ENDOCRINE TUMOURS

Progressive metastatic medullary thyroid carcinoma: first- and second-line strategies

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Abstract

The treatment for metastasised medullary thyroid cancer is still a topic of discussion. One of the main challenges remains to find effective adjuvant and palliative options for patients with metastatic disease. The diagnostic and treatment strategies for this tumour are discussed and possible new developments commented. Approaches that target rearranged during transfection (RET) are preferable to those that target RET downstream proteins as, theoretically, blocking RET downstream targets will block only one of the many pathways activated by RET. Combining several agents would seem to be more promising, in particular agents that target RET with those that independently target RET signalling pathways or the more general mechanism of tumour progression.

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Introduction

Medullary thyroid cancer (MTC) is an uncommon disease accounting for ~5% of all thyroid cancers. This malignant neuroendocrine tumour is derived from the parafollicular C cells. In 1906, Jacquet (1) first described MTC in a patient as a 'malignant goiter with amyloid', and Hazard (2) more than 50 years later defined a case of thyroid carcinoma with a solid non-follicular structure with amyloid in the stroma as a MTC. MTC can occur sporadically (75%) or as part of a familial syndrome called MEN2. The hereditary forms are caused by a

mutation in the 'rearranged during transfection' (*RET*) gene, of which familial MTC (FMTC), MEN2A and MEN2B variants are discerned. Other clinical manifestations of the MEN2 syndrome are pheochromocytoma and hyperparathyroidism (MEN2A) or pheochromocytoma, marfanoid habitus and mucosal neuromas (MEN2B: Table 1). In the case of a proven *RET* mutation, carriers of these familial tumour syndromes will be offered a prophylactic thyroidectomy. The timing of this prophylactic procedure is still a matter of

Invited Author's profile

Prof. Thera P Links is President of the working party for national guidelines for the treatment of thyroid cancer and of the Dutch Von Hippel–Lindau Association and involved in national and international studies on endocrine tumours. She has a lot of experience on working with rare familial syndromes, with working in multidisciplinary teams of different institutes and countries. Her research focuses on thyroid cancer and rare familial tumour syndromes such as Multiple Endocrine Neoplasia and Von Hippel–Lindau disease.

Table 1 Clinical expression of familial MTC-associated syndromes.

	FMTC (%)	MEN2A (%)	MEN2B (%)
MTC	100	100	100
Phaeochromocytoma	0	10–60	50
Hyperparathyroidism	0	10–30	0
Marfanoid habitus	0	0	100
Intestinal ganglio-neuromatosis	0	0	60–90
Mucosal neuromas	0	0	70–100

discussion and is accepted at a young age when an aggressive mutation is present (3). Basal and stimulated calcitonin levels can be used in the decision making, but the balance between the risk of the complications of an early thyroidectomy and the possible risk of disease development when this procedure has been delayed is still difficult (4).

Most MTC patients present with an asymptomatic palpable solitary thyroid nodule and/or suspicious enlarged cervical lymph node(s). Some patients may have symptoms of a more local or even advanced disease such as dysphagia, coughing, hoarseness and dyspnoea. Owing to excessive calcitonin production, diarrhoea or flushing can be one of the presenting symptoms, especially in more advanced disease (5). In very rare and advanced cases, ectopic adrenocorticotrophin production of the neuroendocrine cells, causing Cushing's syndrome, has been described (6, 7).

At presentation, ~50% of the MTC patients show lymph node metastases, 10% already had distant metastases and more than 20% of the patients will die from progressive metastatic disease (8). Although the prognosis is generally favourable when diagnosed and treated at an early localised stage, it strongly depends on disease stage, with a 10-year overall survival (OS) of 95% in patients with localised disease to 75 and 40% in patients with regional and metastasised disease respectively (9). Treatment for metastasised MTC, as for the prophylactic procedure, remains a topic of discussion, but progress has been made by American and European Taskforces (10, 11). However, one of the main challenges in the treatment of MTC patients is to find effective adjuvant and palliative options for patients with metastatic disease.

In the pathogenesis, both sporadic and inherited MTC mutations in the *RET* proto-oncogene are of major importance. Other pathways, including the vascular epidermal growth factor (VEGF) pathway and the mesenchymal–epithelial transition (MET) pathway, also seem to play a role in MTC development. Overexpression or mutations in the *MET* gene, with activation of the receptor c-MET/hepatocyte growth factor (HGF) receptor, are observed in MTC (12, 13, 14). Interestingly, activation

of mTOR and RAS is also observed in *RET*-mutated tumours, as is the case for PI3K (15).

In this review, we discuss the diagnostic and treatment strategies for MTC and comment on possible new developments.

Prediction of progressive MTC at diagnosis

For carriers of *RET* germline mutations, MTC is commonly curable in an early stage or when identified upon preventive surgery. Upon diagnosis, most patients with MTC present with a solitary thyroid nodule and cervical nodal or distant metastasised disease, expressing its heterogeneous character. It is therefore difficult to establish the behaviour of the tumour – both locally and systemically; this is, however, necessary in order to determine the therapeutic management of MTC. Localised and limited locoregional diseases are treated by curative intended resections, while in more advanced localised or residual/recurrent disease a multimodality approach is generally recommended for local control and to reduce tumour progression. Moreover, early identification of clinically relevant systemic progression or irresectability is important to choose a more appropriate therapeutic intervention that may delay symptomatic deterioration, maintaining quality of life and possibly increasing survival.

Several tools are available to support the most appropriate surgical approach. First, we need an adequate diagnosis, which is generally made using fine-needle aspiration of cervical nodules with immunohistochemical examination for calcitonin and carcinoembryonic antigen (CEA). We then need appropriate staging of nodal and distant disease, using cervical ultrasonography and magnetic resonance imaging and an ¹⁸F-FDG-PET(CT) or an ¹⁸F-DOPA-PET(CT) on indication, to perform adequate initial treatment with curative intent.

Optimal initial surgery is important to obtain loco-regional control and eventually cure MTC. The standard treatment of MTC with palpable lesions consists of a total thyroidectomy with central compartment dissection completed by an ipsilateral or bilateral neck lymphadenectomy. Additional lateral neck surgery is still a matter of debate and depends on the clinical relevance of the extent of the nodal dissection.

Several factors may help to predict tumour progression and enhance treatment effectiveness

Lymph node involvement ► Different surgical approaches are proposed by the guidelines of the

American and British Thyroid Association. Both tumour size and lymph node involvement have been shown to be the most important predictors for disease-free and OS (16). The ATA recommends total thyroidectomy with central dissection (level VI) and ipsilateral lymph node dissection (LND) of level II–V when nodal involvement is suspected, while the BTA advocates bilateral selective LND in pT2–4 tumours or palpable lymph nodes in the central or lateral compartment (10, 17). However, it remains difficult to cure patients with extensive nodal involvement, and the reported variation of biochemical cure ranged from 5 to 35% after reoperation. Systematic extended LND has improved biochemical cure, but the survival benefits remain contradictory (18, 19, 20). When extensive metastatic disease is present upon diagnosis, one must carefully consider whether the advantages of surgery to obtain local tumour control weigh up against the disadvantages and risks of extensive surgery. Recently, we have shown that ATA-compliant surgery resulted in fewer local reoperations and more biochemical cure. Adequate surgery according to ATA guidelines has been executed most often in the participated referral centres where MTC patients less often underwent surgical re-interventions (16).

Calcitonin doubling time ► Calcitonin is one of the specific tumour markers for MTC, and detectable calcitonin after apparently curative treatment indicates persistent disease. CEA is less specific, but is used as a useful marker to observe progressive disease. Currently, many investigators consider short calcitonin and CEA doubling times to be the best available indicators to assess progressive disease (21, 22). Giraudet *et al.* (21) found that 94% of patients with doubling times <25 months had progressive disease according to RECIST. However, a disadvantage of this method is that calcitonin and CEA levels commonly fluctuate so greatly that serial measurements must be performed over a considerable time (3–6 months) in order to accurately determine doubling time.

¹⁸F-FDG-PET uptake ► Recently, it has been shown that both ¹⁸F-FDG-PET and ¹⁸F-DOPA-PET are useful in guiding therapeutic steps in patients with MTC with different indications (23, 24). ¹⁸F-DOPA-PET is preferably used to assess the extent of the disease, while ¹⁸F-FDG-PET seems to be better for identifying more progressive MTC (25).

Mutation analysis ► Mutations in the *RET* oncogene are found in the familial forms of MTC and in more than 45% of sporadic MTC (26, 27, 28). MEN2A and FMTC patients

commonly have a better treatment outcome than those with sporadic MTC, who are frequently diagnosed at a more advanced stage. The aggressiveness also differs between FMTC and different types of MEN2 and the related *RET* mutations have been stratified into low, high, and very high risks (levels 1–3). Level 1 includes patients with *RET* codon 768, 790, 791, 804 and 891 mutations; level 2, patients with MEN2A/FMTC-related mutations (codons 609, 611, 618, 620, 630 and 634); and level 3, patients with MEN 2B mutations in codon 883 or 918 (3). As reported previously in 1994, somatic mutations in *RET* can be identified in 30–50% of all sporadic MTC (29). The most common and more aggressive somatic *RET* mutation in sporadic MTC is the replacement of methionine by threonine at codon 918 (Met918Thr), although mutations and deletions have been described at a number of other codons. It is as yet unclear whether factors other than the genes described previously (*RAS/c-MET/HGF*) and mechanisms (VEFG/mTOR pathways) are involved in the development or progression of MTC. However, it has been shown that aggressive inherited and sporadic medullary thyroid carcinomas display comparable expression profiles (30), suggesting that activation and de-activation of specific pathways may be related to invasion and metastatic behaviour.

Treatment options for progressive disease

Somatostatin analogues

Reports have been published on several trials that study the effect of somatostatin analogues on MTC. Currently available somatostatin analogues with a high affinity for SSTR2 and SSTR5 (octreotide and lanreotide) do not seem to have an effect on survival but do in some patients show fewer complications such as flushing and diarrhoea (31). SSTR receptors are present in <40% of the MTCs (32), so only those patients with SSTR positivity will have the clinical benefits. The use of somatostatin analogues can be considered for symptomatic treatment of diarrhoea if other drugs are ineffective (10).

Radiofrequency ablation

Radiofrequency ablation can be applied for local tumour control or as a tumour debulking procedure in case of severe uncontrolled diarrhoea. It has been described as a useful treatment modality for liver metastases in differentiated thyroid carcinoma and may therefore also be applied for MTC metastatic disease (33).

Adjunctive value of radiotherapy

The benefits of postoperative radiotherapy for local tumour control have undergone poor, and only retrospective, evaluation. External beam radiotherapy (EBRT) may be indicated to improve locoregional disease control in high-risk patients, especially in cases of microscopic and even macroscopic residual tumour in the neck after incomplete surgery, or severe local extratumoural spreading (34).

For distant metastases that cannot be approached surgically, EBRT can be indicated for palliative treatment of painful bone metastases or prevention of paraplegia upon threat of spinal cord involvement; it can also be indicated as an adjuvant therapy after surgery (11).

Chemotherapy

Currently, there is no employable standard chemotherapeutic regimen, but the most frequently described cytotoxic drug in MTC patients is doxorubicin, used either alone or in combination with cisplatin. However, responses are partial and reported in up to 22% of patients, and only for a few months. Other combinations with 5-fluorouracil, dacarbazine, streptozocin, cyclophosphamide and vincristine have been described (35); however, none of these compounds are commonly used. Therefore, future perspectives on useful chemotherapeutic options are still very limited as all known studies have as yet failed to demonstrate relevant objective responses or survival benefit (11).

Targeted therapies

Tyrosine kinase inhibitors ► New therapeutic options, particularly tyrosine kinase inhibitors (TKIs) targeting RET protein, have been studied extensively and have recently become available for the systemic treatment of MTC patients.

In general, activation of a tyrosine kinase receptor (TKR) starts with binding of specific ligands to the extracellular parts of the receptor, resulting in case of RET in a homodimer, which triggers autophosphorylation, subsequently resulting in downstream activation of several signalling pathways. For RET, this is slightly more complicated as RET first needs to bind to GFR α 1, after which glial cell line-derived neurotrophic factor binds to this protein complex, resulting in autophosphorylation. RET autophosphorylation leads to downstream activation of many pathways, including the RAS–MAPK, PI3–AKT and JAK pathways.

The TKIs work by blocking the ATP pocket of the TKR, thereby preventing autophosphorylation of the TKR. TKRs are highly homologous proteins and, as the inhibitors usually target many TKRs, they are called multikinase inhibitors. In most cases, RET is one of the many kinases targeted for such a TKI. Table 2 gives an overview of studies published in the past few years regarding systemic treatment with TKI targeting RET.

As is clear in Table 2, many different TKIs have been tested, but because study outcomes are inconclusive, comparisons between these studies are sometimes

Table 2 Results in MTC with kinase inhibitors.

	Molecular target	No.	ORR (%)	Stable disease > 6 months (%)	References
Imatinib	Bcr-Abl, PDGFR α and PDGFR β , c-Fms, c-Kit, RET	15 9	0	27 56	(63) (64)
Gefitinib	EGFR	4	0	0	(65)
Motesanib	VEGFR1, VEGFR2 and VEGFR3, PDGFR, c-Kit, RET	91	2	48	(66)
Axitinib	VEGFR1, VEGFR2 and VEGFR3	11	18	NR	(67)
Sorafenib	RAF, VEGFR2 and VEGFR3, PDGFR, RET	21 15	21 13	53 NR	(68) (69)
Vandetanib	VEGFR, EGFR, RET	30 19 331	20 16 45	53 53 NR	(70) (71) (37)
Sunitinib	VEGFR1, VEGFR2 and VEGFR3, PDGFR, c-Kit, RET, FLT3	25 15	32 33	NR NR	(72) (73)
Lenvatinib	VEGFR1, VEGFR2 and VEGFR3, RET, c-Kit, FGFR1, FGFR2, FGFR3 and FGFR4, PDGFR	59	36	NR	(40)
Cabozantinib	VEGFR2, MET, c-Kit, FLT3, Tie2	37 330	27 28	41 NR	(74) (38)
Pazopanib	VEGFR 1-3, c-Kit, PDGFR α and β	35	14	NR	(39)

difficult. Moreover, many questions remain such as: which TKI should be used? Can all MTC be treated with the same TKI? Should the mutational status of the tumour be taken into account? When should we start treating the patients with TKI? *In vitro* studies could answer some of these questions. For example, in an *in vitro* study comparing four TKIs, vandetanib and cabozantinib were found to be the most potent inhibitors of tumour progression in MTC. More specifically, it was demonstrated that XL184 is the most potent inhibitor (with cell proliferation as an outcome measure) in cell lines harbouring MEN2A- and PTC-associated mutant RET proteins, and vandetanib was proven most effective for cell lines harbouring MEN2B-mutated RET proteins. This study indicates that mutation-specific therapies could be beneficial in treating MTC (36). This was also confirmed in two phase III clinical trials, which showed that these TKIs had a significant effect on

progression-free survival (37, 38). Besides RET, other TKRs, mostly based on overexpression, could also play a role in MTC. Figure 1 gives an overview of the interaction of RET, EGFR and VEGFR pathways. EGFR, overexpressed in 35% of MTC metastases, and VEGFR2 overexpression stimulated by angiogenesis have been found in the majority of MTC tumours and particularly in their metastases. As these TKRs probably also play a role in MTC development, inhibition of the TKRs by TKI has been extensively explored. We now will discuss some of these important TKIs.

Pazopanib, a multikinase inhibitor inhibiting c-KIT, FGFR, PDGFR and VEGFR, showed partial responses in 14.3% (39). Lenvatinib is also a multikinase inhibitor, acting most potently on FGFR, a mechanism that resists VEGF/VEGFR inhibitors. Preliminary results of a phase 2 trial with lenvatinib showed a partial response rate of

Figure 1

Schematic representation of downstream pathways of the RET receptor and other tyrosine kinase receptors (e.g. EGFR) with possible targets for therapeutic interventions.

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36% (40). Everolimus has also been tested in phase 2 studies, but without convincing effects as yet (41).

Although a number of TKIs show encouraging results, no benefits of any of these inhibitors on OS have yet been demonstrated. Therefore, further studies with adequate follow-up are required. Moreover, currently studied TKIs, including those directed against the RET protein, were found to have a considerable dose-dependent toxicity in the majority of patients. For patients with metastasised MTC who still have a considerable life expectancy, the benefits of progression-free survival often do not outweigh the side effects caused by these drugs (42).

If first-line treatment fails and the patient develops drug resistance, it is important to have an alternative drug available. However, there are no published studies that include only patients who failed after treatment with a specific TKI, and, as yet, there are no data on cross-resistance among TKIs. Thus, there is no standard treatment protocol to follow treatment with first-line TKI.

New developments

New RET inhibitors ► Ponatinib (AP24534) is a TKI that preferentially binds the protein at its inactive form and has shown to be a potent inhibitor of RET. De Falco *et al.* (43) studied this drug in human *RET/PTC1* (TPC-1), *RET M918T* (MZ-CRC1) and *RET/C634W* (TT) cell lines and TT xenografted tumours in mice, and showed inhibition of RET kinase. Mogni (44) also demonstrated that ponatinib inhibits all four forms of the RET kinase: the fusion protein with the WT sequence (*RET/PTC1*), the receptor carrying an activation mutation in the extracellular domain (*RET/C634W*), the full-length protein with the *RET M918T* mutation and the drug-resistant V804M/L gatekeeper mutant. They therefore called this drug a pan-RET inhibitor. Gild *et al.* (45) also demonstrated that AST487, a RET kinase inhibitor, suppressed growth and inhibited mTOR signalling in MZ-CRC-1 cell lines.

Other RET-related approaches ► One might consider targeting RET proteins with heat shock protein 90 (HSP90). This HSP90 is necessary for the folding and stability of WT and mutant molecules (46). Nelfinavir is a HIV protease inhibitor that can target HSP90. Nelfinavir has been shown to inhibit MTC cells and to decrease RET expression (47).

Current research has focused on different steps in these complex processes using monotherapy and

combination therapy, including RET-dependent and -independent signalling.

Monotherapy

PI3K/AKT/mTOR pathway ► The idea of using RAD001 (everolimus) has been based on the presence of AKT/mTOR activation, proven by immunohistochemical staining, in more than 50% of MTC cells. It should be noted that RET can activate the AKT/mTOR signalling pathway (see for comprehensive review) (15).

The use of everolimus to treat MTC tumours induced in mice resulted in a significantly lower tumour volume when compared with controls (48).

Lin *et al.* (49) studied the effect of the PI3K/mTOR inhibitor NVP BEZ235 as a single agent in cell lines of all thyroid cancer types. Anaplastic cell lines were the most sensitive to this agent, suggesting that refractory cancers that develop PI3K/mTOR signalling during the process of dedifferentiation would be the most responsive to this therapy. However, the authors could not show a correlation between the sensitivity of the cells to NVP BEZ235 and the genetic alterations found in the PI3K/mTOR pathways. Another agent inhibiting mTOR, which has been tested in *in vitro* MTC cell lines, is INK128 (45). This kinase inhibitor showed inhibitory effects on both MZ-CRC and TT cell proliferation, although no effects on RET autophosphorylation were observed, suggesting that the PI3K/mTOR activation is not RET related in this specific cell line. Novel experiments with anolide derivatives have also demonstrated an inhibitory effect on RET phosphorylation as well as on the mTOR signalling in MTC-TT and DRO 81-1 cells (50). The fact that RET activation stimulates mTOR signalling could imply that the observed inhibition of mTOR signalling is the direct result of the inactivation of RET. However, two other compounds, vandetanib and cabozantinib, also tested in this study and shown to inhibit RET, did not affect mTOR signalling in the specific cell line.

Akt is a downstream target of PI3K, and specific Akt inhibition by MK-2206, an Akt specific inhibitor, did significantly suppress MTC cell proliferation. This inhibitor, similar to INK128, did not suppress RET phosphorylation (51); this again shows that it is probably RET independent.

These studies show that inhibition of pathways that are independent of RET or pathways that are activated by RET can be targeted with possible beneficial effects for the patient. This can also be concluded from the studies on JAK/STAT.

JAK/STAT pathway ► The JAK/STAT pathway is another important pathway for gene transcription and can be activated by many pathways including RET (52, 15). Couto *et al.* (53) demonstrated experiments with thyroid cancer cell lines and xenografts with AZD1480, a JAK 1,2 inhibitor that can block cell growth and induce cell death. They used cell lines harbouring distinct forms of oncogenic RET, such as *RET/PTC1* (TPC-1), *RET* M918T (MZ-CRC1) and *RET/C634W* (TT). In particular, the *RET* mutation associated with MEN2B (MZ-CRC1) was highly sensitive to the inhibitory effects of AZD1480, thereby illustrating the potential benefit of this drug for treating aggressive MTC. They also suggested an effect on the microenvironment based on the decrease in vascularity and tumour necrosis via *JAK*/phosphor-STAT 3 inhibition in endothelial cells.

Combined targeted therapy

Combined targeted therapy is also currently under investigation in the treatment of MTC. The antiproliferative effects of sorafenib – the RAF kinase inhibitor – were significantly augmented in MTC human cell lines (harbouring the 634 and 918 *RET* mutations), when it was combined with the MEK inhibitor AZD6244, thereby underscoring the potential of this combined approach (54). A phase 1 study in 13 patients with MTC, combining sorafenib with tipifarnib (a RAS inhibitor), showed a partial response with acceptable toxicity in five out of 13 patients (55). Combined blockage of the PI3K/mTOR pathway and Raf inhibition as published by Jin also potentially inhibits growth in MTC cell lines (56).

However, alternative approaches seem to be promising. Metformin is an antidiabetic agent that decreases proliferation of cancer cells through the 5-AMP-activated protein kinase inhibition of mTOR. Metformin also inhibits growth of MTC cell lines, thereby underscoring the significance of the mTOR pathway in this type of tumour (57). Metformin is now used in various clinical trials in combination with other drugs and in a neoadjuvant setting. Gild *et al.* (45) also showed that a combination of AST487 and INK128 suppressed growth and induced apoptosis in the MZ-CRC-1 cell line, thereby supporting the use of combined treatments for thyroid cancers with oncogenic *RET* mutations.

Other targets

Targets for therapeutic agents could also be independent of the mutational status of a tumour: one could focus on

more general mechanisms such as apoptosis or proliferation. A drug that can target tumour cell apoptosis, reduction of proliferation and suppression of tumour-induced angiogenesis is enzastaurin, a protein kinase C (PKC) inhibitor playing pivotal roles in these activities. Molè *et al.* (58) have demonstrated that targeting PKC may be a useful approach for controlling MTC proliferation.

Another approach might be to change the methylation status of the tumour. Aberrant genomic DNA methylation is a hallmark of cancer and gene expression is dependent on the methylation status. A recent paper has demonstrated that MTC is characterised by general hypomethylation. Although the role of hypomethylation in cancer remains yet to be unravelled, it may suggest another approach to treatment (59).

Besides changing the methylation status of a tumour, one might also change its acetylation status. Histone deacetylases regulate gene expression and thereby cell cycle, proliferation and apoptosis. Histone deacetylase inhibitor PXD101 has been shown to suppress proliferation of thyroid cancer cells, including the MTC TT cell line (60).

Side effects of TKIs

Many side effects are related to the degree of inhibition by TKIs and to patient-related comorbidities, but can be TKI specific; these are referred to as on-target toxicity, such as that occurs in cardiotoxicity, where the TKI target regulates both cancer cell and normal cardiomyocyte survival (61). Small-molecule kinase inhibitors usually block multiple kinase proteins (multitargeting) with crossover activity and therefore more diversified related side effects, diminishing the quality of life. Several adverse events (AEs) and serious adverse events (SAEs) are reported in 30–60% and 2% of patients respectively. Many of these AEs are commonly related (fatigue, headache and muscle cramps), but with some severe cutaneous side effects (dry skin, rashes, hyper/hypopigmentations, hand-foot syndrome/erythrodysesthesia and musculoskeletal pain). Other frequently described AEs are gastrointestinal related events (loss of appetite, vomiting, diarrhoea, obstipation and abdominal pain or haematological toxicity). Many of these AEs can be treated symptomatically, while some AEs are reduced during the first 1–2 years (62).

The more severe SAEs are different in origin and frequently cardiovascular related: from myositis/dermatitis with even peripheral arterial occlusive diseases to ischaemic heart disease with congestive heart failure or ischaemic cerebrovascular disease. Other problems are

hepatotoxicity, even including liver failure, pulmonary arterial hypertension and the development of second malignancies.

Conclusion

MTC is a rare heterogeneous malignant disease, which frequently presents with metastases that are difficult to manage. Standardisation and centralisation of surgery are desirable for an optimal initial treatment. Subsequent systemic treatment of advanced MTC is currently not available, although many types of drugs are being tested.

Treatment of metastasised MTC always involves a balance between the effect of the drug on the tumour and the side effects of the drug. Most of the drugs that are tested are TKIs, targeting RET, encoded by the major gene in MTC pathology.

Of these TKIs, vandetanib and cabozantinib are currently the only systemic therapy approved in the European Union (EU) for the treatment of aggressive and symptomatic advanced MTC. However, after treating tumour progression with a first-line TKI, there is no standard treatment, and several new agents are under development.

Several other different strategies for the treatment of MTC are currently being considered, many of which target downstream proteins of RET. We do believe that approaches that target RET are preferable to those that target RET downstream proteins as, theoretically, blocking RET downstream targets will block only one of the many pathways activated by RET. Combining several agents would seem to be more promising. In particular, combining agents that target RET with those that independently target RET signalling pathways or the more general mechanism of tumour progression do have our preference.

Finally, what we did not discuss extensively is that the mutational status of *RET* is related to the effect of the agents used (36). This is a field that needs more attention.

Between *in vitro* testing and clinical application lies a long road. Clinical testing with small numbers of patients is challenging and time consuming. We therefore advocate international collaboration, preferably in a multicentre clinical trial, to find the most effective treatment for patients with progressive MTC.

Declaration of interest

Prof. T P Links is on the Advisory Board of Astra Zeneca, Bayer and Genzyme. All other authors have no conflicts of interest.

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