Review Article

State of the art of chemotherapy for the treatment of central nervous system metastases from non-small cell lung cancer

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Contributions: (I) Conception and design: A Inno; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Chemotherapy is the mainstay of treatment of advanced non-small cell lung cancer (NSCLC) without molecular drivers. Despite a low penetration of central nervous system (CNS), chemotherapy drugs demonstrated encouraging activity against CNS metastases from NSCLC. Based on the available data, chemotherapy should be considered as an important part of the multidisciplinary treatment of CNS metastases. Particularly, platinum-based regimens represent the most active combinations and pemetrexed is associated with a meaningful clinical benefit for patients with non-squamous histology. How to integrate chemotherapy and radiotherapy for newly diagnosed brain metastases (BMs) is still debated. Although flawed by some limitations, the available evidence suggests a role for upfront chemotherapy for the treatment of NSCLC patients with synchronous, asymptomatic BMs, thus allowing a delay of radiotherapy. Despite the introduction of modern and more effective chemotherapy, however, the prognosis of NSCLC patients with CNS metastases remains poor, especially for those with progressive BMs or leptomeningeal carcinomatosis (LC).

Keywords: Chemotherapy; central nervous system (CNS); brain metastases (BMs); leptomeningeal carcinomatosis (LC); non-small cell lung cancer (NSCLC)

Submitted Jul 26, 2016. Accepted for publication Aug 22, 2016.
doi: 10.21037/tlcr.2016.11.01
View this article at: http://dx.doi.org/10.21037/tlcr.2016.11.01

Introduction

The development of central nervous system (CNS) metastases, including brain metastases (BMs) and leptomeningeal carcinomatosis (LC), represents a common event in the natural history of non-small cell lung cancer (NSCLC) (1). Among patients with NSCLC, 10–25% present with CNS metastases at the time of diagnosis and up to 50% will develop CNS metastases at some point during the course of their disease (2,3). The incidence of CNS metastases seems to have further increased over the last years (4), possibly due to a more widespread use of magnetic resonance imaging (MRI) leading to early diagnosis (5), and to the improved efficacy of systemic therapies in controlling extracranial disease and prolonging survival, therefore allowing CNS micro-metastases to grow and become clinically evident (6). Unfortunately, the development of CNS metastases has a negative impact on quality of life, resource utilization and survival of patients with NSCLC (7).

The optimal management of the individual patient with NSCLC and CNS metastases involves a multidisciplinary approach including supportive therapy, local therapies as surgery, stereotactic radiosurgery (SRS) and whole brain radiotherapy (WBRT), and systemic therapy (8).

Despite active treatments, prognosis of patients with NSCLC and BMs remains poor, with a wide heterogeneity

of outcomes depending on several prognostic variables (9-11). In 1997, the Radiation Therapy Oncology Group (RTOG) developed a prognostic index for NSCLC patients with BMs performing a recursive partitioning analysis (RPA) from a historical database of 1,200 patients treated with WBRT from three RTOG trials (12). Three prognostic classes were identified based on Karnofsky performance score (KPS), age, control of primary tumor and extent of extracranial disease with median survival ranging from 3.4 months for patients in class III (KPS <70) to 7.1 months for those in class I (KPS ≥70, age <60, controlled primary tumor and no extracranial disease) (12). Since then, several other scoring classifications have been developed (9,10,13,14). A comparative review of five of these prognostic tools (15) suggests that the lung-graded prognostic assessment (lung-GPA) index (10), which is based on KPS, age, presence of extracranial disease and number of BMs, may be the most powerful in predicting survival for patients with newly diagnosed CNS metastases from lung cancer. Generally the prognostic class and the number of BMs guide the clinical decision-making. For patients in RPA class III the best supportive care is a reasonable option (16). For patients in class I/II, WBRT is usually offered to patients with more than three BMs and SRS is the preferred treatment of 2 to 3 BMs, whereas single brain metastases can be treated either by surgery or SRS with equal results for appropriately selected patients (16).

Recent advances in the understanding of NSCLC biology, along with the development of highly active targeted drugs for tumors with a specific genetic alteration, have helped to redefine the prognosis of NSCLC patients with BMs (17). Target therapy, however, is restricted to the minority of patients with NSCLC harboring a druggable molecular target, whereas for most patients with advanced NSCLC chemotherapy still represents the cornerstone of systemic therapy. This review focuses on the role of chemotherapy for the treatment of CNS metastases from NSCLC and how to integrate chemotherapy into a multidisciplinary approach.

The over-rated importance of the blood-brain barrier

The role of chemotherapy for the treatment of CNS metastases from NSCLC has been neglected for years because of the prevailing belief that chemotherapeutic drugs cannot cross the blood-brain barrier (BBB) (18). The BBB is composed by a monolayer of specialized endothelial cells connected by tight junctions, surrounded by a basement membrane and characterized by absence of fenestration, thus being a highly selective barrier separating systemic circulation from cerebrospinal fluid (CSF) (19). BBB maintains CNS homeostasis by enabling the transport of selected substances necessary for the brain, while blocking most other molecules, including toxic metabolites and xenobiotics (20). Free diffusion of molecules across the BBB requires both lipophilicity and a molecular mass smaller than 0.5 kDa. Chemotherapy drugs are generally more than 150 kDa large, hydrophilic, and often protein-bound molecules, therefore unable to penetrate an intact BBB (21). Furthermore, chemotherapy drugs are often substrate of active efflux transport proteins, such as P-glycoprotein, which can be highly expressed by the BBB and it is responsible for the transport of compounds from the brain into the circulation (22). In fact, most chemotherapy agents have low CSF concentrations, with relevant liquor permeability reported only for temozolomide, methotrexate and topotecan (23-25).

However, there is growing evidence that the presence of macroscopic CNS metastases causes BBB disruption. This process is probably sustained by tumor neo-angiogenesis leading to new vessels that lack the structural and physiological features of normal BBB (26). The disruption of BBB in presence of CNS metastases is evidenced by peritumoral edema and accumulation of contrast media during MRI and computed tomography and, as more recently observed, penetration of CNS metastases by nuclear medicine tracers such as 18-Sodium Fluoride (27). This paradigm allows for the investigation of upfront systemic therapy in patients with macroscopic BMs. BBB disruption may be further enhanced by WBRT (28), thus favoring the passage of drugs into the brain and providing a biologic rationale for the use of concomitant or sequential chemo-radiotherapy.

Clinical activity of chemotherapy against BMs from NSCLC

Platinum-based doublets are the cornerstone treatment in the first-line setting for patients with metastatic NSCLC without molecular drivers (29). Although cisplatin and carboplatin have limited CNS penetration rates (3.7% and 2.6%, respectively), as reported by a pharmacokinetic study in nonhuman primates (30), they demonstrated clinical activity in newly diagnosed NSCLC patients with asymptomatic CNS metastases. Several clinical trials with

Table 1 Upfront platinum-based chemotherapy for BMs from NSCLC

Author (Ref.)	Regimen	No. of patients	IRR (%)	mOS (months)
Cotto *et al*. (31)	Cisplatin/fotemustine	31	23	5
Minotti *et al*. (32)	Cisplatin/teniposide	23	35	5.2
Franciosi *et al*. (33)	Cisplatin/etoposide	43	37	8
Fujita *et al*. (34)	Cisplatin/ifosfamide/irinotecan	30	50	12.7
Bernardo *et al*. (35)	Carboplatin/vinorelbine/gemcitabine	22	45	7
Cortes *et al*. (36)	Cisplatin/paclitaxel/vinorelbine or cisplatin/paclitaxel/gemcitabine	26	38	5.3

BMs, brain metastases; NSCLC, non-small cell lung cancer; IRR, response rate; mOS, median overall survival.

upfront platinum-based chemotherapy reported intracranial response rates (RRs) ranging from 23% to 50% (31-36) (*Table 1*). Interestingly, in these studies intracranial RRs were correlated with and almost comparable to systemic RRs (37). On the other hand, when temozolomide, a drug that for its small size and lipophilic properties is deemed able to cross the BBB, was administered in a phase 2 study to NSCLC patients with or without BMs as first-line treatment, no objective responses were observed in the brain nor in the lung (38). Taken together, these data suggest that effective cytotoxic drug combinations result in intracranial responses, and that the choice of upfront systemic chemotherapy should be based mainly on the established activity on the extracranial sites rather than on its theoretically expected ability to penetrate the BBB.

Epipodophyllotoxins etoposide and teniposide have been investigated as systemic therapy for NSCLC BMs. High dose etoposide (1.5 g/m^2 in six infusions over 3 days) administered to a heterogeneous population of patients with NSCLC or SCLC and BMs achieved an intracranial RR of 29% (39), but at the cost of high toxicity rates, mainly hematologic, with an unacceptable number of toxic deaths (40). Teniposide has comparable activity with a more favorable safety profile. A study of single agent teniposide on 13 patients with newly diagnosed or pretreated BMs from NSCLC reported intracranial objective response in 3 patients and neurological improvement in 7 patients (41). The addition of cisplatin to tenoposide translated into a RR of 35% including three complete responses in 33 patients with newly diagnosed NSCLC BMs, although the median overall survival (OS) was only 21 weeks (32). These data suggest a possible role of teniposide in the treatment of NSCLC BMs, but they are not conclusive due to the small sample size and non-comparative design of the studies.

Which chemotherapy regimen may represent the best choice for the treatment of asymptomatic BMs from NSCLC has not been clearly determined yet. In a randomized, phase 3 clinical trial comparing three different chemotherapy regimens (carboplatin plus gemcitabine, paclitaxel plus gemcitabine, or paclitaxel plus carboplatin), in the subgroup of 194 patients with clinically stable BMs (previously treated with surgery or radiation therapy), no chemotherapy regimen was proven to be superior to the others in terms of RR, time to progression and OS, regardless of histology (42).

More recently, the multi-target antifolate pemetrexed has demonstrated efficacy in the treatment of patients with advanced NSCLC, but its clinical benefit is limited to non-squamous histology (43,44). Based on results from phase 3 trials, pemetrexed is currently approved both in combination with platinum compounds in first line setting (43), and as single agent in maintenance or second line setting (45-47), for the treatment of patients with advanced, non-squamous NSCLC. Despite a penetration of CNS of less than 5% (48), pemetrexed demonstrated a consistent activity against BMs from NSCLC. One of the first evidence of pemetrexed activity against BMs came from a retrospective Italian study on 39 NSCLC patients with CNS metastases treated with pemetrexed as second or third line (49). Although the patients were unselected for histology, the study reported an intracranial RR of 30.8%, with clinical benefit obtained in 69% of patients (49). Subsequent studies demonstrated that the addition of platinum compounds to pemetrexed can slightly improve the outcome. In a phase 2 trial on 43 chemotherapy naïve NSCLC with BMs (93% with non-squamous histology) treated with pemetrexed and cisplatin at standard doses for six cycles, the intracranial RR was 41.9% (50). A comparable intracranial RR of 40% was obtained when pemetrexed was combined with carboplatin, as reported by an observational study on 30 patients with NSCLC adenocarcinoma and BMs (51) (*Table 2*).

Taken together, results from clinical trials consistently

Table 2 Pemetrexed for the treatment of BMs from NSCLC

Author (Ref.)	Regimen	Study design	Histology	Prior radiation	Prior chemotherapy	No. of patients	IRR (%)	mOS (months)
Bearz *et al*. (49)	Pemetrexed	Retrospective	NSCLC	Heterogeneous	Yes	39	38.4	10
Barlesi *et al*. (50)	Pemetrexed/cisplatin	Phase 2	93% NSq NSCLC	No	No	43	41.9	7.4
Bailon *et al*. (51)	Pemetrexed/carboplatin	Observational	Adenocarcinoma	No	No	30	40	9.7
Dinglin *et al*. (52)	Pemetrexed/cisplatin	Phase 2	Adenocarcinoma	Concurrent WBRT	No	42	68.3	12.6

BMs, brain metastases; NSCLC, non-small cell lung cancer; IRR, intracranial response rate; mOS, median overall survival; NSq, non-squamous; WBRT, whole brain radiotherapy.

showed that chemotherapy drugs, specifically platinum-based regimens, are active against BMs from NSCLC and that pemetrexed-containing regimens achieve high RRs in patients with non-squamous histology. It should be emphasized, however, that these studies have some important limitations, mainly because of the low number of patients enrolled and the selection of patients with good prognosis, therefore the transferability of the results can be questionable. Recently, a *post-hoc* analysis of a large prospective observational European study on 1,564 patients with newly diagnosed advanced NSCLC receiving a platinum-based regimen as first-line treatment, showed that in the subset of 263 patients with BMs the median OS was 7.2 months, ranging from 5.6 months for those treated with cisplatin plus gemcitabine up to 9.3 months for those treated with platinum plus pemetrexed (53). Interestingly, only 34% of patients had previously received cranial radiotherapy. Results from this real-life study were comparable to those from the previously reported clinical trials and contributed to corroborate the role of chemotherapy for the treatment of NSCLC patients with newly diagnosed, asymptomatic BMs.

Concurrent chemotherapy and radiotherapy for BMs from NSCLC

WBRT is widely used for the treatment of multiple, inoperable BMs from NSCLC. Several clinical trials have evaluated the addition of chemotherapy to WBRT in order to improve the outcome.

A randomized, phase 3 trial compared WBRT versus WBRT plus concurrent carboplatin in treatment-naïve patients with NSCLC and BMs. There was no significant difference between the two treatment arms in terms of RRs (10% and 29% in the radiotherapy alone arm and in the combined treatment arm, respectively) and OS (4.4 and 3.7 months in the radiotherapy alone arm and in the combined treatment arm, respectively), although no definitive conclusions could be driven from this study because it was closed early due to poor accrual, after the enrolment of only 42 patients (54).

Two randomized, phase 2 trials compared temozolomide plus WBRT with WBRT alone in previously untreated patients with BMs from different tumors, primarily lung cancer. Both studies reported an improvement in RRs with the combined treatment, but no significant differences were observed in terms of OS (55,56). Similarly, results from a randomized phase 3 trial, closed early due to slow accrual after enrolment of 95 of 550 planned patients, showed no significant survival benefit from the addition of temozolomide to WBRT compared with WBRT alone, with enhanced toxicity in terms of nausea, vomiting, alopecia, fatigue, anorexia, and constipation (57). Therefore, the benefit of temozolomide plus WBRT remains unproven.

Single agent topotecan added to WBRT did not demonstrate improvement in OS when compared to WBRT alone in a randomized 3 phase trial on patients with BMs from lung cancer, both SCLC and NSCLC. Also for this study, the accrual was terminated early, after the enrolment of 96 of 320 planned patients, and the number of patients was too low to detect a small advantage with the combined treatment (58).

A meta-analysis of 19 clinical trials involving 1,343 patients with BMs from lung cancer reported that compared to WBRT alone, WBRT plus chemotherapy is more effective in terms of RR (OR 2.30; 95% CI: 1.79–2.98; P<0.001), with increased toxicity and no available data on long-term survival (59). The authors of a Cochrane meta-analysis that included nine studies comparing WBRT alone versus WBRT plus chemotherapy concluded that the combination of WBRT and chemotherapy should be still considered an experimental approach (60).

Interestingly, a single-arm phase 2 study evaluated

safety and efficacy of cisplatin plus pemetrexed regimen combined with WBRT in 42 patients with BMs from lung adenocarcinoma, reporting an intracranial RR of 68.3%, intracranial PFS of 10.6 months and median OS of 12.6 months (52). Although these data are very promising, it is unclear whether WBRT in combination with cisplatin plus pemetrexed is more effective than WBRT alone or cisplatin plus pemetrexed alone, given the non-comparative design of the study.

Up-front chemotherapy or radiotherapy for BMs from NSCLC

How to sequence radiotherapy and chemotherapy in the context of newly diagnosed multiple BMs is still debated. In a phase 3 study, Robinet *et al*. (61) randomized 166 patients with NSCLC and BMs treated with cisplatin and vinorelbine to receive early WBRT (given concurrently with cycle 1 of chemotherapy) or delayed WBRT (administered in absence of intracranial response to chemotherapy). Although in the early WBRT arm a greater number of complete intracranial responses was observed (7 *vs*. 1), there was no statistically significant difference in terms of overall RRs, intracranial RRs, 6-month survival and OS between the two arms. These results suggest that the timing of WBRT do not influence survival of NSCLC patients with BMs receiving chemotherapy.

Another randomized trial (62) compared gemcitabine plus vinorelbine followed by WBRT versus the reverse sequence in 48 chemotherapy-naïve NSCLC patients with clinically silent BMs. Again, RRs and survival outcomes in the primary chemotherapy arm were no statistically different from those in the WBRT-first arm (overall RRs 28% *vs*. 31.1%, progression-free survival 3.6 *vs*. 4.4 months and OS 9.1 and 9.9 months). Importantly, safety profile of primary chemotherapy seemed more favorable than WBRT followed by chemotherapy. In fact, in the WBRT-first arm, grade 3 or 4 neutropenia was more frequent (79% *vs*. 40%) during chemotherapy and 4 patients (17.4%) did not receive further chemotherapy because of early death or poor performance after WBRT. Furthermore, a deterioration of quality of life parameters was observed when WBRT was given first. The authors also reported that, among 182 patients with NSCLC enrolled in different phase 2 trials with different chemotherapy regimens conducted by the same research group (63-65), 32 patients had BMs and were treated with chemotherapy alone without WBRT achieving a median OS of 10.6 months (62). Interestingly, 28% of them never received WBRT later in the course of their disease and their cause of death was progressive systemic diseases rather than progression of BMs with an OS of 11.3 months (62).

Although these studies are flawed by some limitations, mainly because of the low number of patients included, they all go in the same direction, suggesting that upfront chemotherapy with deferred WBRT is a reasonable option for NSCLC patients with multiple synchronous, asymptomatic BMs. In fact, this strategy has been endorsed as an option by the European Society for Medical Oncology (16).

Further data in support of upfront chemotherapy can be derived from retrospective studies. Results from a survey on 156 patients treated in six Italian oncologic centers (66) showed that there was no significant difference in brain response between the 110 patients treated with upfront chemotherapy (intracranial RR of 27%) and the 46 patients treated with WBRT followed by chemotherapy (intracranial RR of 35%). Another retrospective analysis included 129 patients with NSCLC and synchronous BMs (67). Among them, 57.8% received systemic chemotherapy only, 20% upfront WBRT followed by chemotherapy and 17.8% patients received upfront SRS and chemotherapy, with no significant difference in OS among the three groups (systemic chemotherapy alone, 13.9 versus upfront SRS followed by chemotherapy, 22.4 versus upfront WBRT followed by chemotherapy, 17.7 months, respectively; P=0.86).

The role of chemotherapy for the upfront treatment of patients with limited BMs is less clearly defined. Lim *et al*. randomized 105 patients with NSCLC and less than 4 BMs to receive SRS followed by a platinum-based doublet or a platinum-based doublet alone (68). Although the study included a smaller sample size than initially anticipated due to early termination, SRS followed by chemotherapy did not improve OS compared with upfront chemotherapy (median OS was 14.6 and 15.3 months in the SRS arm and upfront chemotherapy arm, respectively). Symptomatic progression of BMs was observed more frequently in the upfront chemotherapy group (26.5%) than the SRS group (18.4%), but without statistical significance. These results may suggest a role for upfront chemotherapy also in the setting of limited BMs. However, a recent secondary analysis of NSCLC patients with BMs and favorable prognosis according to lung-GPA suggested an improved survival with WBRT plus SRS versus SRS alone (69). This raises the question whether the combination of WBRT

plus SRS is superior to upfront chemotherapy in NSCLC patients with asymptomatic oligo-BMs.

Chemotherapy as salvage treatment for progressive BMs

Unfortunately, in pretreated patients, whether they were previously exposed to chemotherapy or radiotherapy, chemotherapy seems to play a more limited role. Single-agent temozolomide achieved a RR of 4–5% in patients who had previously received WBRT for BMs from different primary tumors, mainly NSCLC (70,71). The addition of vinorelbine to an intensive schedule of temozolomide did not increase the RR compared to previous studies with single-agent temozolomide at standard doses (72). Interestingly, among the 39 patients enrolled in the above reported retrospective study with single agent pemetrexed (49), in the subset of 22 patients with active BMs (either radiotherapy naïve or progressed after WBRT and before starting pemetrexed) pemetrexed obtained CNS partial response in five patients and stable disease in ten patients.

More recently, patupilone, which is a blood-brain barrier-penetrating, microtubule-targeting cytotoxic agent, was investigated in a phase 2 study on 50 patients with NSCLC and BMs. Among the patients enrolled in this study, 98% had received prior therapy for brain metastases. Paputilone showed a promising activity in such a heavily pretreated population: 36% of patients were progression-free at 9 weeks, with a median OS of 8.8 months and a 6-month survival rate of 65% (73).

The role of chemotherapy for the treatment of LC from NSCLC

LC occurs in approximatively 5–18% of patients with lung cancer, and more than 75% of cases are associated with adenocarcinoma histology (74). A retrospective analysis indicated a poor median survival of only 3 months for patients with LC and no difference in survival for patients who received WRBT (75). A retrospective study of 149 NSCLC patients with cytologically proven LC identified poor ECOG performance status, high protein level of CSF and high initial CSF white blood cell count as predictive factors of poor prognosis in a multivariate analysis (76). In the treatment of LC, surgery and radiotherapy have only a limited role and they are mainly deserved for palliation of hydrocephalus or symptoms resulting from focal lesions, whereas intrathecal or systemic chemotherapy are more widely used (77). Although some retrospective studies suggested an improvement in symptomatic palliation and a survival benefit with intrathecal chemotherapy for LC (76,78), the optimal dose and schedule as well as the real efficacy of intrathecal chemotherapy remain elusive, due to the lack of large randomized clinical trials (74).

In a randomized study including 52 assessable patients (12 with lung cancer) intrathecal methotrexate and thiotepa obtained similar OS times (15.9 weeks for methotrexate and 14.1 weeks for thiotepa) and neither reversed fixed neurologic deficits (79). Another study evaluated 61 patients with LC (10 with lung cancer) and found a better median time to neurological progression for intrathecal liposomal cytarabine over intrathecal methotrexate (58 *vs.* 30 days, P=0.007), but not significant differences in median survival (105 *vs.* 78 days, respectively; P=0.15) (80). A multicenter phase 2 clinical trial investigated the activity of intrathecal topotecan for the treatment of LC in 62 patients (13 with lung cancer). The study showed a CSF clearance of malignant cells in 21% of patients, with an OS of 15 weeks (81). A combination of three intrathecal agents (methotrexate, hydrocortisone and cytosine arabinoside) was compared with single agent methotrexate in a randomized study on 55 patients with LC from different solid tumors (33 lung cancers). In this study, combination therapy was superior to single agent in terms of cytological response rate (38.5% *vs.* 13.8%, P=0.036) and OS (18.6 *vs.* 10.4 weeks, P=0.029), with manageable toxicity (82). However, other trials did not demonstrate superiority of intrathecal combination therapy over single-agent (83,84), therefore the role of a combination therapy remains uncertain. In addition to the most frequently used drugs, intrathecal administration of gemcitabine (85) or etoposide (86) has resulted in clinical activity in some case reports. Finally, a more recent prospective, single-arm study evaluated the efficacy and safety of intrathecal chemotherapy (methotrexate) combined with concomitant involved-field radiotherapy in 59 patients with LM from various solid tumors (42 lung cancers) and showed an encouraging efficacy (RR of 86.4% and median OS of 6.5 months), with acceptable toxicity (87).

Prospective data on the efficacy of systemic chemotherapy in the treatment of LC from NSCLC are lacking. However, retrospective studies suggest a role for systemic chemotherapy in this setting. A retrospective analysis evaluating 50 patients with LC from NSCLC (96% of patients received intrathecal chemotherapy) showed that patients receiving systemic therapy such as chemotherapy or EGFR tyrosine kinase inhibitor (TKI) had prolonged

survival compared with those not receiving systemic therapy (11.5 *vs.* 1.4 months, P<0.001) (88). In another retrospective series of 30 patients, those receiving modern systemic therapy, defined as pemetrexed, bevacizumab or TKI, had decreased hazard of death (HR 0.24; P=0.007).

Conclusions

Chemotherapy is the mainstay of treatment for disseminated NSCLC without a druggable molecular target. Despite chemotherapy drugs have low penetration of CNS, they showed clinical activity against BMs from NSCLC. Platinum-based regimens represent the most active combinations, with high clinical benefit of platinum plus pemetrexed combinations for patients with non-squamous histology. How to integrate chemotherapy and radiotherapy is still debated. Although flawed by several limitations, the available evidence suggests that up-front chemotherapy may represent the treatment of choice for selected NSCLC patients with asymptomatic BMs, thus delaying the need for radiation therapy. Despite active chemotherapy, the prognosis of patients with NSCLC and BMs remains poor, particularly for patients with LC or progressive BMs. The development of effective drugs against NSCLC-derived BMs therefore represents an unmet clinical need. Unfortunately, NSCLC patients with BMs are often excluded from clinical trials (89) and more efforts should be done to investigate more explicitly the CNS benefit of new drugs.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Inno A, Di Noia V, D'Argento E, Modena A, Gori S. State of the art of chemotherapy for the treatment of central nervous system metastases from non-small cell lung cancer. Transl Lung Cancer Res 2016;5(6):599-609. doi: 10.21037/tlcr.2016.11.01

