Perspective

Updating advances on recombinant human endostatin combined with radiotherapy for non-small cell lung cancer with brain metastasis

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Abstract: Brain metastases (BM) heavily affects the prognosis of advanced non-small cell lung cancer (NSCLC). Although whole-brain radiotherapy remains the mainstream therapy for BM caused by NSCLC, the effectiveness is unsatisfactory. Endostar, a recombinant human endostatin (RHES), has shown certain therapeutic effect on advanced NSCLC. This article reviews the feasibility of Endostar combined with radiotherapy in the treatment of BM caused by NSCLC.

Keywords: Recombinant human endostatin (Endostar); radiotherapy; brain metastases; non-small cell lung cancer

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Introduction

Brain metastases (BM) is a common complication of many malignancies and occurs in about 20-40% of the patients with extracranial malignant tumor. In the patients with BM, 18-64% are from lung cancer and 2-21% from breast cancer (1). The incidence of BM is about 40% in patients with non-small cell lung cancer (NSCLC), and the prognosis usually is poor, with a survival of 1-3 months (2). Many therapies including surgical management, chemotherapy, stereotactic radiotherapy, and molecular targeted therapy have been developed for BM, while whole brain radiotherapy (WBRT) remains the commonest method (3) due to its wide indications, quick response, and relatively high effectiveness rate (70-90%) (1,4). However, BM often recurs after radiotherapy (5), indicating that WBRT has certain limitations in the treatment of BM. About 30-50% of BM patients die of uncontrolled or recurrent intracranial lesions (6). In addition, BM is usually accompanied with brain edema (which leads to intracranial hypertension), while WBRT can induce edema in normal brain tissue. Therefore, new drugs should be actively developed to treat BM caused by NSCLC.

Endostar, a recombinant human endostatin (RHES), is a novel anti-tumor drug created by Chinese scientists. It can prevent vascular endothelial growth factor (VEGF) from binding with endothelial cells through vascular endothelial growth factor receptor (VEGFR), and thus blocks the effect of VEGF. Meanwhile, by directly downregulating the mRNA and protein expressions of VEGF, it can block the signal transduction of VEGFR and thus inhibit VEGF-mediated endothelial cell migration and angiogenesis (7).

Relationship between NSCLC-caused BM and VEGF

Many studies have denonstrated that tumor invasion and metastasis are positively correlated with VEGF over-expression (8). The growth of metastatic cancer is highly depended on the nutrition provided by neovessels in the new micro-environment (9). During the tumor neovascularity, intratumoral vascular endothelial cells undergo proliferation, migration, and angiogenesis; as a result, the formation, growth, invasion, and metastasis of tumors occur. BM is a typical blood vessel-dependent malignancy. It has been demonstrated that microvessel density is positively correlated with malignancy and prognosis in primary tumors (10). Many vasoactive factors including VEGF, basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) are involved, among which VEGF plays a key role in BM angiogenesis and growth and in the development of brain edema (11,12).

High expression of VEGF has been found in *in vitro*

incubated NSCLC cells, tumor-bearing mouse NSCLC models, and human NSCLC cells (13). VEGF expression is strongly associated with lymph node and distant metastasis, especially with BM, and the incidence of lymph node and distant metastasis is significantly increased in the patients with positive VEGF (14). Kopczynska *et al.* found (15,16) that higher serum VEGF level in the patients with NSCLC predicted more advanced cancer, wider range of infiltration, and more frequent metastasis.

Relationship between radiosensitivity and VEGF

Radiosensitivity is closely related to VEGF. When killing tumor cells, radiotherapy also induces high VEGF expression to protect endothelial cells from apoptosis (17,18). In addition, the existing blood vessels can not effectively provide oxygen due to rapid proliferation of tumor cells, leading to tumor cell hypoxia, which in turn promotes high expression of VEGF. The high expression of VEGF can cause angiogenesis. Tumor neovessels are very disordered and tortuous, and form larger capillaries, sinusoid and abnormal arteriovenous anastomosis, increasing futile cycling and aggravating tumor hypoxia (19). Hypoxia also induces VEGF expression, which further promotes tumor angiogenesis. The vicious cycle eventually leads to tumor resistance to radiotherapy. Lee *et al.* (20,21) have found that radiotherapy can induce VEGF secretion in a variety of malignant tumor cells.

Application and mechanism of anti-angiogenic drugs

Since angiogenesis plays an important role in BM, the role of anti-angiogenic treatment for BM has increasingly been studied. Many anti-angiogenic drugs with different mechanisms have been used in the treatment of BM.

Bevacizumab, a recombinant human anti-VEGF monoclonal antibody, mainly neutralizes VEGF to block its binding with VFGER on endothelial cells; by doing so, it not only inhibits tumor neovascularity but also relieves peritumoral edema (22). However, bevacizumab can also block many normal physiological effects of VEGF including repairing gastrointestinal mucosa, maintaining glomerular filtration, and protecting liver. Therefore, it may produce many adverse effects. Furthermore, the premature drug discontinuance may induce tumor progression, while long-term administration leads to high treatment cost (23) and more complications (24,25). As time goes on, tumor cells may produce other angiogenesis factors, which result in drug resistance. This process is quite similar to the "acquired drug-resistance" induced by cytotoxic chemotherapy. Therefore, more broader-spectrum angiogenesis inhibitors should be explored for long-term treatment of cancer.

Compared with bevacizumab, endostar, as a broad-spectrum angiogenesis inhibitor, has significantly less severe adverse effects such as bleeding and high blood pressure, and its efficacy seems not being affected by post-operative wound healing time. Animal experiments have indicated that endostatin extensively regulates the signal network of angiogenesis, inhibits more than 65% of tumor types, and midifies 12% of angiogenesis-associated human genome expression (26). Endostar, a negative regulatory factor of angiogenesis, can effectively inhibit endothelial cell activation to prevent neovascularization; however, it has certain effect on non-activated endothelial cells, and thus may produce limited adverse effects on the normal physiology of blood vessels. In a multi-center clinical study using endostatin combined with chemotherapy for the treatment of NSCLC in stage III/IV, the median time to tumor progression (TTP) was 6.3 months, which was significantly longer than that of chemotherapy alone (3.6 months); meanwhile, endostatin did not increase the adverse reactions of chemotherapy (27). Endostatin was included in *NCCN Non-small Cell Lung Cancer Clinical Prectice Guidelines* (Chinese Edition) in 2006. Endostatin combined with chemotherapy have been used in the treatment of recurrent and metastatic NSCLC.

Feasibility of Endostar combined with radiotherapy in the treatment of BM

Whether endostatin can be concurrently used in the patients receiving radiotherapy remains controversial. It is traditionally believed that therapies with vascular endothelial cells as the target points can destroy tumor vascular network, and thus aggravate hypoxia and decrease radiotherapeutic effectiveness. However, many laboratory studies have found that anti-angiogenic targeted therapy can increase radiotherapeutic effectiveness. In Ling *et al.'s* study (28), endostatin gene was transduced into pulmonary adenocarcinoma A549 cells with retrovirus as carrier, followed by radiotherapy; the results indicated that endostatin gene combined with radiotherapy had synergetic repression on angiogenesis and growth of pulmonary adenocarcinoma. LUO *et al.* (29) also confirmed that endostatin gene combined with radiotherapy showed certain efficacy for lung cancer.

What is the synergetic mechanism of endostatin and radiotherapy? The abnormal structure and functions of tumor neovessels can lead to tumor hypoxia. Hypoxia allows tumor become resistant to chemoradiation and make tumor invasion more severe. Jain *et al.* (30) found that angiogenesis inhibitors can allow tumor vasculature to normalize *in vivo*, and thus relieves tumor hypoxia. On one hand, angiogenesis inhibitors reduce the density of tumor vessels; on the other hand,

andgiogenesis inhibitors can improve blood supply, relieving tumor hypoxia. These inconsistent changes are resulted from the elimination of immature tumor vessels and the decrease in cellular oxygen consumption and vascular permeability. Winkler *et al*. (31) found that DC101, a VEGFR2 antibody, can induce the normalization of tumor vasculature within a specific period in mouse brain tumor models and thus relieve tumor hypoxia. However, the normalization of tumor vasculature is transient (often lasts only one to five days after administration, known as "normalization window"). During the "normalization window", partial pressure of oxygen raises initially and then decreased, showing an inverted U curve. Therefore, radiotherapy can produce better therapeutic effectiveness during the "normalization window". Huand *et al*. (32) also found the presence of the "normalization window" of endostatin in animal models. Jiang *et al*. (33) observed the inhibitory effect of radiotherapy combined with weekly RHES on the human pulmonary adenocarcinoma A549 xenografts in nude mice, and found that the use of endostatin in the first week after radiotherapy obtained better therapeutic effects, which may be reasonably explained by the use of endostatin in the "normalization window". However, it has been reported that normalization of tumor vasculature may be reversible in patients with glioblastoma receiving AZD2171 (34), suggesting that the normalization of tumor vasculature may be a more complicated process. Tumor angiogenesis results from the imbalance between angiogenesis factors and angiostatin (35). When the balance between angiogenesis factors and angiostatin is re-stored, apoptosis of intratumoral abnormal capillaries begins and neovessels gradually become normal (36). Therefore, downregulation of VEGF expression makes angiogenesis factors and angiostatin reach a new balance; under such conditions, intratumoral neovessels begin to become normal, which not only improves tumor hypoxia (which increases radiosensitivity) but also reduces blood vessel-derived leakage (which relieves peritumoral edema). It has been reported that anti-VEGF therapy can not only inhibit the growth of brain metastasis tumor, but also relieve peritumoral edema (37,38). Angiogenesis inhibitors have been found to be able to reverse the up-regulation of VEGF induced by ionizing radiation and thus increase tumor radiosensitivity (39).

Application of Endostar combined with radiotherapy

The conventional protocol for Endostar combined with radiotherapy is as follows: 7.5 mg/m^2 of Endostar is intrvenously injected over 3-4 hours daily from the first day to the fourteenth day in each treatment cycle. Although this usage is clinically safe and effective, it may be further optimized. Administration time and dosage plays important roles in the normalization of tumor blood vessels (40,41). In fact, the therapeutic effects of anti-angiogenic drugs are highly time-dependent, while their dependence on dose is not obvious. Therefore, Endostar should be administered at a low dose and for a long period. It is reported that the continuous administration of Endostar has better therapeutic effects than short-term administration of the same dose (42). Jiang *et al*. (43) have reported that patients with NSCLC who were intravenously administered with 15 mg/d Endostar and concurrently underwent radiotherapy tended to have better short-term therapeutic effects, higher local control rate, and less severe adverse reactions. Continuous intravenous infusion of Endostar is beneficial to properly control drug concentration and reach the best blood drug concentration.

Conclusions

In summary, continuous intravenous infusion of Endostar combined with radiotherapy in the treatment of NSCLC-caused BM has shown promising therapeutic effects both in theory and in clinical practice. Bone marrow suppression, gastrointestinal reactions, and other adverse effects are mild and can be well controlled. Therefore, Endostar combined with radiotherapy may play an important role in improving the life quality of the patients with advanced lung cancer. However, the ultimate clinical benefits, in terms of total response rate, progression-free survival, and overall survival, need to be further elucidated in more large-scale, multi-center, randomized, and controlled studies.

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