SPECIAL REPORT

To treat or not to treat

Developments in the field of advanced differentiated thyroid cancer

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ABSTRACT

Background: Thyroid cancer is the most prevalent endocrine malignancy. Based on the increased understanding of thyroid tumourigenesis, novel therapeutic agents have been identified. However, given the low incidence, the good prognosis of the majority of these tumours and the limited evidence of different treatment modalities, a wide variety of treatment strategies are available. These are mostly based on small studies, data from retrospective analyses and the particular experiences of treating physicians. We discuss the recent developments in the treatment of advanced differentiated thyroid cancer.
Case description: Three cases demonstrate the considerations involved in treatment decisions for patients with advanced thyroid cancer. The first patient achieved stable disease for over five years with different targeted therapies. The second patient shows the potential (severe) toxicity of these drugs and the third patient illustrates the indolent nature of this disease.
Conclusion: The treatment of patients with extensively metastasised thyroid cancer is very complicated. The timing of initiation of therapy and the potential toxicity of targeted therapies are important in the clinical decision to treat or not to treat because of the slowly progressive course of differentiated thyroid cancer. When targeted therapy is considered, it remains of great importance to enrol patients in clinical studies in order to further determine the position of these therapies, to develop more effective (combination) treatment schemes, and above all, to identify those patients that truly benefit.

KEYWORDS

Advanced differentiated thyroid cancer, outcome, targeted therapies, toxicity

INTRODUCTION

Thyroid cancer accounted for 95% of cancers of the endocrine system and 66% of endocrine cancer mortality in 2010.[1] The incidence of thyroid cancer is globally increasing, which is largely due to an increase in the number of detected small tumours (T1). In 2011, 185 men and 426 women were diagnosed in the Netherlands with thyroid malignancy.[2] Thyroid cancer is a heterogeneous disease that is classified into differentiated thyroid carcinoma (DTC 80-90%), undifferentiated (anaplastic) thyroid carcinoma (ATC 5-10%) and medullary thyroid carcinoma (MTC 5%). DTC covers papillary (60-70%) and follicular (also including the oncocytic variant, known as Hürthle cell carcinoma) subtypes (20-30%). The majority of DTC is slowly progressive and, when identified at an early stage, frequently cured with adequate surgical management and radioactive iodine (RAI) ablation therapy. However, metastatic DTC that has become inoperable or refractory to RAI therapy is associated with a less favourable prognosis (*table 1*). Based on the understanding of thyroid tumourigenesis, potential targets and novel therapeutic agents have been identified (*figure 1*). Based on the patients presented here, we discuss the recent developments in the treatment of advanced differentiated, RAI refractory thyroid cancer and the considerations involved in treatment decision-making.

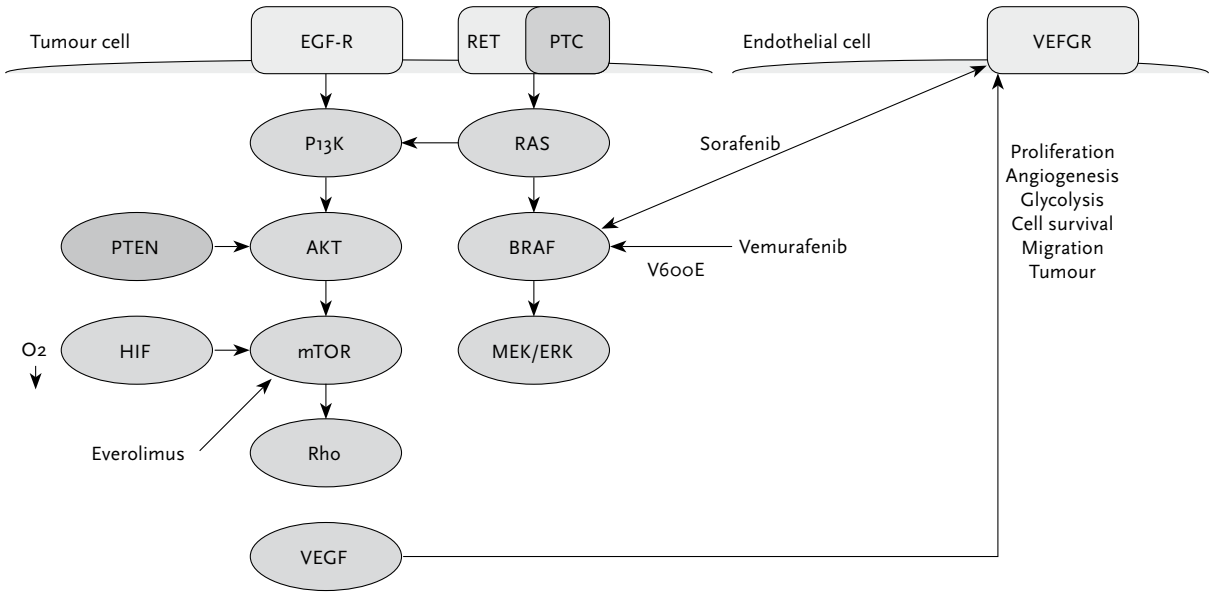
Patient A was a 47-year-old man when he was diagnosed with a multifocal papillary T2N0M0 thyroid carcinoma in 1995. He underwent a total thyroidectomy, followed by RAI ablation therapy (50 millicurie (mCi)) and thyroid-stimulating hormone (TSH) suppression therapy. Besides hypertension, his medical history revealed no other diseases. In 2002, he developed multiple lung and mediastinal lymph node metastases and was treated with additional RAI therapy (cumulative dose 545 mCi). The

Table 1. *Thyroid cancer: tumour type, age, prevalence and survival*

Tumour type		Age (years)	Prevalence	10-year survival	
				Non metastatic disease	Metastatic disease
Differentiated	Papillary Follicular	10-60 25-70	60-70% 20-30%	90-95%	5-10%
Medullary		10-60	5%	75%	10%
Anaplastic		>60	5-10%	<5%	0

Schlumberger M, Pacini F. Thyroid tumors. Paris, France: Editions Nucléon 2006.

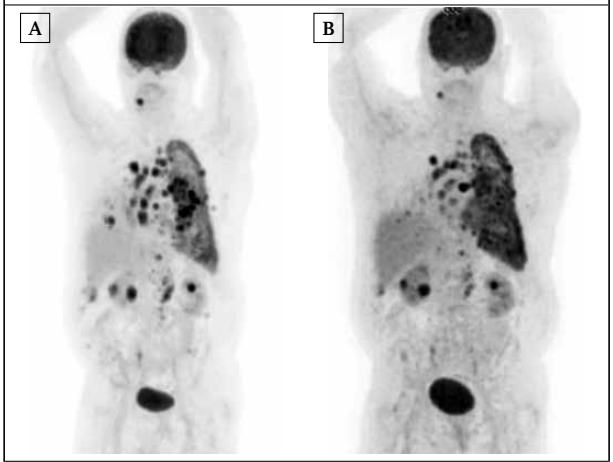
Figure 1. *Signalling pathways involved in thyroid tumourigenesis*



last post-therapeutic whole body scan was negative. In 2008 the lung metastases were progressive so he started sorafenib 400 mg twice daily in a phase II study in 2008. Revision of the tumour showed a B-type Raf kinase (BRAF) V600E mutation. Due to grade 3 diarrhoea sorafenib was reduced from 800 mg to 200 mg daily, which resulted in a partial response according to the Response Evaluation Criteria In Solid Tumours (RECIST).[3] Two years later the patient showed progressive disease with pleuritis carcinomatosis. Sorafenib was discontinued and the patient underwent pleurodesis and therapeutic punctures. After progression of his pulmonary metastases he was enrolled in a phase II trial with everolimus at the end of 2010 resulting in stable disease. He tolerated everolimus treatment well after a 50% dose reduction to 5 mg daily because of mucositis. In August 2012 the disease became progressive again and everolimus was discontinued. One month later the patient started on vemurafenib in a phase II study. He tolerated the standard dose (960 mg twice daily) well and stable disease was achieved (*figure 2*). One year after initiation of vemurafenib, he developed progressive dyspnoea and haemoptysis and died at the age of 65, most likely due to a massive haemorrhage from a pulmonary metastasis.

Patient B is a 74-year-old man diagnosed with a follicular variant of a papillary thyroid carcinoma (T4aN0M0) in 2004. A total thyroidectomy was performed followed by RAI therapy (cumulative dose 450 mCi) and TSH suppression therapy. He underwent a coronary artery bypass graft in 2006 for three-vessel coronary artery disease. In 2007, the patient presented with local, pulmonary and bone metastases of his thyroid tumour. He was enrolled in the phase II study with sorafenib and received 400 mg twice daily. Due to complaints of grade 3 diarrhoea the dose was reduced to 200 mg twice daily. After six months, the patient showed a partial response and good tolerance of the sorafenib. Late 2009 he was hospitalised with a myocardial infarction followed by severe heart failure. Coronary angiography showed no

Figure 2. *F-FDG PET scan from patient A before (a) and after 4 weeks (b) of vemurafenib treatment*



Physiological 18F-FDG uptake in brain, bladder, liver and spleen; pathological uptake in osseous, pulmonary and lymph node metastases, and carcinomatous pleuritis prior to vemurafenib (a). After 4 weeks of treatment slight decrease of FDG accumulation in some metastases: the centre of the left lung, dorsobasal in the right lung and two mediastinal lymph nodes, no new FDG-avid lesions (b).

significant stenosis. Given the possible role of sorafenib in luxating coronary spasms and thereby myocardial infarction this treatment was discontinued. No other therapeutic options were available for his thyroid tumour and the patient was followed in the referral hospital. Upon inquiry, the patient received radiotherapy for a local recurrence in the neck in May 2013. At the end of 2013, he was in a reasonable condition with a relatively good quality of life.

Patient C is a 79-year-old female who underwent a subtotal left hemithyroidectomy in 1985 because of a 'follicular lesion', histologically diagnosed as a follicular adenoma. In 2003 she presented with a mass in the neck and lung metastasis. Revision of the pathological specimen from 1985 revealed a follicular thyroid carcinoma. The patient underwent a completion thyroidectomy. RAI therapy (450 mCi) was followed by surgical excision of three RAI refractory lung metastases. In 2005 she had recurrent disease in the neck and new lung metastases. Surgical re-exploration of the neck was followed by radiotherapy (70 Gy in 35 fractions). In 2009, the lung metastases became progressive and a new occipital skull metastasis was treated with radiotherapy (10x3 Gy). The patient declined systemic therapy. In August 2011, she presented with pain, based on an impending pathological fracture of the femoral neck. She underwent an hemiarthroplasty after embolisation. Once more the patient declined systemic treatment. At the end of 2013 she experienced no other limitations of her metastatic disease, except from blindness of her right eye due to a metastasis.

These cases demonstrate both the (long-term) benefits that can be achieved with targeted therapy (case A), the potential (severe) toxicity (case B) of these agents, and the slowly progressive course of metastatic differentiated thyroid carcinoma (DTC) (case C).

TARGETED THERAPIES

Preclinical studies have shown that inhibition of kinases that play a role in signalling pathways involved in thyroid tumours may lead to a decrease in tumour growth. Several of these kinase inhibitors have been investigated with encouraging results (*table 2 and 3*). Here we discuss the agents previously mentioned in our case presentations (*figure 1*).

Sorafenib (BAY 43-9006) is an orally active tyrosine kinase inhibitor (TKI) targeting BRAF, vascular endothelial growth factor receptor 1 and 2 and rearranged during transfection (RET), resulting in pro-apoptotic and antiangiogenic actions. Several phase II trials with sorafenib in patients with advanced DTC have been conducted, showing promising results.[4-6] In a recently performed phase III study, investigating the efficacy and safety of sorafenib in patients with advanced, RAI-refractory DTC, 417 patients were randomised between sorafenib twice daily 200 mg and placebo with the option of crossover in case of disease progression. The median progression-free survival in the placebo and sorafenib group was 5.8 months and 10.8 months respectively (HR 0.587; $p < 0.0001$).[7]

Everolimus (RAD001) is an orally available derivative of rapamycin that interferes with the regulation of cell cycling, cell growth and cell survival mechanisms through binding to the mammalian target of rapamycin. Recently published data of a phase II study of everolimus in patients with advanced thyroid cancer of all histological subtypes (n=38) reported a median PFS of 47 weeks.[8] Currently, a phase II study with everolimus in patients with unresectable or metastatic DTC, ATC and MTC is being conducted in the Netherlands. Results of this trial will be known at the end of 2014.

Vemurafenib (PLX 4032) is a TKI that specifically inhibits the BRAF V600E and V600K mutated kinases. Recent data of a phase II study in patients with a papillary thyroid carcinoma (PTC) reported a median progression-free survival of 15.6 and 6.8 months in treatment-naive patients and patients previously treated with a TKI, respectively.[9]

Although targeted therapies are better tolerated than cytotoxic chemotherapy, many patients develop side effects that require dose reduction or additional medication. The most common adverse events per targeted agent are summarised in *table 4*.

Table 2. *Summary of studies in thyroid cancer*

Drug	Tumour type	N	RR	SD	PFS	Referentie
Sorafenib	DTC	41 30 26 207	15% 23% 27% 12%	56% (≥24 weeks) 53% 58% 42% (≥26 weeks)	15 months 79 weeks 18 months 11 months	Kloos et al. 2009 Gupta et al. 2008 Schneider et al. 2012 Brose et al. 2013
Everolimus	All types	38	5%	45% (≥24 weeks)	47 weeks	Lim et al. 2013
Vemurafenib	DTC	3 51	33% 61%	66% -	12 months 16 months+ 7 months+	Kim et al. 2013 Brose et al. 2013
Motesanib	DTC+MTC DTC	71 93	7% 14%	49% (>12 weeks) 35% (>24 weeks)	- 40 weeks	Rosen et al. 2007 Sherman et al. 2008
Vandetanib	DTC	72	1%	56%	11 months	Leboulleux et al. 2009
Sunitinib	DTC	12 31	8% 13%	67% 68%	- -	Ravaud et al. 2009 Cohen et al. 2009
Thalidomide~	DTC+MTC	28	18%	32%	-	Ain et al. 2007
Gefitinib	All types	18	0%*	24% (>24 weeks)*	16 weeks*	Pennell et al. 2008
Pazopanib	DTC	37	32%	65%	12 months	Bible et al. 2009
Axitinib	DTC	45	31%	42%	18 months	Cohen et al. 2008
Lenalidomide	DTC	18	23%	45%	-	Ain et al. 2008

RR = response rate; SD = stable disease; PFS = progression free survival; DTC = differentiated thyroid cancer; MTC = medullary thyroid cancer; - not reported; + 15.6 months in the TKI naive group and 6.8 months in the group previously treated with a TKI, c-KIT stem cell factor receptor; TNFα = tumour necrosis factor alpha; * overall results; ° DTC+MTC results.

Table 3. *Kinase inhibitors and their targets*

Drug	Target(s)
Sorafenib	BRAF VEGFR 1,2 RET
Everolimus	mTOR
Vemurafenib	BRAF V600E
Motesanib	VEGFR 1-3 RET c-KIT
Vandetanib	VEGFR 2,3 RET EGFR
Sunitinib	VEGFR 1-3 RET RET/PTC 1-3
Thaliodomide*	VEGFR TNFα
Gefitinib	EGFR
Pazopanib	VEGFR 1-3 c-KIT
Axitinib	all VEGFRs
Lenalidomide*	VEGFR TNFα

*** exact mechanism of action unknown.**

DISCUSSION

Up to 50% of follicular and 12% of Hürthle cell malignancies contain RAS mutations.[10] The RAF proteins are cytoplasmic serine/ threonine protein kinases that are effected downstream by RAS. Of these, BRAF is the most efficient at phosphorylating mitogen-activated protein kinase (MAPK) and is important in proliferative as well as apoptotic pathways.[11] Point mutations leading to BRAF signalling independent of binding to RAS have been reported in 35-70% of PTCs, underlining the significance of the RAS/RAF/MAPK pathway in thyroid cancer.[12] BRAF is an important regulator of thyroid-specific protein expression and proliferation.[13] BRAF mutations are associated with recurrent and persistent disease, a higher rate of lymph node metastasis and a higher tumour-node metastasis stage.[14] In human thyroid cancer, BRAF V600E is associated with vascular endothelial growth factor overexpression, which in turn is associated with increasing tumour stage and invasiveness.[15]

Furthermore, BRAF is a putative downstream signal transducer for RET/PTC. A translocation of the RET/ PTC oncogene is seen in 25% of PTCs, resulting in the generation of chimeric oncogenes and proteins responsible for the initiation of tumour formation. Based on evidence that BRAF is involved in the development of PTC in the

Table 4. *Most common side effects (≥ 1/10 patients) per system organ class per targeted therapy*

System organ class	Sorafenib	Everolimus	Vemurafenib
General	Fatigue Headache	Fatigue Headache Fever Weight loss	Fatigue Headache Fever Anorexia
Blood and lymphatic system disorders	Lymphopenia	Anaemia Thrombocytopenia	
Cardiac disorders	Hypertension Bleeding	Peripheral oedema	Peripheral oedema
Respiratory disorders			Cough
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	Diarrhoea Nausea Vomiting	Diarrhoea Nausea Vomiting Constipation
Musculoskeletal and connective tissue disorders			Myalgia Arthralgia Back pain
Skin disorders	Alopecia Rash HFS Erythema Pruritus	Mucositis Rash Pruritus Dry skin	Photophobia Rash Actinic keratosis Pruritus Erythema Dry skin Alopecia Hyperkeratosis
Laboratory disorders	Hypophosphataemia Elevated amylase Elevated lipase	Hypercholesterolaemia Hypertriglyceridaemia Hyperglycaemia	Elevated gammaGT
Neoplasms			SCC of the skin Seborrhoeic keratosis Skin papilloma

HFS = hand foot syndrome, SCC = squamous cell carcinoma.

progression of anaplastic carcinoma, BRAF is an attractive target in thyroid cancer.[16]

The AKT pathway plays an important role in cell proliferation and survival and has been found by others to be aberrantly activated in thyroid tumours.[17-20] An important player in this pathway is the PI3KCA subunit that in turn is also regulated by RAS. Activation of the PI3K/AKT pathway is seen in thyroid adenomas, follicular thyroid carcinomas and ATCs.

Since the knowledge of the biological basis of thyroid cancer has increased, systemic treatment options for metastatic DTC have changed. There are a wide variety of treatment strategies for patients with extensively metastasised thyroid cancer, although this type of cancer is rare and often has a slowly progressive course. The evidence for these different treatment strategies is limited. To date, only sorafenib is available as standard systemic treatment for patients with progressive, RAI-refractory disease. However, in case of slowly progressive disease, the side effects of systemic treatment outweigh the potential benefits. Therefore, patients must show at least progressive disease within 12-14 months before initiation of therapy based on the RECIST criteria.

Given the low incidence of (metastatic) thyroid carcinoma, its slowly progressive course and the potential toxicity of targeted therapies, the timing of initiation of therapy is a delicate issue. It is of great importance to take the natural course of disease into account and to value not only possible benefits but also toxicity before starting a targeted therapy. Hence, initiation of systemic therapy preferably has to be coordinated in a specialised centre and if possible to enrol patients in clinical studies in order to further determine the position of targeted therapies, to develop more effective (combination) treatment schemes, and above all, to identify those patients that truly benefit.

DISCLOSURES

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