EFFICACY AND SAFETY OF MULTI-TARGETED KINASE INHIBITORS IN PROGRESSIVE, RADIOIODINE-REFRACTORY DIFFERENTIATED THYROID CANCERS: A META-ANALYSIS

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Abstract:

Purpose: A meta-analysis was conducted to evaluate the impact of oral multitargeted kinase inhibitors (MTKIs) in radioactive-iodine refractory locally advanced, recurrent/metastatic differentiated thyroid cancer (DTC) on disease control rate (DCR), progression free survival (PFS) and overall survival (OS) rates.

Materials and methods: The PubMed/MEDLINE, CANCERLIT, EMBASE, Cochrane Library database, and other search engines were searched to identify randomized controlled trials (RCTs) comparing MTKIs with placebo in locally advanced, recurrent/metastatic DTC. Pooled data were expressed as odds ratio (OR), with 95% confidence intervals (CIs; Mantel–Haenszel fixed-effects model).

Results: Three RCTs with a total patient population of 954 patients were identified. The use of MTKIs was associated with improved PFS (OR: 0.262, 95% confidence interval (CI): 0.19–0.35; heterogeneity (I²) = 22.4%; P < 0.0001), improved DCR (complete and partial responses + stable disease), P < 0.0001), and improved OS 0.66, 95% CI: 0.46-0.96 (I²=43%, P = 0.034). Lenvatinib (compliance = 87%) was associated with more Grade ≥ 3 hypertension. However, its other adverse effects were much lower than Sorafenib (compliance = 56%) and Vandetanib.

Conclusion: In RAI-refractory recurrent, metastatic DTC patients, Lenvatinib and Sorafenib were associated with improved PFS, DRC and OS rates, while the compliance was better with Lenvatinib.

Key words: Radioactive iodine refractory, progressive differentiated thyroid cancer, multi-targeted kinase inhibitors, meta-analysis.

Introduction

Differentiated thyroid cancers (DTC), which include papillary, follicular and poorly differentiated subtypes constitutes 90% of all thyroid malignancies. DTC have generally an excellent outcome after the traditional treatment which includes, surgery, thyroid stimulating hormone (TSH) suppression therapy, and radioactive iodine (RAI) therapy, and in some cases radiation therapy. Despite this, 10% - 25% DTC patients experience locoregional recurrence and distant metastasis which needs additional treatment measures in the form of surgery or RAI for cure or significant palliation. Patients with iodine-avid recurrent or metastatic disease from DTC may continue to receive multiple sessions of RAI. Subsequently, about two thirds of such patients become refractory to RAI uptake. Systemic chemotherapy has been found relatively ineffective with poor response rates (10% - 37%) and has shown to be associated with significant toxicities.
During the last decade, aberrant signaling pathways have been investigated in the development, progression, and metastasis of DTC such as BRAF and RAS point mutations and rearrangement of the RET proto-oncogene in papillary cancers; RAS point mutations and rearrangement of the PPARG and PAX8 genes in follicular cancers; and RAS point mutations, EGFR, VEGF receptors overexpression and PIK3CA in poorly differentiated cancers. Identification of these potential targets have led to the development of novel multitargeted kinase inhibitors (MTKIs) for RAI-refractory recurrent, metastatic DTC. However, efficacy, safety profile and impact on treatment outcome by MTKIs has not been well studied in DTC patients.

We conducted a meta-analysis to assess the impact of MTKIs in RAI-refractory, locally advanced, recurrent, metastatic DTC on progression free survival (PFS), disease control rate (DCR), toxicity profile, and overall survival (OS).

**Materials and Methods:**

**Studies and study population**

Eligible studies had to be either complete reports of prospective, randomized controlled trials (RCT) or well-controlled retrospective studies. The abstracts from which full details were available were also included. The PubMed/MEDLINE, CANCERLIT, EMBASE, Cochrane Library database, Web of Science, Academic Search Premier, and CINAHL were searched (period 2000-2015) using the terms “(thyroid cancer, differentiated thyroid cancer, carcinoma), (papillary, follicular, poorly differentiated thyroid cancer, carcinoma), (tyrosine kinase inhibitors, multitargeted kinase inhibitors, Sorafenib, Sunitinib, Axitinib, Motesanib, Vandetanib, Pazopanib, Lenvatinib), the efficacy and safety”. These terms were then combined to search for eligible studies. The relevant articles were selected by two investigators. Only studies that met the following criteria were included.

Inclusion criteria were (a) histologically confirmed DTC (papillary, follicular and poorly differentiated cancers), (b) RAI-refractory recurrent or metastatic DTC and (c) treated with oral MTKIs as monotherapy. Patients with DTC who received anti-angiogenic drugs other than MTKIs or Histone Deacetylase Inhibitors, peroxisome proliferator-activated receptor gamma (PPARG) agonists, Retinoid receptor agonists and Proteasome inhibitors were excluded.

**Outcome measures and review analysis:**

The outcome measures were PFS, DCR, toxicity profile and OS. All analyses were carried out on an intention to treat analysis basis. For the categorical variables, weighted odds ratios and their 95% confidence intervals (95% CI) were calculated. The results were tested for heterogeneity (I2) using Cochran’s Q test at the significance level of p < 0.05. If there was evidence of heterogeneity, a random effects model was used for meta-analysis; otherwise fixed effects model was used. The odds ratio and 99% CI were calculated for each RCT and presented in forest plot. The disease control rate (DCR) was defined as, complete response (CR) + partial response (PR) + stable disease (SD) based on Response Evaluation Criteria in Solid Tumours (RECIST) criteria and follow up period mentioned in each RCT. Publication bias was evaluated using the funnel graph, the Begg-Mazumdar adjusted rank correlation test and the Egger test. All analyses were performed using comprehensive meta-analysis software version 3.3.070.

**Results:**

The electronic search revealed 23,204 relevant citations, out of which 352 were selected. Finally, three RCTs were identified that fulfilled the criteria.
**Progression free survival:**

All three RCTs with a population of 954 patients analysed the PFS rate as one of the outcomes. PFS rates were significantly higher in patients treated with MTKIs especially Lenvatinib and Vandetanib ($p < 0.0001$). The pooled OR was 0.262 (95% CI: 0.19–0.35; $I^2 = 22.4\%$) Figure 2.

**Disease control rate:**

Two RCTs with 809 patients examined the DCR as one of the outcomes. MTKIs especially Lenvatinib was associated with significantly higher DCR ($p < 0.0001$) Figure 3.

**Overall survival:**

All three RCTs, with 954 patients, addressed the OS as one of the outcomes. Two RCTs of Sorafenib and Lenvatinib showed a significant improvement in the OS, while one RCT of Vandetanib showed no survival benefit. The pooled OR was 0.66, 95% CI: 0.46-0.96 ($I^2=43\%, P = 0.034$) Figure 4.
Table 1: Prospective randomized, phase II/III trials in refractory differentiated thyroid cancer with multitargeted kinase inhibitors included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients (TKI/Control)</th>
<th>Year</th>
<th>RCT type/Country</th>
<th>TKI type</th>
<th>Control</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leboulleux S, et al 10</td>
<td>145 (72/73)</td>
<td>2007-2008</td>
<td>Multicentre/ France</td>
<td>Vandetanib 300 mg PO daily</td>
<td>Placebo</td>
<td>PFS</td>
<td>TTP, ORR and DCR, toxicity profile</td>
<td>20 months</td>
</tr>
<tr>
<td>DECISION trial 11</td>
<td>417 (207/210)</td>
<td>2009-2011</td>
<td>Multicentre/UK, Germany, Italy, Poland, Denmark, France, South Korea, USA, Netherlands</td>
<td>Sorafenib 400 mg PO twice daily</td>
<td>Placebo</td>
<td>PFS</td>
<td>OS, TTP, ORR and DCR, toxicity profile</td>
<td>36 months</td>
</tr>
<tr>
<td>SELECT trial 12</td>
<td>392 (261/131)</td>
<td>2011-2012</td>
<td>Multicentre/ USA, Australia, France, UK, Japan, Canada, South Korea, Italy, Brazil</td>
<td>Lenvatinib 24 mg PO daily every 28 days</td>
<td>Placebo</td>
<td>PFS</td>
<td>OS, TTP, ORR and DCR, toxicity profile</td>
<td>36 months</td>
</tr>
</tbody>
</table>

Abbreviations: TKI = Tyrosine Kinase Inhibitors, RCT= randomized control trial, PO = per oral, PFS = progression free survival, TTP= time to progression, ORR = objective response rate, DCR = disease control rate

Table 2: Inclusion and exclusion criteria of included studies in meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean age</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Previous therapy</th>
<th>Definition of DCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leboulleux S, et al 10</td>
<td>-</td>
<td>Aged ≥18 years, with locally advanced/ metastatic refractory DTC (papillary, follicular, or poorly differentiated)</td>
<td>Prior targeted therapy, thalidomide, or chemotherapy</td>
<td>Radioactive iodine ablation</td>
<td>A complete or partial Response (CR or PR) or durable stable disease (SD) for ≥23 weeks</td>
</tr>
<tr>
<td>DECISION trial 11</td>
<td>63 years</td>
<td>Aged ≥18 years, with locally advanced/ metastatic refractory DTC (papillary, follicular, or poorly differentiated)</td>
<td>Prior targeted therapy, thalidomide, or chemotherapy</td>
<td>Radioactive iodine ablation</td>
<td>A complete or partial Response (CR or PR) or durable stable disease (SD) for ≥23 weeks</td>
</tr>
<tr>
<td>SELECT trial 12</td>
<td>64 years</td>
<td>Aged ≥18 years with locally advanced, metastatic refractory DTC, at least one measurable lesion without iodine uptake on any iodine-131 scan</td>
<td>Prior targeted therapy, or chemotherapy</td>
<td>Radioactive iodine ablation within 12 months</td>
<td>A complete or partial Response (CR or PR) or durable stable disease (SD) for ≥23 weeks</td>
</tr>
</tbody>
</table>

Abbreviations: DTC = Differentiated thyroid cancer, DCR = disease control rate, CR = complete response, PR = partial response, SD = stable disease

Toxicity profile:
All three TCTs with 954 patients reported the toxicities, dose reductions and compliance as one of the outcomes. Lenvatinib (compliance = 87%) was associated with more Grade 3 hypertension, however other adverse effects were much lower than Sorafenib (compliance = 56%) and Vandetanib (compliance not reported) Table 3.

**Table 3:** Incidence of toxicity profile ≥ grade 3 in included studies in meta-analysis

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Vandetanib (%)</th>
<th>Sorafenib (%)</th>
<th>Lenvatinib (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>20</td>
<td>41.8</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10</td>
<td>11</td>
<td>8.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>11</td>
<td>9.2</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>-</td>
<td>42</td>
<td>3.4</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>-</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>-</td>
<td>-</td>
<td>2.7</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>-</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>-</td>
<td>-</td>
<td>5.4</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Skin/desquamation</td>
<td>-</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>14</td>
<td>-</td>
<td>1.5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>-</td>
<td>-</td>
<td>3.8</td>
</tr>
</tbody>
</table>

**Publication bias**

The resultant funnel plot was significantly narrower with statistical significance by Egger test of *P* = 0.05 Figure 5.

**Discussion:**

![Funnel plot of publication bias](image)
In present meta-analysis, the pooled analysis showed that MTKIs (Lenvatinib, Sorafenib and Vandetanib) significantly improve the PFS and DCR rates, in RAI refractory DTC patients. Further, Lenvatinib and Sorafenib showed a trend of increased OS rates. Past experience obtained from using MTKIs has shown that the adverse effects associated with VEGFR inhibition includes hypertension, proteinuria, delayed wound healing, bleeding, bowel perforation, and thrombosis. In the present meta-analysis, the incidence of severe hypertension was much higher with Lenvatinib, which warrants its use with extreme caution in hypertensive patients. On other hand Sorafenib resulted in more grade 3 ≥ hand-foot syndrome and Vandetanib resulted in significant QTc prolongation. Possible explanation for relatively higher adverse effects in DTC patients as compared to patients of renal and hepatocellular cancers treated by similar MTKIs could be the prior multiple RAI sessions or high RAI cumulative dose, which suggest possible radiosensitizing effects of MTKIs; however, future phase I and II trials can give answers by use of MTKIs in RAI naïve DTC patients. Patient related compliance was significantly higher with Lenvatinib. In contrast to present meta-analysis, previous meta-analysis which was conducted by Klein Hesselink EN and colleagues was criticized mainly for two reasons, (a) primary objective was limited only to response rates and (b) medullary carcinoma of thyroid was not excluded to see absolute benefit of MTKIs in DTC; however, this study concluded that MTKIs in thyroid cancer show a modest response rates; and among MTKIs response rates were promising with Lenvatinib and Vandetanib.

The strengths of our meta-analysis were; (1) completeness of the search strategy, including searching multiple databases, trial registries, and conference proceedings for RCTs comparing MTKIs to the placebo group in RAI refractory locally advanced/metastatic DTC patients; (2) DCR rates; and (3) evaluation of the PFS and OS benefit and toxicity profile of MTKIs. The limitations of our meta-analysis were (1) inherent methodological issues in the included trials (risk of bias); (2) attrition bias and (3) reporting bias in included RCTs.

Conclusion:

In view of this meta-analysis and magnitude of the problem of RAI refractory recurrent, metastatic DTC and efficacy and safety of MTKIs, Lenvatinib and Sorafenib were associated with improved PFS, DCR and OS rates, while the compliance was better with Lenvatinib. However, oncologists and endocrinologists should be aware of proper case selection, adverse effects and precautions, nursing care, frequent follow-ups to improve quality of life and reduce morbidity and mortality in these patients.

References:


