Original Article

Evaluating the effectiveness of targeted therapies for thyroid carcinoma: an updated meta-analysis

Shuai Lin[1,2], Jun Shen[3], Wanjun Zhao[1], Xiaofei Wang[1], Xiaoqing Wang[2], Jingqiang Zhu[1]

[1]Thyroid and Parathyroid Surgery Center, West China Hospital, Sichuan University, Chengdu 610041, China; [2]Department of Thyroid Breast Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, China; [3]Department of General Surgery, The Second Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, China

Contributions: (I) Conception and design: Si Lin; (II) Administrative support: J Zhu; (III) Provision of study materials or patients: S Lin, J Shen, W Zhao, X Wang; (IV) Collection and assembly of data: S Lin, J Shen, W Zhao, X Wang, X Wang; (V) Data analysis and interpretation: S Lin, J Shen, W Zhao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jingqiang Zhu. Thyroid and Parathyroid Surgery Center, West China Hospital, Sichuan University, No. 37 Guo Xue Xiang, Chengdu 610041, China. Email: zjq-wkys@163.com.

Background: At present, most of the targeted therapies for thyroid carcinoma are in the clinical trial stage, and there is still no strong evidence to confirm their clinical effect. The aim of this meta-analysis was to evaluate the outcome of targeted therapies and provide quantitative evidence.

Method: Ovid, PubMed, EMBAS, ClinicalTrails.gov, and Cochrane Library electronic databases were searched until September 1, 2019. Randomized controlled studies (RCTs) studies that compared the treatment of thyroid carcinoma with the targeted therapies of utility and complications were analyzed.

Results: The study included 5 studies with a total of 1,615 patients, with 991 cases in the drug group and 624 cases in the placebo group. The meta-analysis indicated that compared with the placebo group, the progression-free survival (PFS) rate of the drug group was significantly improved. The PFS of the drug group was 10.8 to 30.5 months, compared with 4 to 19.3 months for the placebo group (6 months PFS: OR =3.23, 95% CI: 2.57 to 4.05, P<0.00001, 12 months PFS: OR =3.38, 95% CI: 2.58 to 4.42, P<0.00001, 18 months PFS: OR =2.48, 95% CI: 1.74 to 3.54, P<0.00001). Overall survival (OS) did not differ significantly in the study (6 months: OR =1.53, 95% CI: 1.00 to 2.35, P=0.05, 12 months: OR =1.26, 95% CI: 0.94 to 1.69, P=0.12, 18 months: OR =1.11, 95% CI: 0.87 to 1.42, P=0.39). The incidence of adverse reactions in the drug group was significantly higher than that in the placebo group (OR =4.76, 95% CI: 3.45 to 6.57, P<0.00001), and the subgroup of adverse reactions was still significantly higher than that in the placebo group.

Conclusions: This meta-analysis revealed that the targeted drugs can significantly prolong PFS in patients with thyroid carcinoma, but the targeted drugs did not prolong the OS. Although the incidence of adverse reactions was significantly higher than that of the placebo group, the patients were still tolerable in drug group.

Keywords: Targeted therapy; thyroid carcinoma; meta-analysis

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Introduction

Thyroid carcinoma is the most common malignant carcinoma of the endocrine system. In the past few years, the incidence of thyroid carcinoma has increased at a greater rate than other tumors, and the number of confirmed cases of thyroid carcinoma is more than double of that in the previous year (1). Surgery is the preferred clinical treatment for thyroid carcinoma, but a few other treatments types are also relatively successful. For most

patients with early thyroid carcinoma, the prognosis is good after surgery, postoperative thyroid stimulating hormone (TSH) inhibition therapy, and radioactive iodine (RAI) therapy. Due to the success of these therapies, the 20-year survival rate is over 90%. However, there still remain a number of refractory thyroid carcinomas, including advanced, recurrent, metastatic thyroid, and anaplastic thyroid carcinomas. As a consequence of the lack of treatment for these conditions, the survival of these patients is very unsatisfactory (2). Targeted drugs that can compensate for the failure of traditional treatment have given hope for the treatment of these thyroid carcinoma types, and finding effective targeted treatments is critical to improving its prognosis.

The current molecular targets for the treatment of thyroid carcinoma include: a variety of kinases, BRAF, AKT, mTOR, VEGFR, and MEK (3-5). Compared with traditional chemotherapy drugs, these drugs are characterized by high efficiency and low toxicity. Early small-scale clinical trials have shown that the use of targeted drugs, such as the multi-target tyrosine kinase inhibitors like axitinib, imatinib, sorafenib, etc. can control the progression of thyroid carcinoma to some extent. Therefore, targeted drug therapy is considered to be one of the most promising treatments for thyroid carcinoma (6,7). At present, most of the studies on molecular targeted therapy for advanced thyroid carcinoma have been single-arm experiments, and there only a few prospective randomized controlled trials have been conducted. This study therefore aimed to use a meta-analysis to evaluate the efficacy and safety of molecular targeted therapy in thyroid carcinoma with the hope of providing a theoretical basis for its application.

Methods

Search strategy

Two authors independently searched all the English-language literature in the Medline, PubMed, EMBASE, ClinicalTrails.gov, Cochrane Library, and Ovid electronic databases published as of September 1, 2019 by. For our search strategy, the following keywords were used in all fields: “thyroid carcinoma” or “thyroid carcinoma” or “thyroid neoplasm” or “thyroid tumor” and “targeted therapy”. The electronic search was supplemented by a manual search of academic papers, dissertations, and conference abstracts published by various magazines.

Study selection

The inclusion criteria of eligible studies were as follows: (I) the literature research methods was a randomized controlled study (RCT), and the efficacy and safety of targeted therapy in thyroid carcinoma was analyzed; (II) studies included more than 50 patients; (III) all the included documents were available for data extraction; (IV) there were cases and controls in each study, and the controls were all placebo. Studies were excluded according to the following criteria: (I) to avoid the extraction of duplicate data, only the latest or most complete report was included if the same case population was published in more than one journal; (II) studies were not English language; (III) the full text of studies could not be accessed on-line or with request to the authors.

Quality assessment and data extraction

The utility index was the patient’s progression-free survival (PFS) rate. The safety index was the adverse reaction of the drug, which mainly included the incidence of various adverse reactions with a severity of ≥3 and the total incidence of all adverse reactions. The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) (8), while the Jadad scoring system was used for RCTs (9).

Statistical analysis

All the statistical analyses in this review were conducted using RevMan 5.3 software. Mean data were measured as mean difference (MD), and count data were expressed as odds ratio (OR or RR) with a 95% confidence interval (95% CI). If the test results did not show statistical heterogeneity ($I^2 \leq 50\%$), the data were combined and analyzed using a fixed effects model. If there was statistical heterogeneity between the two study groups without clinical heterogeneity, a random effects model was used for analysis. A sensitivity analysis of the literature was performed if heterogeneity arose from low-quality studies, while a declarative analysis was used if the heterogeneity between the two groups was too large or the source of the data could not be found.

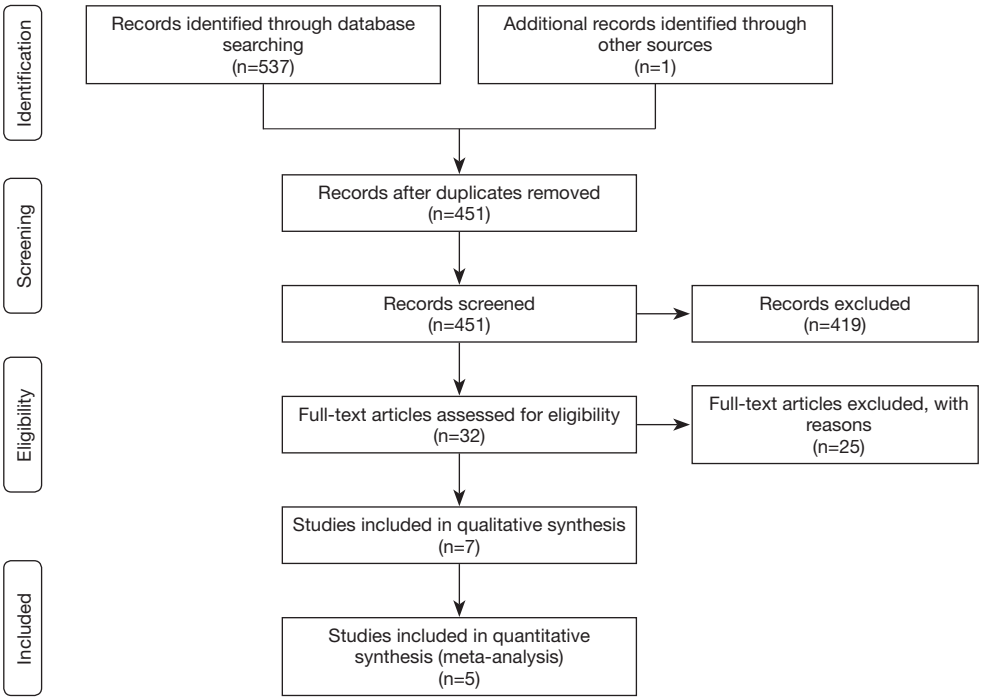

Figure 1 Search flow diagram.

Table 1 Basic characteristics of studies included in the meta-analysis

Trial (year)	Tested agent	Study design	Dose (mg)	Pathological type	Number of patients		Progression free survival	Overall survival
					Drug	Placebo		
Wells 2012	Vandetanib	Randomized controlled	300	MTC	231	100	30.5 (95% CI, 0.31 to 0.69) months	NE (95% CI, 0.48 to 1.65)
Leboulleux 2012	Vandetanib	Randomized controlled	300	MDC	73	72	11.1 (95% CI, 7.7 to 14.0) months	NE (99.24% CI, 0.4 to 2.15)
Elisei 2013	Cabozantinib	Randomized controlled	140	MTC	219	111	11.2 (95% CI, 0.19 to 0.40) months	NA
Brose 2014	Sorafenib	Randomized controlled	800	MDC	207	210	10.8 (95% CI, 0.45 to 0.76) months	NE (95% CI, 0.54 to 1.19)
Schlumberger 2015	Lenvatinib	Randomized controlled	24	RAIR-DTC	261	131	18.3 (99% CI, 0.14 to 0.31) months	NE (22.0–NE)

MTC, medullary carcinoma; MDC, metastatic differentiated carcinoma; RAIR-DTC, differentiated thyroid cancer, iodine-131-refractory; NA, not applicable or not reported; NE, not estimable.

Results

Eligible articles

According to the search strategy, a total of 537 related articles were retrieved. After reading the title and abstract of the literature, the screening criteria were used for screening, resulting in 7 RCT research literatures which were read and analyzed. After 2 duplicated data sets were excluded, 5 RCT studies remained (*Figure 1*) comprising a total of 991 cases in drug group and 624 cases in the placebo group (*Table 1*).

Study characteristics and quality

Quality analysis was performed on the 5 RCT studies included

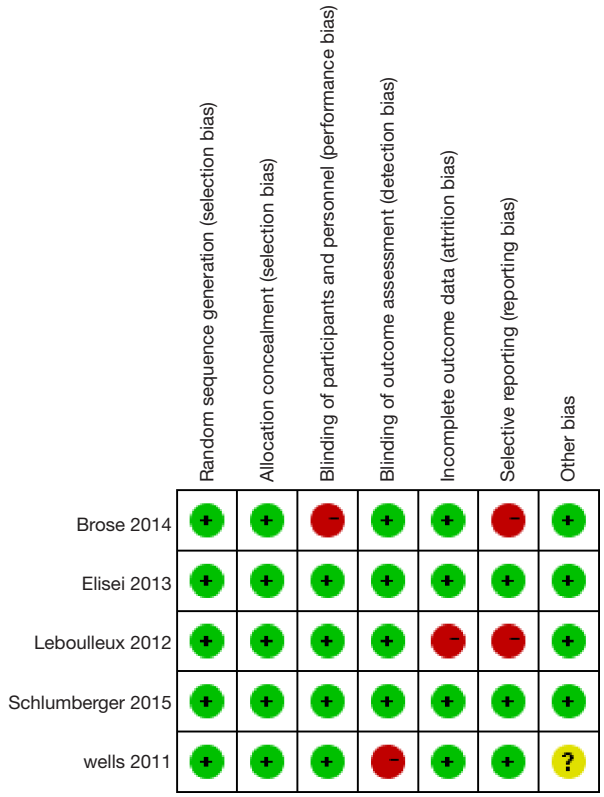

Figure 2 Targeted treatment of thyroid carcinoma included in the literature quality evaluation.

using the Cochrane Risk Bias Assessment Tool. All 5 articles were RCTs (10-14). Four of the studies were rated as high quality and one was evaluated as medium quality (*Figure 2*).

Results of statistical meta-analysis

Drug efficacy analysis

The 5 RCT studies included 991 cases in the drug group and 624 cases in the placebo group. The primary evaluation index of efficacy was PFS, and the secondary indicator was overall survival (OS). In the 5 studies, the PFS for the drug group was 10.8–30.5 months, compared with only 4.0–19.3 months for the placebo group (*Table 1*). In the respective comparison of PFS at 6, 12, and 18 months between the drug and placebo group, the PFS rate of the drug group was significantly improved (6 months PFS: OR =3.23, 95% CI: 2.57 to 4.05, P<0.00001, 12 months PFS: OR =3.38, 95% CI: 2.58 to 4.42, P<0.00001, 18 months PFS: OR =2.48, 95% CI: 1.74 to 3.54, P<0.00001) (*Figure 3*). OS did not differ significantly in the study (6 months: OR =1.53, 95% CI: 1.00 to 2.35, P=0.05, 12 months: OR =1.26, 95% CI: 0.94 to 1.69, P=0.12, 18 months: OR =1.11, 95% CI: 0.87 to 1.42, P=0.39) (*Figure 4*).

Security analysis

The major adverse reactions in 5 studies are shown in *Table 2*. The most frequent treatment-emergent adverse events in the sorafenib group were hand-foot skin reaction (76.3%), diarrhea (6.6%), alopecia (67.1%), and rash or desquamation (50.2%) (10). Common cabozantinib-associated adverse events included diarrhea, palmar-plantar erythrodysesthesia, decreased weight and appetite, nausea, and fatigue, which resulted in dose reductions in 79% of patients and holds in 65% of patients (14). The most common grade 3 or worse adverse events were QTc prolongation [10 (14%) of 73 patients in the vandetanib group *vs.* none in the placebo group], diarrhea [7 (10%) *vs.* none], asthenia [5 (7%) *vs.* 3 (4%)], and fatigue [4 (5%) *vs.* none] (13). Treatment-related adverse effects of any grade, which occurred in more than 40% of patients in the lenvatinib group, were hypertension (in 67.8% of the patients), diarrhea (in 59.4%), fatigue or asthenia (in 59.0%), decreased appetite (in 50.2%), decreased weight (in 46.4%), and nausea (in 41.0%) (12). Common adverse events (any grade) occurred more frequently with vandetanib compared with placebo, including diarrhea (56% *vs.* 26%), rash (45% *vs.* 11%), nausea (33% *vs.* 16%), hypertension (32% *vs.* 5%), and headache (26% *vs.* 9%) (11). However, in the study, we mainly analyzed the incidence of serious ≥3 adverse reactions.

The incidence of adverse reactions in the drug group was significantly higher than that in the placebo group (OR =10.06, 95% CI: 7.46 to 13.55, P<0.00001) (*Figure 5*), and the subgroup of adverse reactions was significantly higher than that in the placebo group.

Diarrhea

There was no statistical heterogeneity between the 5 studies (P=0.95, I^2 =0%). Meta analysis showed that the incidence of diarrhea in the drug group was significantly higher than that of the control group (OR =8.44, 95% CI: 3.86 to 18.47, P<0.000001) (*Figure 5*).

Fatigue

There was no statistical heterogeneity between the 5 studies (P=0.98, I^2 =0%). Meta analysis showed that the incidence of fatigue in the drug group was significantly higher than that of the control group (OR =4.46, 95% CI: 2.31 to 8.64,

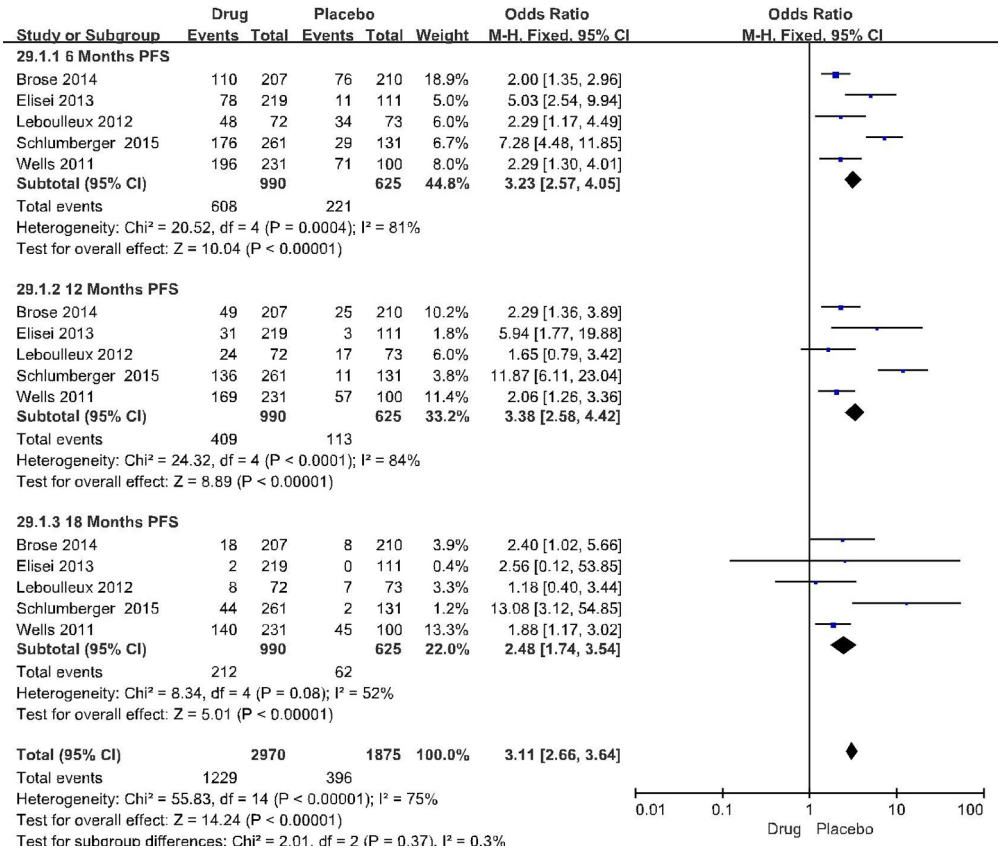

Figure 3 Meta-analysis PFS results for the utility of thyroid carcinoma targeted therapy in the drug and control groups. PFS, progression-free survival.

P<0.00001) (*Figure 5*).

Decreased appetite

There was no statistical heterogeneity between the 5 studies (P=0.21, I^2 =34%). Meta analysis showed that the incidence of decreased appetite in the drug group was significantly higher than that of the control group (OR =5.24, 95% CI: 1.79 to 15.36, P=0.003) (*Figure 5*).

Hypertension

There was no statistical heterogeneity between the 5 studies (P=0.31, I^2 =17%). Meta analysis showed that the incidence of hypertension in the drug group was significantly higher than that of the control group (OR =5.03, 95% CI: 2.50 to 10.12, P<0.00001) (*Figure 5*).

Dyspnea

There was statistical heterogeneity between the 5 studies (P=0.05, I^2 =61%). Meta analysis showed that the incidence of dyspnea in the drug group was not significantly different than that of the control group (OR =0.61, 95% CI: 0.33 to 1.11, P=0.11) (*Figure 5*).

Discussion

The objective of the current study was to evaluate the effectiveness of targeted therapies for thyroid carcinoma. Five RCTs were included. The meta-analysis indicated that targeted therapies, as compared with placebo, were associated with more significant improvements in PFS and in the response rate among patients with thyroid carcinoma. Patients who received targeted therapies had more adverse effects, but the patients were still tolerant. To our knowledge this is the first systematic review and meta-analysis that evaluates the effectiveness of targeted therapies for thyroid carcinoma.

Thyroid carcinoma is the most common malignant tumor of the endocrine system, and has shown the fastest growing

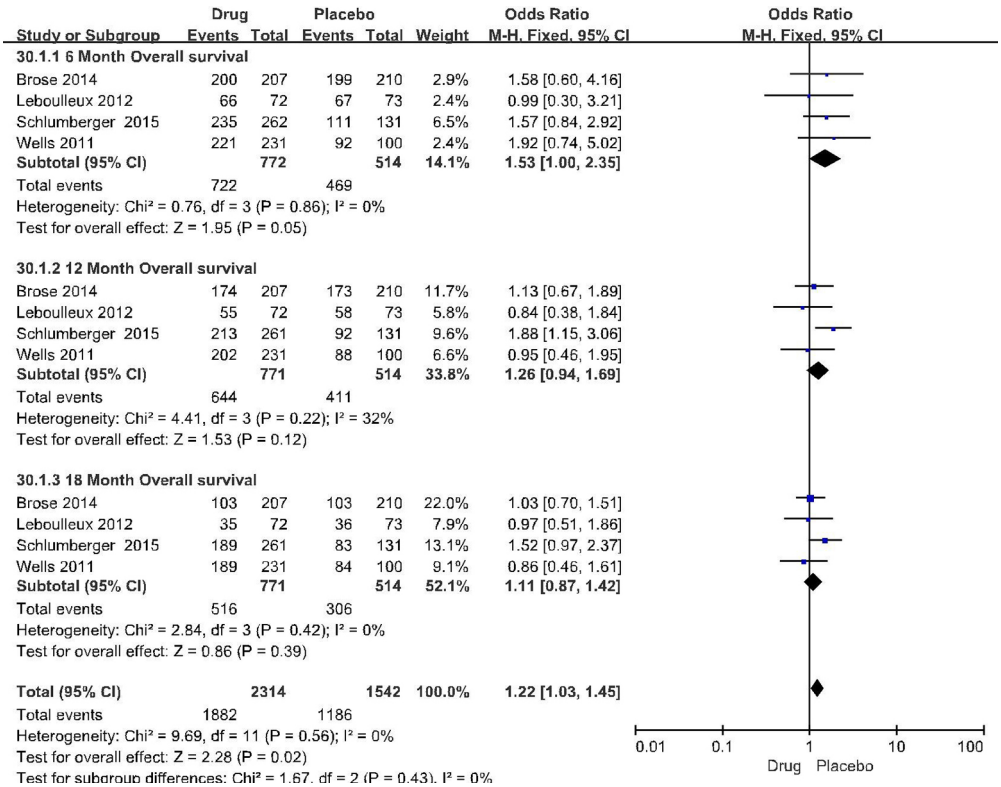

Figure 4 Meta-analysis results for overall survival related to the utility of thyroid carcinoma targeted therapy in the drug and control groups.

Table 2 Targeted thyroid carcinoma targeted therapy included in the study of major adverse reactions

Study number	1st author (year)	Drug	Diarrhea		Fatigue		Decreased appetite		Hypertension		Dyspnea	
			Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
1	Wells 2012	Vandetanib	25/231	2/99	13/231	1/99	9/231	0/99	20/231	0/99	3/231	3/99
2	Leboulleux 2012	Vandetanib	7/73	0/72	4/73	0/72	1/73	2/72	0/73	0/72	2/73	3/72
3	Elisei 2013	Cabozantinib	34/214	2/109	20/214	3/109	10/214	1/109	18/214	1/109	5/214	11/109
4	Brose 2014	Sorafenib	12/207	2/209	12/207	3/209	5/207	0/209	20/207	5/209	10/207	6/209
5	Schlumberger 2015	Lenvatinib	21/261	0/131	24/261	3/131	14/261	0/131	11/261	3/131	0/261	0/131

incidence in recent years, with age standardized (world population) rates of 6.10 and 1.90 per 100,000 persons (15). Thyrotropin (TSH) inhibition or RAI treatment after surgery, can have the most benefit as a routine treatment for thyroid carcinoma, with the 5-year survival rate of patients with thyroid carcinoma increasing to 97.8% (16). However, 7–23% of patients develop distant metastases (17), and so there are still a large number of refractory thyroid carcinomas, such as advanced, recurrent, metastatic thyroid, medullary, and anaplastic thyroid carcinoma. Due to a lack of treatment, the survival of patients is very unsatisfactory (18,19). In the context of today's precision medicine era, molecular targeted therapy is increasingly valued and is playing an ever-growing role in the treatment of thyroid carcinoma; its development has offered these patients a new hope.

At present, most of the research on targeted therapy of thyroid carcinoma is Phase I study and Phase II single-

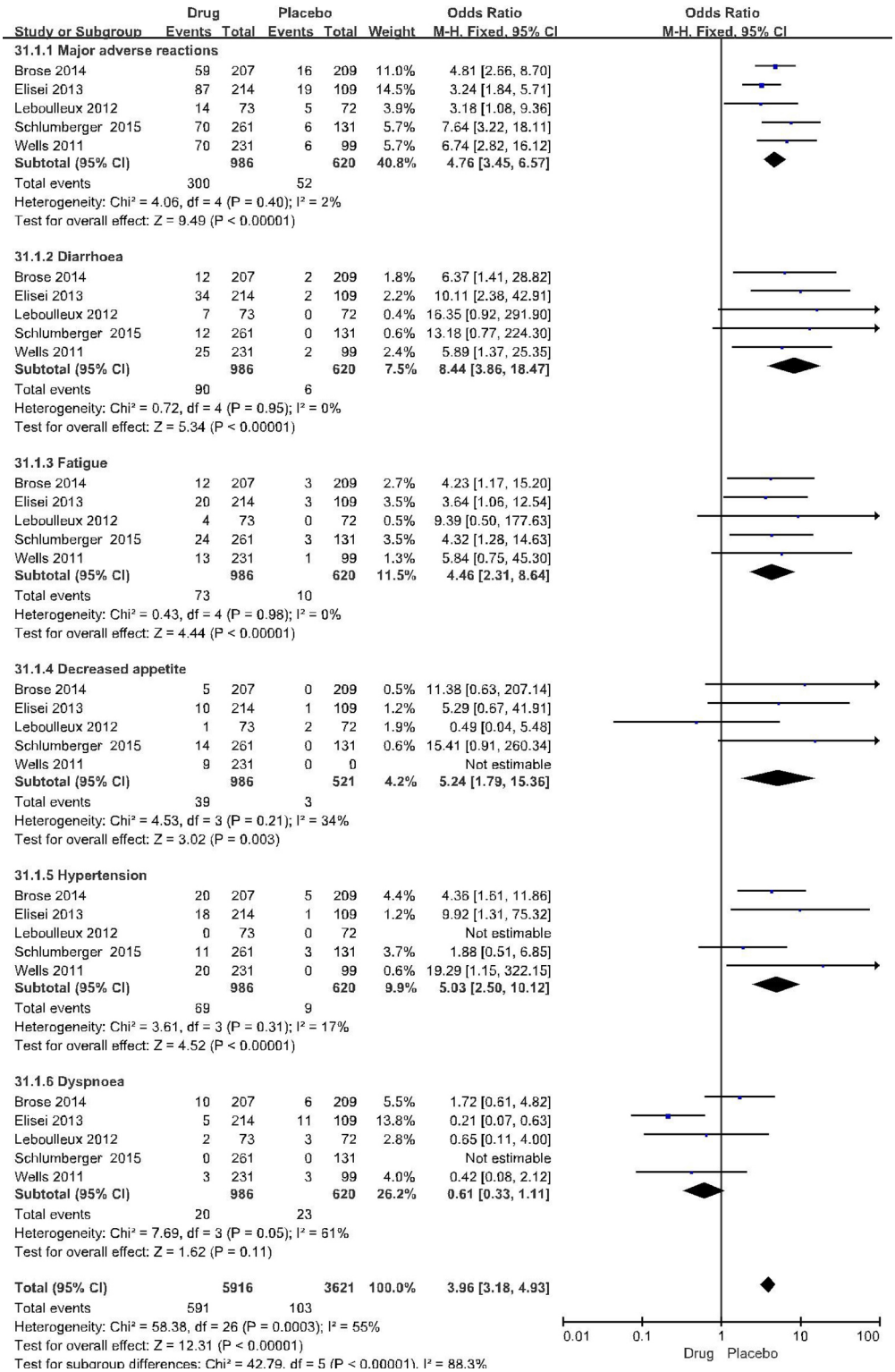

Figure 5 Meta-analysis results of adverse reactions in thyroid carcinoma targeted therapy.

arm study. There are still a few Phase III and RCT clinical studies. Therefore, this study evaluated the efficacy and safety of targeted drugs by meta-analysis. The drugs included in the study were lenvatinib, vandetanib, cabozantinib, and sorafenib (10-14). Sorafenib, a tyrosine kinase inhibitor that inhibits VEGFRs 1, 2, and 3, PDGFR β, Raf-1, RET, and BRAF, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of iodine-131-refractory thyroid carcinoma on the basis of results of a phase 3 trial showing a 5-month improvement in median PFS (10). Lenvatinib is an oral, multi-targeted tyrosine kinase inhibitor of the VEGFRs 1, 2, and 3; the FGFRs 1 through 4; and the PDGFR α, RET, and KIT signaling networks (20,21). Cabozantinib is a TKI that targets three relevant pathways in MTC: MET, VEGFR2, and RET (22). Vandetanib is a once-daily oral agent that selectively targets RET, VEGFR, and EGFR signaling (23,24).

This study showed that targeted drugs effectively improve patients' PFS (6 months PFS: OR =3.23 , 95% CI: 2.57 to 4.05, P<0.00001, 12 months PFS: OR =3.38, 95% CI: 2.58 to 4.42, P<0.00001, 18 months PFS: OR =2.48, 95% CI: 1.74 to 3.54, P<0.00001). The total PFS of drug group was more than 3 times that of the control group(OR =3.11, 95% CI: 2.66 to 3.64, P<0.00001) (*Figure 3*), indicating that the targeted therapy has a stable therapeutic effect.

This study also discussed several serious adverse events (incidence of serious adverse event ≥ grade 3) with the highest incidence of each drug group, the incidence of adverse reactions in the drug group was significantly higher than that in the placebo group (OR =10.06, 95% CI: 7.46 to 13.55, P<0.00001) (*Figure 5*). Serious adverse reactions common to the four drugs included diarrhea, fatigue and high blood pressure. Hypertension was the most common adverse event in the lenvatinib group (in 67.8% of the patients), and the most common adverse events (any grade) that occurred with vandetanib were diarrhea [seven (10%) *vs.* none]. The most frequent treatment-emergent adverse events in the sorafenib group were hand-foot skin reaction, but diarrhea was the most adverse event in cabozantinib, which is consistent with the previous research (25-28). By supporting treatment or reducing the dose of the drug, almost all patients can tolerate these adverse reactions until the end of the trial. The adverse reactions were significantly reduced after the reduction of the drug dose (11,12,14), but there was no RCT to prove the efficacy at low doses, and further research is needed.

There are still many targeted drugs under study. In 2011, the first BRAFV600E targeted inhibitor, vemurafenib, was approved by the US FDA. A current phase II clinical trial on Willofini is also underway (29).

The MEK1/2 inhibitor AZD6244 (selumetinib) is a potent and highly selective MEK1 inhibitor that is considered to be an adjuvant therapy for patients with inadequate response to RAI. In 2013, selumetinib was awarded the orphan drug qualification by the US FDA for the treatment of advanced differentiated thyroid carcinoma (DTC), demonstrating potential in the treatment of radioiodine-refractory (RR)-DTC patients (30). In addition, there are many other targets for the treatment of refractory thyroid carcinoma, such as RET, ALK, RAS, MEK, BRAF, MEK1/2, histone deacetylase (HDAC) and mechanistic target of rapamycin (MTOR). Phase I and phase II trials of these targeted drugs are ongoing.

There are several limitations in our meta-analysis. First, although all the included studies were prospective RCTs, the patient population and study sample were small, and thus bias was inevitable. Secondly, there was no stratified analysis of factors that might have influenced effectiveness, such as gender, age, and type of genetic mutation. Finally, the confounding effect of different experience of physician in different medical institutions was not accounted for.

In summary, the findings of this study indicate that targeted drugs can significantly prolong PFS in patients with thyroid carcinoma. Although the incidence of adverse reactions was significantly higher than that of the control group, the patient was still tolerant. At present, most of the targeted research on refractory thyroid carcinoma is in the clinical trial stage, and there is still no strong evidence to confirm its clinical effect. Therefore, the potential risks and benefits must be considered comprehensively before targeted therapy can proceed. It is believed that with the emergence of more targeted therapies, breakthroughs can be made in the clinical treatment of refractory thyroid carcinoma with more substantial benefits being brought to patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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