REVIEW

Advanced medullary thyroid cancer: pathophysiology and management

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Abstract: Medullary thyroid carcinoma (MTC) is a rare malignant tumor originating from thyroid parafollicular C cells. This tumor accounts for 3%–4% of thyroid gland neoplasias. MTC may occur sporadically or be inherited. Hereditary MTC appears as part of the multiple endocrine neoplasia syndrome type 2A or 2B, or familial medullary thyroid cancer. Germ-line mutations of the *RET* proto-oncogene cause hereditary forms of cancer, whereas somatic mutations can be present in sporadic forms of the disease. The *RET* gene encodes a receptor tyrosine kinase involved in the activation of intracellular signaling pathways leading to proliferation, growth, differentiation, migration, and survival. Nowadays, early diagnosis of MTC followed by total thyroidectomy offers the only possibility of cure. Based on the knowledge of the pathogenic mechanisms of MTC, new drugs have been developed in an attempt to control metastatic disease. Of these, small-molecule tyrosine kinase inhibitors represent one of the most promising agents for MTC treatment, and clinical trials have shown encouraging results. Hopefully, the cumulative knowledge about the targets of action of these drugs and about the tyrosine kinase inhibitor-associated side effects will help in choosing the best therapeutic approach to enhance their benefits.

Keywords: medullary thyroid carcinoma, proto-oncogene *RET*, tyrosine kinase inhibitors

Introduction

Medullary thyroid carcinoma (MTC) is a rare malignant tumor originating from parafollicular C cells of the thyroid, first described by Hazard et al.[1] This tumor accounts for 3%–4% of all thyroid gland neoplasias.[2] Calcitonin, the main secretory product of MTC, is a specific and highly sensitive biomarker for C-cell disease. The carcinoembryonic antigen (CEA) is also produced by neoplastic C cells. These molecules are widely used as prognostic markers during the follow-up of MTC patients.[3,4] The reported 10-year mortality rate for patients with MTC varies from 13.5% to 38%.[5,6]

MTC may occur sporadically (75% of cases), or as part of the inherited cancer syndrome known as multiple endocrine neoplasia (MEN) type 2.[7,8] The term MEN was introduced by Steiner et al in 1968 to describe disorders that include a combination of endocrine tumors. The Wermer syndrome was designed as MEN 1, and the Sipple syndrome as MEN 2.[9] Later, MEN 2 was subdivided into three distinct syndromes: MEN 2A, MEN 2B, and familial medullary thyroid carcinoma (FMTC). Hereditary MTC is usually preceded by C-cell hyperplasia, and these tumors are generally bilateral and multicentric. The mean age at diagnosis is around 45 years.[6,10]

The MEN 2A subtype constitutes approximately 70%–80% of cases of MEN 2 and is characterized by the presence of MTC (95%), pheochromocytoma (30%–50%) and hyperparathyroidism (10%–20%). Adrenomedullary disease is usually multicentric and

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bilateral (65%–78%), generally detected after the onset of MTC.[11,12] Two rare variants of MEN 2A have been described: one with cutaneous lichen amyloidosis, a pruriginous lesion of the scapular region characterized by amyloid deposition, and the other with Hirschsprung's disease, caused by the absence of autonomic ganglia in the terminal hindgut that results in colonic dilatation, obstipation, and constipation.[13,14] The clinical course of MTC in patients with MEN 2A is variable, and the disease progression is associated with codon-specific mutations.[11,15]

The MEN 2B syndrome accounts for about 5% of the cases of MEN 2. MEN 2B is characterized by a single phenotype, which includes diffuse ganglioneuromatosis of the tongue, lips, eyes, and gastrointestinal tract, and Marfanoid habitus. MEN 2B patients present with MTC (>90%), pheochromocytoma (45%), ganglioneuromatosis (100%), and Marfanoid habitus (65%).[11,12] MTC in the setting of MEN 2B develops earlier and has a more aggressive course, compared with MTC in other MEN 2 subtypes.[6,16]

The FMTC subtype constitutes 10%–20% of the cases of MEN 2.[11] MTC is the only manifestation of FMTC, thereby it is necessary to demonstrate the absence of a pheochromocytoma or hyperparathyroidism in two or more generations of the same family or the identification of related mutations to confirm the diagnosis. The clinical presentation of MTC occurs later, and the prognosis is more favorable compared to the other forms of MTC.[17]

Sporadic MTC generally presents as a palpable thyroid nodule or cervical lymph node. Diagnosis tends to be late, generally in the fifth or sixth decade of life.[18] Lymph-node metastases are detected in at least 50% of these patients at diagnosis, while distant metastases occur in around 20% of cases.[19,20] A minority of patients with MTC present systemic manifestations that include diarrhea, flushing, or painful bone metastases.[16]

Epidemiology, etiology, and pathophysiology of familial and sporadic medullary thyroid cancer

MTC represents approximately 3%–4% of malignant thyroid gland neoplasias.[2] The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute showed that MTC patients had a median age of 50 years at diagnosis and were white in the majority of the cases. There is no difference in the frequency of this tumor between sexes.[21,22]

Hereditary MTC affects approximately one in 30,000 individuals and is associated with germ-line mutations in the *RET* (Re arranged during Transfection) proto-oncogene, an autosomal dominant disease with a high penetrance and variable phenotype. *RET* point mutations affect mainly exons 10, 11, and 16. Less common mutations occur in exons 5, 8, 13, 14, and 15.[21,23]

The *RET* gene encodes a receptor tyrosine kinase (RTK), expressed in cells derived from the neural crest: thyroid parafollicular cells (C cells), parathyroid cells, and chromaffin cells of the adrenal medulla and enteric autonomic plexus. The RET protein is constituted by three domains: extracellular, transmembrane, and intracellular. The extracellular domain includes regions homologous to the cadherin family of cell-adhesion molecules and a large region rich in cysteine residues that performs the transduction of extracellular signals of cell proliferation, differentiation, migration, survival, and apoptosis. The intracellular domain encloses two tyrosine kinase subdomains – TK1 and TK2 – which contain the tyrosine residues involved in the activation of the signaling intracellular pathways. The *RET* gene is subject to alternative splicing of the 3′ region, generating three distinct protein isoforms, with 9 (RET9), 43 (RET43) and 51 (RET51) amino acids in the carboxy-terminal tail downstream from glycine 1063. RET9 and RET51, consisting of 1072 and 1114 amino acids, respectively, are the main isoforms.[24,25]

The majority of families with MEN 2A (>90%) present point mutations in the *RET* proto-oncogene (missense type), involving codons located in the extracellular region: 609, 611, 618, and 620 (exon 10) and 634 (exon 11). The most frequent mutations are located in codon 634, occurring in more than 60% of all genetically identified MTC.[11,17,21,26] Codon 634 mutations have been associated with the presence of pheochromocytoma and hyperparathyroidism,[27] and rarely with cutaneous lichen amyloidosis.[28] Nevertheless, we observe a variety of phenotypic expressions in families with the same *RET* mutation.[11,29–32] Patients harboring the genotype C634R (TGC/Cys → CGC/Arg, exon 11) present significantly more distant metastases at diagnosis than groups C634W (Cys/TGC → Trp/TGG, exon 11) and C634Y (Cys/TGC → Tyr/TAC, exon 11), suggesting that a change of specific amino acids may modify the natural development of the disease.[32] The *RET* C634W mutation is associated with high penetrance for MTC and pheochromocytoma.[26] The risk profiles and penetrance estimations in MEN 2A caused by germ-line *RET* exon 10 mutations were recently analyzed by Frank-Raue et al in a large multicenter study that

included 340 subjects from 103 families. It was observed that mutations affect mainly the cysteine codons 609, 611, 618, and 620, and 50% penetrance was achieved by the age of 36 years for MTC, by 68 years for pheochromocytoma, and by 82 years for hyperparathyroidism.[30]

MEN 2B occurs, in approximately 95% of the cases, through a specific M918T mutation (exon 16), resulting in structural change of the intracellular domain of the RET protein. The genotype A883F (GCT → TTT, exon 15) accounts for about 2%–3% of cases, and[33,34] a double-mutation V804M/Y806C at codon 804 (Val/GTG → Met/ATG, exon 14) and 806 (Tyr/TAC → Cys/TGC) in the same allele was described in a patient with MEN 2B. Patients presenting with "atypical" MEN 2B harboring the germ-line double-point mutation in codons 804 and 904 (V804M and S904C) were also reported.[35,36] Mutations in codons 883 and 918 are associated with younger age of MTC onset and higher risk of metastases and disease-specific mortality.[10,11,37]

In FMTC, germ-line mutations are distributed throughout the *RET* gene; approximately 86%–88% of FMTC families present mutations in exon 10 (codons 609, 611, 618, 620) and exon 11 (codon 634) of *RET*.[31,38] Substitutions in the intracellular domain of *RET* in exon 13 (codon 768, 790, 791), exon 14 (codon 804 and 844), and exon 15 (codon 891) are less common. Interestingly, the most frequent mutation observed in MEN 2A, C634R, has not been described in FMTC families.[11,38–41]

On the other hand, the molecular mechanisms involved in sporadic MTC have not yet been clarified. About 50%–80% of cases present the somatic *RET* mutation M918T (Met/ATG → Thr/ACG, exon 16).[42,43] Somatic mutations in codons 618, 603, 634, 768, 804, and 883 and partial deletion of the *RET* gene have been identified in a few tumors.[19,20] However, the mutation does not appear to be uniform among the various cell subpopulations in the tumor or in the metastases, suggesting that sporadic MTC might be of polyclonal origin, or that the mutations in the *RET* proto-oncogene are not initial events in MTC tumorigenesis.[42,44]

The presence of a somatic *RET* (M918T) mutation correlates with higher probability of persistent disease and lower survival rate in a long-term follow up.[19,20]

In recent years, the presence of *RET* variant sequences or polymorphisms have been associated with susceptibility for the development or progression of MTC. Several studies have described increased prevalence of *RET* polymorphisms in individuals with hereditary or sporadic MTC when compared with the population.[43,45–49]

Overview of current therapeutic strategies

Surgery is the only curative treatment for MTC.[10,16,50] There are no effective therapeutic options for distant metastatic disease, since chemotherapy and external beam radiation therapy for metastatic or cervical recurrent disease have limited response rates.[51,52] A large study of an American cohort of MTC patients demonstrated that age at diagnosis, stage of disease, and extent of surgery are important predictors of survival. Patients with tumor confined to the thyroid gland had a 10-year survival rate of 95.6%, whereas patients with regional stage disease or distant metastasis at diagnosis had overall survival rates of 75.5% and 40%, respectively.[22]

The main challenge in the management of MTC is patients with advanced and progressive disease, because conventional therapeutic options have poor results for these individuals. Nevertheless, in the last few years, several studies have upgraded our knowledge on the molecular events associated with MTC. RTKs, such as RET and vascular endothelial growth factor-A (VEGFA), involved in proliferation and cell survival, play an important role in the tumorigenesis process. In response to binding of extracellular ligands, such receptors are phosphorylated and activated downstream signaling pathways, such as mitogen-activated protein kinase and phosphatidylinositol 3-kinase pathways, and many signaling effectors, like β-catenin and nuclear factor-kappa B.[53,54] Thus, the molecules involved in these processes serve as potential therapeutic targets for new drugs.[55]

Review of therapies targeting receptor tyrosine kinases

The cumulative knowledge on the distinct signaling pathways and multiple genetic abnormalities involved in the pathogenesis of cancer has allowed the development of targeted molecular therapies. The protein kinases regulate the processes of cell proliferation, differentiation, migration, and antiapoptotic signaling. Protein kinases are characterized by their ability to catalyze the phosphorylation of tyrosine amino acid residues in proteins and thus activate various intracellular signaling pathways. Therefore, tyrosine kinase inhibitors (TKIs) may act as therapy for cancer by blocking the tyrosine kinase-dependent oncogenic pathways. TKIs can be specific to one or several tyrosine kinase receptors, most designed to inhibit multiple signaling pathways.[55,56]

Tyrosine kinase activation plays a key role in the development of MTC; therefore, small-molecule TKIs represent one of the most promising agents for MTC treatment, and

clinical trials have shown encouraging therapeutic results. The objective Response Evaluation Criteria in Solid Tumors index has been used to evaluate tumor response and is classified as follows: complete response (the disappearance of all target lesions), partial response (at least a 30% decrease in the sum of the longest diameter of target lesions), progressive disease (at least a 20% increase in the sum of the longest diameter of target lesions), and stable disease (SD; neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease).[57] Interestingly, the reduction in serum levels of tumor markers (calcitonin and CEA) observed with these medications occurs independently of radiological response.[58,59] Another relevant question concerns the different responses of the parenchymal target lesions (for example, metastasis to lung, liver, bone) vs nonparenchymal target lesions (metastasis in lymph nodes); one possible explanation is that the parenchymal lesions are better perfused.[60]

The most studied TKI drugs for MTC treatment are vandetanib, cabozantinib, motesanib, sorafenib, sunitinib, axitinib, and imatinib (Tables 1 and 2).

Vandetanib (ZD6474, Zactima)
Vandetanib is an agent that selectively targets RET, vascular endothelial growth factor receptors (VEGFRs), and epidermal growth factor receptors (EGFRs).[61,62] In human MTC cell lines, vandetanib inhibited the cell proliferation and phosphorylation of RET receptors, EGFR, and mitogen-activated protein kinase pathways.[63]

The activity profile of this drug made it a good choice as a treatment for patients with unresectable MTC. A phase II clinical trial assessed the efficacy of vandetanib (300 mg once daily) in patients with advanced hereditary MTC. A total of 30 patients were enrolled; a partial response was achieved in 20% of these patients, and durable SD for ≥24 weeks was reported in 53% of the patients. Therefore, the disease-control rate was 73%, and serum calcitonin levels decreased 50% or more in 80% of the patients.[64] Similar results were described in 19 patients with metastatic hereditary MTC receiving 100 mg/day vandetanib, where the disease-control rate was 68%.[65] However, no direct comparison of the efficacy at each dose level – 100 or 300 mg/day – has been conducted.

More recently, in a large trial, 331 adults with metastatic MTC (90% with sporadic disease) were randomized to receive either vandetanib at a dose of 300 mg daily or placebo. A significant improvement in progression-free survival was observed for patients randomized to receive vandetanib (hazard ratio 0.46, 95% confidence interval 0.31–0.69). The rate of mortality at 2-year follow-up was 15%. A subgroup analysis of progression-free survival in sporadic MTC patients suggested that *RET* M918T mutation-positive patients had a higher response rate to vandetanib compared with *RET* M918T mutation-negative patients.[64,66]

Table 1 Summary of clinical trials with tyrosine kinase inhibitors in medullary thyroid carcinoma

Drug	Targets	N° of patients	Partial response (%)	Stable disease (%)	Reference
Clinical trials phase I and II					
Vandetanib (ZD6474)	VEGFR-1, VEGFR-2, VEGFR-3, RET, EGFR	30	20	53	64
		19	16	53	65
Cabozantinib (XL 184)	VEGFR-2, RET, MET	37	29	41	69
Motesanib (AMG 706)	VEGFR-1, VEGFR-2, VEGFR-3, c-Kit, RET, PDGFR	91	2	48	73
		5	40	40	77
Sorafenib (BAY 43-9006)	VEGFR-2, VEGFR-3, c-Kit, RET	16	6	50	58
		15	25	–	78
Sunitinib (SU 11248)	VEGFR-1, VEGFR-2, VEGFR-3, RET, c-Kit	7	28[a]	46[a]	86
		15	33.3	26.7	87
Axitinib (AG-013736)	VEGFR-1, VEGFR-2, VEGFR-3, c-Kit	11	18	27	89
Imatinib (STI571)	RET, c-Kit, PDGFR	9	0	55	91
		15	0	27	92
			PFS drug vs placebo (months)	**Hazard ratio**	
Clinical trials phase III					
Vandetanib (ZD6474)	VEGFR-1, VEGFR-2, VEGFR-3, RET, EGFR	331	30.5 vs 19.3	0.46	66
Cabozantinib (XL 184)	VEGFR-2, RET, MET	330	11.2 vs 4.0	0.28	70

Note: [a]Results for the total number of patients with advanced thyroid cancer, not only MTC patients.
Abbreviations: PFS, progression-free survival; VEGFR, vascular endothelial growth-factor receptor; EGFR, epidermal growth-factor receptor; PDGFR, platelet-derived growth-factor receptor.

Table 2 Summary of most common reported adverse events of tyrosine kinase inhibitors*

Adverse events (%)	Vandetanib (ZD6474)	Carbozantinib (XL 184)	Motesanib (AMG 706)	Sorafenib (BAY 43-9006)	Sunitinib (SU 11248)	Axitinib (AG-013736)	Imatinib (STI571)
Gastrointestinal disorders							
Diarrhea	47–77	15.9–57	41	71	26	48	43
Dyspepsia	–	–	–	10	–	–	30
Nausea	16–63	43	26	14	9	33	–
Vomiting	14–40	24	–	14	9	13	–
Oral pain	–	19	–	62	–	–	–
Stomatitis	–	–	–	48	–	25	–
Abdominal pain	14	–	–	29	–	–	–
Skin events							
Acne	20	–	–	–	–	–	–
Alopecia	–	–	–	48	–	–	–
Dry skin	15	12	–	76	–	–	–
Hand-foot-skin reaction	–	16.6	–	76	26	15	–
Pruritus	–	–	–	33	–	–	–
Rash	45–67	26	–	67	–	15	–
Respiratory disorders							
Cough	10	–	–	–	–	–	
Epistaxis	–	–	–	14	–	–	–
Cardiovascular disorders							
Hypertension	33–41	7.9–16	27	43	3	28	–
QTc prolongation	22	–	–	–	–	–	–
Blood system							
Leucopenia	–	–	–	52	31	–	–
Neutropenia	–	–	–	33	34–60	–	8
Thrombocytopenia	–	–	–	58	3–70	–	7
Anemia	–	–	–	38	6–10	–	–
Others							
Fatigue	24–63	9.3–55	41	5	26	50	70
Anorexia	16–43	–	27	8	3	30	31
Headache	26–47	–	–	7	–	13	–
Proteinuria	–	–	–	–	–	18	–

Notes: *Irrespective of causality; –, not reported.

Based on these results, the US Food and Drug Administration (FDA) approved vandetanib for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.[67] Meanwhile, it is important to emphasize that preclinical studies have evidenced that *RET*-activating mutations at codon 804 (V804L, V804M) cause resistance to some TKIs, such as vandetanib.[68]

Cabozantinib (XL184)

XL184 is a potent inhibitor of MET, VEGFR-2, and RET. A phase I study of XL184 (maximum tolerated dose 175 mg daily) was conducted in 37 patients with MTC. Overall, 68% of patients had SD for 6 months or longer or confirmed partial response.[69] Data about a phase III study with XL184 in metastatic MTC, presented at the 2012 Annual Meeting of the American Society of Clinical Oncology, demonstrated in an interim analysis that the XL184 treatment resulted in prolongation of progression-free survival when compared with placebo (11.2 vs 4.0 months, respectively).[70] The XL184 was also recently approved by the FDA for the treatment of MTC, in November 2012.

Motesanib (AMG 706)

Motesanib is a multikinase inhibitor that targets VEGFR-1, -2, and -3, platelet-derived growth-factor receptor (PDGFR) and stem cell-factor receptor (c-Kit). In a previous study, this compound potently inhibited angiogenesis in a variety of in vivo models, and it was able to induce regressions of large established tumor xenografts.[71] Recently, the effects of motesanib on wild-type and mutant RET activity in a mouse model of MTC were described. Treatment with motesanib resulted in substantial inhibition of RET tyrosine phosphorylation and VEGFR-2 phosphorylation in TT tumor cell xenografts.[72]

A single-arm phase II study investigated the efficacy of motesanib (125 mg once daily) in 91 patients with

advanced MTC. Eighty-one percent of patients had SD, and 48% had durable SD (≥24 weeks); however, the overall response rate observed was only 2%. The clinical benefit rate was 51% (objective response and durable SD).[73] Another study found that changes from baseline in serum placental growth factor and soluble VEGFR-2 levels, after initiation of therapy with motesanib, predicted therapeutic responses in patients with metastatic medullary thyroid cancer.[74]

Sorafenib (BAY-43-9006)

Sorafenib is a multikinase inhibitor with potent activity against Raf and RTKs. Sorafenib inhibits oncogenic RET kinase activity in NIH3T3 cells, while it induces growth arrest in TT cells (C634R *RET* mutation-positive MTC cell line). Moreover, sorafenib inhibits the growth of cells carrying *RET* V804L or *RET* V804M, both mutants that are resistant to other TKIs.[75] In cell-based assays, sorafenib exhibits potent inhibition of several RTKs involved in tumor angiogenesis and is able to block autophosphorylation of VEGFR-2, VEGFR-3, PDGFR, FMS-like tyrosine kinase 3 (FLT3), and c-Kit.[76]

A small observational study investigated the efficacy of sorafenib in five patients with progressive MTC; after 6 months, two patients showed a partial response, and two patients exhibited SD.[77] In a phase II trial, 21 patients with metastatic or locally advanced MTC, hereditary or sporadic form, were enrolled to receive 400 mg sorafenib orally twice daily. The hereditary arm of the study was prematurely closed, and it was therefore not possible to conclude on the effect of sorafenib; in the sporadic MTC group, 50% of the patients demonstrated durable SD ≥ 15 months, with only one partial response (6%). Eleven patients had a decrease in calcitonin and CEA.[58] More recently, another phase II trial examined a total of 15 patients with metastatic MTC treated with sorafenib. The radiological response rate was achieved for 25% of patients.[78]

To investigate the hypothesis that combinations of drugs with different therapeutic targets are synergistically effective and thereby could be a better option to treat thyroid malignancies, the combination of sorafenib and tipifarnib – a selective oral farnesyltransferase inhibitor – was employed in a phase I trial. Of the 35 patients studied, 13 had MTC and 22 differentiated thyroid cancer. The MTC partial response rate was 38% and the SD rate, of at least 6 months, was 31%.[79] More recently a synergistic effect of sorafenib and AZD6244 (a mitogen-activated protein kinase kinase inhibitor) was demonstrated in the inhibition of human MTC cells, in vitro.[80] Despite limitations in comparing different studies,

it seems that combined treatment offers higher rates of partial response than the use of sorafenib only. Sorafenib is currently approved by the FDA for renal cell and hepatocellular carcinomas.

Sunitinib (SU11248)

Sunitinib is a small molecule that inhibits members of the RTK family, including VEGFR-1, VEGFR-2, PDGFR, c-Kit, and RET.[81–83]

Recently, two patients with metastatic MTC received sunitinib (50 mg/day for 28 days, followed by 14 days of no treatment), with a satisfactory response.[84,85] In a phase II study, 35 patients with advanced thyroid cancer – seven of them with MTC – received sunitinib at a dose of 37.5 mg daily. The objective response included one complete response (3%), ten partial responses (28%), and 16 patients (46%) with SD.[86]

An ongoing phase II trial aims to determine the efficacy of sunitinib in patients with locally advanced or metastatic thyroid cancer. The partial results of the 15 patients with MTC show 33.3% partial response and 26.7% SD for ≥12 weeks.[87]

The FDA has approved sunitinib for treatment of advanced renal cell carcinoma and gastrointestinal stromal sarcomas.

Axitinib (AG-013736)

Axitinib is an oral TKI with selectivity and potency against VEGFR-1, VEGFR-2, and VEGFR-3.[88] A multicenter, open-label, phase II study of 60 patients with advanced thyroid cancer, of whom 18% had MTC, was conducted using 5 mg daily of axitinib. In MTC patients only, the confirmed partial response rate was 18%, and the SD rate was 27%.[89]

Imatinib (STI571)

Imatinib is a TKI used to treat chronic myelogenous leukemia and gastrointestinal stromal tumors. In MTC-derived cell lines expressing mutant RET receptors, imatinib inhibited RET Y1062 phosphorylation and induced cell-cycle arrest and apoptotic cell death. However, the half-maximal inhibitory concentration of imatinib necessary to inhibit RET in vitro is higher than other small-molecule kinase inhibitors of RET activity.[90] An open-label trial evaluated nine patients with unresectable and progressive MTC treated with imatinib (600 mg daily) for 12 months. A complete or partial response was not seen; after 6 months, five patients had SD, and after 12 months only one.[91] Similar results were found in another clinical trial with imatinib at the same doses. Of

the 15 patients with disseminated MTC treated for up to 12 months, four patients had SD over 24 months.[92]

A recent study compared the effect of four TKIs (axitinib, sunitinib, vandetanib, and XL184) on cell proliferation, RET autophosphorylation, and extracellular signal-regulated kinase activation in three cell lines: MZ-CRC-1 (M918T *RET* mutation), MTC-TT (C634W *RET* mutation), and TPC-1 (RET/PTC-1 rearrangement) cells. The results showed that all four TKIs were capable of reducing cell proliferation, yet XL184 was the most efficient inhibitor for MEN 2A and vandetanib was the most potent inhibitor for MEN 2B.[93] These data suggest that the use of specific treatments for each mutation could provide additional benefits in the management of metastatic MTC.

Safety and tolerability of receptor tyrosine kinase inhibitor therapies and implications for disease management

The TKIs are used as chronic therapies, and therefore it becomes important to understand the profile of adverse effects. Generally, these effects are tolerable, and the majority of patients have manageable toxicity. However, TKI-related serious adverse events leading to death have been also observed and include aspiration pneumonia, respiratory arrest, respiratory failure, sepsis, *Staphylococcus* infection, and acute heart failure and arrhythmia.[66,94,95]

Common adverse events associated with TKIs are diarrhea, rash, fatigue, and nausea. Other adverse events related to use of TKIs include hypertension, neutropenia, leucopenia, hand-foot syndrome, stomatitis, proteinuria, abdominal pain, facial edema, thrombocytopenia, malaise, laryngeal mucosal swelling, and QTc prolongation, among others (see Table 2).[58,64–66,69,73,77,78,86,87,89,91,92] Endocrine dysfunctions are often a side effect of TKI treatment. The most frequent is hypothyroidism, which required an increase in thyroid replacement dose in approximately 50% of patients. However, the mechanism of hypothyroidism induction is still unclear.[96]

Conclusion and future directions

Until recently, patients with advanced or metastatic MTC received only palliative care to relieve disabling symptoms, since chemotherapy and radiotherapy have unsatisfactory results. In recent years, cumulative knowledge of molecules and intracellular signaling pathways involved in the pathogenesis of MTC has allowed the use of new targeted therapies.

Different TKIs have been studied in the management of metastatic MTC. The results have demonstrated that TKIs are able to induce partial responses or stabilization of tumor growth. However, it is important to remember that TKIs also interact with physiological functions, causing a number of highly toxic side effects. Moreover, most of the clinical trials were performed on a small number of patients with a brief follow-up period, since tumor growth is very slow in MTC. Therefore, caution is essential in identifying patients who will benefit with such therapies. Gathering information about the targets of action of these drugs as well as TKI-associated side effects will help in choosing the best therapeutic approach to enhance their benefits.

Disclosure

The authors report no conflicts of interest in this work.

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