Clinics in Oncology

Research Article
Published: 21 Jun, 2024

Stereotactic Radiotherapy Plus Anlotinib with or without Toripalimab in Newly Treated Non-Small Cell Lung Cancer Patients with Brain Oligometastatic-Metastases: A Prospective Study Multi-Cohort Phase Ib Clinical Study Trial

*Jia Ma[1], Jianping Bi[1], Guoliang Pi[1], Ying Li[1], Hanping He[1], Yanping Li[1], Shi H[1], Zeng F[1], Vivek V[2], Desheng Hu[1] and Han G[1]**

[1]Department of Radiation Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, China

[2]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, USA

Abstract

Lung cancer harbors the highest mortality in the world and China, which is a devastating disease to people and poses a huge burden to both families and society. At present, the main treatment methods of driver mutation-negative advanced Non-Small Cell Lung Cancer (NSCLC) are chemotherapy, immunotherapy, anti-angiogenic therapy, and radiotherapy etc. However, the treatment effect still cannot meet the needs, and the side effects of therapy are sometimes severe and several patients just can't struggle it. In this article, we propose a clinical trial in the NSCLC patients with brain metastasis. This is a single-center, multi-cohort phase Ib clinical trial (NCT05021328) that evaluates the safety and efficacy of combining immune checkpoint inhibition, angiogenesis pathway inhibitors, and Stereotactic Radiotherapy (SRT) in driver mutation-negative NSCLC patients with 1-5 brain metastasis (oligometastasis). The patients will be assigned into two cohorts: SRT of brain metastasis (35Gy/5fx) and concurrent anlotinib, or SRT (35Gy/5fx) plus concurrent anlotinib and toripalimab. After brain SRT, both groups will receive maintenance toripalimab combined with anlotinib for up to 1 year. The primary endpoints are safety and intracranial Overall Response rate (iORR). The secondary endpoints include intracranial progression-free survival, local control, overall survival, and the maximum response rate of lesions in non-irradiated areas, the distant effect of radiotherapy enhanced by toripalimab, quality of life, and cognitive function. It is hoped that this chemotherapy-free regimen will merit further investigation for brain metastases from NSCLC.

Keywords: Non-small lung cancer; Brain metastases; Stereotactic radiotherapy; Anlotinib; Toripalimab

OPEN ACCESS

Correspondence:
Guang Han, Department of Radiation Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China,

Received Date: *24 May 2024*
Accepted Date: *13 Jun 2024*
Published Date: *21 Jun 2024*

Citation:
Jia Ma, Jianping Bi, Guoliang Pi, Ying Li, Hanping He, Yanping Li, et al. Stereotactic Radiotherapy Plus Anlotinib with or without Toripalimab in Newly Treated Non-Small Cell Lung Cancer Patients with Brain Oligometastatic-Metastases: A Prospective Study Multi-Cohort Phase Ib Clinical Study Trial. Clin Oncol. 2024; 9: 2081.

ISSN: 2474-1663

Copyright *© 2024 Guang Han. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

Introduction

Lung cancer is the most common malignant tumor in China, accounting for 23.8% of all cancer deaths [1]. Non-Small Cell Lung Cancer (NSCLC) accounts for about 85% of all lung cancers, and 20% to 56% of NSCLC patients develop Brain Metastases (BMs) during disease progression [2,3]. Once BMs occur, prognosis remains very poor, and the natural survival time is only 2 to 3 months [4]. At present, Whole Brain Radiotherapy (WBRT) or Stereotactic Radiotherapy (SRT) is the most important method of BM management, but improvements in local control and survival are still required. In recent years, with the development and application of Tyrosine Kinase Inhibitors (TKIs), the prognosis of BM patients associated with driver mutations, such as Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK), Recombinant C-Ros Oncogene 1 (ROS1) has achieved breakthrough clinical benefits [5-7]; however, for patients without driver mutations, the prognosis remains very poor. Therefore, it is necessary to combine radiotherapy with other treatments to further improve the comprehensive therapeutic effect.

Current status of immunotherapy in BM

Immune Checkpoint Inhibitors (ICIs) and antiangiogenic drugs are now standard of care for

many settings of NSCLC. Macromolecular monoclonal antibody drugs can also successfully pass through the Blood-Brain Barrier (BBB) into the brain [8]. Some studies have shown that, compared to the primary tumor, BMs of NSCLC patients are relatively immunosuppressed. Tumor infiltrating CD8-positive T-lymphocytes, tumor associated macrophages, and inhibition of the expression of Vascular Cell Adhesion Molecule-1 may lead to reduced T cell infiltration in BMs [9]. Another research using high-dimensional single-cell approaches revealed that the composition of immune cells in brain tumors was tumor-specific, as brain metastases were characterized by higher infiltration of peripherally derived leukocytes, especially CD8+ T cells, thus brain metastases are relatively hot or active tumors that can be targeted by T-cell based immunotherapies [10].

In terms of the safety of immunotherapy for patients with BMs, a publication of 88 patients from CheckMate 017/057/063 showed that the safety of nivolumab was similar in patients with or without BMs. The Overall Survival (OS) was slightly longer in metastatic NSCLC patients with BM treated with nivolumab (8.4 months *vs.* 6.2 months), and the incidence of new intracranial lesions was slightly lower after 6 months (13% *vs.* 17%) [11]. A prospective study showed that in newly diagnosed NSCLC patients with brain metastases (PD-L1 ≥ 1%), 10 mg/kg pembrolizumab was administered twice a week. Eleven of 37 NSCLC patients (29.7%) of brain metastases were relieved, and this treatment were safe and tolerable [12].

Ahmed and colleagues analyzed 17 NSCLC patients (49 BM sites) who received brain radiotherapy combined with pembrolizumab/durvalumab [13]. The 6- and 12-month OS after combined treatment reached 81% and 51%, respectively. The study also found that if radiotherapy was given before/during immunotherapy, the intracranial distant metastasis control rate was 57% after 6 months, compared to 0% if immunotherapy was given before radiotherapy. Another retrospective study analyzed the efficacy of 260 patients with BM (157 NSCLC patients) who received Stereotactic Radiosurgery (SRS). The median OS of patients receiving SRS/SRT alone (n=181), SRS/SRT plus immunotherapy (n=27), and SRS/SRT with sequential immunotherapy (n=51) was 12.9, 24.7 and 14.5 months, respectively, and the median number of subsequent brain metastases was 4, 2, and 4 respectively [14]. Lastly, Wu et al. [15] studied the efficacy of radiotherapy combined with immunotherapy in various metastatic organs of NSCLC. Through the combined analysis with hematological indexes, it was revealed that the brain was associated with the best immune activation effect and prognosis (ORR 49%).

Current status of anti-angiogenesis therapy in BM

Angiogenesis is mainly mediated by the Vascular Endothelial Growth Factor (VEGF) pathway. A complex process, it plays an important role in maintaining the tumor microenvironment, promoting tumor growth, and metastasis [16].

Antiangiogenic drugs, especially the small molecular multi-target receptor TKIs (such as apatinib, alotinib, etc.) offer several advantages to NSCLC and BM. Preclinical data show an interaction between the angiogenesis pathway and radiation-induced injury. From experiments in some tumor cell lines, there may be a dose-effect relationship between radiation dose and VEGF level. Inhibiting the expression of VEGF can significantly inhibit the hypoxia of tumor cells, thereby increasing the radiosensitivity of tumor cells and improving efficacy [17]. This synergistic effect has been confirmed in many other tumor cell lines [18]. A retrospective study of apatinib combined with brain radiotherapy conducted by our research team showed that apatinib combined with brain radiotherapy (whole brain 37.5 Gy, boost to 52.5 Gy) was a safe and effective method for the treatment of NSCLC patients with BM. This treatment model yields high intracranial progression free survival (median 16.5 months) and the overall survival (median 26 months) [19]. At present, a clinical trial evaluating the aforementioned paradigm is underway [20].

Anlotinib is a new small molecular multi-target receptor TKI, approved for the treatment of advanced NSCLC, recurrent refractory Small Cell Lung Cancer (SCLC), and advanced soft tissue sarcoma in China. Subgroup analysis of the ALTER0303 and ALTER1202 studies showed that anlotinib has brain activity, can effectively delay the progression of intracranial lesions, and does not cause an increased rate of cerebral infarction/hemorrhage over placebo [21-23].

Anti-VEGF combined with ICI, on the one hand, anti-angiogenic drugs can reverse VEGF-induced immunosuppression by promoting antigen presentation, activating cytotoxic CD8+ T cells, promoting lymphocyte infiltration and migration [24-27]. On the other hand, ICIs can normalize tumor vessels by activating effector T cells and upregulating the secretion of Interferon-γ (IFN-γ), thus potentiating the efficacy of anti-angiogenic drugs and enhancing the infiltration and killing function of effector T cells [28]. Chu et al. conducted a clinical trial (NCT03628521) to evaluate the first-line chemotherapy-free strategy of anti-PD-1 combined with anlotinib in the treatment of IIIB/IV stage NSCLC patients. Four of the 22 patients had BM at baseline. The ORR was 73% and DCR was 100% [29]. Another real-world retrospective study included 69 NSCLC patients to explore the efficacy of ICIs combined with antiangiogenic therapy. The results suggested that early use of ICIs combined with antiangiogenic drugs was more effective in patients with BM [30]. Therefore, the use of anti-vascular small molecule TKIs combined with ICIs is also a highly active area of research in the treatment of BM.

With regard to radiotherapy, a publication found that combining radiotherapy (particularly SRS) and ICIs can significantly improve the Local Control Rate (LCR) of intracranial metastasis, along with the potential to increase OS. A prospective study also showed that anlotinib combined with toripalimab can safely and effectively treat advanced NSCLC patients and improve survival [31,32]. However, there is no clinical study on the combination of anti-vascular therapy, immunotherapy, and SRT in the treatment of BM patients with mutation-negative NSCLC. Toripalimab is the first anti-tumor PD-1 monoclonal antibody independently developed in China, which has been approved for the treatment of melanoma, nasopharyngeal carcinoma, urothelial cancer, esophageal cancer, and NSCLC [33-36]. The combination of toripalimab and chemotherapy of first-line therapy has brought significant survival benefits and controllable safety for stage IV NSCLC without driver mutations.

Our proposed single-center phase Ib trial builds on the aforementioned clinical data by combining the three treatments (toripalimab combined with anlotinib and SRT) in NSCLC patients with BM. The aim of this clinical trial is to verify the effectiveness and safety of this combined treatment model, and lay the foundation for the development of follow-up large-scale clinical studies.

Patients and Methods

Objectives

The primary endpoints are early/late adverse reactions (1 month, 3 months, and 1 year after radiotherapy) and intracranial ORR (iORR). The secondary endpoints include intracranial Progression-

Free Survival (iPFS), OS, 1-year LCR, 1-year maximum response rate of unirradiated lesions, along with Quality of Life (QOL) and cognitive function assessment at 0, 1, 3, 6, 9, and 12 months.

Inclusion criteria

The trial will enroll NSCLC (diagnosed by pathology or histopathology) patients age ≥ 18 years old, ECOG score 0-1, and life expectancy longer than 3 months. Driver mutations are required to be negative (EGFR, ALK and ROS-1). Within 2 weeks of enrollment, MRI must confirm a total of 1 to 5 intracranial metastases that are suitable for linear accelerator-based SRT. Systemic disease status was allowed to be variable, including *de novo* treatment-naïve disease, or cases with prior therapy for NSCLC who relapsed with BM after 6 months. All patients had to have the ability to complete neurocognitive tests and QOL questionnaires independently, to sign written informed consent, and (patients of childbearing age) to use appropriate methods of contraception or surgical sterilization during and within 3 years after treatment.

Exclusion criteria

In addition to the lack of meeting the above criteria, additional ineligibility criteria were previous treatment history of CTLA-4, PD-(L)1, and/or VEGF targeted therapy. Contraindications to the study drugs include active autoimmune diseases that require hormone or immunomodulator treatment (*e.g.* rheumatoid arthritis, ankylosing spondylitis, type I diabetes, psoriasis, vitiligo, immune-associated thyroid dysfunction (except after normal hormone replacement therapy)); acute or chronic infectious diseases such as hepatitis B, hepatitis C, tuberculosis or HIV; and/or prior allergic reactions to components of the study drugs.

BMs located in the brainstem, leptomeninges, or other areas not suited for SRT were excluded. Patients actively participating in other interventional clinical studies were also not eligible (or with receipt of other research drugs or organ/bone marrow transplant within 4 weeks of enrollment). Previous history of head trauma, central nervous system and neurological defects, non-cancerous intracranial conditions such as cerebral infarction, intracranial vascular malformations, etc.; recent history of steroid treatment or active infection; alcohol or drug abuse; and diabetic patients with a history of frequent hypoglycemic attacks.

Treatment plan

This study was divided into two cohorts, each of which would enroll 5 patients.

Cohort A: SRT 35Gy/5fx (once a day) and concurrent oral anlotinib 12 mg d1-d14.

Cohort B: SRT 35Gy/5fx (once a day) combined with concurrent toripalimab 240 mg d1, and concurrent oral anlotinib 12 mg (d1-d14).

During the maintenance phase, each cohort was treated with toripalimab (240 mg d1 Q3W) and anlotinib (12 mg d1-d14 Q3W) for up to 1 year, unless the disease progressed, the toxicity was intolerable, the informed consent was withdrawn, or the researchers determined that the medication must be discontinued for other unforeseen reasons.

Statistical analysis

There was no similar prospective study data in the past to use for reference, so each cohort randomly enrolled 5 patients to determine the initial safety and efficacy, and to evaluate whether further exploration would be carried out in the expanded sample group.

Conclusion

The limited survival of driver mutation-negative NSCLC patients with BM highlight the urgency of elucidating alternative paradigms. This phase Ib trial (NCT05021328), which aims to recruit 10 patients, evaluates SRT and anlotinib with or without toripalimab. The main endpoints are safety and iORR. The secondary endpoints include iPFS, 1-year LCR, OS, and 1-year the maximum response rate of non-irradiated lesions, the distant effect of radiotherapy enhanced by toripalimab, and QOL & cognitive function. It is hoped that this chemotherapy-free regimen will merit further investigation for brain metastases from NSCLC.

Acknowledgement

This clinical trial was supported from National Natural Science Foundation of China (No. 82373197), Research Projects of Biomedical Center of Hubei Cancer Hospital (grant number 2022SWZX17), and CSCO Chaoyang Cancer Research Foundation Project (Y-Young2022-0325).

References

1. Xia C, Dong X, Li H, Cao M, Sun D, He S, et al. Cancer statistics in China and United States, 2022: Profiles, trends, and determinants. Chin Med J (Engl). 2022;135(5):584-90.
2. Wang P, Zou J, Wu J, Zhang C, Ma C, Yu J, et al. Clinical profiles and trend analysis of newly diagnosed lung cancer in a tertiary care hospital of East China during 2011-2015. J Thorac Dis. 2017;9(7):1973-9.
3. Sudmeier L, Tian S, Higgins KA. Multidisciplinary Management of brain metastases from non-small cell lung cancer in the era of immunotherapy. Curr Treat Options Oncol. 2021;22(9):77.
4. Park HS, Decker RH, Wilson LD, Yu JB. Prophylactic cranial irradiation for patients with locally advanced non-small-cell lung cancer at high risk for brain metastases. Clin Lung Cancer. 2015;16(4):292-7.
5. Camidge DR, Kim HR, Ahn MJ, Yang JCH, Han JY, Hochmair MJ, et al. Brigatinib versus Crizotinib in ALK inhibitor-naive advanced ALK-positive NSCLC: Final results of phase 3 ALTA-1L trial. J Thorac Oncol. 2021;16(12):2091-108.
6. Zhao B, Wang Y, Wang Y, Chen W, Zhou L, Liu PH, et al. Efficacy and safety of therapies for EGFR-mutant cancer with brain metastasis: An evidence-based pooled study of multivariable survival analyses. Aging. 2020;12(14):14244-70.
7. Schuler M, Wu YL, Hirsh V, O'Byrne K, Yamamoto N, Mok T, et al. First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. J Thorac Oncol. 2016;11(3):380-90.
8. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. Nature. 2015;523(7560):337-41.
9. Kudo Y, Haymaker C, Zhang J, Reuben A, Duose DY, Fujimoto J, et al. Suppressed immune microenvironment and repertoire in brain metastases from patients with resected non-small-cell lung cancer. Ann Oncol. 2019;30(9):1521-30.
10. Friebel E, Kapolou K, Unger S, Núñez NG, Utz S, Rushing EJ, et al. Single-cell mapping of human brain cancer reveals tumor-specific instruction of tissue-invading leukocytes. Cell. 2020;1626-42.e20.
11. Goldman JW, Crino L, Vokes EE, Holgado E, Reckamp KL, Pluzanski A, et al. Nivolumab (Nivo) in patients (pts) with advanced NSCLC and central nervous system metastases. J Clin Oncol. 2016;34(15_suppl):9038.

12. Goldberg SB, Schalper KA, Gettinger SN, Mahajan A, Herbst RS, Chiang AC, et al. Pembrolizumab for management of patients with NSCLC and brain metastases: Long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. Lancet Oncol. 2020;21(5):655-63.

13. Ahmed KA, Kim S, Arrington J, Naghavi AO, Dilling TJ, Creelan BC, et al. Outcomes targeting the PD-1/PD-L1 axis in conjunction with stereotactic radiation for patients with non-small cell lung cancer brain metastases. J Neurooncol. 2017;133(2):331-8.

14. Chen L, Douglass J, Kleinberg L, Ye X, Marciscano AE, Forde PM, et al. Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung cancer, melanoma, and renal cell carcinoma. Int J Radiat Oncol Biol Phys. 2018;100:916-25.

15. Wu M, Liu J, Wu S, Liu J, Wu H, Yu J, et al. Systemic immune activation and responses of irradiation to different metastatic sites combined with immunotherapy in advanced non-small cell lung cancer. Front Immunol. 2021;12:803247.

16. Manzo A, Montanino A, Carillio G, Costanzo R, Sandomenico C, Normanno N, et al. Angiogenesis Inhibitors in NSCLC. Int J Mol Sci. 2017;18(10):2021.

17. Sofia Vala I, Martins LR, Imaizumi N, Nunes RJ, Rino J, Kuonen F, et al. Low doses of ionizing radiation promote tumor growth and metastasis by enhancing angiogenesis. PLoS One. 2010;5(6):e11222.

18. Hoang T, Huang S, Armstrong E, Eickhoff JC, Harari PM. Enhancement of radiation response with bevacizumab. J Exp Clin Cancer Res. 2012;31(1):37.

19. Ma J, Bi J, Tuo X, Pi G, Li Y, Li Y, et al. Efficacy and safety of Apatinib combined with whole-brain radiation therapy with a simultaneous integrated boost for brain metastases from non-small cell lung cancer: A multicenter retrospective study. J Thorac Dis. 2022;14(2):455-63.

20. Ma J, Pi G, Bi J, Li Y, He H, Li Y, et al. Concurrent Apatinib and brain radiotherapy in patients with brain metastases from driver mutation-negative non-small-cell lung cancer: Study protocol for an open-label randomized controlled trial. Clin Lung Cancer. 2021;22(2):e211-4.

21. Han B, Li K, Wang Q, Zhang L, Shi J, Wang Z, et al. Effect of Anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: The ALTER 0303 phase 3 randomized clinical trial. JAMA Oncol. 2018;4(11):1569-75.

22. Cheng Y, Wang Q, Li K, Shi J, Liu Y, Wu L, et al. Anlotinib *vs.* placebo as third- or further-line treatment for patients with small cell lung cancer: A randomised, double-blind, placebo-controlled phase 2 study. Br J Cancer. 2021;125(3):366-71.

23. Jiang S, Liang H, Liu Z, Zhao S, Liu J, Xie Z, et al. The impact of Anlotinib on brain metastases of non-small cell lung cancer: Post hoc analysis of a phase III randomized control trial (ALTER0303). Oncologist. 2020;25(5):e870-4.

24. Long J, Hu Z, Xue H, Wang Y, Chen J, Tang F, et al. Vascular Endothelial Growth Factor (VEGF) impairs the motility and immune function of human mature dendritic cells through the VEGF receptor 2-RhoA-cofilin1 pathway. Cancer Sci. 2019;110(8):2357-67.

25. Voron T, Colussi O, Marcheteau E, Pernot S, Nizard M, Pointet AL, et al. VEGF-A modulates expression of inhibitory checkpoints on CD+ 8 T cells in tumors. J Exp Med. 2015;212(2):139-48.

26. Mauge L, Terme M, Tartour E, Helley D. Control of the adaptive immune response by tumor vasculature. Front Oncol. 2014;4:61.

27. Missiaen R, Mazzone M, Bergers G. The reciprocal function and regulation of tumor vessels and immune cells offers new therapeutic opportunities in cancer. Semin Cancer Biol. 2018;52(Pt 2):107-16.

28. Huang Y, Kim BYS, Chan CK, Hahn SM, Weissman IL, Jiang W. Improving immune-vascular crosstalk for cancer immunotherapy. Nat Rev Immunol. 2018;18(3):195-203.

29. Chu T, Zhong R, Zhong H, Zhang B, Zhang W, Shi C, et al. Phase 1b study of Sintilimab plus Anlotinib as first-line therapy in patients with advanced NSCLC. J Thorac Oncol. 2021;16(4):643-52.

30. Qiu L, Zhao X, Shi W, Sun S, Zhang G, Sun Q, et al. Real-world treatment efficacy of anti-programmed death-1 combined with anti-angiogenesis therapy in non-small cell lung cancer patients. Medicine. 2020;99(24):e20545.

31. Zhang L, Hao B, Geng Z, Geng Q. Toripalimab: The first domestic anti-tumor PD-1 antibody in China. Front Immunol. 2022;12:730666.

32. Enright TL, Witt JS, Burr AR, Yadav P, Leal T, Baschnagel AM. Combined immunotherapy and stereotactic radiotherapy improves neurologic outcomes in patients with non-small-cell lung cancer brain metastases. Clin Lung Cancer. 2021;22(2):110-9.

33. Wang Z, Wu L, Li B, Cheng Y, Li X, Wang X, et al. Toripalimab plus chemotherapy for patients with treatment-naive advanced non-small-cell lung cancer: A multicenter randomized phase III trial (CHOICE-01). J Clin Oncol. 2023;41(3):651-63.

34. Wang ZX, Cui C, Yao J, Zhang Y, Li M, Feng J, et al. Toripalimab plus chemotherapy in treatment-naïve, advanced esophageal squamous cell carcinoma (JUPITER-06): A multi-center phase 3 trial. Cancer Cell. 2022;40(3):277-88.e3.

35. Tang B, Yan X, Sheng X, Si L, Cui C, Kong Y, et al. Safety and clinical activity with an anti-PD-1 antibody JS001 in advanced melanoma or urologic cancer patients. J Hematol Oncol. 2019;12(1):7.

36. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, et al. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: A multicenter randomized phase 3 trial. Nat Med. 2021;27(9):1536-43.