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Mini-Review

Targeted Lung Cancer Treatments and Eye Metastasis

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ABSTRACT

Lung cancer remains the leading cause of death due to cancer. We do not have effective tools for the early detection of lung cancer, so patients are usually diagnosed at an advanced stage. However, novel therapies based on molecular pathways (such as those involving the epidermal growth factor receptor, anaplastic lymphoma kinase, serine/threonine-protein kinase B-Raf, proto-oncogene tyrosine-protein kinase ROS, c-Met proto-oncogene protein, and RET proto-oncogene protein) are now commonly used in the treatment of lung cancer. In particular, these therapies are considered as first-line treatments for non-small-cell lung cancer. This manuscript outlines previous research on these targeted treatments, focusing on whether they are effective against eye metastasis.

KEY WORDS

Lung cancer; Epidermal Growth Factor Receptor; Anaplastic Lymphoma Kinase; Serine/Threonine-Protein Kinase B-Raf; Proto-Oncogene Tyrosine-Protein Kinase ROS; C-Met Proto-Oncogene Protein; RET Proto-Oncogene Protein

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INTRODUCTION

Lung cancer remains underdiagnosed due to the lack of early-stage symptoms. Moreover, there are no blood markers for the early detection of lung cancer (unlike for cancers such as prostate, colorectal, and gynecological cancers) (1). In the past, non-specific cytotoxic agents were the first choice of treatment for patients with stage IV non-small-cell lung cancer (NSCLC; either adenocarcinoma or squamous cell carcinoma) (2, 3).

However, in the last decade, novel molecular pathways have been found to be involved in adenocarcinoma and squamous cell carcinoma of the lung, and, as a result, targeted treatments are now being used. The most important of these are the treatments that target the epidermal growth factor receptor (EGFR), anaplastic

lymphoma kinase (ALK), serine/threonine-protein kinase B-Raf (BRAF), proto-oncogene tyrosine-protein kinase ROS (which is encoded by the ROS1 gene), c-Met proto-oncogene protein (which is encoded by the MET gene), and RET proto-oncogene protein (which is encoded by the RET gene found on chromosome 10) (4, 5). An issue that has yet to be clarified is whether these targeted treatments are effective against eye metastasis. This issue is discussed in the following section, which is based on data that were obtained via a search of the US National Center for Biotechnology Information's PubMed service on February 19, 2017.

Overview of the Use of Targeted Treatments in Relation to Eye Metastasis

Currently, oral tyrosine kinase inhibitors (TKIs) are being used to treat EGFR- and ALK-positive patients. In particular, for EGFR-positive patients, erlotinib, gefitinib, and afatinib (the first two of which are first-generation TKIs that target EGFR, and the third of which is a second-generation TKI that targets EGFR) are the treatments of choice. If an EGFR-positive patient being treated with TKI experiences a relapse (as assessed using the Response Evaluation Criteria In Solid Tumors (RECIST) (6)), a rebiopsy should be performed (7). However, if the patient's condition does not allow for a rebiopsy, a liquid biopsy should be performed (8). In particular, if the EGFR T790M mutation is detected, osimertinib (a TKI that targets EGFR) should be administered (9).

Research indicates that gefitinib could be an effective agent against choroidal metastasis, and it should be used if such a metastasis exists (10). In the case of brain metastasis, research indicates that afatinib may be effective as a first-line treatment (11). Furthermore, a recent study showed that osimertinib was rapidly effective against brain metastasis, and it negated the need for radiotherapy (12).

Regarding patients with ALK mutations, crizotinib (a TKI that targets ALK) is used as the first-line treatment (13). In particular, crizotinib has been shown to be effective against uveal and choroidal metastasis (14, 15). The human epidermal growth factor receptor 2 (HER2) has been found to be overexpressed in patients with lung cancer (16) and, in these cases, trastuzumab (a monoclonal antibody that targets HER2) may be administered (17). Research has indicated that this drug is able to control ocular metastasis (18). However, it is important to take into consideration that fact that trastuzumab can also induce adverse ocular effects (19).

In addition to ALK mutations, BRAF mutations have been observed in patients with lung cancer (20). In these cases, the patients could be treated with ipilimumab (a monoclonal antibody that targets cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)). In particular, ipilimumab has been successfully used for uveal metastasis (20-24). However, orbital myositis and retinopathy have been observed in patients treated with ipilimumab (22, 23), and other immunotherapies such as nivolumab and pembrolizumab (both of which are monoclonal antibodies that target programmed cell death protein 1 (PD-1)) are currently being tested (20, 21).

In some patients with lung cancer, the ROS1 pathway has been found to be upregulated (25). In these cases, crizotinib should be administered (26). Furthermore, research has indicated that eye metastasis that involves ROS1 upregulation can be efficiently controlled with crizotinib (14). Alternatively, cabozantinib (a TKI that targets c-Met and vascular endothelial growth factor receptor 2 (VEGFR-2)) can be used in cases involving crizotinib resistance (27).

The RET pathway has also been found to be upregulated in some patients with lung cancer (25). In these cases, crizotinib (a TKI that targets ALK and ROS1) or alectinib (a TKI that targets ALK) should be administered (28, 29, 30) Cabozantinib may also be effective (31).

Lastly, the c-Met pathway has been also shown to be upregulated in some patients with lung cancer (32). Furthermore, a previous study has suggested that, in patients with melanoma, c-Met overexpression is associated with uveal metastasis, but more data are required to clarify this association (34). A previous study indicated that crizotinib is effective against uveal metastasis that involves the upregulation of the c-Met pathway in a melanoma model (15). However, for NSCLC, cabozantinib should be used in cases involving upregulation of the c-Met pathway (33).

DISCUSSION

Overall, the data on the use of TKIs or immunotherapy to control eye metastasis are limited. We recommend that if a patient experiences a cancer relapse, biopsies should be taken from the sites of relapse. We are currently waiting for trials with larger numbers of patients with BRAF, MET, RET, and ROS mutations. In these trials, data with the control of eye metastasis should be collected so that clear conclusions can be drawn regarding the optimum treatment approaches.

DISCLOSURE

Conflicts of Interest: None declared.

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