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Lessons learned and questions unanswered from use of multitargeted kinase inhibitors in medullary thyroid cancer

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SUMMARY

Objectives: To review studies of novel multitargeted kinase inhibitors studied in patients with medullary thyroid cancer (MTC).
Materials and methods: Search of relevant references in PubMed and Google Scholar on "chemotherapy" and "medullary thyroid cancer".
Results: Multitargeted kinase inhibitors have revolutionized the role of chemotherapy for progressive MTC, providing for the first time tolerable therapeutic options that can improve outcomes in patients with progressive disease. Drugs thought to inhibit the RET kinase have advanced the furthest for this disease, but these agents also target the VEGF receptor along with other kinases that may be relevant to both beneficial and adverse effects. Vandetanib improved progression-free survival from 19.3 to 30.5 months compared with placebo in patients with metastatic disease, whereas cabozantinib improved progression-free survival from 4.0 months to 11.2 months in a population with more aggressive disease. However, "cure" remains elusive, adverse events frequent, and exactly how such "targeted" agents actually function within MTC remains unclear.
Conclusions: New approaches to clinical trial design and the preclinical development of targeted agents may be required to optimize the combination of maximum efficacy with minimal toxicity for patients with metastatic MTC.

Introduction

The development of targeted therapies for cancer has been based on the premise that pharmacologic alteration of key intracellular signaling pathways will interfere with processes that promote cellular proliferation, tumor invasion, and metastasis or that permit the neoplasm to escape apoptosis, thereby leading to control or eradication of the cancer. Use of such treatments for advanced thyroid cancers has revolutionized the role of chemotherapy for these diseases, providing for the first time tolerable therapeutic options that can improve progression-free survival in patients with progressive disease. However, "cure" remains elusive, and exactly how such "targeted" agents actually function within thyroid cancers remains unclear. This review will discuss the recent studies that have led to regulatory approval of multitargeted kinase inhibitors for medullary thyroid carcinoma (MTC), emphasizing the important lessons learned and the questions yet to be answered about how these agents may work in this disease.

Medullary thyroid carcinoma

In the United States, about 2–4% of all newly diagnosed cases of thyroid carcinoma represent MTC. This variant of the disease arises from the neuroendocrine parafollicular or C cells within the gland, which are responsible for production of calcitonin as a vestigial regulator of calcium flux into and from bone. Patients who develop locally advanced disease cannot be cured by surgical intervention, and often develop significant morbidity from invasive disease. In the setting of distant metastases, morbidity from progressing structural disease and from oversecretion of various hormonally active peptides, which leads to intractable diarrhea among other symptoms, presents significant clinical management challenges, and mortality is considerable.[1] Historically, systemic chemotherapy has been reported to yield response in up to 30% of patients with metastases of MTC involving liver, lung or bones, but these were generally reported from small cohorts of patients and considerable toxicity was also reported.[2] Thus, interest focused on identifying molecular targets that might be based upon known genetic abnormalities thought to drive the growth and invasive behavior of these tumors.

About 20% of cases of MTC occur in one of several familial syndromes (multiple endocrine neoplasia types 2A and 2B) along with

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familial MTC. Germline mutations in the *RET* proto-oncogene were identified as causative of these hereditary forms of MTC in two landmark 1993 studies.[3,4] Today, more than 99% of all cases of hereditary MTC can be attributed to one of numerous point mutations in *RET* that cause activation of the tyrosine kinase function of this receptor, which signals downstream primarily through RAS kinase. The most common germline mutation, a cysteine-to-arginine substitution at codon 634 (denoted C634R), accounts for at least half of all cases of MEN 2A, and has also been extensively studied *in vitro* in the well-characterized TT cell line.[5] This mutation is found in the cysteine-rich extracellular domain of RET, a region responsible for ligand-dependent dimerization. However, in the setting of the C634R mutation, RET is capable of ligand-independent dimerization, leading to autophosphorylation of the intracellular tyrosine residues that are responsible for interaction with downstream signaling pathways. In contrast, a methionine-to-threonine substitution at codon 918 (denoted M918T) is associated with the more aggressive phenotype of MEN 2B. The M918T mutation occurs in the intracellular domain of RET, changing the conformation of the tyrosine kinase domain and allowing marked enhancement of autophosphorylation in the absence of dimerization or ligand binding. Additionally, allelic imbalance, due to either increased copy number of the mutant *RET* allele or deletion of part or all of the wild type allele, has been reported in several cases of MEN 2A as well as the TT cell line itself. In sporadic MTC, which is not associated with germline abnormalities, somatic *RET* mutations have been commonly reported in up to half of cases. In this instance, the most frequent somatic mutation is the M918T alteration, and its presence is associated with worse overall survival.[6] Activating abnormalities in RET signaling have also been reported as result of chromosomal rearrangement (in papillary thyroid carcinoma, chronic myleomonocytic leukemias, and nonsmall cell lung cancers), copy number alteration (in pheochromocytoma and MTC), and overexpression (including carcinomas of the breast, prostate and pancreas).[7] Thus, given both the contributory role of *RET* mutations in many malignancies as well as its association with more aggressive disease in sporadic MTC, the mutant RET kinase has been an attractive target for consideration of novel chemotherapies.[8]

The proof-of-concept that targeting mutant RET kinase could alter growth of MTC cells involved use of a hammerhead ribozyme, a catalytic RNA enzyme capable of site-specific cleavage of complementary RNA sequences.[9] Using a ribozyme targeting the C634R mutant RET, the activated kinase function of RET could be inactivated, thus preventing the transforming effects of the mutation without affecting function of the wild type protein. The same group subsequently demonstrated that a more potent ribozyme could effectively block proliferation of TT cells containing the C634R mutation.

Multitargeted kinase inhibitors in MTC

Laboratory investigation of pharmacologic intervention focusing on the RET kinase was advanced with the recognition that the structure of the RET kinase was in fact quite similar to that of the vascular endothelial growth factor receptor (VEGFR) kinase family, and that inhibitors of VEGFR could often also inhibit RET. One of the earliest efforts to evaluate a multitargeted kinase inhibitor for its potential therapeutic application to RET targeting was a study of vandetanib (ZD6474).[10] In this early report, vandetanib, a tyrosine kinase inhibitor primarily developed as an inhibitor of VEGFR and EGFR, was shown to block autophosphorylation of the RET mutant M918T, which causes MEN2B and is found in more aggressive sporadic MTC tumors. A subsequent study showed a dose-dependent inhibition by vandetanib of tumor growth in a xenograft model derived from a sporadic MTC tumor bearing the C634R mutation in *RET*.[11] Tumor cells expressing the vandetanib-resistant V804M *RET* mutation are not similarly inhibited, however, suggesting that at least in this *in vitro* model, a responsive mutant RET kinase is required for action of the drug.[12]

Based on these *in vitro* findings, a multicenter, open-label phase II trial studied the efficacy of the drug in patients with metastatic familial forms of MTC.[13] Thirty patients were enrolled, starting therapy with vandetanib, 300 mg daily. Confirmed partial response was reported in 21% of these patients and unconfirmed responses in another 17%. Calcitonin levels dropped by more than 50% in most patients, but given that blocking RET may lead to a direct inhibition of calcitonin gene expression, independent of tumor volume changes, the significance of these biomarker changes was uncertain.[14] A second phase II trial in familial MTC, with a lower starting dose of 100 mg daily, reported similar results.[15]

A pivotal multicenter, randomized phase III trial (ZETA) in patients with metastatic MTC, either sporadic or inherited, was performed to test the hypothesis that progression-free survival would be improved with vandetanib compared with placebo in patients with advanced or metastatic disease.[16] Unlike the phase II studies, there was no requirement that the tumor contain a *RET* mutation, but a secondary goal of the study was to try to determine whether *RET* mutation status affected the outcomes. A key design feature of the study was to permit unblinding of patient's drug assignment upon disease progression, as well as the subsequent option to "cross over" to vandetanib for post-progression therapy if the patient had initially been randomized to the placebo arm. For the primary endpoint, median progression-survival was improved from 19.3 months in the placebo arm ($n = 100$) to 30.5 months in the vandetanib arm ($n = 231$), with a hazard ratio of 0.46 (95% confidence interval 0.31–0.69). At the time of the primary analysis, only 15% of the patients in the study had died (30% of the targeted 165 needed for final analysis), and there was no significant difference in overall survival yet observed between the two arms of the study (hazard ratio 0.89, 95% confidence interval 0.48–1.65). Whether the inability to detect a survival benefit from vandetanib therapy at this point in the study was due to: (a) the potentially confounding effect of allowing cross over between treatment arms, (b) the availability of other possibly effective therapies to be used after progression, (c) the lack of relationship between improvements in progression-free and overall survival, or (d) simply the small number of observed events remains to be determined as the long term follow portion of the study is still ongoing. As for the dependence upon *RET* mutation (as originally hypothesized) for vandetanib's action, no difference in key outcomes was observed between patients with tumors documented to contain *RET* mutations and those documented to be *RET* wild type; however, a large number of tumors could not be successfully genotyped to absolutely exclude the presence of any *RET* mutation, and thus the question remained unsettled. Despite these unanswered questions, vandetanib was approved in the United States and Europe in 2011 as the first effective chemotherapy for treatment of patients with progressive MTC.

A second multi-targeted kinase inhibitor has also been extensively studied and now approved for MTC, cabozantinib (XL184). Initially studied as an inhibitor of VEGFR and MET kinases, it also demonstrated marked *in vitro* potency against RET as well.[17] In a phase I dose-escalation study, 10 of 35 MTC patients (29%) achieved a confirmed partial response.[18] Stable disease of at least 6 months duration was observed in 15 of 37 patients with MTC, and the overall disease control rate (combining partial responses and stable disease of at least 6 months duration) was 68%. In particular, responses were seen in patients regardless of the *RET* mutation status of their tumors, suggesting that the drug is active in patients without *RET* activating mutations.