Clinical Response and Toxicities of TKLS in Advanced Medullary Thyroid Cancer: Systematic Review and Meta-Analysis

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Abstract

Background and aim: Several randomized controlled trials (RCTs) have investigated the effectiveness of different TKIs. However, these studies have not been able to provide conclusive results. The aim of this systematic review and Meta-analysis was effectiveness and safety of different TKIs and toxicities of TKIs in patients with advanced or metastatic thyroid cancer.

Methods: MEDLINE, PubMed, Cochrane Library, Embase, ISI, google scholar were used as electronic databases to perform a systematic literature until 2019. A commercially available software program (Endnote X9) was used for electronic title management. Searches were performed with keywords, "thyroid", "cancer OR carcinoma OR neoplasm", "vandetanib OR motesanib OR lenvatinib OR sorafenib OR axitinib OR sunitinib OR imatinib OR cabozantinib OR selumetinib OR pazopanib", "tyrosine kinase inhibitor", "VEGF inhibitor OR therapy OR target therapy" "protein kinase inhibitor".

Results: All trials investigated the OS of patients receiving TKI treatment. lenvatinib showed significantly higher OS than control group. No significant difference in OS was observed between groups among the MTC patients. Except of vandetanib, sorafenib, cabozantinib and lenvatinib had a significant better partial RRs than control, respectively. Pooling result of all TKIs exhibited a significantly higher partial RR than did the control group.

Conclusions: these drugs is important to manage AEs efficiently and proactively, and determine if the drug is no longer effective.

Keywords: Medullary Thyroid Cancer, MTC, TKI.

Introduction

Medullary thyroid cancer (MTC) which arises from par follicular cells is less common than differentiated thyroid cancer (DTC) constituting between 2 and 5% of all thyroid malignancies [1, 2]. 13–15% of patients of MTC present with distant metastasis (DM) and have a 10-year survival of approximately 20% [3]. The medullary thyroid carcinoma (MTC) occurs in two forms: sporadic (75%) and hereditary (25%), in most cases with mutations in the proto-oncogene tyrosine-protein kinase receptor gene RET. Upon diagnosis, the most common treatment method of the disease is surgical intervention, including total thyroidectomy and central neck dissection, given that metastatic spread to cervical lymph nodes is a common event. Surgical cure is possible, but in progressive cases of the disease and distant metastatic spread, this treatment method is not sufficient [4, 24]. Disease-form of MTC needs a systemic treatment, but is insensitive to conventional chemotherapy, external beam radiation, and radioactive iodine therapy for thyroid cancer (TC). Therefore, a targeted therapy is needed. Tyrosine kinase inhibitors (TKIs), such as pazopanib and cabozantinib are proposed as a promising new therapeutic option. TKIs work by blocking internal signaling cascades involved in the induction of angiogenesis, an important process for the tumor to acquire enough nutrients for further expansion [5, 6]. In addition, several drugs acting on other steps of the molecular pathway to MTC are being investigated with promising results. The application of targeted radionuclide therapy also provides an effective treatment modality with good QOL [5]. Two pharmacological approaches are available to interrupt VEGF signaling. First is the direct inhibition of VEGF using monoclonal antibodies, preventing the binding to their receptors [19-21]. However, it has been shown that cancers are able to develop resistance towards these drugs, which in turn can lead to an increase in expression of hepatocyte growth factor receptor MET, the only known receptor for HGF. Consecutively, this leads to an increase in aggressiveness and metastatic progression of the tumor [7]. The second pharmacological approach to

prevent tumor progression is the inhibition of the RTKs, prompting a blockage of consecutive intracellular phosphorylation cascades. This is the method of action of cabozantinib, pazopanib, and vandetanib [8, 18]. However, such therapies also have adverse effects (AEs), and for tyrosine kinase inhibitors, two of the most common side effects are proteinuria and hypertension [4, 6, 22]. Several randomized controlled trials (RCTs) have investigated the effectiveness of different TKIs. However, these studies have not been able to provide conclusive results. The aim of this systematic review and Meta-analysis was effectiveness and safety of different TKIs and toxicities of TKIs in patients with advanced or metastatic thyroid cancer.

Material and Methods

Search strategy

MEDLINE, PubMed, Cochrane Library, Embase, ISI, google scholar were used as electronic databases to perform a systematic literature until 2019. A commercially available software program (Endnote X9) was used for electronic title management. Searches were performed with keywords, "thyroid", "cancer OR carcinoma OR neoplasm"," vandetanib OR motesanib OR lenvatinib OR sorafenib OR axitinib OR sunitinib OR imatinib OR cabozantinib OR selumetinib OR pazopanib"," tyrosine kinase inhibitor", "VEGF inhibitor OR therapy OR target therapy" "protein kinase inhibitor".

Study inclusion and exclusion criteria

The following inclusion criteria were applied:

1. Outcome of TKI therapy in patients with locally advanced, unrespectable, or metastatic thyroid cancer
2. Full text available
3. TKI regimens
4. The stage of thyroid cancer, and the definition and evaluation of prognostic outcomes.
5. Randomized controlled study
6. Studies limited to humans

The following exclusion criteria were applied:

1. Inclusion of less than twenty patients.
2. Patients received systemic anticancer therapy for <3 weeks
3. Patient cohorts were reported in duplicate

Quality assessment of selected studies

The methodological quality of each study by using the risk of bias method recommended by the Cochrane Collaboration. Several domains were assessed, including the adequacy of the randomization, allocation concealment, blinding of the patients and outcome assessors, length of follow-up, information provided to the patients regarding study withdrawals, whether intention-to-treat analysis was performed, and freedom from other biases.

Data Extraction and method of analysis

Baseline and outcome data were independently abstracted, study designs, study population characteristics, inclusion and exclusion criteria, thyroid cancer types, TKI regimens, and adverse events were extracted. Heterogeneity between RCT's, meta-analysis (weighted mean difference and 95% confidence interval), forest plots were assessed using a commercially available software program (Comprehensive Meta-Analysis Stata. V14).

Results

A total of 154 potentially relevant titles and abstracts were found during the electronic and manual search. During the first stage of study selection, 81 publications were excluded based on title and abstract. For the second phase, the complete full-text articles of the remaining 73 publications were thoroughly evaluated. A total of 67 papers had to be excluded at this stage because they did not fulfil the inclusion criteria of the present review. Finally, a total of six publications fulfilled the inclusion criteria required for this systematic review (Figure 1).

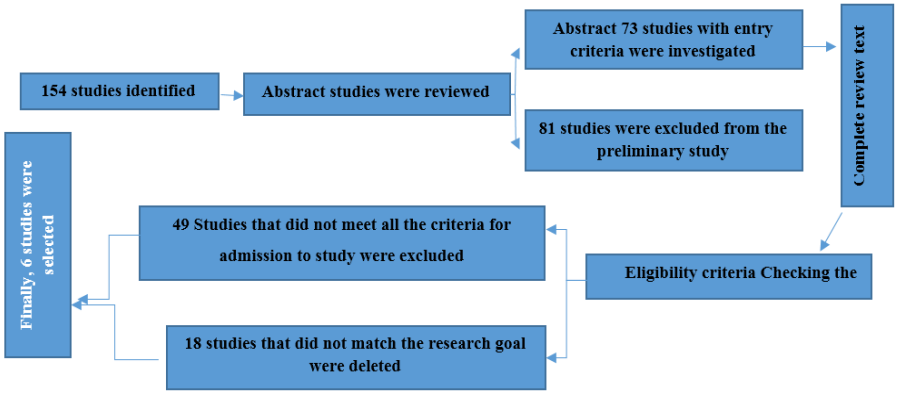

Figure-1: Study Attrition Diagram

Among table 1, Schlumberger et al, Kiyota et al and Wirth et al analyzed patient outcomes from the same trial (the phase 3 SELECT trial) [13-15]. Kiyota et al, mainly focused on analyzing the outcome of TKI treatment in Japanese patients [14]. 303 Patients received vandetanib in two trials [9, 10, 223], 219 Patients received Cabozantinib in one trial (11), 207 Patients received sorafenib in one trial [12] and 783 Patients received lenvatinib in three trial [13-17]. The median PFS was investigated in all trials. 887 Patients were placed in the placebo group. Also Table 2 shows a summary of the methodological quality of the included trials. All trials investigated the OS of patients receiving TKI treatment. lenvatinib showed significantly higher OS than control group. No significant difference in OS was observed between groups among the MTC patients (figure 2). In MTC patients, cabozantinib treatment groups also showed a significantly higher PFS than control. TKIs treatment exhibited significantly higher PFS than did the control group in MTC (figure3). Response rate All 6 trials investigated the RR of TKI treatments. Total 1512 patients treated with TKIs. Except of vandetanib, sorafenib, cabozantinib and lenvatinib had a significant better partial RRs than control, respectively. Pooling result of all TKIs exhibited a significantly higher partial RR than did the control group (Figure 4).

Table-1: Studies Included in the Meta-analysis

	Study/year	Cancer type	No. of patients		Age, y		intervention
1	Leboulleux et al / 2012 (9)	PTC/FTC/poorly differentiated	V: 72	P: 73	V: 63 (29-81)	P: 64 (23-87)	V: Vandetanib 300 mg qd P: Placebo
2	Wells et al / 2012 (10)	MTC	V: 231	P: 100	V: 50.7*	P: 53.4	V: Vandetanib 300 mg qd P: Placebo
3	Elisei et al / 2013 (11)	MTC	C: 219	P: 111	C: 55 (20-86)	P: 55 (21-79)	C: Cabozantinib 140 mg qd P: Placebo
4	Brose et al / 2014 (12)	PTC/FTC/Hurthle cell/poorly differentiated/others	S: 207	P: 210	S: 63 (24-82)	P: 63 (30-87)	S: Sorafenib 400 mg twice P: Placebo
5	Schlumberger et al/ 2015 (13)	PTC/FTC/poorly differentiated	L: 261	P: 131	L: 64 (27-89)	P: 61 (21-81)	L: Lenvatinib 24 mg qd P: Placebo
6	Kiyota et al / 2015 (14)	PTC/FTC/poorly differentiated	L: 261	P: 131	L: 64 (27-89)	P: 61 (21-81)	L: Lenvatinib 24 mg qd P: Placebo
7	Wirth et al / 2018 (15)	DTC	L: 261	P: 131	NA	NA	2:1 to lenvatinib (24 mg/d on a 28-day cycle) or placebo

C, cabozantinib; DTC, differentiated thyroid cancer; FTC, follicular thyroid cancer; L, lenvatinib; MTC, medullary thyroid cancer; P, placebo; PTC, papillary thyroid cancer; S, sorafenib; V, vandetanib; Data are presented as the median (range) except where* indicates the mean.

Table-2: Methodological quality assessment of included studies

Study/year	Allocation generation	Allocation concealment	Blinding of patients and assessors	Loss to follow-up (%)	Selective reporting
Leboulleux et al / 2012 (9)	Computer generated	Unclear	Double blinded	0	Low risk
Wells et al / 2012 (10)	Unclear	Unclear	Double blinded	0.30	Low risk
Elisei et al / 2013 (11)	Unclear	Unclear	Double blinded	5	Low risk
Brose et al / 2014 (12)	Computer generated	Unclear	Double blinded	1.2	Low risk
Schlumberger et al/ 2015 (13)	Computer generated	Unclear	Double blinded	0	Low risk
Kiyota et al / 2015 (14)	Computer generated	Unclear	Double blinded	0	Low risk
Wirth et al / 2018 (15)	Computer generated	Unclear	Double blinded	0	Low risk

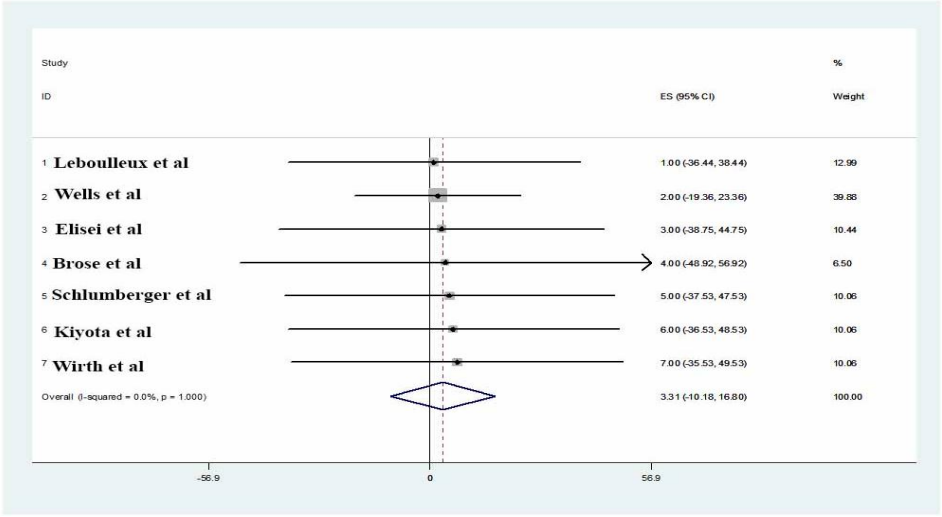

Figure-2: Heterogeneity chi-squared = 0.08 (d.f. = 6): z= 0.44 p = 0.0019 CI= 95%

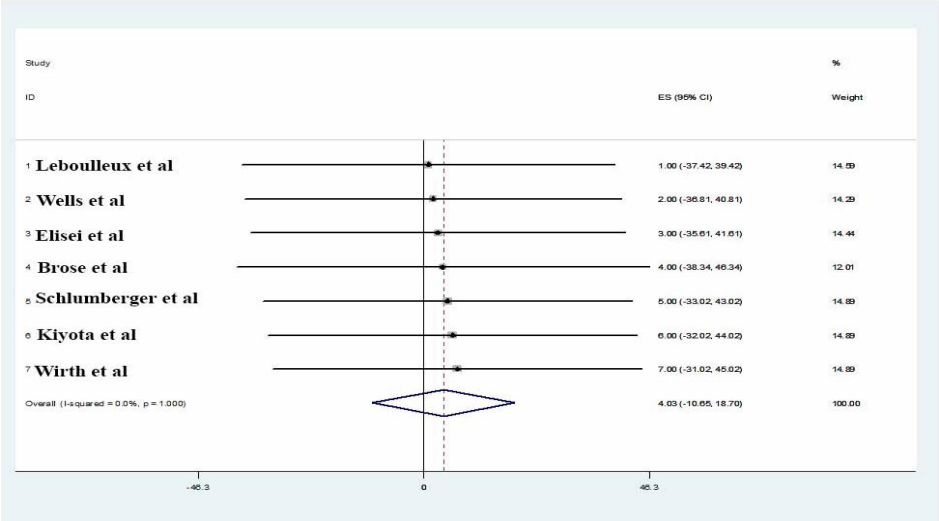

Figure-3: Heterogeneity chi-squared = 0.07 (d.f. = 6): z= 0.63 p = 0.007. CI=95%

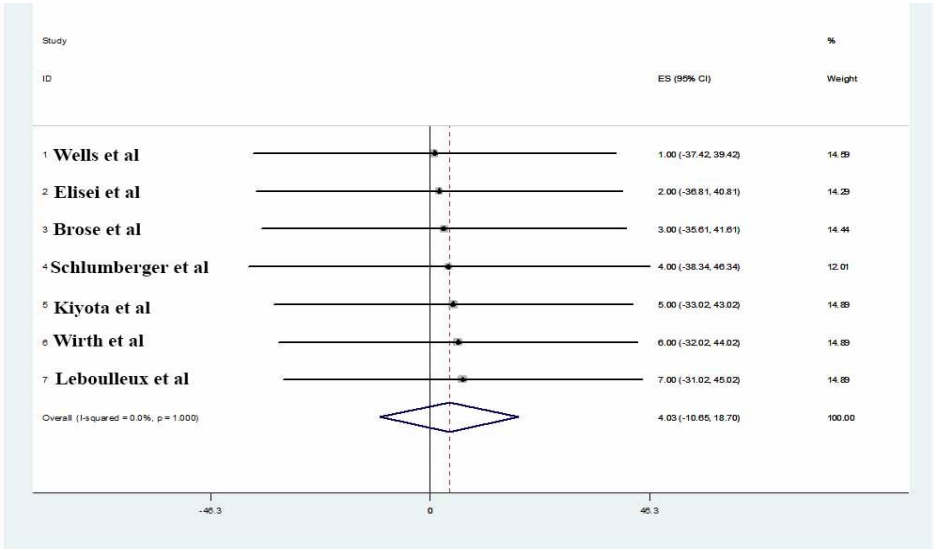

Figure-4: Heterogeneity chi-squared = 0.01 (d.f. = 5): z= 0.54 p = 0.001. CI=95%

Discussion

A concern when treating any condition is that the efficacy of the chosen drug should always be sufficient enough to make up for the often rather extensive AEs. As specified above, hypertension is a common AE in treatments with TKIs, but also other serious AEs such as proteinuria, hemorrhage, pulmonary embolism/venous thrombosis, nausea, vomiting, diarrhea, and skin toxicity are of relevance and affect quality of life [6]. Hypertension as a side effect is not a problem, patients complain about it due to its asymptomatic nature. Therefore, it is not hypertension, but the cardiovascular complications following hypertension that are of concern and necessitate treatment. Tyrosine kinase inhibitors like pazopanib, cabozantinib, or vandetanib act by inhibiting the VEGF signaling cascade and have an anti-angiogenetic effect, preventing tumor growth and providing a promising treatment option to otherwise untreatable cancers [4]. The drugs do not come without AEs though, the most common effect is hypertension. Hypertension is manageable in most cases, either through a lowering of TKI doses or through treatment with antihypertensive drugs. Unfortunately, in a few cases, the hypertension is so severe that the risk-benefit-ratio requires the discontinuation of TKI treatment. In all other cases, treatment with TKIs significantly prolongs progression-free survival for patients with progressive MTC. In addition, the treatment also prolongs overall survival, though not always to a statistically significant level.

Therefore, developing treatment strategies for the AEs are required in order to secure TKI treatment for all patients with progressive MTC. Treating thyroid cancer with TKIs is unavoidably followed by certain AEs, which deteriorate the quality of life of patients. According to a meta-analysis of RCTs, at least 20% of patients discontinue treatment because of potential AEs. The general side effects of TKIs, including fatigue, weight loss, diarrhea, hypertension, and skin problems, are typically manageable. The symptoms of rash and alopecia have been reported to occur with a high ratio when patients were treated with sorafenib and vandetanib [10, 12]. Outcomes for Japanese patients were assessed by Kiyota et al in relation to those for the overall population in Schlumberger trial [13, 14]. Efstathiadou et al showed, TKI treatment in MTC exhibited a significant benefit in terms of reducing progression of the disease. The results were similar to the present study, also Liu et al in meta-analysis study showed TKIs significantly improved PFS and RR in patients with advanced or metastatic DTC or MTC. All TKI treatments evaluated in TC are related to gastrointestinal toxicities, which deeply impact on patient's adherence to treatment and quality of life. We recommend thoroughly evaluating patients' health status and cautiously using TKIs to maximize their benefits and minimize their toxicity.

Conclusion

TKI treatment in MTC exhibited a significant benefit in terms of reducing progression of the disease, however, careful monitoring of patients on these drugs is important to manage AEs efficiently and proactively, and determine if the drug is no longer effective.

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