

Alternative Therapeutic Approaches in the Treatment of Primary and Secondary Dedifferentiated and Medullary Thyroid Carcinoma

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The prognosis of patients with surgically unresectable differentiated thyroid tumors deteriorates significantly if radioiodine therapy is or becomes ineffective, considering the limited role of conventional chemotherapies in these patients. Several alternative approaches have been investigated for the treatment of patients with advanced thyroid malignancies in recent years. Among targeted therapies, tyrosine kinase inhibitors have resulted in the most encouraging responses and could soon be, along with redifferentiation therapy, the possible palliative strategies. Radiopeptide therapy, especially with beta emitter-labeled DOTANOC, which shows a great affinity to the somatostatin receptors expressed by thyroid tumor cells, might also be an attractive approach considering its comparatively low rate of side effects. However, the indication should be evaluated on individual basis. Medullary thyroid carcinoma shows a worse overall prognosis compared with the other differentiated thyroid tumors especially because of its natural resistance to radioiodine therapy. However, among possible palliative strategies, ^{131}I -meta-iodobenzylguanidine therapy is a noteworthy therapeutic approach in patients experiencing metastasized medullary thyroid carcinoma. In summary, recent developments in the treatment of patients with advanced thyroid malignancies have shown promising results, raising the hope for better outcomes in these patients in future.

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The most frequent primary thyroid malignancies arise from follicular cells in differentiated thyroid carcinomas (DTCs), accounting for 85%-95% of all thyroid tumors. They show generally an excellent prognosis and even metastatic cases can be cured, especially young patients with solely micronodular lung metastases.¹ Standard therapy procedure consists of thyroidectomy, including resection of involved lymph nodes, radioiodine ablation therapy, and thyrotropin (ie, thyroid-stimulating hormone)-suppressive therapy, especially in high-risk patients. However, an increasing rate of differentiated carcinomas with higher initial tumor stages, lack of the ability to accumulate radioiodine sufficiently, and therefore worse prognosis is observed in older patients.²

The prognosis deteriorates significantly if radioiodine therapy is or becomes ineffective in patients with surgically unresectable tumor remnants or recurrences. This applies especially to patients with medullary thyroid carcinoma

(MTC), originating from parafollicular cells, which doesn't accumulate radioiodine and is curable only in cases of limited disease. MTC occurs in the sporadic form in approximately 70% of cases, whereas the remaining 30% is represented by 3 familial forms: multiple endocrine neoplasia type 2 A (MEN 2 A), multiple endocrine neoplasia type 2 B (MEN 2 B), and familial MTC not associated with MEN.³ Total thyroidectomy, including resection of lymph nodes of the central and both lateral compartments, is the general therapeutic approach in these patients.

Anaplastic thyroid carcinomas, characterized by extremely aggressive growth and extensive resistance against radiation and conventional chemotherapy, display the worst prognosis among the thyroid malignancies. Conventional chemotherapies in this type of thyroid cancers have been reported only anecdotal to be efficient in cases of advanced disease. As a result, anaplastic carcinomas show rapid progression, and survival time seldom exceeds 6 months.

In primary or secondary dedifferentiated thyroid cancers, redifferentiating cancer cells to induce radioiodine-uptake in formerly radioiodine-negative tumor lesions combined with conventional chemotherapy with doxorubicin and cisplatin

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Table 1 Compounds Used in Recent Clinical Trials for Thyroid Cancer

Class	Compound	Target	Clinical Study	Reference
Tyrosine-kinase inhibitor	Sorafenib	BRAF, PDGFR, ret, VEGFR	Phase 3	Clinical Trials NCT00984282*
	Sunitinib	PDGFR, ret, VEGFR	Phase 2	32
	Motesanib	Kit, PDGFR, VEGFR	Phase 2	34
	Axitinib	VEGFR	Phase 2	30
	Pazopanib	PDGFR, VEGFR	Phase 2	36
	Gefitinib	EGFR	Phase 2	37
Ras inhibitor	Tipifarnib	Farnesyl transferase	Phase 1 (in combination with sorafenib)	29
Histone deacetylase inhibitor	Valproic acid	Class I HDAC	Phase 2	Clinical Trials NCT00525135† and NCT01182285‡
	Voronostat (SAHA)	Class I, II HDAC	Phase 2	43
Cyclooxygenase inhibitor	Celecoxib	Cyclooxygenase-2	Phase 2	46
Angiogenesis inhibitor/immunomodulation	Thalidomide	Unknown (ie, inhibition of TNF- α synthesis in immune cells)	Phase 2	38
	Lenalidomide (thalidomide analogue)	Unknown (ie, inhibition of TNF- α synthesis in immune cells)	Phase 2	39
Cell differentiation agent	Retinoic acids	Retinoic acid receptors (RXR)	Phase 2	53
	Rosiglitazone	Peroxisome proliferator-activated receptor	Phase 2	56

EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; TNF, tumor necrosis factor alpha; VEGFR, vascular endothelial growth factor receptor.

*<http://clinicaltrials.gov/ct2/show/NCT00984282>. Accessed September, 27, 2010.

†<http://clinicaltrials.gov/ct2/show/NCT00525135>. Accessed September, 27, 2010.

‡<http://clinicaltrials.gov/ct2/show/NCT01182285>. Accessed September, 27, 2010.

has been investigated as a possible palliative approach with limited impact on patient's survival.⁴⁻⁹

Recently, targeted therapies, including novel agents like angiogenesis inhibitors and tyrosine kinase inhibitors, proved to yield at least stable disease in several patients with radioiodine resistant dedifferentiated, medullary, and anaplastic cancers, raising hope for an improvement in therapeutic modalities.¹⁰ By contrast, the expression of somatostatin receptors on thyroid cells and their malignant counterparts, proven by somatostatin receptor scintigraphy, has been the basis of the administration of beta emitting-labeled somatostatin receptor agonists as a palliative therapy in patients with thyroid cancer. It has shown varying impact on patients' outcome especially due to heterogeneity of published studies. However, considering the limited success of conventional therapy strategies in advanced stages of the thyroid malignancies, novel therapeutic strategies have become promising treatment modalities in recent years.

Conventional Chemotherapy

Most experiences regarding chemotherapy in advanced thyroid cancers have been made with doxorubicin as monotherapy or in combination with cisplatin. The overall response, based on the data mostly collected before year 2000, is estimated to be in the range of approximately 30%. However, it is difficult to make a definite statement about therapeutic efficacy of these therapy regimes because of the heterogeneity of study designs and investigated cancer types.¹¹⁻¹³

Furthermore, World Health Organization (WHO) criteria for response evaluation used in most of these studies have been almost completely replaced by response evaluation criteria in solid tumors (RECIST), which were developed in the late 1990s and published in February 2000.

Side effects of doxorubicin are common, consisting of nausea, vomiting, mouth sore, diarrhea, weight, and hair loss, as well as hematologic toxicity. Severe cardiotoxicity became less important after its use as the liposomal form.

Argiris and colleagues¹⁴ investigated the therapeutic efficacy of the combination of doxorubicin and interferon alpha in patients with locally recurrent or metastatic, radioiodine-refractory, non-MTC. The combination proved to be only of limited benefit: in 16 patients assessable for response, 1 patient (6%), who had follicular thyroid carcinoma (FTC), achieved a partial response whereas 10 patients (62.5%) showed stable disease as best response.

Table 1 gives an overview of the above mentioned therapeutic approaches.

Targeting Therapies

Biomolecular Background

RET gene encodes a transmembrane tyrosine kinase receptor that is a part of a receptor complex for ligands of the glial-derived neurotrophic factor family. In case of chromosomal rearrangements aberrant forms of the receptor are produced, resulting in abnormal activation of the ras/extracellular sig-

nal-regulated kinase and PI3-kinase/V-akt cascades¹⁵ and therefore augmented gene transcription, which leads to malignant cell-growth. This type of *RET* gene rearrangement is well known in papillary thyroid carcinoma (PTC), with the greatest prevalence of *RET/PTC1* and *RET/PTC3* occurring in 5%-30% of adult sporadic and in 50%-80% of radiation-induced papillary carcinomas.¹⁶⁻¹⁷ Interestingly, these *RET/PTC* expressions are especially frequent in occult PTC, interpreted as a sign of early event in tumorigenesis.¹⁸ Therapeutic approach consists of protein kinase inhibitors that are not monospecific for *RET*.

Development of PTC could also be the result of a disorder in the *ras/Raf/mitogen-activated protein kinase* signaling pathway. *Ras* proteins are plasma membrane attached small GTPases activated by growth factor receptors, nonreceptor tyrosine kinases, and to lesser extent G protein-coupled receptors.¹⁵ These proteins are involved in proliferation, differentiation, and cell survival. Mutations of the *ras* oncogenes are highly prevalent in follicular adenomas and carcinomas and less frequent in papillary thyroid cancer. *Ras* proteins are possible targets of antisense oligonucleotides and are investigated in clinical trials.

Raf proteins, the second part of the *ras/Raf/mitogen-activated protein kinase* pathway, are serine/threonine kinases consisted of 3 isoforms namely *ARAF*, *BRAF*, and *CRAF*. The most common genetic alterations in these proteins are mutations in *BRAF* encoding gene, usually in point mutations in papillary thyroid cancer, not to be found in other forms of well-differentiated follicular neoplasms.¹⁹ Present data indicate clearly that papillary thyroid cancers with *BRAF* mutations show comparatively aggressive growth, metastasize more frequently, and have a worse prognosis. Several *RAF* small molecule kinase inhibitors as well as inhibitors of downstream kinases (eg, mitogen-activated protein kinase/extracellular signal-regulated kinase) are being tested for the treatment purposes.²⁰

A key factor inducing the growth of thyroid cancer is the stimulated angiogenesis because of increased secretion of vascular endothelial growth factor (VEGF).²¹ Soh and colleagues²² demonstrated that the expression of VEGF was significantly greater in patients with DTC comparing to those with normal thyroid or benign thyroid disease. VEGF receptors antagonizing substances have been used for therapy in several malignancies, including thyroid cancers.

Another receptor that is highly expressed in thyroid carcinomas as well as in a significant portion of well-differentiated benign thyroid nodules is epidermal growth factor receptor (EGFR).²³ Furthermore, results of a study published by Chen et al suggest that autocrine activation of platelet-derived growth factor alpha (PDGF- α) receptor also plays a crucial role in the carcinogenesis of thyroid cells.²⁴ The expression of these 2 receptor types may display further targets for small molecule-therapy.

Tyrosine Kinase Inhibitors

One of the most extensive studied new antitumor compounds for thyroid cancer treatment is sorafenib (BAY 43-

9006), which is approved by Food and Drug Administration and the European Medicines Agency for the treatment of renal cell carcinoma and hepatocellular carcinoma. It is a multikinase inhibitor which targets VEGF receptors 1-3, PDGF receptor, *BRAF*, and *RET*. Kloos and colleagues evaluated therapeutic efficacy and side effects of sorafenib in a phase 2 study in patients with mainly papillary thyroid cancer.²⁵ Five of 33 patients with PTC (15%) demonstrated partial response in this study, assessed by RECIST. However, the therapeutic effect of sorafenib was rather underestimated, considering the size reduction of the target lesions, which was present in almost all patients with stable disease (57%), though not attaining a tumor shrinkage of 30%. The median progression-free survival time was 15 months. Treatment was generally well tolerated but dose reduction was necessary in about half of the patients. Gupta-Abramson and colleagues²⁶ reported higher rates of partial response (23%) and median progression-free survival (21 months) using similar dose in 30 patients with advanced thyroid cancer. This study was again a phase 2 trial with mainly DTC patients. The authors reflected the limitations of RECIST and emphasized the resulting underestimation of therapeutic effects. They mentioned that RECIST ignores the disappearance or decrease of subcentimeter lesions as well as appearance of tumor necrosis although these findings indicate therapeutic response. A comparable partial response rate of 25% and an estimated median progression free survival rate of 15 months was observed in another phase 2 trial on 31 patients with advanced, radioiodine-refractory DTC treated with sorafenib.²⁷ However, patients with bone metastases profited less from the therapy and radioiodine-uptake was not reduced under sorafenib medication.

In younger ages thyroid carcinomas are highly differentiated and markedly iodine-avid. Radioiodine-refractory DTC in adolescents are an extremely rare condition. Waguespack and colleagues²⁸ reported an 11-year-old girl experiencing an advanced papillary thyroid cancer with extrathyroidal spread, lymph node- and distant metastases in the lungs. She showed evidence of progressive disease despite radioiodine therapy which could be stopped with sorafenib administration.

As the result of promising results of treatment with sorafenib, a phase 3 multicenter study (DECISION) has been initiated, including patients with advanced, radioiodine-refractory DTC. Preliminary results are expected in year 2012.

The most common side effects of sorafenib are fatigue, palmar-plantar erythema, rash, fatigue, stomatitis, weight loss, and musculoskeletal pain. Less frequently, other side effects, such as hypertension, diarrhea, pruritus, anxiety, and elevated lipase and amylase, can also occur. In this case, doses must be reduced or interrupted at least temporarily.

Recently, Cabanillas and colleagues²⁹ researched treatment efficacy of the combination of sorafenib and tipifarnib, an inhibitor of farnesyl transferase that prevents the activation of *ras*, in patients with metastatic DTC. In this phase 1 study, in which the authors also used RECIST to determine tumor response, only 1/15 patients (7%) with DTC showed partial response, whereas stable disease was present in 13/15

patients (86%). The median progressive-free survival rate was 20 months.

Sunitinib, a tyrosine kinase inhibitor of VEGF1, -2, and -3, PDGFR, and RET, is used for treatment of renal cell carcinoma similar to sorafenib. Information regarding treatment efficacy in patients with thyroid malignancies is scarce and exists predominantly in form of meeting abstracts presented at the annual meeting of the American Society of Clinical Oncology in year 2008 and 2009. Cohen and colleagues evaluated the impact of sunitinib on patients' outcome in a phase II study.³⁰ Of 31 evaluable DTC-patients with initial evidence of progressive disease partial response was evident in 13% and stable disease in 68%. Most common drug-related side effects were fatigue, diarrhea, palmar-plantar erythrodysesthesia and gastrointestinal tract problems. Simultaneously, Ravaud, and colleagues presented interim-analysis regarding sunitinib-therapy in 17 patients with histologically different thyroid malignancies, of which 8 with papillary thyroid cancer, who showed a disease progression during the last 6 months before tyrosine kinase-onset.³¹ Partial response or stable disease for longer than 12 weeks was achieved in 2 of 12 patients. Another phase 2 trial studied sunitinib-therapy in 33 patients with metastatic, radioiodine-refractory, FDG-PET-positive thyroid malignancies who predominantly experienced DTC (80%).³² Recently, published data verified overall partial response in 31% and stable disease in 46% after being in the study for 8.5 months. Noteworthy, in patients with MTC, partial response according to RECIST was observed in 50%. The patients were mainly treated with sunitinib (n = 35), whereas 2 patients were pretreated with sorafenib and 2 patients with motesanib. Interestingly, 1 patient with a refractory disease under sorafenib and 1 patient with pretreatment with motesanib showed partial response under sunitinib with significant reduction in tumor size.

Motesanib (AMG706) is another oral tyrosine kinase inhibitor, targeting VEGF1, -2, and -3, PDGFR, and KIT. A phase 1 study in which the authors evaluated treatment efficacy of motesanib in patients with solid tumors proved partial response in 2 of 5 patients with DTC.³³ It is followed by a phase 2 study of 93 patients with locally advanced or metastatic DTC and documented evidence of disease progression.³⁴ Partial response, assessed according to RECIST, was present in 14%, and stable disease was confirmed in 67%. Twelve patients (13%) discontinued treatment as the result of adverse events, most commonly diarrhea, hypertension, fatigue, and weight loss, whereas 2 patients with progressive disease died because of pulmonary hemorrhage. Further studies might clarify the therapeutic efficacy and safety of motesanib in DTC compared with other tyrosine kinase inhibitors.

Sporadically, experiences with other drugs, such as axitinib, pazopanib, and gefitinib in therapy of advanced DTC have also been published. In a 2008 released study axitinib, inhibiting predominantly and selectively VEGFR 1-3, was applied in 45 DTC-patients as well as in 15 patients with thyroid malignancies of other histology.³⁵ Partial response occurred in 31% whereas stable disease was present in 42% with a median progression free survival-rate of 18 months in

the whole cohort. Treatment was generally well tolerated with side effects consisting of fatigue, diarrhea, nausea, anorexia, hypertension, stomatitis and proteinuria.

Pazopanib, a small molecule inhibitor of all VEGFR subtypes and of PDGFR, was also studied in a phase II trial on patients with advanced and progressive DTC. The preliminary results of the treatment of 37 evaluable patients have been recently published showing a 49% partial response-rate using RECIST for therapeutic assessment.³⁶

In contrast, therapy with gefitinib, a small molecule inhibitor of the EGFR, resulted in no objective response in DTC-patients, although 5 of 16 patients featured a decrease in thyroglobulin-level.³⁷ The authors assumed a therapeutic effect because of prolonged stable disease in several patients.

Inhibitors of BRAF kinases may also play a role as therapeutic agents in BRAF-mutant PTC in the future. However, to the best of authors' knowledge, no published paper regarding their therapeutic efficacies exists to date.

Angiogenesis Inhibitors

Thalidomide and their derivative lenalidomide are believed to express their antitumor effects at least partially by inhibiting angiogenesis. Ain and colleagues investigated the tumorigenic effect and toxicity of thalidomide on a mixed cohort of patients with rapidly progressive thyroid cancers with distant metastases.³⁸ Five twenty-eighths evaluable patients (18%) achieved a partial response, whereas 9 patients (32%) showed a stable disease. Most common side effect was fatigue, whereas grade 3-4 infections (n = 4), pericardial effusion (n = 1) and pulmonary embolus (n = 1) were less frequent. In general, side effects were numerous, including severe teratogenicity, sedation, drowsiness, constipation, dermatologic manifestations mostly in the form of skin eruptions but even epidermal necrolysis, hypothyroidism and more rarely deep vein thrombosis, hepatotoxicity, pulmonary hypertension and hyperkalemia.

More recently, lenalidomide has been investigated by the same authors in a similar setting. Preliminary results in 21 evaluable patients yielded partial response in 22% and stable disease in 44%.³⁹ Lenalidomide is an oral therapeutic agent with clinical activity in multiple myeloma, lymphoma and myelodysplasia. The exact mechanism of action of lenalidomide is uncertain. However it has been reported, *inter alia*, also to promote immune activation and interference with tumor cell microenvironment.⁴⁰

Histone Deacetylases Inhibitors

Only sporadic data exists with regard to therapy efficacy of agents inhibiting histone deacetylases, such as romidepsin (depsipeptide),^{41,42} vorinostat,^{43,44} and valproic acid.⁴⁵ Primary results indicate only limited effect on tumor progression which needs further clinical trials to shed light on the matter.

Another therapeutic approach was investigated by Mrozek and colleagues⁴⁶ based on the knowledge of increased expression of cyclooxygenase COX-2 mRNA and protein levels in thyroid cancer tissue compared with nonneoplastic and

benign thyroid tissues.⁴⁷⁻⁴⁹ Results were disappointing with 23 of 32 patients receiving celecoxib, a selective COX-2 inhibitor, suffered from progressive disease or stopped therapy due to severe toxicity. Only 1 patient achieved partial response and 1 patient remained stable for 12 months on treatment with celecoxib.

Redifferentiation Therapy

Induction of redifferentiation in primary and secondary DTCs is a possible therapeutic approach by the positive relation between the tumor's grade of differentiation and the likelihood of a slow growth and its ability to accumulate radioiodine.⁵⁰ One important precondition for the latter is expression of sodium-iodine symporter (ie, NIS), which co-transporters 2 sodium ions along with 1 iodine ion. In vitro studies showed successful redifferentiation of thyroid carcinoma cell lines by increasing the expression of some thyroid specific proteins⁵¹ and sodium/iodide symporter.⁵²

Retinoic acids, including all-*trans*-retinoic acid (RA), 9-*cis*-RA, and 13-*cis*-RA, are chemically related to vitamin A. Several authors have investigated the clinical benefit of their oral administration at doses of 1-1.5 mg/kg body weight for several weeks to induce ¹³¹I uptake in formerly iodine resistant tumor lesions.⁴⁻⁹ Treatment was generally well tolerated but almost all patients experienced side effects, usually grade 1-2, such as dryness of lips, mucosa and skin as well as hypertriglyceridemia.

Interestingly, a common effect under retinoic acid regimen is the rise of thyroglobulin, interpreted as a sign of redifferentiation in regaining the ability to produce thyroid cell-specific proteins.⁵³ Therefore, the measurement of this tumor marker for restaging may not be accurate or even feasible in this setting. According to the existing data, re-uptake of radioiodine can be achieved in approximately one-third of patients (Fig. 1). It is worth mentioning that there are reported indications for therapeutic effects even in tumors not showing re-uptake of radioiodine. However, clinical benefit in form of tumor shrinkage or even stable disease is limited, preventing general use of retinoic acids in patients with radioiodine-refractory thyroid cancers.

Peroxisome proliferator-activated receptor-binding agonists, such as thiazolidinediones, commonly used in therapy of patients with diabetes mellitus type 2, (glitazones) could also demonstrate antiproliferative and redifferentiating effects in thyroid cancer cell lines.^{54,55} Kebebew and colleagues⁵⁶ investigated efficacy and side effects of rosiglitazone therapy in patients with radioiodine-refractory DTC. Although radioiodine uptake occurred in 5/20 patients after 8 weeks of rosiglitazone treatment, no objective response could be revealed using RECIST criteria, indicating a similar impact on tumor behavior as retinoic acids.

In a case report presented on "International Conference on Radiopharmaceutical Therapy" in 2005, Hofmann, and colleagues reported radioiodine uptake in a patient with previously radioiodine negative tumor lesions following the administration of a statin for 4 weeks.⁵⁷ However, to the authors' knowledge, the validation of any significant impact

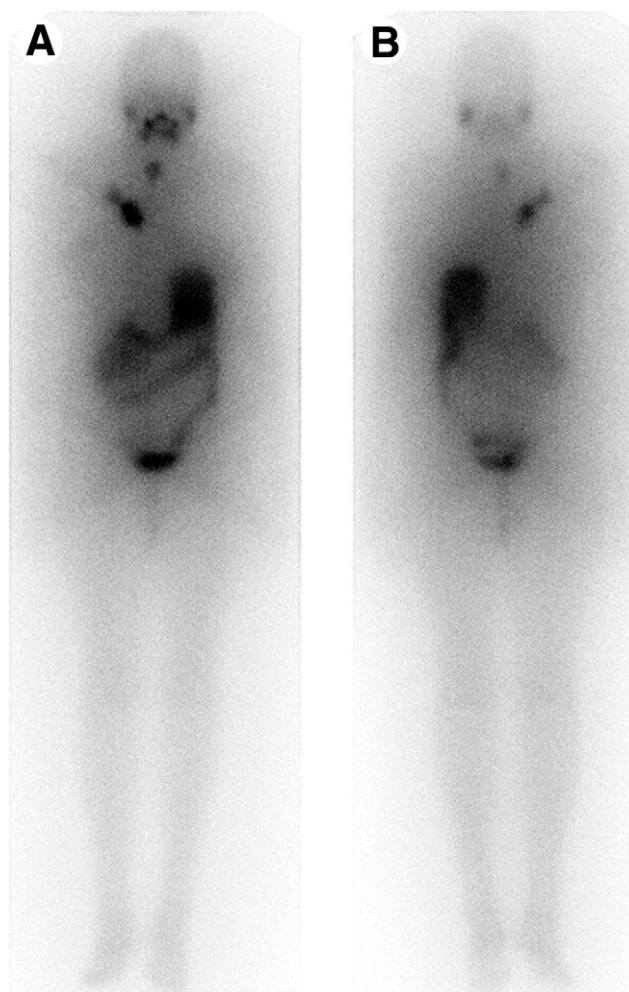


Figure 1 (A) Lack of I-131-Uptake in known pulmonary metastases (low-dose whole-body scan) in a patient with follicular thyroid carcinoma (FTC). (B) Significant ¹³¹I uptake in pulmonary metastases after redifferentiation therapy with retinoic acid (after high-dose ¹³¹I therapy).

of statins on radioiodine-refractory thyroid cancer is still missing. Other factors varying radioiodine uptake, such as the type of hypothyroidism (endogenous vs exogenous), the amount of administered radioiodine as well as the previous exposure to iodide radioiodine therapy should also be taken into account.

Radiopeptide Therapy

In a significant proportion of patients with radioiodine negative DTC, the expression of somatostatin receptors on tumor lesions can be proven by scintigraphy with the somatostatin analog 111-In-diethylenetriaminepentaacetic acid(0) (DTPA)-octreotide⁵⁸⁻⁶¹ or 68-Ga-DOTA(0)-Phe(1)-Tyr(3)octreotid (DOTATOC)-PET.⁶² The implication was to treat these carcinomas with beta emitting-labeled somatostatin receptor agonists. Treatment of gastroenteropancreatic neuroendocrine tumors (GEPNETs) with beta emitting-labeled somatostatin receptors has already proved to improve the patients' disorders, caused by hormonal overproduction, accompanied by an objective tumor response in a significant portion.

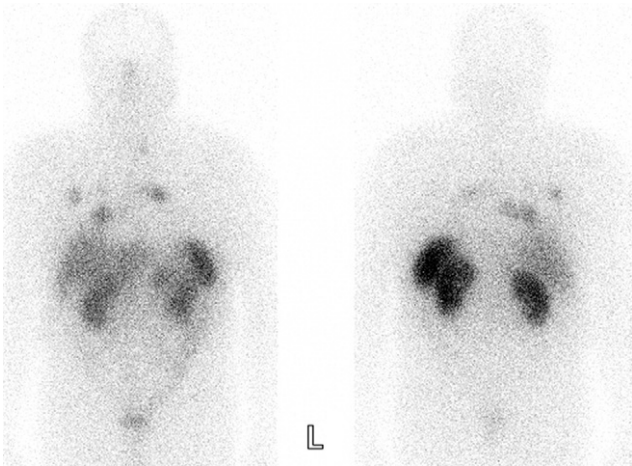


Figure 2 Uptake of Lu-177-DOTATE in pulmonary (iodine-negative) metastases of papillary thyroid carcinoma.

However initial studies on GEPNET, in the absence of beta emitting-labeled somatostatin receptors, the use of ^{111}In -DTPA-octreotide resulted in significant symptom relief but with limited effect on tumor response.⁶³⁻⁶⁴

In present days peptide receptor radionuclide therapy is mainly performed with either 90-Y-DOTATOC or 177-Lu-DOTATATE with encouraging (complete- and partial-) response rates of approximately 30% whereas one to two-thirds of patients with GEPNETs showed stable disease (Fig. 2).⁶⁵⁻⁶⁸ Therapy is generally well tolerated with mild side effects consisting of mainly moderate nausea, vomiting and hematological toxicity WHO grade 1 or 2. In contrast, more severe side effects, such as hematological toxicity WHO grade 3 or 4, myelodysplastic syndrome and renal insufficiency occur only rarely. The absorbed dose to the kidneys and the resulted kidney toxicity can be significantly diminished by coinfusion of amino acids. Although fixed dose regimens show a high rate of tolerance there's an increased risk of undertreatment compared with regimens, including individualized dosimetry.⁶⁹

Data regarding peptide receptor radionuclide therapy in thyroid carcinomas are scarce. Teunissen and colleagues published the results of 177-Lu-DOTATATE-therapy in 5 patients with radioiodine-refractory DTC, including 3 patients experiencing Hürthle cell carcinomas.⁷⁰ Stable disease, minor response (tumor shrinkage between 25% and 50%) and partial remission (shrinkage $\geq 50\%$) each was achieved in 1 patient with Hürthle cell carcinoma. One patient with PTC showed stable disease and one with FTC-progressive disease. The authors mentioned the difficulties in comparing their findings with those of the other studies^{60,63,71-76}: to date scientific releases regarding therapy with beta emitting-labeled somatostatin receptor agonists in DTC comprise small sample sizes, treated with different radiolabeled somatostatin analogs and individually variable administered doses. Particular attention must be given to the heterogeneity of the expression of different somatostatin receptor subtypes (SSTR). Although differentiated gastroenteropathic neuroendocrine tumors, effectively treated by peptide receptor therapies, ex-

press predominantly SSTR2 and SSTR1,⁷⁷ thyroid cancer cells express mainly SSTR3 and SSTR5, and SSTR2 is only faintly detectable in these tumors.⁷⁸ These distinctive features need to be set in the context of different somatostatin receptor subtypes targeted by the known somatostatin analogs. Although DOTATATE has a 9-fold greater affinity for the SSTR2 than does DOTATOC, the affinity to SSTR3 and SSTR5 were found to be lower.⁷⁹ To date there is no sufficient data concerning imaging and therapy of thyroid cancer using ^{111}In - or ^{90}Y -labeled DOTA-1-Nal(3)-octreotide (DOTA-NOC), characterized by affinity for SSTR3 and SSTR5 besides SSTR2. Nevertheless, beta emitter-labeled DOTA-NOC might be an encouraging approach considering its comparatively low rate of side effects. With regard to hitherto existing data, the indication of peptide receptor radionuclide therapy in patients suffering from thyroid carcinoma should be evaluated on individual basis.

MIBG Therapy in Medullary Thyroid Carcinoma

The overall prognosis of MTC is worse than DTC despite being comparable in case of limited disease. The presence of lymph node and especially distant metastases reduces survival times of patients with MTC more significantly compared with DTC cases—10-year survival rates account for 75% and 40%, respectively.⁸⁰ MTC releases predominantly calcitonin and carcinoembryonic antigen (CEA), but occasionally neuron-specific enolase, serotonin, chromogranin, gastrin-releasing peptide, substance P, pro-opiomelanocortin-derived products, and somatostatin can also be secreted.⁸¹ Hormone-related symptoms, including flushing, diarrhea, and the ectopic corticotrophin syndrome often are associated with an advanced stage of the disease.⁸² Complete resection of the tumor and metastases is the only curative treatment while alternative approaches have to be applied as palliative treatment strategies for unresectable cases. Currently available palliative therapies include radiotherapy, chemotherapy, targeted therapies and radiolabeled peptide therapy as well as therapy with radioiodinated meta-iodobenzylguanidine (MIBG). MIBG is a radiopharmaceutical specific for tumors originating from the neural crest, including MTC. MIBG is structurally similar to norepinephrine. It is taken up actively and transported into the intracellular catecholamine storing granules of sympathomedullary tissues. Chemotherapy with different cytotoxic drugs, such as Adriamycin, cyclophosphamide, vincristine, dacarbazine, 5-fluorouracil and doxorubicin, or even combined regimes have shown only minor responses with considerable hematologic, nephrologic, cardiologic, or gastrointestinal toxicities and without indicators of a benefit regarding long-term survival. Furthermore, chemotherapy has only negligible effects on neuroendocrine symptoms of the MTC patients (flushing, diarrhea, electrolytic disorders, Cushing syndrome). Therefore, it is used predominantly in patients with rapidly progressing metastatic disease. Overall, chemotherapy is not a particularly attractive option for patients with metastatic MTC.⁸³⁻⁸⁵

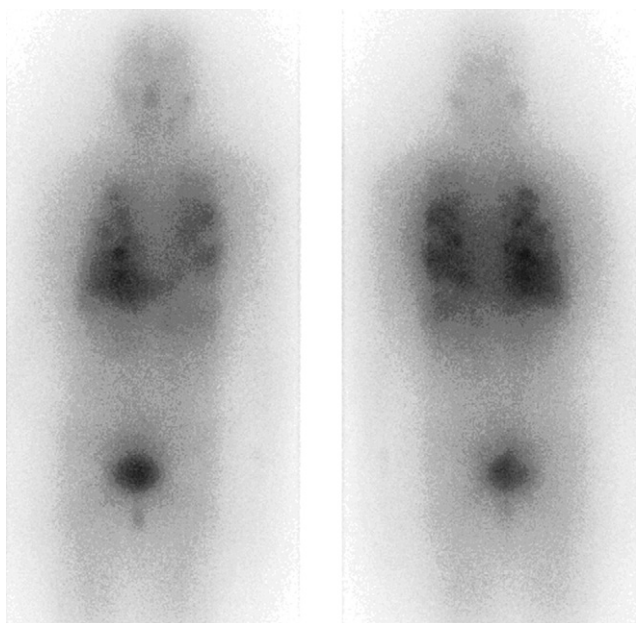


Figure 3 Whole-body ^{131}I MIBG posttherapy scan shows multiple lung metastases in a patient with MTC.

For diagnostic purposes MIBG can be labeled both with ^{131}I and ^{123}I . Although the former (364 keV photon energy, half-life 8 days) is easily available is of low cost and allows for prolonged studies (useful for dosimetric evaluation), ^{123}I MIBG (159 keV photon energy, half-life 13.3 h) by contrast has a more favorable dosimetry, better image quality and the possibility of single photon emission computed tomography studies. Its physiological distribution is in the pararenal glands, liver, spleen, heart and salivary glands. It has a very high specificity and sensitivity in pheochromocytoma and neuroblastoma with, respectively 90% and more than 95%, respectively. However, the sensitivity in MTC is as low as 25%-30%, despite the overall specificity of around 95%.^{86,87}

Treatment with ^{131}I MIBG is indicated for the patients either with tumor progression or quality-of-life compromising symptoms, such as calcitonin-induced diarrhea. Surgical options should be excluded beforehand and diagnostic MIBG uptake should be prominent to allow successful treatment, which is the case in approximately one-third of patients (Fig. 3).⁸⁸ Several medications interfering with MIBG like sympathomimetics, calcium channel blockers or reserpine should be withdrawn according to their biological half-life.⁸⁹ Blockade of the thyroid gland is necessary to avoid iodine uptake. This can be achieved by high amounts of potassium iodide, starting 12-24 hours before and lasting for about 2-4 weeks or by the use of perchlorate, starting 4-12 hours before and lasting for about 1 week.⁹⁰

Treatment protocol in present time is similar to that applied for malignant pheochromocytoma either with fixed doses of activity or according to patient weight or body surface. Several centers administer high activities of 7.4-11.1 GBq (200-300 mCi) ^{131}I MIBG. The infusion should linger at last 45-60 minutes to avoid acute side effects and regular monitoring of patients' vital signs, in particular blood pres-

sure, is advisable. If blood pressure rises, especially α -blockers demonstrate potent therapeutic effectivity. Side effects like nausea and hypothyroidism can be treated easily in general. Although it is mainly eliminated via the kidneys (40%-55% within 24 h and 70%-90% within 96 h), significant radiation effects on this organ are usually not observed. Thus, although dose reductions might be considered in individual cases, presence of renal disease is no limiting factor for the ^{131}I MIBG therapy. However, reduced doses should be applied for patients with leukopenia to avoid hematologic toxicity. This particularly applies for patients previously treated by chemotherapies. Additionally, blood count controls are necessary within the first 6 weeks after therapy with ^{131}I MIBG in this setting.

Posttherapeutic scintigraphies within the subsequent days reveal tracer distribution in tumor lesions. The minimum interval of 3 months and a maximum total activity of 11.1 GBq has shown a considerable symptomatic and hormonal improvement, moderate tumor regression/stabilization and improved quality of life with minimal adverse effects in patients with medullary cancer treated with ^{131}I MIBG.^{88,91,92} Response is evaluated by symptom palliation, biochemical response (reduction in calcitonin and CEA levels) and tumor regression.⁹³ Although data with regard to objective response are scarce, both partial response and stable disease can be expected in 30% of treated cases,⁹³ whereas symptom-relief may be achieved in 60%.⁹⁴ In the study published in 2008 by Castellani, and colleagues 8 of 11 evaluable patients showed at least stable disease (4/11) under the therapy.⁹⁵ Combined pretherapeutic imaging with ^{111}In -DTPA-octreotide and $^{131}\text{I}/^{123}\text{I}$ MIBG has been recommended to predict the benefit of targeted radiotherapy and to choose the effective radiopharmaceuticals.⁹¹ In this setting, positive imaging with ^{111}In -DTPA-octreotide may indicate the feasibility of 90-Y-DOTATOC therapy. By contrast, positive imaging with $^{131}\text{I}/^{123}\text{I}$ MIBG may suggest ^{131}I MIBG therapy. In summary, ^{131}I MIBG therapy is a noteworthy alternative therapeutic approach in patients experiencing advanced MTC and should be especially considered if conventional therapies, such as chemotherapies, show disappointing effects.

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