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Study on The Current Situation of Drug Therapy for Differentiated Thyroid Cancer

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Abstract: Thyroid cancer (TC) is a common endocrine tumor. At present, surgery is still the main treatment for this disease. In addition to conventional surgical treatment, common TC drug treatments include radioactive iodine therapy (RAIT), molecular targeted drug therapy, thyroid stimulating hormone (TSH) inhibition therapy, neoadjuvant chemotherapy, and traditional Chinese medicine treatment, etc. This article aims to review the research status of drug therapy for differentiated thyroid cancer (DTC), so as to provide reference for its treatment ideas.

Keywords: differentiated thyroid cancer; drug treatment; molecular mechanism; side effect

Thyroid cancer (TC) is a common malignant tumor in the human endocrine system, including differentiated thyroid cancer (DTC), medullary thyroid cancer (MTC), and anaplastic thyroid cancer (NPC) thyroid cancer, ATC ） ，DTC includes papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC). Currently, the main treatment for DTC is surgical treatment. In addition to surgical treatment, radioactive iodine therapy (RAIT), molecular targeted therapy, thyroid stimulating hormone (TSH) inhibition therapy, neoadjuvant chemotherapy, and traditional Chinese medicine treatment have broad application prospects. This article aims to review the research status and application progress of DTC drug treatment methods based on relevant literature at home and abroad, in order to improve the understanding of DTC drug treatment.

1 DTC drug treatment method

1.1 RAIT

There may be benign residual thyroid tissue after total thyroidectomy, and the purpose of RAIT is to ablate these residual tissues and monitor treatment status through thyroglobulin (TG). Radioactive iodine has three objectives: ① ablation of residual material: eradication of residual thyroid cells, not aimed at improving patient survival, but to enhance the sensitivity of TG monitoring and subsequent ^{131}I imaging quality; ② Adjuvant therapy: eliminate potential lesions of local or distant metastasis in TC tissue, reduce the risk of recurrence, and improve disease-specific survival rate and progression free survival rate; ③ Treatment of known diseases: Treatment can improve disease-free survival and overall survival rates for refractory or recurrent diseases[1]. The mechanism of radioactive iodine is that iodine is absorbed and concentrated in thyroid follicular cells through membrane sodium iodide transporters. DTC can concentrate iodine, express thyroid stimulating hormone (TSH) receptors, and produce TG. ^{131}I is absorbed by thyroid follicular cells, emitting beta rays to cause clear local damage to thyroid tissue, and emitting gamma rays for imaging detection of any residual or metastatic diseases.

Recently, a retrospective study included 1487 patients with moderate risk PTC after total thyroidectomy. Among them, 1349 patients received RAIT and 138 patients did not receive RAIT. After 51 months of follow-up, 30 patients experienced recurrence, including 11 structural recurrence and 19 biochemical recurrence. After propensity score matching, the structural recurrence rate (5/138 vs. 5/552, P=0.046) and biochemical recurrence rate (6/138 vs. 4/552, P=0.005) in the non RAIT group were higher than those in the RAIT group, indicating that RAIT can reduce the recurrence risk and improve the survival rate of

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intermediate risk PTC patients[2].

1.2 Molecular Targeted Therapy

Some patients with postoperative 131I adjuvant therapy may experience recurrence or metastasis due to lack of iodine uptake or insufficient iodine uptake, resulting in poor prognosis. This type of DTC is called refractory differentiated thyroid cancer (RR-DTC), which is insensitive to RAIT and chemotherapy. In this context, the role of targeted drugs is highlighted.

1.2.1 Molecular mechanism of TC

TC is mainly associated with the activation of two signaling pathways, namely the mitogen activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K) pathway, and abnormalities in other genes also play important roles[3]. The activation of MAPK pathway is considered to be the key to the occurrence of PTC, while the activation of PI3K signaling pathway is considered to be the key to the occurrence of FTC. The RAS gene, as a molecule that exists simultaneously in the two pathways mentioned above, mainly functions to transmit mitotic signals and plays an important role in regulating cell growth, division, and proliferation. Mutations in the RAS gene lead to the sustained activation of these two pathways, causing abnormal cell proliferation and ultimately leading to the occurrence of tumors. The development of tumor blood vessels promotes tumor growth and metastasis, and vascular endothelial growth factor (VEGF), as an important cytokine that promotes vascular growth, plays a crucial role in this process. In DTC, the expression of VEGF increases, and its targeted drugs act on the VEGF signaling pathway, which can inhibit the generation of neovascularization endothelial cells, thereby suppressing the proliferation and migration of tumor cells. In addition, there are also some gene mutations closely related to the occurrence of TC. The V-Raf murine sarcoma viral oncogene homolog B (BRAF) mutation is a common gene mutation in the occurrence of DTC, among which the BRAF V600E mutation is very common in DTC. Tumors driven by BRAF V600E exhibit high extracellular signal regulated kinase (ERK) phosphorylation, leading to uncontrolled cell proliferation and inhibition of genes required for radioactive iodine response in TC. RET/PTC rearrangement is a common oncogenic driver of PTC. Transmembrane receptor tyrosine kinase is rearranged to encode RET oncogene during transfection and activated by chromosomal rearrangement or point mutation in PTC, which can activate the MAPK and PI3K signaling pathways, leading to carcinogenesis of normal cells. The Prkar1a gene is involved in encoding protein kinase A (PKA), and thyroid growth is driven by the TSH/cAMP/PKA signaling pathway. Studies have shown that in mouse models, genetic ablation of the Prkar1a gene can activate the TSH/cAMP/PKA signaling pathway, leading to FTC.

1.2.2 Current status of DTC targeted therapy drug application

Currently, multi enzyme inhibitors targeting different subtypes of TC have achieved certain results in clinical applications. The molecular targeted drugs for DTC are mainly lenvatinib and sorafenib. Lenvatinib is an oral medication that inhibits multiple growth factors and RET. A phase III randomized, double-blind, multicenter study on RR-DTC showed a median progression free survival of 18.3 months in the lenvatinib group and 3.6 months in the placebo group (hazard ratio for progression or death was 0.21; 99% CI was 0.14-0.31; P<0.001). Sorafenib is a multi kinase inhibitor with anti proliferative and anti angiogenic properties both in vitro and in vivo. In the phase III clinical trial of using sorafenib to treat RR-DTC, it was shown that sorafenib significantly prolonged median progression free survival compared to placebo [sorafenib 10.8 months vs. placebo 5.8 months (HR 0.59; 95% CI 0.45-0.76; P<0.0001)], and reduced the risk of cancer progression or death by 41% during double-blind treatment. Although there was no significant difference in overall survival rate between the treatment groups, the objective response rate of the sorafenib group was 12.2%, which was better than the placebo group's 0.5% (P<0.0001). This indicates that sorafenib significantly improved progression free survival in patients with progressive radioactive iodine RR-DTC compared to placebo. Based on the above research, the US Food and Drug Administration has approved these two drugs for the treatment of DTC.

In addition, some scholars have proposed using targeted drugs for DTC that cannot be treated surgically. A study has found that anlotinib inhibits the cell viability of TC and ATC cell lines, possibly due to abnormal spindle assembly, G2/M arrest, and TP53 activation after anlotinib treatment; In addition, anlotinib inhibits the migration of TC cells and the growth of mouse xenograft thyroid tumors in vitro. Data shows that anlotinib has significant anti-cancer activity in TC and may provide an effective treatment strategy for advanced TC patients. Scholars have reported a case of DTC that could not be directly treated with neoadjuvant targeted therapy before Apatinib surgery. Apatinib (oral, 500 mg/time, once a day) was used to treat the patient as neoadjuvant therapy. After 6 weeks, the tumor rapidly shrank from 56 mm × 37 mm to 29 mm × 26 mm. Complete tumor resection was completed through a neck incision 10 days after Apatinib discontinuation. This strongly suggests that preoperative short-term targeted therapy for locally advanced DTC that cannot be operated on may become a promising new adjuvant

therapy, which can reduce tumor size and improve staging, making it possible to completely and safely remove the lesion.

1.2.3 Side effects of targeted drug therapy for TC.

The use of targeted drugs has certain side effects on the body. Common side effects generally include gastrointestinal reactions, nausea, hypertension, fatigue, weight loss, rash, acne, dry skin, etc. Some drugs may have specific adverse reactions, such as hand foot skin reactions, taste disorders, and oral inflammation, which may occur during the use of cabozantinib. Diarrhea is the most common gastrointestinal adverse reaction during targeted drug therapy. Diarrhea is usually mild to moderate, and about 10% of patients may experience severe diarrhea during medication. The occurrence of diarrhea may be related to the vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) in the intestinal mucosa. Other gastrointestinal reactions such as gastrointestinal bleeding, gastrointestinal perforation, and other side effects may be related to the anti angiogenic properties of such drugs . In addition, fistula formation is a rare adverse reaction related to this mechanism, and patients with a history of neck radiation or surgery, or with important structures in the neck being invaded, are more likely to develop this complication. During the medication process, some patients may experience symptoms of hypertension, which may be related to a decrease in endothelial nitric oxide (NO) concentration. NO It plays an important role in regulating vascular homeostasis. The decrease in endothelial NO concentration can lead to increased vascular tension and hypertension, while the inhibition of VEGFR activates the endothelin system to reduce the activation of endothelial nitric oxide synthase, resulting in a decrease in NO levels. Patients may experience fatigue during the medication process, which is also the most common side effect of targeted drugs. Some patients may experience unexplained weight loss during the treatment process, which is generally painless, especially in patients taking lenvatinib who have a higher probability of experiencing this condition. Rash, acne, and dry skin can also occur from time to time. The side effects of such drugs on the skin are usually mild and self limiting.

1.3 TSH suppression therapy

TSH suppression therapy refers to the use of high-dose TSH after TC surgery to suppress pituitary TSH secretion through a negative feedback mechanism, while correcting thyroid dysfunction caused by thyroidectomy. Pituitary tumor transforming gene 1 (PTTG1) can induce proliferation, proliferation, and dedifferentiation of thyroid cells and other epithelial cells. TSH receptor activation increases the expression of PTTG1, which is usually associated with the proliferation and invasiveness of TC. The research conclusion of the National Thyroid Cancer Treatment Cooperative Research Group (American Thyroid Cancer Registry Association) in the United States is that active TSH suppression therapy is not valuable for patients with low recurrence risk, but beneficial for high-risk patients. The 2022 National Comprehensive Cancer Network (NCCN) Oncology Clinical Practice Guidelines TC section states that for patients with residual cancer lesions or high risk of recurrence, TSH levels should be maintained below 0.1 mU/L within 5 years; The TSH level of patients with low recurrence risk should be maintained at half of the normal level. Although maintaining low TSH levels has a certain effect on avoiding tumor recurrence and metastasis, long-term excessive TSH intake can also cause adverse events such as bone and heart dysfunction, psychological, social, and physical quality of life damage to the human body. Research has found that the lower the TSH level, the less significant the decrease in bone density, but the lower the lumbar spine trabecular score. This suggests that female patients may experience a decrease in bone strength during TSH suppression therapy after surgery. This indicates that although TSH suppression therapy can reduce the tumor recurrence rate after DTC surgery, there are still potential treatment risks. Therefore, the American Thyroid Association recommends the use of graded TSH suppression methods based on initial and ongoing risk assessments.

1.4 Neoadjuvant chemotherapy

The vast majority of TCs are not sensitive to chemotherapy, and chemotherapy can only be attempted as palliative treatment or after other methods have failed. However, cytotoxic chemotherapy is only considered when the tumor exhibits widespread metastasis, rapid progression, or poses a serious threat to the patient's life, and other methods such as targeted therapy drugs are ineffective. Neoadjuvant chemotherapy refers to chemotherapy performed before surgery, with the aim of reducing tumor volume, improving surgical outcomes, and reducing postoperative complications. At present, there is not much research on neoadjuvant chemotherapy for TC. Two studies by scholars have obtained similar results. In 2012, they administered a total of 67 cycles of neoadjuvant chemotherapy to 29 inoperable DTC patients, and the tumor size of 13 patients decreased by more than 50%; In patients with and without distant metastasis, the size of the primary tumor decreased by 17% and 65%, respectively (P=0.02). In a 2013 study, after 40 cycles of neoadjuvant chemotherapy using vincristine combined with doxorubicin in 16 patients with inoperable DTC, the tumor size of all patients decreased, with 7 patients (44%) experiencing a tumor size reduction of ≥ 50% and 9 patients experiencing a tumor size reduction

of<50%. This indicates that neoadjuvant chemotherapy may have a certain therapeutic effect on DTC, but currently neoadjuvant chemotherapy has not been widely promoted in clinical practice, and there is little research on this method for treating TC, which cannot well prove the effectiveness of neoadjuvant chemotherapy.

1.5 Traditional Chinese Medicine Treatment

Traditional Chinese medicine plays a significant role and has great potential in the adjuvant treatment of cancer. The advantages of traditional Chinese medicine lie in its high efficiency and minimal side effects on the human body. Studies have shown that the active ingredients of traditional Chinese medicine or natural medicines can induce tumor cell aging, selectively eliminate senescent cells, reduce inflammatory reactions, enhance immune system function, thereby delaying the progression of age-related diseases and promoting health. In addition, traditional Chinese medicine can inhibit autophagy and apoptosis of tumor cells, as well as suppress cancer invasion and migration through angiogenesis outside the tumor. Some traditional Chinese medicine formulas have certain effects on the treatment of TC, but there are many types of traditional Chinese medicine and their interaction mechanisms have not yet been elucidated. Therefore, the anti-tumor effect of a single traditional Chinese medicine has become a current research hotspot. Huanglian Su is an effective ingredient in the traditional Chinese medicine Huanglian, which has therapeutic effects on various types of cancer. Studies have shown that berberine can induce mitochondrial apoptosis, G0/G1 cell cycle arrest, and inhibit migration through the PI3K-AKT and MAPK signaling pathways to suppress TC cells.

2 Conclusion

At present, surgical treatment, RAIT and TSH suppression therapy are still the main treatments for iodine RR-DTC. Surgical treatment has significant therapeutic effects on most patients, and there is currently no clear drug treatment plan for iodine RR-DTC. Molecular targeted therapy, neoadjuvant chemotherapy and traditional Chinese medicine treatment provide new ideas for the treatment of iodine RR-DTC. However, the efficacy of neoadjuvant chemotherapy is not clear, and traditional Chinese medicine treatment lacks evidence-based medicine. Molecular targeted therapy also has problems such as large side effects and high medical costs. But more drugs are being invested in DTC treatment, providing diverse options for future DTC drug therapy.

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