Review Article

Novel targeted therapies for the treatment of advanced thyroid cancer: a review

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Abstract: Thyroid cancers are often considered the "darling" form of cancer as the 5-year survival rate for non-recurrent well differentiated thyroid carcinoma are some of the highest amongst malignancies. However, the advanced and aggressive forms of thyroid carcinoma are rare and aggressive. For advanced medullary thyroid cancer (MTC), radioactive iodine-refractory differentiated thyroid cancer (DTC), and anaplastic thyroid cancer, there were limited options before the advent of new targeted and biologic therapies. Tyrosine kinase inhibitors (TKIs) and multikinase inhibitors (MKIs) inactivate cell proliferation signals in these cancers and show promise in slowing disease progression of these more aggressive subtypes of thyroid cancer. In addition, several new small-molecule therapies are being developed which are increasingly specific to certain subsites involved in cell proliferation. With the advent of precision-based medicine, these new tools will treat patients based on their tumor's genetic profile on an individualized basis to improve overall survival of these patients. We discuss the successes, failures, and current investigations into the biologic treatments of this more aggressive group of thyroid cancers.

Keywords: Tyrosine kinase inhibitor (TKI); tyrosine kinase; multikinase; inhibitors; medullary; anaplastic; RAI-refractory

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Introduction

Medullary thyroid cancer (MTC) arises from the calcitonin producing parafollicular cells within the thyroid gland. This cancer accounts for 2% of all thyroid malignancies; however, it accounts for 13.4% of all the deaths (1-4). Patients with intrathyroidal tumors have a 10-year survival rate of 95.6%, whereas patients with regional stage disease or distant metastasis at diagnosis present overall survival rates of 75.5% and 40%, respectively (5). It is inherited approximately 20–25% of the time and arises from sporadic mutations 75–90% of the time. All of the inherited mutations are germline mutations of the RET (Rearranged during Transfection) proto-oncogene and somatic RET mutations are frequently present in sporadic disease (6,7). This gene, RET, encodes a transmembrane receptor which phosphorylates tyrosine kinases that triggers intracellular pathways. Currently, the only curative treatment for MTC is surgery.

Differentiated thyroid cancer (DTC) encompasses both papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC). These two cancers account for 97% of all thyroid cancer and while 85% are cured with standard treatment, 15% are recurrent, metastatic, or refractory to standard treatment (8). The standard of care for most patients who have recurrent or metastatic DTC is radioactive iodine (RAI). Patients who receive RAI with metastatic or recurrent DTC and achieve complete remission have greater than a 90% 10-year overall survival (9). However,

up to 50% of these patients are not susceptible to RAI and are deemed RAI-refractory, which makes treatment difficult in this cohort (9).

It is believed that DTC can completely de-differentiate and become anaplastic thyroid cancer (ATC). ATC is a rare, but rapidly progressive and one of the most aggressive malignancies in humans (10). There have been few improvements in the treatment of this cancer since it was identified. The generally accepted median survival is about 6 months (11). Currently, the most aggressive treatment regimen involves surgery, chemotherapy, and hyper-fractionated external beam radiation; however, commonly treatment is palliation.

Receptor tyrosine kinases are a family of receptors that play an integral role in cell growth, differentiation, survival, and programmed cell death. The proto-oncogene RET and vascular endothelial growth factor (VEGF) are examples of this family of receptors and are associated with the development of medullary thyroid cancer and radioactive iodine refractory differentiated thyroid cancer, respectively (12-14). Specifically, tyrosine kinases activate proteins through signal transduction, generally through phosphylation. Tyrosine kinase inhibitors (TKIs) are small molecules that specifically work to inhibit the signal transduction of tyrosine kinases through competitive alkaline tri-phosphate inhibition at their catalytic binding site (15). Multikinase inhibitors (MKIs) target more than one kinase, increasing their potency synergistically (16). In thyroid cancer, two TKIs, Vandetanib and Cabozantinib, are approved for recurrent or metastatic MTC (17). Both Sorafenib and Lenvatinib are approved in radioactive iodine refractory metastatic DTC patients (18-20). In addition, other TKIs such as sunitinib are being used for both types of malignancies (21). Here we discuss current and potential uses of TKIs and MKIs in thyroid cancer as well as current and possibly unknown side effects associated with use and new advances driving precision based care.

Methods

Using search concepts for TKIs and thyroid malignancy comprehensive search terms were developed with the assistance of a medical librarian. PubMed, EMBASE, Web of Science, Scopus, and Cochrane were performed from their inception through July 2019. Nine hundred and four articles were identified and exported to Endnote9. 364 duplicates were removed. Fifty-six candidate titles and abstracts were independently reviewed by two authors (CJ Britt, E Thorpe) using the below inclusion criteria. Manuscripts meeting inclusion criteria described either patient satisfaction topics or telemedicine in thyroid malignancies. Non-English language studies without an available translation and studies describing benign thyroid disease only were excluded. Bibliographic review was then performed, and additional eligible articles identified.

Discussion

Medullary thyroid cancer

Initial trials of TKIs in thyroid cancer centered around Imatinib and were generally unsuccessful (22,23). Sorafenib was the first successful TKI used for MTC (24). Today, Several MKIs were tested for MTC treatment, including motesanib, sorafenib, sunitinib, axitinib, imatinib, pazopanib, anlotinib, lenvatinib, vandetanib, and cabozantinib (25-35). As previously stated, Vandetanib and Cabozantinib are the only MKIs approved for advanced MTC treatment. The first approved compound for thyroid malignancies, vandetanib, selectively targets RET, VEGF, and epidermal growth factor receptors (36).

The efficacy of vandetanib was evaluated in a phase III randomized, double-blinded, placebo control trial of 331 individuals with documented MTC progression and demonstrated a significant increase in progression free survival (PFS) in the vandetanib-treated group (30.2 *vs.* 19.2 months; HR =0.46, 95% CI: 0.31–0.69) (35). Similarly, a phase III randomized, double-blinded, placebo control of cabozantinib showed that cabozantinib-treated group improved PFS (11.2 *vs.* 4.0 months; HR =0.28, 95% CI: 0.19–0.40, P<0.0001) (34). Unfortunately, overall survival (OS) versus placebo is currently unknown, without evidence of improvement in OS (34,35). However, there may be specific patients where a more durable response with improvement in OS may be seen. Patients with sporadic MTC harboring a somatic *RET* M918T mutation showed improved response rate versus those without and in the cabozantinib trial. Patients with *RET* mutation showed more durable PFS with cabozantinib versus placebo (60 *vs.* 20 weeks), and patients with the mutation *RET* M918T achieving the longest PFS (61 *vs.* 17 weeks). These results show again that while results are promising, with further individualization of treatment, they may prove increasingly favorable.

As previously stated, medullary cancer has a much higher incidence of mortality than differentiated thyroid cancer.

A significant contributor to this mortality rate is the lack of treatments other than surgical therapy. Radiotherapy has a limited scope in medullary thyroid cancer for disease control and has not been shown to improve OS (37). While randomized control trials for TKIs have not demonstrated improved OS for MTC, both trials evaluated only progressive MTC, not MTC in a purely adjuvant setting. As the safety and efficacy of these drugs becomes better established, a role for adjuvant therapy in advanced stage disease may be more common and thus demonstrate improved survival in non-progressive advanced disease.

Poorly differentiated thyroid cancer and RAI refractive thyroid cancer

Two phase 3 trials examined the efficacy of TKIs in RAI refractory thyroid cancer, both of which showed similar efficacy to the advanced MTC TKIs. The DECISION trial examined the use of Sorafenib in either locally advanced or metastatic differentiated cancer in a double-blinded, randomized control trial (20). This study found that there was a significantly longer PFS (10.8 *vs.* 5.8 months, HR 0.59, 95% CI: 0.45–0.76, P<0.000) and response rate (12.2% *vs.* 0.5%); however, there was no significant improvement in OS (HR 0.80, 95% CI: 0.54 to 1.19; P=0.14) compared to placebo (20). Similarly, in the SELECT trial, Lenvatinib, an oral MKI of VEGFR1–3, FGFR 1–4, PDGFR alpha, RET, and KIT, was compared in a randomized double-blinded, placebo controlled trial with patients with RAI-refractory DTC (19). Lenvatinib demonstrated improved PFS and response rate (median PFS 18.3 *vs.* 3.6 months; HR 0.21, 99% CI: 0.14 to 0.31, P<0.001; ORR 64.8% *vs.* 1.5%, P<0.001); however, the OS was not significant (HR 0.73, 95% CI: 0.50 to 1.07; P=0.10) (19). Adverse reactions to both these drugs in each trial were high, and those events are delineated later in the manuscript. While these are powerful new tools useful for a disease with few options, expectations should be tempered by these results given the lack of OS.

When examining different aspects of these trials, Age was one of the most significant prognosticators. In a subgroup analysis of the SELECT study, patients over the age of 65 years receiving lenvatinib had improved OS versus placebo (HR 0.53, 95% CI: 0.31 to 0.91; P=0.020) (38). In addition, patients in this trial had significantly improved OS for FTC (HR 0.41, 95% CI: 0.18 to 0.97; P<0.035) that was not present for PTC (39). Just as certain expectations should be tempered, there are times when these therapies should be strongly considered. These scenarios, along with certain circumstances such as brain metastases, metastases that compromise patient's quality of life, and disease burden that can lead to increased bleeding are reasons to consider TKI treatment in these conditions. Overall, we see promise in the treatment of RAI refractive thyroid cancer with TKI, but no study has demonstrated improved OS. The improved progression free survival does suggest some activity in slowing disease.

Anaplastic thyroid carcinoma

As stated, ATC is an extreme variant of thyroid cancer. The treatment options have been limited, aggressive, and ineffective thus far. Ha *et al.* used imatinib in 11 patients and less than 20% obtained a partial response and only 27% had a 6-month PFS. The 6-month OS was only 46% (40). In a study of 16 patients Nagaiah obtained some disease control in 40% of patients (41). There is some suggestion that some new MKIs may prove more effective in these cancers, but evidence is lacking (42). Currently the standard approaches for ATC are doxorubicin and cisplatin or paclitaxel and carboplatin. Although disappointing, the results of these regimens are the current standard of care.

Side effects of TKI

Side effects of TKIs are less severe than traditional chemotherapeutic agents but mild adverse effects (AEs) are common. In the trials associated with MTC, the most frequent adverse events are diarrhea, rash, fatigue, and nausea. The most common AEs are usually of mild intensity (grade 1 or 2) and can be prevented or managed with symptom-related treatment but dose reduction (up to 79% for cabozantinib and 35% for vandetanib) was ultimately needed in two large clinical trials (34,43). MKI-induced hypothyroidism is also frequent and requires an increase in the levothyroxine dose. More severe adverse events (G3-G4) are uncommon, occurring in 5–10% of cases. MKI-related grade 5 adverse events are also reported (25,26,30,33-35,44).

Caution is warranted when prescribing MKIs for patients with a medical history of hemoptysis, tumor invading vital structures of the neck, and radiation treatment of the neck or mediastinum since they are at higher risk for hemorrhages and fistula formation, a rare but life-threatening antiangiogenic MKI adverse event (45). Vandetanib carries a higher risk for prolongation of the QT interval and should be avoided in patients with heart

conduction disorders (46,47). Wound healing issues are also reported, especially for patients who have undergone tracheoesophageal puncture status post laryngectomy (48).

VEGF-targeted TKI specifically cause a number of adverse events, including hypertension, hand-foot syndrome, anorexia, fatigue, diarrhea, proteinuria, thrombosis and myocardial ischaemia (49). While proteinuria may occur, staying on trial was not shown to be associated with serious renal dysfunction (50). Sorafenib in particular saw interruptions, reductions, or withdrawals because of adverse events occurred in 66.2%, 64.3% and 18.8% of patients, respectively (20). Lenvatinib saw greater than 40% major treatment for adverse events with a 14.2% discontinuation of therapy because of events (19). Approximately 65% of patients required at least one dose reduction in both trials, highlighting the poor tolerability of these TKIs at the approved starting dose (34,35). Finally, deaths resulting from drug-related toxicities were rare (0.5% for sorafenib and 2.3% for lenvatinib) (19,20). Drug response should be assessed at 3-month intervals, but clinical responses to side effect profiles should be assessed more frequently, especially during the first two months (8). Decisions to limit treatment should be based on clinical reviews and response to the drug.

Future directions

Despite the advances in the management of metastatic MTC in the last decade, the clinical experience with the TKIs and MKIs are somewhat disappointing. While TKIs and MKIs have increased the PFS, no definitive evidence of improved OS has been demonstrated yet. Almost all studies demonstrate a relatively low rate of partial responses, absence of complete response, and eventual tumor progression due to acquired drug resistance, which is most commonly due to secondary mutations in the kinase domains that sterically block the binding of TKIs and MKIs in the target genes (51). Several other options are being investigated for such cases including immunotherapy and highly specific small molecule targets.

There are several ongoing phase II trials examining therapies targeting programmed death ligand 1 (PDL1) with the use of pembrolizumab (52). Several small molecule drugs are currently being tested which have highly specific targets. Loxo-292 is an oral, highly active RET inhibitor that is effective against multiple RET alterations. Only one phase I trial has been performed, that showed a 45% response rate and a 49% tumor reduction with an adverse event rate less than 10%. Most patients stayed on treatment (53). Blu 667 is another RET inhibitor that is greater than 10 times more potent than TKIs. While data for the phase 1 trial is preliminary, it seems to show similar efficacy and side effect profile to loxo-292 (53). Finally, larotectinib is a pan-tropomyosin receptor kinase inhibitor that has demonstrated activity against thyroid cancers with TRK fusion mutations (54).

These therapies are becoming increasingly patient specific. As tumor genetic profiling becomes more accessible, precision medicine will become increasingly common. Precision medicine considers tumor genetics, patient genetics, and patient environment and lifestyle. As therapies become progressively specific, precision medicine will take a more important role in the management of refractory thyroid cancer.

Conclusions

TKIs and MKIs are successfully used to prolong disease free survival in progressive MTC, RAI-refractory DTC, and recurrent DTC in phase III trials. However, their impact on OS is not proven for these disease processes. Their side effect profile, while generally modest, can include serious side effects with a non-zero risk of mortality. As familiarity grows, these medicines will be increasingly used in an adjuvant role for advanced thyroid malignancies. They already provide additional options for advanced MTC and ATC, two rare, but aggressive forms of thyroid cancer that previously had limited options. As the number of options increases for these types of cancer and as medicine becomes more precise, we may see an increase in overall survival for these more aggressive diseases; however, currently, this is yet to be seen.

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