an exclusion criterion.

Lorlatinib (PF-06463922), a selective and potent third-generation ALK and ROS1 TKI, has been recently developed and rationally designed to minimize P-gp-mediated drug efflux and optimize CNS penetration [95]. In preclinical models, it has shown antitumor activity in the CNS and has demonstrated strong activity against all known *ALK* resistance mutations identified in patients with crizotinib-resistant disease [96]. A phase I trial ($n = 54$) reported promising activity among *ALK*- and *ROS1*-positive NSCLC patients and brain metastases [97]. The ongoing phase II trial (NCT01970865) will evaluate the efficacy of lorlatinib among treatment-naïve and pretreated *ALK*- and *ROS1*-positive NSCLC patients, and patients with LM are eligible for this trial.

There is not yet enough patient experience to define separate guidelines for *ALK*-rearranged LM, but treatment with alectinib or a first-generation ALK TKI with concurrent ITC are likely to be the most effective option.

Other molecular alterations: HER2 and BRAF mutations

HER2 mutations are reported in 1–2% of lung adenocarcinomas. In the EUHER2 cohort, 6% of *HER2*-positive adenocarcinoma patients reported brain metastasis, but incidence of LM among this subpopulation is unknown [98]. In breast cancer, *HER2* status is not associated with an increased risk of developing LM [99]. Although anti-HER2 therapies, such as the humanized monoclonal antibody trastuzumab, combined with chemotherapy seem to have a positive impact on the outcome of *HER2*-mutant NSCLC patients [98], the role of trastuzumab for treating LM is limited due to its molecular size of 185 kDa [100] (blood-brain-barrier limits penetration of molecules >200 kDa into the CNS), with a serum:CSF trastuzumab ratio in breast cancer patients with brain metastasis of 420:1 prior to radiotherapy [101]. Investigation of intrathecal trastuzumab for LM is thus underway, notably among *HER2*-positive breast cancer patients [102]. In a recent pooled analysis ($n = 17$), intra CSF-trastuzumab was administered at varying doses (5–100 mg) with clinical and cytological success in *HER2* positive breast cancer patients [99], suggesting it is a promising treatment for LM among *HER2*-positive cancer patients. This strategy is ongoing in a phase I/II trial (NCT01325207) in breast cancer patients. However, further studies are warranted for defining the dose, the optimal schedule, combination treatments (with or without intrathecal methotrexate) and standardized response criteria. Intrathecal methotrexate could probably be used as a rescue treatment concomitant to intra-CSF-trastuzumab in case of lack of response. Also, efficacy of this strategy in other patients than *HER2*-positive breast cancer patients merits further evaluation.

BRAF mutations have been described in 2–4% of lung cancers, especially adenocarcinoma, without ethnicity or gender predominance. The *V600E* mutation accounts for 50% of cases [103]. Vemurafenib, an oral selective inhibitor of BRAF kinase [104] and dabrafenib, another BRAF kinase inhibitor, in combination with trametinib, a MEK signaling downstream inhibitor [105] have reported efficacy in *BRAF* V600E-mutated pretreated NSCLC patients, but the limited number of patients with CNS disease does not allow firm conclusions to be drawn about the efficacy of these agents in this population. Among melanoma patients, activity of vemurafenib and dabrafenib has been reported in BRAF *V600E*–

mutated melanoma patients, including in melanoma patients with brain or leptomeningeal metastases [106–108]. In six melanoma patients treated with vemurafenib, low CSF vemurafenib penetration was reported (the mean ratio of CSF: plasma concentration rationwas 0.98 ± 0.84%), suggesting high inter-individual variability for vemurafenib diffusion into the CSF. This could be explained because vemurafenib is a substrate for P-gp and breast-cancer resistance protein, which can reduce penetration of vemurafenib into the CSF. Also, previous treatment, such as surgery and WBRT, may alter CSF-vemurafenib penetration [109]. More evidence is needed to confirm the role of BRAF TKI at standard doses and/or combined with ITC in *BRAF*-mutant cancer patients with LM. Also the efficacy of these agents among non-*V600E BRAF*-mutant NSCLC patients is unknown.

Immunotherapy

Four randomized phase III, two with nivolumab [110,111], one trial with pembrolizumab [112] (both anti-PD-1 agents); and one trial with atezolizumab [113] reported that immunotherapy significantly improved survival compared to docetaxel in previously-treated patients advanced NSCLC patients, even among the subpopulation of patients with pre-treated brain metastases. The efficacy of immunotherapy among patients with symptomatic or untreated brain metastases is unknown. In a recent phase II trial [114], pembrolizumab was tested in 18 PD-L1-positive (>1%) NSCLC patients with at least one untreated or progressive brain metastasis between 5 and 20 mm in diameter without associated neurologic symptoms or the need for corticosteroids. A brain metastasis response was achieved in 33% of patients lasting at least 6 months. However, effectiveness of immunotherapy in cytologically confirmed and symptomatic leptomeningeal carcinomatosis is unknown. Recently, stabilization of asymptomatic leptomeningeal carcinomatosis for 10 weeks with nivolumab was reported in one patient [115]. Taken toghether, these data suggest intracranial activity of immunotherapy, however no predicitive factors are currently available and efficacy in molecularly-selected NSCLC patients is unknown.

Conclusions

LM is an increasing complication among cancer patients. Incidence of LM is 3.8% in the overall NSCLC population, and can increase to 9% in *EGFR*-mutant NSCLC patients. Prognosis remains poor, even with the use of personalized treatments, principally due to low penetration into the CSF of currently used TKI and cytotoxic agents. However, third generation EGFR and ALK TKIs have been developed with better brain-barrier penetration, which may have an impact as therapeutic strategies among molecularly-selected patients with LM. For unselected NSCLC patients a combination of systemic treatment and intrathecal chemotherapy is an appropriate strategy for treating LM. Also, further studies are warranted for defining the dose, the optimal schedule, combination treatments (with or without intrathecal methotrexate) and standardized response criteria in molecular selected and LM NSCLC patients.

Conflicts of interests

The authors declare don't have any conflict of interest.

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