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Clinical outcomes in intracranial and extracranial lesions with fist-line systemic therapies in patients with brain metastases from lung cancer.

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Abstract

Background: Lung cancer is the most common type of cancer to develop the Brain Metastases (BM), along with poor prognosis. This study evaluated the responses of different courses of fist-line systemic therapies including single chemotherapy and targeted agents or their combination for intracranial and extracranial lesions in patients with BM from lung cancer.

Patients and methods: Twenty patients, diagnosed with lung cancer with BM and received fist-line chemotherapies, targeted agents or their combination, were retrospectively analyzed between 2010 and 2016. Treatment responses of intracranial and extracranial lesions after 2, 4 cycles of systemic therapies were assessed respectively.

Results: Twenty patients were evaluated for treatment responses. After 2 cycles of therapies, fourteen patients had simultaneously assessable intracranial and extracranial lesions. No significant difference was observed between intracranial and extracranial lesions (Z=1.000, P=0.317). The results revealed similar efficacy (Z=0.000, P=1.000) of intracranial and extracranial lesions after 4 cycles of therapy, but there were only nine patients remaining evaluated. Besides, there were consistency efficacy (Z=0.905, P=0.366) of intracranial and extracranial lesions after 2-4 cycles of therapy.

Conclusion: Fist-line systemic therapies seem to achieve similar efficacy and responses between intracranial and extracranial lesions in lung cancer patients with BM. Further studies will be needed to confirm the treatment responses between intracranial and extracranial lesions and their underlying mechanisms.

Keywords: Lung cancer, Brain metastases (BM), Fist-line chemotherapies, Targeted agents, Intracranial and extracranial lesions.

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Introduction

Lung cancer, the leading cause of cancer-related death around the world, is characterized by a high incidence of solid tumor-related Brain Metastases (BM), with approximately 40% patients developing BM at some point during their disease course [1-3]. The rising incidence of BM is related to the better treatment of systemic disease, the consequent prolonged survival and the improvement in neuroimaging in detecting smaller lesions. BM is a significant cause of morbidity and mortality, with 4 to 5 months of median survival time [4]. Whole Brain Radiotherapy (WBRT) is the standard care for patients presented with BM, but the prognosis is poor [5]. Compared with WBRT, surgery combined with WBRT and stereotactic radiosurgery have been demonstrated to ameliorate survival. Nevertheless, this approach is only available for a small and selected subgroup of patients with solitary lesions and inactive extracranial disease. Thus, more effective treatments are urgently needed.

There are controversies in the role of systemic chemotherapy because of the weak penetration of most potential agents

beyond the Blood Brain Barrier (BBB), which may not have efficacy against the tumor that metastasized to the brain. However, clinical studies revealed comparable responses on intracranial lesions and extracranial lesions in breast cancer and germ cell tumor [6,7]. In the meantime, several studies have demonstrated that some chemotherapeutic agents seems to be candidates for treating BM in small-cell lung cancer, and can cause the recovery of intracranial lesions [8-10]. Concerning NSCLC occupied the majority of lung cancer, only a few clinical trials have reported the activity of cisplatin in BM [11]. Cortes et al. reported the efficacy of vinorelbine or gemcitabine combination with intracranial response rate in 38% of patients [12]. Moreover, a series of case reports suggest that gefitinib, the Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs), has clinical activity on brain metastases of NSCLC [13-16]. In fact, these activities are considered to be attributed to partial disruption of the BBB in BM [17,18].

Although the activities of some systemic therapies against BM from lung cancer have been documented, the knowledge about the effectiveness or response of BM with fist-line systemic therapies aiming at primary lung tumor is still insufficient. On the basis of the available clinical date, we carried out a retrospective study to assess the anti-tumor efficacy and responses on intracranial and extracranial lesions of primary lung tumor in lung cancer patients with BM during different courses with fist-line systemic medicine therapies.

Patients and Methods

Patients

In this study, we retrospectively analyzed lung cancer patients with BM who received fist-line chemotherapies, targeted agents, or chemotherapies plus targeted agents between 2010 and 2016 at Dongguan People Hospital (Dongguan, People's Republic of China). The diagnosis of lung cancer was confirmed pathologically, and brain metastases were documented by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). 20 patients who met the above criteria were identified.

Clinicopathological data, including sex, age, histology, metastatic sites, therapies, and treatment responses by radiographic assessment were retrieved from patient's medical records.

Treatment and response assessment

All patients enrolled were either given alone fist-line chemotherapies, targeted agents, or chemotherapies plus targeted agents until disease progression, death, or unacceptable toxicity. Clinical outcomes in intracranial and extracranial were assessed by radiologic images from 2 to 4 cycles of systemic therapies until disease progression.

Tumor response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors, including Partial Remission (PR), Stable Disease (SD) and Progression Disease (PD) of the intracranial and extracranial lesions [19]. Tumor responses for intracranial and extracranial diseases were evaluated separately. The disease control rate for intracranial lesions and extracranial lesions were compared separately.

Statistical analysis

All tests and Confidence Intervals (CIs) were two-sided and the significance level of statistical analysis was defined as $P<0.05$. All statistical analyses were performed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

From January 2010 to December 2016, 20 lung cancer patients with BM were analyzed, of whom received fist-line chemotherapies, targeted agents, or chemotherapies plus targeted agents. The baseline characteristics of these 20 patients are summarized in Table 1. The median age of these patients was 63 y (ranged from 39 to 82 y). 9 patients were male and 11 were female. The lung cancer cases included 12 adenocarcinoma, 6 poorly differentiated carcinoma and 1 small cell carcinoma. RPA showed that 9 patients were in RPA class I, 4 in class II, and 7 in class III. Of the 20 patients, 4 patients only had intracranial lesion, while 16 had concurrent other metastases. 12 patients were treated with fist-line chemotherapy, 4 with fist-line targeted agents, and 4 had concomitant use of first-line chemotherapies and targeted agents.

Table 1. *Patient characteristics (n=20).*

Clinical variables	N	%
Age (Y)		
Median (range)	63 (39-82)	
<65	10	50
≥ 65	10	50
Sex		
Male	9	45
Female	11	55
Histology		
Adenocarcinoma	12	60
Squamous	0	0
Large-cell	0	0
Small cell	1	5
Poorly differentiated	6	30
NC	1	5
RPA class		
Class I	9	45

Class II	4	20
Class III	7	35
Presence of metastases		
Intracranial only	4	20
Intracranial+Extracranial	16	80
Number of locations involved		
1	4	20
2	5	25
3	6	30
4 or more	5	25
Medications		
First-line chemotherapies	12	60
First-line targeted agents	4	20
Fist-line chemotherapies+targeted agents	4	20

Evaluation of treatment responses

Clinical outcomes in intracranial and extracranial lesions after 2 cycles of first-line systemic therapies: Fourteen patients had simultaneously assessable intracranial and extracranial lesions after 2 cycles of therapy. The clinical outcomes were documented in Table 2. Lesions Partial Response (PR) was presented in 4 patients (30%), stable disease (SD) in 1 patient (10%) for both of intracranial and extracranial diseases. The disease control rate for intracranial lesions was 90% and 80% for extracranial lesions. No significant difference was observed between intracranial and extracranial lesions (Z=1.000, P=0.317).

Table 2. *Comparison of tumor response of intracranial and extracranial lesions after 2 cycles of treatment.*

Intracranial response	Extracranial response		
	PD	SD	PR
PD	0 (0.0%)	1 (10.0%)	0 (0.0%)
SD	1 (10.0%)	1 (10.0%)	1 (10.0%)
PR	2 (10.0%)	4 (20.0%)	4 (30.0%)

Diversity test, Z=1.000, P=0.317; PD: Progression Disease; SD: Stable Disease; PR: Partial Response.

Clinical outcomes in intracranial and extracranial lesions after 4 cycles of first-line systemic therapies: With respect to 4 cycles of therapies, nine patients had simultaneously assessable intracranial and extracranial lesions. The clinical outcomes were listed in Table 3. Four patients (30%) both had PR. 1 achieved PR on intracranial lesions, but SD extracranial lesions. While 2 achieved PR on extracranial lesions, but SD intracranial lesions the disease control rate for intracranial lesions was 88.8% and 77.7% for extracranial lesions. The results showed similar efficacy (Z=0.905, P=0.366) of intracranial and extracranial lesions after 4 cycles of therapies.

Table 3. *Comparison of tumor response of intracranial and extracranial lesions after 4 cycles of treatment.*

Intracranial response	Extracranial response		
	PD	SD	PR
PD	1 (11.1%)	0 (0.0%)	0 (0.0%)
SD	1 (11.1%)	0 (0.0%)	2 (22.2%)
PR	0 (0.0%)	1 (11.1%)	4 (44.4%)

Diversity test, Z=0.000, P=1.000; PD: Progression Disease; SD: Stable Disease; PR: Partial Response.

Clinical outcomes in intracranial and extracranial lesions after 2-4 cycles of first-line systemic therapies: Restaging imaging examination was performed after 2-4 systemic treatment. 14 patients had imaging scans available for assessment of response. The response rates were summarized in Table 4. According to RECIST criteria, 14 patients showed comparable tumor response: 4 both PRs, 1 both SDs and 1 both PDs. The disease control rate for intracranial lesions was 85.7%, and 64.3% for extracranial lesions. The outcomes indicated there was no significant difference of efficacy (Z=0.905, P=0.366) between intracranial and extracranial lesions with combination systemic therapy.

Table 4. *Comparison of tumor response of intracranial and extracranial lesions after 2-4 cycles of first-line systemic therapies.*

Intracranial response	Extracranial response		
	PD	SD	PR
PD	1 (7.1%)	1 (7.1%)	0 (0.0%)
SD	2 (14.3%)	1 (7.1%)	2 (14.3%)
PR	1 (7.1%)	2 (14.3%)	4 (28.6%)

Diversity test, Z=0.905, P=0.366; PD: Progression Disease; SD: Stable Disease; PR: Partial Response.

Discussion

Globally, Non-Small-Cell Lung Cancer (NSCLC) accounts for 80%-90% of all lung cancer cases [20]. Approximately 50% of brain metastases originate from NSCLC and their presence considerably worsens the prognosis of these patients [21]. To date, treatment of patients with advanced stages of lung cancer with BM remains a significant therapeutic challenge. Most of these patients present multiple, unresectable brain lesions, often combined with active systemic disease [11]. Whole Brain Radiotherapy (WBRT) is a standard treatment for BM when surgery or radiosurgery is not possible, but it may not be the optimal choice since it induces cognitive dysfunction and fails to improve cerebral progression-free survival [22,23]. As an alternative to WBRT, other therapeutic approaches may be available to treat BM. Recently research hotspots have been

focused on whether the use of fist-line systemic therapy initially responsible for primary lung tumor is also effective for BM.

It is well known that WBRT may accelerate the opening of the BBB and thereby improve penetration of chemotherapeutic agents or molecular targeted drugs into the brain [24]. Whereas in our retrospective study, none of patients had undergone WBRT prior to the drug administration. To our knowledge, this study firstly compared the changes of intracranial and extracranial lesions in lung cancer patients with BM after different course of therapy, who were received fist-line systemic therapies initially aimed at primary lung tumor. Our data showed interesting results that fist-line systemic therapies with 2 or 4 cycles of therapies aimed at primary lung tumor also provide activity against BM. Moreover, fist-line chemotherapies plus concomitant targeted therapy could effectively control intracranial lesions in lung cancer. In the results, there were no significant differences in our study between intracranial or extracranial response rates, no matter during 2 (Z=1.000, P=0.317) or 4 (Z=0.905, P=0.366) or 2-4 (Z=0.905, P=0.366) cycles of therapies.

Fist-line medicine therapy regimens in this study included platinum-based chemotherapy and targeted agents. For lung cancer patients with BM, platinum-based chemotherapy is often used as the first-line treatment [25]. Pemetrexed is currently approved as a first-line treatment for NSCLC, in association with platinum-based chemotherapy [21]. Interestingly, pemetrexed-based regimen can be effective against BM reported by a recent trial [26]. In our study, all patients received fist-line chemotherapies were platinum-based regimens, 4 of them were administrated pemetrexed in combination with platinum regimen. On the other hand, the other fist-line medicine therapy regimen EGFR-TKIs, the drugs with a small molecular weight targeting mutated *EGFR* genes, have been shown to be highly effective when administered systemically, as they are reported to be able to partly cross the BBB with improving penetration into the Central Nervous System (CNS) [27]. Moreover, a relatively high concentration of erlotinib was detected in the cerebrospinal fluid of patients with BM from NSCLC and the standard dose of erlotinib may be regarded as a treatment option for this patient population [28,29]. Several reports demonstrated that gefitinib, Erlotinib and icotinib are linked with a favourable response in lung adenocarcinoma with BM, particularly in cases harbouring EGFR mutations [30-34].

Few studies have assessed the effect of chemotherapy as fist-line treatment for BM from NSCLC, but several prospective trials in NSCLC patients have investigated the activity of first-line chemotherapy for BM from NSCLC, which has the response rates ranging from 23% to 50% for cisplatin containing combinations [11,12,35,36]. Compared with above reports of response rates, the response rates for BM in our study were relatively higher. Additionally, in our result, the response rates in intracranial diseases were higher than extracranial diseases after 2 (90% *vs.* 80%) and 4 (88.8% *vs.* 77.7%) cycles of systemic therapies respectively. The responses seem to be less impressive in the lung than in the brain, possibly because of the larger extra-cerebral lesions, and correlation with lymphangitis carcinomatosis, bone metastases, or pleural lesions. Whereas, there is another reason should be taken into account. Of note, patients in our study were selected for targeted therapy based on the likely phenotype associated with EGFR mutation. 4 patients received gefitinib, 2 received erlotinib and 1 received icotinib either mono-therapy or combination with fist-line chemotherapy. Zimmermann et al. reviewed that response rate of BM to EGFR-TKI in patients with NSCLC harbouring EGFR mutations reaches 60-100%, with a rate of complete response as high as 40%. Besides, 1 patient received bevacizumab, the recombinant monoclonal antibody targeting VEGF, with concomitant chemotherapy. The activity of fist-line platinum-based chemotherapy might also be improved by the addition of bevacizumab in NSCLC patients with BM and encouraging efficacy and acceptable safety results have been reported with this combination [37]. There was another possibility that tumor regression in the brain could be partially induced by concomitant steroids administration, which could not be excluded. Together with these, it may contribute to the results that response rates for BM were higher than other reports, and intra-cerebral response rates were higher than systemic rates. So far, less information has been available in some case reports about whether there is any correlation between the efficacy of fist-line medicine therapy for brain metastases and extracranial diseases. Particularly, the patients whose intracranial lesions showed partial remission were highly likely to remain PR in extracranial lesions with fist-line medicine therapy. The reason that why the intracranial response to fist-line therapy was similar with extracranial response is currently unexplained and further studies is recommended.

The BBB is consisted of microvascular endothelial cells, pericytes and perivascular astrocytic end-feet. Prevailing belief consider that systemic therapy for brain metastases has been hampered, while BBB prevents drugs from entering the cerebrospinal fluid through blood circulation and only permits small lipid-soluble molecules can permeate it [38]. Consequently, most chemotherapeutic agents do not cross the intact barrier, and the temozolomide, methotrexate and topotecan, whose relevant liquor permeability was known were also excluded in our study, because there were only a few regimens based on lipid soluble agents practically. It is reported that when brain parenchymal metastases reached at a given tumor size, accompanied by the required neovessels, the structure and function of the BBB would be disrupted, which might induce the drugs to pass through the brain parenchyma [39,40]. Similarly, animal experiment has revealed that BBB is partly damaged with a reduction of hampering drugs [41]. In general, the activities of fist-line systemic treatments against intracranial lesions are probably benefit from the disruption of BBB in the presence of BM.

Despite the classical concept of the BBB, in our study, 2-4 cycles fist-line therapies including chemotherapy and targeted therapy appeared to produce a 85.7% response rate in the brain, while this was not statistically significant compared with

64.3% response rate obtained by extracranial lesions. Our data supported the notion that fist-line systemic therapies retain their effectiveness in the treatment of BM, which also demonstrated that the BBB did not impede the effectiveness of systemic therapy to some extent. In this regard, it has been speculated that fist-line systemic therapies initially aimed at primary lung tumor may also exert clinical benefits for intracranial lesions in these patient population, which was in consistent with recent evidence that the chemosensitivity of the primary tumour characterize the response to systemic treatment of brain metastases [42]. Furthermore, a major protein constituent in the BBB is P-glycoprotein (P-gp), which pumps natural product chemotherapy drugs and toxins out of the CNS. Whereas in tumors with low intrinsic P-gp expression, such as SCLC, NSCLC, chemotherapy that is effective against the primary may also be effective against the brain metastasis [43]. In contrast, temozolomide, a lipophilic methylating drug penetrating the BBB to 30-40% of its plasma concentration, has only minor efficacy as a single agent in NSCLC, SCLC, and breast cancers [43]. Consequently, a good activity against the systemic disease, rather than the lipid solubility, of the therapeutic agents may play a more crucial role for determining the treatment efficacy of brain lesions.

Despite clinically significant findings, our current study did have some limitations. With limited statistical power due to small numbers, there were no significant difference in the response rates, and further analysis for subgroup could not be performed and the efficacy and response analysis in this study were of a descriptive nature only. Furthermore, our study did not report any toxicities or survival related with fist-line systemic therapy for lung cancer patients with BM which raise concern. Finally, this is a retrospective study. Further prospective study with lager number of patients is needed to confirm the results.

In conclusion, fist-line systemic therapies seem to achieve similar efficacy and responses between intracranial and extracranial lesions in lung cancer patients with BM. However, the clinical benefits of fist-line systemic therapies in lung cancer patients with BM require confirmation by further investigations.

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Conflict of interest

None.

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