

# The clinical efficacy of Apatinib plus Ba Zhen granules in the treatment of advanced unresectable differentiated thyroid cancer and their influence on immune factors

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**Abstract:** The aim of this study was to analyze the clinical efficacy of Apatinib plus Ba Zhen granules in advanced unresectable differentiated thyroid cancer and its influence on immune factors. Sixty patients with advanced unresectable differentiated thyroid cancer in our hospital between January 2018 and December 2019 were selected and randomized to the control group and the observation group (30 cases in each group). After treatment, the observation group yielded higher serum levels of Cyfra21.1 and Gal-3, but lower SIL-2R levels than the control group. After treatment, the two groups obtained a marked increase in CD3+ and CD4+ levels and a decrease in CD8+ level, in which the observation group has higher levels of CD3+ and CD4+ and lower levels of CD8+ than the control group. After treatment, the serum FT3 and FT4 levels sharply increased and serum TSH levels declined significantly, with higher levels of FT3 and FT4 and lower levels of TSH observed in the observation group. The incidence of adverse reactions didn't significantly differ between groups. In advanced unresectable differentiated thyroid cancer, apatinib remarkably inhibits disease development. The combination of Apatinib and Ba Zhen granules adjusts immune factors and improves thyroid function, with a low incidence of adverse reactions and promising efficacy.

**Keywords:** Thyroid cancer, thyroid function, Ba Zhen granules, Apatinib, efficacy.

## INTRODUCTION

87% of thyroid cancers are differentiated thyroid cancer (DTC) which is considered curable with surgery in most cases (Xu *et al.*, 2021). However, given the location of the thyroid and its relations to important tissues such as the trachea, recurrent laryngeal nerve and parathyroid glands, radical resection of DTC by surgery is rather negative, with a recurrence rate of 30%. Factors, such as tissue adhesion, keloid, edema and the blur anatomical layers caused by the second operation pose greater difficulties to radical resection, easily resulting in damage to normal tissues (Liu *et al.*, 2020). It is reported that the injury rate of recurrent laryngeal nerve reaches as high as 17% after the second operation. Although 131 residual and recurring lesions were cured to a certain extent after surgery, recurrence may predispose patients to radiation thyroiditis, cervical edema and radiation sialadenitis (Niu *et al.*, 2020). Radiotherapy for DTC requires high target doses given the insensitivity of DTC to radiotherapy. However, radiotherapy is limited by the dose to normal tissues such as the larynx, trachea, esophagus, spinal cord, and parotid gland, which is virtually impossible to reach a radical dose for the total tumor volume (Meng *et al.*, 2020). Therefore, treatment method with remarkable efficacy and mild damage for patients with advanced DTC is considered rather extravagant. Apatinib mesylate is a small tyrosine kinase inhibitor (TKI) that is mainly involved in regulating vascular endothelial growth factor receptor of tumor angiogenesis, with favorable efficacy

for the treatment of solid tumors (Su *et al.*, 2019). Accordingly, the objective of this study was to explore the clinical efficacy of Apatinib plus Ba Zhen granules in the treatment of advanced unresectable differentiated thyroid cancer and its influence on immune factors, with an aim to provide a new theoretical basis for clinical treatment.

## MATERIALS AND METHODS

### General materials

This study was conducted on sixty patients with advanced unresectable differentiated thyroid cancer in our hospital between January 2018 and December 2019. 30 patients were assigned to the control group and 30 patients were assigned to the observation group according to different treatment methods. The control group was given Apatinib, and the observation group received Apatinib plus Ba Zhen granules. The observation group included 12 males and 18 females with a mean age of (45.20±1.49) years. In the control group, there were 14 males and 16 females, with a mean age of (45.80±3.04) years. The two groups showed no significant difference in baseline data ( $p>0.05$ ). table 1.

Inclusion criteria for patients were as follows (Cheng *et al.*, 2019): 1) Patients who were diagnosed with typical radioiodine refractory thyroid cancer through pathological examination. 2) Patients without insufficiency or severe insufficiency of heart, liver and kidney. 3) Patients with no allergy to apatinib. 4) Patients with normal coagulation function. 5) All patients and their family members voluntarily participated in this study and signed the informed consent form.

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**Methods**

The control group was treated with Apatinib (Jiangsu Hengrui Pharmaceutical Co., Ltd.), 750mg, once per day, at half an hour after meals, and a course of treatment spanned four weeks. The treatment was discontinued upon the occurrence of positive treatment efficacy or severe adverse reactions. During treatment, if grade 3 or higher adverse reactions associated with apatinib occurred, apatinib was discontinued or reduced as appropriate according to the physician's instructions. An increase in dosage without permission was prohibited. The observation group received Apatinib combined with Ba Zhen granules. Patients were orally given Ba Zhen granules (Sichuan Hebang Sunshine Pharmaceutical Co., Ltd., 3.5 g\*16 bags), one bag respectively after breakfast and dinner.

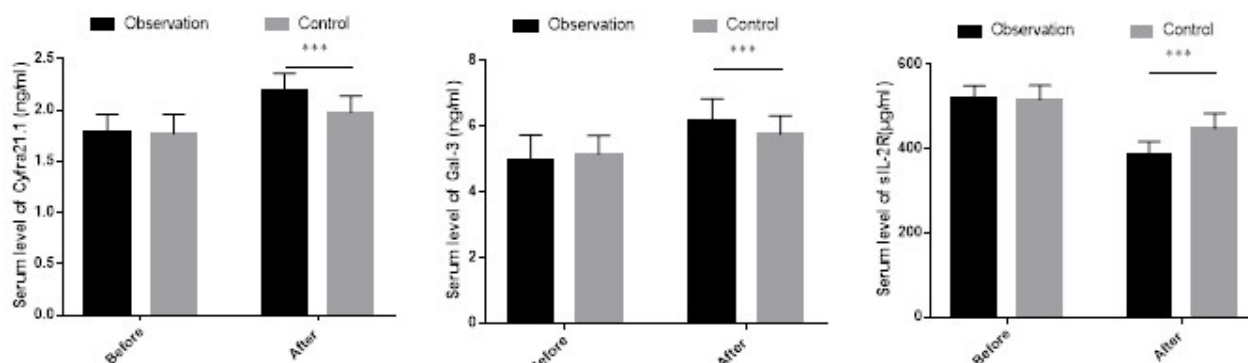
**Observation indicators**

The specific criteria for evaluating the clinical efficacy of the two groups after treatment were as follows (Agrawal *et al.*, 2018). 1) The disappearance of clinical symptoms represented a markedly effective treatment efficacy, the improvement of clinical symptoms represented an effective treatment efficacy, and no significant changes in clinical symptoms represented an ineffective treatment efficacy. Overall efficacy = (markedly effective + effective) cases/total cases × 100%. 2) 5ml of fasting venous blood was collected from all patients before and after treatment and the ratio of CD3+, CD4+ and CD8+ in whole blood was determined using flow cytometry

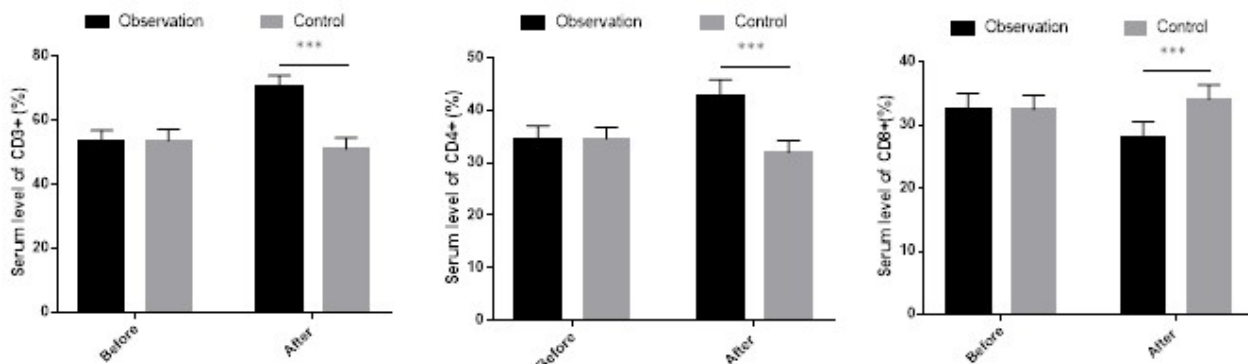
(Beckman Coulter, USA). 4) Before and after treatment, 5 ml of fasting venous blood was collected from the two groups in the morning, centrifuged at 3000 r/min for 15 min to obtain the serum. The serum levels of free triiodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) were determined using an automatic chemical analyzer (German Siemens IMMULITE1000). 4) 5ml of venous blood was collected from all patients before treatment and after one month of treatment to determine serum levels of soluble interleukin-2 receptor (sIL-2R), galectin-3(Gal-3) and cytokeratin 19 fragment antigen (Cyfra 21.1). The blood samples were then centrifuged at a low temperature to obtain the supernatant and the three indexes were determined using an enzyme-linked immunosorbent assay. The kits were purchased from Thermo Fisher Scientific Company, and the ELISA kits were purchased from Merck Sigma 5) The adverse reactions of the two groups were recorded after treatment, including mental symptoms such as anxiety, irritability and gastrointestinal reactions.

**Evaluation of quality of life**

The general conditions of patients were scored according to Karnofsky Performance Scale (KPS). In the quality-of-life questionnaire, there were four items including appetite, spirit, fatigue and daily life, with five grades for each item and a corresponding score for each grade. The score was directly proportional to the quality of life.



**Fig. 1:** Comparison of tumor indicators, \*\*\* indicated p <0.001



**Fig. 2:** Comparison of immune cytokines, \*\*\* indicated p <0.001

**Table 1:** Comparison of general data

	Gender (Male/Female)	Age	Hypertension	Smoking	Drinking	Diabetes
Observation group	12/18	45.20±1.49	21	16	19	22
Control group	14/16	45.80±3.04	19	17	16	20
$\chi^2/t$	0.271	0.969	0.300	0.067	0.617	0.317
P	0.602	0.337	0.584	0.795	0.432	0.573

**Table 2:** Comparison of thyroid function

	FT <sub>3</sub> (pg/ml)		FT <sub>4</sub> (pg/ml)		TSH ( $\mu$ U/ml)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group (n=30)	7.36±0.91	13.59±1.03	20.29±1.93	31.66±2.10	3.94±0.35	1.59±0.36
Control group (n=30)	7.35±0.89	7.56±0.88	20.39±1.91	21.36±1.89	3.92±0.34	3.81±0.33
t	0.014	24.239	-0.201	19.883	0.219	24.309
P	0.989	<0.001	0.841	<0.001	0.828	<0.001

**Table 3:** Comparison of KPS scores

	N	Before treatment	After treatment	t	p
Observation group	30	50.93±3.62	89.13±3.81	39.753	<0.001
Control group	30	49.90±2.97	68.40±3.28	22.858	<0.001
t		1.206	22.562		
P		0.233	<0.001		

**Table 4:** Comparison of adverse reactions

	N	Mental symptom	Gastrointestinal reaction	Incidence
Observation group	30	2	1	3 (10.00)
Control group	30	1	1	2 (6.67)
$\chi^2$				0.218
P				0.640

### **Ethical approval**

This trial was reviewed, approved, and monitored by the ethics committee of Cangzhou Central Hospital (License number CZCH 2018.195).

### **STATISTICAL ANALYSIS**

The data in this study were processed using SPSS25.0 software. Independent paired t-test or one-way analysis of variance was performed on the measurement data which were represented by (mean  $\pm$  standard error). The chi-square test was performed on the enumeration data which were represented by [n (%)]. P<0.05 was considered statistically significant.

### **RESULTS**

#### **Comparison of tumor indicators**

Before treatment, no difference in the levels of Cyfra21.1, SIL-2R and Gal-3 was found between groups (p>0.05). After treatment, both groups obtained an increase in the Cyfra 21.1 and Gal-3 levels and a decrease in the SIL-2R

levels (p<0.05), in which the observation group presented higher Cyfra 21.1 and Gal-3 levels and lower SIL-2R level as compared with the control group (p<0.05) (fig. 1).

#### **Comparison of immune cytokines**

After treatment, CD3+ and CD4+ levels decreased and CD8+ levels increased in the two groups (p<0.05), with higher levels of CD3+ and CD4+ and lower levels of CD8+ in the observation group (p<0.05) (fig. 2).

#### **Comparison of thyroid function before and after treatment**

No significant difference in serum FT<sub>3</sub>, FT<sub>4</sub> and TSH levels was observed between the two groups and also between before and after treatment (P>0.05). After treatment, the observation group had higher levels of FT<sub>3</sub> and FT<sub>4</sub> and a lower TSH level when compared with the control group (p<0.05) (table 2).

#### **Comparison of quality of life**

The comparison of KPS scores between one month before and after treatment showed statistical significance (p<0.05) and a more significant increase existed in the observation group as compared with the control group

( $p < 0.05$ ) (table 3).

### **Comparison of adverse reactions**

After treatment, the control group had 2 cases with mental symptoms and 1 case with gastrointestinal reaction and the observation group had 1 case with mental symptoms and 1 case with gastrointestinal reaction. The two groups showed no significant difference in terms of incidence of adverse reactions ( $p > 0.05$ ) (table 4).

## **DISCUSSION**

Thyroid cancer, a common endocrine system tumor with hidden symptoms in the early stage (Feng *et al.*, 2018). Thyroid masses appear, invade surrounding tissues and metastasize to ears, shoulders, local lymph nodes and distant organs (Chang *et al.*, 2019), which can be cured by surgery supplemented with endocrine therapy, radiotherapy and chemotherapy. DTC accounts for over 90% of thyroid cancers and most cases obtain a good prognosis after standardized treatment (Nagayama, 2018). However, some DTC is developed into unresectable advanced stages in the natural state or during treatment. Research has shown (Zhang *et al.*, 2018) that the 10-year survival of patients is less than 10%, which underlines the importance of the follow-up treatment of radioiodine refractory thyroid cancer in the current medical field. Moreover, the 5-year survival of patients with unresectable advanced differentiated thyroid cancer is less than 10% and its following treatment remains one of the pressing issues to be addressed (Scott, 2018). Apatinib is a small molecule tyrosine kinase inhibitor that inhibits vascular endothelial growth factor receptor-2 (VEGFR-2), with a mechanism to selectively compete for the joints of VEGFR-2 in cells and block the signal transmission after the combination of vascular endothelial growth factor (VEGF), thereby suppressing the cardiovascular formation of tumor tissues (Tuttle, 2018). The objective of this study is to explore the short-term efficacy and safety of Apatinib for the treatment of advanced unresectable differentiated thyroid cancer. Results of this study indicated that Apatinib had a certain clinical efficacy and significantly improved the patients' quality of life.

Serum Cyfra21.1 level is an important indicator to predict the recurrence and metastasis of thyroid cancer (Wang *et al.*, 2018). It has been found that the Cyfra 21.1 level in patients with DTC significantly decreases, whose expression is closely correlated with the severity of tumors. Gal-3 is a galectin composed of three specific structures and regulates cell proliferation and apoptosis, promotes angiogenesis and interacts with extracellular substances and its expression is closely associated with the development and metastasis of tumors (Na and Choi, 2018). SIL-2R is a glycoprotein derived from activated T cells. It was found that patients with malignant tumors have many times more SIL-2R levels than those with

benign tumors and their serum levels are also relevant to the severity of thyroid cancer (Cai *et al.*, 2018). Herein, the development of tumors was assessed through Cyfra 21.1, Gal-3 and SIL-2R levels and the results revealed that after treatment, the observation group presented higher Cyfra 21.1 and Gal-3 levels as compared with the control group ( $p < 0.05$ ) and lower SIL-2R levels ( $p < 0.05$ ), indicating that the combination of Apatinib and Ba Zhen granules better promoted the recovery of patients.

T lymphocyte subsets partly reflect the immune status of the body. The cellular immune function of patients with cancer declines in most cases, which results in changes in T lymphocyte subsets (Jin *et al.*, 2017). Specific peripheral blood CD3+ cells, CD4+ cells and cell ratios were lower in patients than in healthy subjects, but CD8+ cells were higher. The reduction in CD3+ cells and CD4+ cells indicates the reduction of immunity of the human body to tumor cells, which becomes more evident with the development of the disease (Lin *et al.*, 2017). The mitigation of such conditions increases the cell ratio increased compared with before, which promotes the recovery of immune function. During chemotherapy, Apatinib may affect the immune system of patients and exert side effects on their immunity to a certain extent (Cabanillas *et al.*, 2016; Venerito *et al.*). Herein, CD3+ and CD4+ levels decreased and CD8+ levels increased in the control group ( $p < 0.05$ ), which was consistent with the results of the above report. After treatment, the observation group had higher CD3+ and CD4+ levels and lower CD8+ levels than the control group ( $p < 0.05$ ), indicating that Ba Zhen granules restore and improve the immune function of cells. Therefore, Ba Zhen granules alleviate cancerous fatigue caused by Apatinib and significantly enhances immune function.

## **CONCLUSION**

In the treatment of advanced unresectable differentiated thyroid cancer, Apatinib remarkably inhibits its development. The combination of Apatinib and Ba Zhen granules reinforces immune factors and improves thyroid function, with a low incidence of adverse reactions and promising efficacy.

## **REFERENCES**

- Agrawal VR, Jodon G, Mushtaq R and Bowles DW (2018). Update on multikinase inhibitor therapy for differentiated thyroid cancer. *Drugs Today (Barc)*, **54**(9): 535-545.
- Cabanillas ME, McFadden DG and Durante C (2016). Thyroid cancer. *Lancet*, **388**(10061): 2783-2795.
- Cai S, Deng H, Chen Y, Wu X and Guan X (2017). Treatment of medullary thyroid carcinoma with apatinib: A case report and literature review. *Medicine (Baltimore)*, **96**(50): e8704.

- Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB and Min L (2019). Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. *Endocr. Rev.*, **40**(1): 17-65.
- Cheng L, Jiao Q, Jin Y, Fu H, Zhang H and Chen L (2019). Initial therapy of advanced anaplastic thyroid cancer via targeting VEGFR-2: A case report. *Oncotargets Ther.*, **12**: 10495-10500.
- Feng H, Cheng X, Kuang J, Chen L, Yuen S, Shi M, Liang J, Shen B, Jin Z, Yan J and Qiu W (2018). Apatinib-induced protective autophagy and apoptosis through the AKT-mTOR pathway in anaplastic thyroid cancer. *Cell Death Dis.*, **9**: 1030.
- Jin Z, Cheng X, Feng H, Kuang J, Yang W, Peng C, Shen B and Qiu W (2017). Apatinib inhibits angiogenesis via suppressing Akt/GSK3 $\beta$ /ANG signaling pathway in anaplastic thyroid cancer. *Cell Physiol Biochem.*, **44**(4): 1471-1484.
- Lin Y, Wang C, Gao W, Cui R and Liang J (2017). Overwhelming rapid metabolic and structural response to apatinib in radioiodine refractory differentiated thyroid cancer. *Oncotarget.*, **8**(26): 42252-42261.
- Liu S, Wu F, Zhang Y, Qin R, Zhu N, Li Y, Wang M, Zeng Q, Xie D, Li Y, Fan J and Han Y (2020). Apatinib combined with radiotherapy enhances antitumor effects in an *in vivo* nasopharyngeal carcinoma model. *Cancer Control*, **27**: 1073274820922553.
- Meng X, Wang H, Zhao J, Hu L, Zhi J, Wei S, Ruan X, Hou X, Li D, Zhang J, Yang W, Qian B, Wu Y, Zhang Y, Meng Z, Guan L, Zhang H, Zheng X and Gao M (2020). Apatinib inhibits cell proliferation and induces autophagy in human papillary thyroid carcinoma via the PI3K/Akt/mTOR signaling pathway. *Front Oncol.*, **10**: 217.
- Na KJ and Choi H (2018). Immune landscape of papillary thyroid cancer and immunotherapeutic implications. *Endocr Relat Cancer*, **25**(5): 523-531.
- Nagayama Y (2018). Thyroid autoimmunity and thyroid cancer - The pathogenic connection: A 2018 update. *Horm Metab Res.*, **50**(12): 922-931.
- Niu Y, Ding Z, Deng X, Guo B, Kang J, Wu B and Fan Y (2020). A novel multimodal therapy for anaplastic thyroid carcinoma: (125) I seed implantation plus apatinib after surgery. *Front Endocrinol (Lausanne)*, **11**: 207.
- Scott LJ (2018). Apatinib: A review in advanced gastric cancer and other advanced cancers. *Drugs*, **78**: 747-758.
- Su M, Gao Y, Ye X, Zhou Q, Zhao L, Cai X, Chen D, Su H, Zhang X and Xie C (2019). Clinical value of apatinib as a salvage treatment in patients with chemo-refractory advanced cervical cancer. *Oncotargets Ther.*, **12**: 9707-9713.
- Tuttle RM (2018). Controversial issues in thyroid cancer management. *J. Nucl. Med.*, **59**(8): 1187-1194.
- Venerito M, Link A, Rokkas T and Malfertheiner P (2016). Gastric cancer - clinical and epidemiological aspects. *Helicobacter*, **21**(Suppl 1): 39-44.
- Wang C, Zhang X, Yang X, Li H, Cui R, Guan W, Li X, Zhu Z and Lin Y (2018). PET response assessment in apatinib-treated radioactive iodine-refractory thyroid cancer. *Endocr Relat Cancer*, **25**(6): 653-663.
- Xu J, Shen J, Gu S, Zhang Y, Wu L, Wu J, Shao G, Zhang Y, Xu L, Yin T, Liu J, Ren Z, Xiong J, Mao X, Zhang L, Yang J, Li L, Chen X, Wang Z, Gu K, Chen X, Pan Z, Ma K, Zhou X, Yu Z, Li E, Yin G, Zhang X, Wang S and Wang Q (2021). Camrelizumab in combination with Apatinib in patients with advanced Hepatocellular carcinoma (RESCUE): A nonrandomized, open-label, Phase II trial. *Clin. Cancer Res.*, **27**(4): 1003-1011.
- Zhang X, Wang C and Lin Y (2018). Pilot Dose Comparison of Apatinib in Chinese patients with progressive radioiodine-refractory differentiated thyroid cancer. *J. Clin. Endocrinol. Metab.*, **103**(10): 3640-3646.