Combining antiangiogenic therapy and radiation in nasopharyngeal carcinoma

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ABSTRACT

يعد العلاج الإشعاعي من العلاجات الأساسية لسرطان البلعوم الأنفي، كما وترتبط مدى فعالية هذا العلاج بمحتوى الأوكسجين في الخلايا السرطانية. وهذا يعني بأنه يجب موازنة التفاعل بين العلاج الإشعاعي والعلاج بمضادات تولد الأوعية في الورم وذلك عند الجمع بينهما من أجل زيادة فعالية العلاج وتحسين نتائجه. وتتضمن عملية الجمع بين هذين العلاجين آليات معقدة متمثلة بالعديد من التفاعلات بين الخلايا السرطانية، والجملة الوعائية، وسدى الورم. كما ويعتمد مدى تضخم الورم السرطاني وانتقاله على عملية تولد الأوعية في الورم حيث يؤدي نمو الورم السريع إلى نقص التأكسد الذي من شأنه أن يقاوم العلاج الإشعاعي. وتعمل مضادات تولد الأوعية على ضبط مجرى الدم في خلايا الورم، وضبط عملية التأكسد وذلك من خلال استهداف الجملة الوعائية السرطانية مما يؤدي إلى زيادة حساسية العلاج الإشعاعي. ونستعرض في هذا المقال مدى تأثير الجمع بين العلاج الإشعاعي والعلاج بمضادات تولد الأوعية في الورم على سرطان البلعوم الأنفي الانتقالي، بالإضافة إلى مراجعة الأبحاث التي تدعم مثل هذه الطريقة العلاجية الواعدة.

Radiation therapy is the primary treatment in nasopharyngeal carcinoma (NPC), and the effect of radiation therapy is strongly related to the oxygen content of cancer cells. That means, it is imperative to balance the interactions between radiotherapy and anti-angiogenesis therapy when giving combination therapy to improve clinical outcomes. The complicated mechanisms between antiangiogenic agents and radiation involve many interactions between the cancer cells, vasculature, and cancer stroma. The proliferation and metastasis of cancer depends on angiogenesis, while rapid growth of cancers will cause hypoxia, which contributes to radioresistance. Antiangiogenic agents can modulate the cancer blood flow and oxygenation through target cancer vasculature, leading to increased radiosensitivity. This study discusses the mechanisms of the synergistic effect of the antiangiogenic therapy with radiation therapy in metastatic NPC, and reviews the data supporting this strategy as a promising treatment for metastatic NPC.

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Nasopharyngeal carcinoma (NPC), as a malignant head and neck cancer, is known for its atypical early symptoms and high-metastatic potential. Unlike other malignant cancers, due to the complexity structure of the nose-pharynx ministry, the characteristics of invasive growth and radiosensitivity, radiotherapy is the first choice for NPC. With the incessant development and update of radiotherapy-associated equipment and technology, the effect of treatment in NPC has been improved greatly, but there still exists some patients who are not sensitive to radiation, and may lead to failures of treatment. Increasing the sensitivity of radiation and improving the local control rate are important approaches to enhance the curative effect of NPC. Radiotherapy combined with chemotherapy has been proven to increase the effect to some extent.[1,2] But more novel targeting strategies are needed in order to improve outcome. In the past years, anti-angiogenesis therapies have showed a rapid ascent into clinical practice. Since angiogenesis is associated with advanced and metastatic cancers, it has its unique characters in cancer. Combining antiangiogenic agents and radiotherapy seems to be feasible. Here, we briefly summarize the effects of antiangiogenic agents added to radiotherapy in NPC, and explain the mechanisms under the current knowledge.

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Hypoxia-inducing factor 1-alpha and radiosensitivity of nasopharyngeal carcinoma. Like the repair of DNA damage, regulation of cell cycle, apoptosis, or others, the oxygenation state of cancer cells is one of the main factors that regulate cancer radiosensitivity. With further research of radiation biology, the influence of hypoxia of tissues or cells to radiosensitivity cannot be simply summarized as enhanced, or reduced. The mechanisms between them are very complicated, even paradoxical to some extent. On the one hand, hypoxia can result in reducing radiosensitivity. Radiation-induced DNA double strand breaks, which causes cell cycle arrest, and cell death is the main mechanism of radiotherapy. Meanwhile, as a potent radiosensitizer, oxygen can facilitate the production of free radicals, which is essential for the induction of radiation-associated DNA damage.[3,4] That means, the growth of cancers, anti-angiogenesis or other factors, which can result in a lack of adequate blood supply or oxygen for regions will lead to radiation resistance as the cancer microenvironment in hypoxia cannot promote radiation-induced DNA damage.[5] On the other hand, hypoxic cancer cells are characterized by up-regulating HIF-1α, an important regulatory factor that enables cancer cells to endure a hypoxic microenvironment.[6,7] The hypoxia tolerance includes regulating the induction of various transcription factors involved in tumor metabolism, invasion, cell death and angiogenesis, including the key angiogenic molecule vascular endothelial growth factor (VEGF).[8,9]

It has been reported that the overexpression of HIF-1α in NPC correlates with carcinogenesis,[10,11] proliferation,[7] and surviving,[12] as well as with poorer prognosis,[13] and advanced cancer stage,[14] while HIF-1α and VEGF play roles in these modulation. The HIF-1α has also been found to have connections with radio resistance.[3,15,16] Hosokawa et al[16] showed that oral squamous cell carcinoma (OSCC) cells of high-level HIF-1α were resistant to radiation and HIF-1α involved in controlling short-term radiosensitivity of cells. Xu et al[17] found that down-regulating the expression of HIF-1α and osteopontin mRNA could radiosensitize the HNE-1 cell. As stated above, HIF-1α caused by radiation exposure can result in the up-regulation of VEGF, estimated glomerular filtration rate (EGFR) and others, followed by high levels of angiogenic growth factors, especially VEGF, endothelial cell survival can be increased, which may participate in radioresistance.[18] Meanwhile, an increased proliferation of cancer cells may result from the promotion or maintenance of cancer vascular system via up-regulated radiation-induced VEGF.[19,20] This may contribute to radiation resistance in many ways, including improved interstitial fluid pressure, or vascular permeability, increased oxygen consumption, and hypoxic microenvironment. There is also evidence to support that HIF-1α can enhance the sensitivity of radiation. The HIF-1α can promote cell cycle arrest and apoptosis to enhance cellular radiosensitivity.[21,22] However, recently Sendoel et al[23] reported HIF-1 could antagonize p53-mediated apoptosis through a secreted neuronal tyrosinase. The outcomes will vary from different conditions. Oike et al[24] found that the expression of HIF-1α did not contribute primarily to the radiosensitivity of lung adenocarcinoma cells under acute hypoxia. At present, most scholars support that increasing HIF-1α can result in radiation resistance, while silencing HIF-1α contributes to an increased radiosensitivity.[16,25]

Vascular endothelial growth factor and its role in nasopharyngeal carcinoma. The VEGF, known as a potent promoter for angiogenesis, plays a primary role in the formation of new blood vessels. Its role in NPC has also been well established.[26] There are 7 ligands of VEGF family, including VEGF A-E. The VEGFR-1/2, which are primarily involved in angiogenesis is known to bind VEGF A-D and PLGF.[27] The VEGF-C and VEGF-D were also found to bind to VEGFR-3, which is involved in lymphatic metastasis. Previous reports indicate that VEGF, especially VEGF-A can bind to 2 receptor tyrosine kinases (VEGFR-1/2) to promote endothelial cell differentiation, proliferation, migration, and induction of matrix metalloproteinase (MMPs). Signaling pathways, such as phosphatidylinositol-3-kinase/Silk threonine protein kinase (PI3K/AKT) and Ras/Mitogen-activated protein kinase (Ras/MAPK) was also activated to help with endothelial cell survival.[18]

In NPC, VEGF-inducted MMPs not only participate in the formation of new blood vessels though degrading endothelial extracellular matrix, but also regulate the invasion and metastasis of cancer, leading to a progression of NPC.[28,29] In addition, it was reported that VEGF has a strong connection with varied regulatory factors, which are involved in angiogenesis. Chen et al[30] indicated that the effects of angiopoietin-2, which can maintain the mature blood vessels, highly rely on the level of VEGF expression. Chen et al[30] found that Celecoxib, an inhibitor of cyclooxygenase-2 -2, has the ability to inhibit the capacity of invasion, suppress the level of VEGF-A expression, and enhance radiosensitivity in NPC.[31] Thus, these could be effective targets to inhibit angiogenesis for the treatment of NPC.

Anti-angiogenesis combined with radiation in nasopharyngeal carcinoma. As the angiogenesis plays an important role in the progress of cancer, targeting angiogenesis agents will be a significant part of the treatment of NPC. Recently, the treatment of anti-angiogenesis combined with radiation has been used in clinical trials, and it has some effects. Bevacizumab had been used in the clinical trial of Head Neck Squamous Cell Carcinoma (HNSCC), and the results showed that combined therapy was feasible.[32,33] Lee et al[34] followed-up 46 NPC patients, and found that adding bevacizumab to standard chemoradiation treatment was feasible. The estimated 2 year locoregional progression-free interval was 83.7% (95% confidence interval [CI]: 72.6-94.9), 2 year distant metastasis-free interval was 90.8% (95% CI: 82.2-99.5), 2 year progression-free survival was 74.7% (95% CI: 61.8-87.6), and 2 year overall survival 90.9% (95% CI: 82.3-99.4). Bevacizumab may delay the progression of subclinical distant disease.[34] Elser et al[35] evaluated 27 patients and determined the efficacy and safety of sorafenib, which could inhibit the growth and angiogenesis of cancer in NPC. They found the median time of progression was 1.8 months (95% CI: 1.6-3.4 months), and overall survival was 4.2 months (95% CI: 3.6-8.7 months). While fatigue, mucositis, lymphopenia, anemia, and hand-foot skin reaction were the most common toxicities.[35,36] Xue et al[37] found that it was tolerable and feasible for a combination of sorafenib, cisplatin (80 mg/m^2), and 5 fluorouracil (FU) (3000 mg/m^2) in NPC recurrent or metastatic, but then requires further randomized trials. Huang et al[38] reported that sorafenib and sunitinib could markedly increase the cytotoxic sensitivity of cancer cells to natural killer cells by up-regulating NKG2D ligands.

In mouse models, it had been reported that the function of radiation in antitumor and antiangiogenesis could significantly increase in NPC by Endostar™ (rh-endostatin, YH-16) (a new recombinant human endostatin developed by Medgenn Bioengineering Co. Ltd., Yantai, Shandong, China), while promoting apoptosis of endothelial cells and cancer cells, increasing hypoxia of cancer cells, and changing proangiogenic factors that contributed to it.[39] Zhou et al[40] found that by Endostar significantly inhibited the growth of NPC cells, the cancer inhibition rates of Endostar + radiation was 86.1%, Endostar was 27.1%, and radiation was 60.5%. Additional, Endostar could enhance the radiosensitivity of NPC cells by lowering VEGF expression. Zhou et al[41] had a similar conclusion. Peng et al[42] also found that Endostar is involved in normalizing tumor vasculature, which could lead to alleviating hypoxia, and sensitizing the antitumor effect of radiation. The increase of pericyte coverage in NPC tumor vessels by the up-regulated PEDF and down-regulated VEGF might play a role in this.[42] In addition to the phase II trial, the efficacy and safety of Endostar combined with gemcitabine and cisplatin chemotherapy in metastatic

Table 1 - The effect of radiation for nasopharyngeal carcinoma cells.

Stage	Cancer blood vessels	Cancer oxygen supply	Cancer radiosensitivity	Influence of cancer
Initial period	Normal or little impairment	Normal or little reduction	High	Kills cancer cells effectively
Interim	Increases the levels of angiogenic growth factors by HIF-1α	Reduced	Reduced	The ability of radiation to kill cancer cells is reduced
Late period	Serious damage	Low	Low	-

HIF-1α - hypoxia inducing factor 1 alpha

Table 2 - The effect of antiangiogenic therapy for nasopharyngeal carcinoma cells in radiation.

Stage	Cancer blood vessels	Cancer oxygen supply	Cancer radiosensitivity	Influence of cancer
Initial period	Inhibit the angiogenesis of cancer	Normal or little reduction	High	Kill cancer cells effectively; reduce the supply for cancer cells
Interim	Against the effect of endothelial cells survival; maintain temporary vascular normalization	Improved	Reduce the radioresistance	Improves the ability of radiation to kill cancer cells
Late period	Reduce the blood vessels strongly	Low	-	The supply is not enough to meet the growth or recurrence of cancer cells

NPC was determined. Twenty-eight patients were included for evaluation. The median progression-free survival (PFS) was 19.4 months (95% CI: 13.6-25.1 months). The confirmed objective response rate was 85.7% (95% CI: 66.4-95.3%) including complete response in 14 patients (50%). The one-year PFS rate was 69.8%, and the one-year overall survival rate was 90.2%. The most common grade 3/4 adverse events were neutropenia (46.4%), and thrombocytopenia (14.3%). This indicated that Endostar combining with gemcitabine and cisplatin chemotherapy would be a potential treatment for NPC.[43]

The mechanism by which the combined treatment has an effect is complicated. On one hand, the formation of cancer blood vessels would be inhibited by targeting VEGF and other targets, as a result, cancer blood supply is insufficient to meet the needs of growth and metastasis, and resulted in an inhibition of cancer progress. Meanwhile, VEGF/VGFR can also activate signaling pathways, such as Ras/MAPK, and PI3K/AKT pathways to promote endothelial cell proliferation and survival.[18,44] Thus, endothelial cells are easily damaged, and the radiosensitivity will be increased by targeting VEGF/ VGFR. Then in terms of the paradoxical effect that hypoxia caused by anti-angiogenesis will reduce the sensitivity of radiation, the theory of vascular normalization window can explain it.[42,45,46] Antiangiogenic therapy can induce a specific "vascular normalization window". During this time, the function, structure of cancer blood vessels, and microenvironment temporarily become normalized, meaning the interstitial fluid pressure is decreased, and blood perfusion is increased. As a consequence, the anticancer drugs can easily penetrate into the cancers; in addition, hypoxia will be temporarily overcome and leads to more DNA damage, cell death, and high sensitivity of radiotherapy by producing more free radicals. Thus, administering radiotherapy during the window period is the key to improve the antitumor efficacy. The effect of radiation for NPC is summarized in **Table 1**, and the effect of antiangiogenic + radiation for NPC is summarized in **Table 2**.

In conclusion, due to the characteristics of NPC, radiotherapy is the main means of treatment. However, the single treatment often cannot meet the need of the expected goal, and combination therapy is a trend for NPC. Anti-angiogenesis, as the main mechanism for blocking the supply of tumor cell growth is a promising treatment for NPC. A high expression of HIF-1α is often induced by radiation, and it regulates the radiosensitivity by modulating the expression of VEGF, or other signaling pathways. Moreover, the vascular normalization window in anti-angiogenesis is considered to be an important factor for the promotion of cancer radiosensitivity. Therefore, the combined therapy does not equate a simple addition of the 2 therapies. More research is needed to obtain a better understanding of the interactive effect. It was found that combining anti-angiogenic therapy with radiotherapy has a clinical value in improving the effect of NPC, but of note, the number of patients in trials is still low, and more specimens are needed to confirm the outcomes. Considering the importance of the vascular normalization window in such treatment, some issues, such as the formative time and duration of the vascular normalization, whether the normalization relies on the dose, or type of drugs is worth further study. In addition, to inhibit the formation of new blood vessels, targeting the existing blood vessels and reducing its function is also involved in antiangiogenic therapy.[47] Radiotherapy combined with antiangiogenic is a promising model for NPC treatment. Considering various factors, such as the type of drugs, delivery time, dose, and the type of ray,[48] and a reasonable therapy scheme are critical to improve the effect of NPC.

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