Witnessing a New Era? – The Emerging Role of Targeted Drugs in the Medical Treatment of Advanced Medullary and Anaplastic Thyroid Cancer

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Abstract
The treatment of advanced thyroid cancer is currently entering a new era due to the introduction of targeted therapy into modern cancer treatment. The growing insight into the molecular biology of thyroid cancer and on the development of numerous mainly multitargeted agents provide the basis for new treatment strategies. In particular, activation of mitogenic and angiogenic signalling pathways are suitable targets as preclinical and clinical data suggest. Several Phase II and a few Phase III studies were launched in thyroid cancer which included medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC) but only a few focused specifically on these subtypes. A number of smaller Phase II trials reported promising response rates and progression-free survival. Results from a randomised Phase III trial in MTC with vandetanib, a combined vascular endothelial growth factor receptor 2 + 3 (VEGF-R2+3) and RET multi tyrosine kinase inhibitor demonstrated significant clinical activity and resulted in the first approval of a kinase inhibitor for the treatment of MTC in 2011. Unlike in MTC, in ATC the prognosis is dismal due to the aggressive nature of the disease. Some mainly vascular targeting agents alone or in combination with chemotherapy have shown interesting activity in this disease and have raised new hope. Particularly the combination of fosfetaxel and a chemotherapy backbone of paclitaxel and carboplatin tripled the one-year survival rate in a recent Phase II trial which included 80 patients with ATC. In this review, we provide a brief overview of the general treatment concept of MTC and ATC and summarise the compiled evidence published on targeted agents in these rare thyroid cancer subtypes.

Keywords
Anaplastic thyroid cancer, medullary thyroid cancer, targeted drugs, multimodality treatment

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Malignancies of the thyroid can be classified as either of follicular cell origin or parafollicular C-cell origin. The cancers of follicular origin include papillary thyroid cancer (PTC), follicular thyroid cancer (FTC) and Hurthle cell cancer commonly referred together as differentiated thyroid cancer (DTC), poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC).¹ Medullary thyroid cancer (MTC) originates from the parafollicular C-cells.¹ PTC and FTC account for more than 80–90 % of all thyroid cancers, MTC for about 4 %, PDTC for about 5–10 % and ATC for 2–5 %.² Although ATC represents only a minority of all thyroid cancer cases, it accounts for approximately 50 % of all thyroid cancer-related death.³ Its highly aggressive nature is underscored by a median survival rate of less than six months following diagnosis.³ While ATC has an almost uniform fatal outcome despite aggressive therapy,¹ unselected patients suffering from MTC have an overall 10-year survival of approximately 70 % following primary successful surgery (see Figure 1). However, until recently, only limited therapeutic options existed for patients with unresectable or metastatic MTC.²

Thus advances in the clinical care of ATC and MTC has been slow and mainly depend on retrospective data analysis or limited case series or even clinical case reports.

Surgery is considered the only curative treatment option in MTC.³ This contrasts with ATC, where the potential and optimal sequence of surgery, radiation and chemotherapy still needs to be defined.¹²

Advances in the understanding of molecular pathology of thyroid cancer led to the identification of a variety of potential molecular targets¹³ which opened the avenue for the introduction of molecular targeted therapy in to the treatment concept for thyroid cancer (see Figure 2 and Table 1 and 2).¹³ This development is highlighted by the recent approval of Vandetanib by the US Food and Drug Administration (FDA) based on data from a randomised trial.

This review summarises the current standard treatment options in MTC and ATC and provides an overview on the emerging role of targeted drugs in the medical treatment of advanced medullary and anaplastic thyroid cancer.
**Medullary Thyroid Cancer**

**Prognosis and Standard Treatment**

Patients age and extent of disease at the time of diagnosis are the main independent indicators for disease relapse and mortality in MTC. The preoperative level of calcitonin is capable to predict the probability for disease-free survival. Post-surgery, if calcitonin is beyond the detection level after pentagastrin stimulation, patients are likely to be free of disease. However, incomplete remission of calcitonin after initial surgery does not rule out long-term survival. Mutation analysis of the RET proto-oncogene identified a specific activating point mutation, M918T which appears to be a strong negative prognostic indicator for progression-free survival (PFS) and OS (OS). The presence of this mutation reduces the 10-year survival by half from about 90 to 45 %.

Patients with RET germline mutations characteristic of the multiple endocrine neoplasia (MEN) type 2A and 8 syndrome are at extreme risk to develop MTC and preventive total thyroidectomy is recommended. In hereditary or sporadic MTC total thyroidectomy combined with lymph node dissection of central compartments is considered the cornerstone of the primary treatment. The additional lateral lymph node dissection is usually indicated in hereditary MTC but should be performed in sporadic MTC only if lymph node metastases are suspected or dependent on the stimulated calcitonin level prior to surgery.

Two to three months following primary resection, calcitonin drops below the detection level in 60–90 % of patients without lymph node involvement. Persistence of calcitonin indicates residual disease and there seems to be a correlation between the level of calcitonin and the remaining tumor burden. In the event of residual disease or disease relapse with tumour mass in the neck or mediastinum, re-operation is usually performed. However, the definitive cure rate is reported to be less than 40 % in this situation. In patients with localised disease with either elevated calcitonin, microscopic residual disease or positive lymph nodes, external beam radiation was shown to reduce the risk of loco-regional tumour recurrence. The main cause of disease-related death are distant metastases which often affect multiple organs including mainly lung, bone and liver. The occurrence of distant metastases considerably affects survival rates which decline at five years to 25 % and at 10 years to 10 %, respectively. In this palliative setting, the relief of symptoms and maintenance of quality of life are the major treatment goals. Calcitonin-induced diarrhoea may temporarily be controlled by either loperamide or somatostatin analogues. Beside the improvement of symptoms, somatostatin analogues alone or in combination with interferon have some efficacy to reduce serum calcitonin levels but rarely induce substantial tumour remissions. Beside the application of bisphosphonates, surgery, external beam radiation or chemoembolisation may be useful to treat bone metastases. In case of clinically dominant liver metastases, chemoembolisation might be effective to reduce tumour burden and provide symptomatic relief.

The effect of chemotherapy on OS is unclear due to the lack of large-scale clinical trials and until recently has been considered for the palliation of symptoms in metastatic disease particularly at the time of rapid tumour progression. Transient tumour responses in up to 20 % have been observed with doxorubicin or dacarbazine alone. Symptomatic improvement and response rates similar to doxorubicin were observed with combinations of 5-fluorouracil/dacarbazine or 5-fluorouracil/s坦托。ticin。 However, in the light of the promising data for molecular treatment approaches a critical re-appraisal of the value of conventional chemotherapy is warranted.

**Figure 1: Prognosis of Thyroid Cancer – Different Thyroid Cancer Subtypes**

The survival time of thyroid cancer of different histological subtypes across all stages is illustrated. ATC = anaplastic thyroid cancer; FTC = follicular thyroid cancer; MTC = medullary thyroid cancer; FTC = papillary thyroid cancer. Source: Survival data were reproduced from Hündahl et al., 1998.

**Anaplastic Thyroid Cancer**

**Prognosis and Current Treatment**

ATC usually manifests itself as a rapidly enlarging anterior neck mass with a doubling time of tumour volume sometimes of less than two weeks. This is often accompanied by dysphagia, dyspnoea or vocal cord paralysis. In most of the cases, ATC is locally advanced, frequently unrectactable and about 50 % of patients have metastatic disease at diagnosis. Prognostic parameters are age, sex, size of the primary tumour, complete resection and extent of the disease. Sugitani et al. defined a prognostic score which is based on the following risk factors: acute symptoms, tumour >5 cm, presence of distant metastases and white cell count >10,000 μl.

As most of the patients die due to local tumour complications within a few month after diagnosis, improving the local disease control might potentially extend the OS. While the treatment standard is still evolving, results from different retrospective studies suggested that single modality treatment is usually insufficient to achieve this goal. Multimodality treatment of ATC typically includes surgery, radiotherapy and chemotherapy. Based on recent clinical data it appears that only a combined treatment approach may improve the clinical outcome in terms of both local and systemic disease control.

The goal of curative surgery is to completely resect the tumour. In fact, a complete tumour resection was recently identified as a prognostic factor in clinical trials in ATC. Moreover, if potentially curative surgery is combined with post-operative adjuvant radiotherapy, this could result in a significantly increase in OS. Given the overall still dismal prognosis, however, surgery should usually be limited to not compromise the functional anatomy of the cervical structures.

Radiation therapy could either be applied as hyperfractionated radiation alone or in combination with chemotherapy as radiosensitiser. The most commonly used drugs for radiochemotherapy are doxorubicin or mitoxantrone. Radiotherapy combined with chemotherapy appeared to result in an improved OS as compared to radiotherapy alone. More recent studies evaluated the curative potential of different radiation doses and data revealed that a hyperfractionated radiation regimen seems more effective than conventional treatment and that doses...
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Figure 2: Simplified Model of Tyrosine Kinase Receptor Pathways and Potential Targets for Molecular Targeted Therapy

The two main signalling pathways for tyrosine kinase (TK) receptors like vascular endothelial growth factor factor-receptor (VEGF-R) or epidermal growth factor-receptor (EGF-R) are the Ras-Raf mitogen-activated protein kinase pathway and the phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR)-pathway. These pathways regulate the phosphorylation status of nuclear transcription factors and thereby regulate cellular proliferation, survival and differentiation. The figure illustrates the main drugs that act along these signal transduction pathways as well as inhibitors of aurora kinases (PF03814735, PF-03814735, BRAF, MEK, ERK), rapamycin; PDGFR = platelet-derived growth factor-receptor; PI3K = phosphoinositide 3-kinase; PPARγ = peroxisome proliferator-activated receptor gamma; VEGF = vascular endothelial growth factor.

Table 1: Overview of Molecular Targets in Anaplastic and/or Medullary Thyroid Cancer

<table>
<thead>
<tr>
<th>Target</th>
<th>Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>ATC, MTC</td>
<td>1, 60</td>
</tr>
<tr>
<td>Aurora B</td>
<td>ATC, MTC</td>
<td>46, 61, 72</td>
</tr>
<tr>
<td>IGF-R</td>
<td>ATC, MTC</td>
<td>73, 74</td>
</tr>
<tr>
<td>Ras</td>
<td>ATC</td>
<td>75</td>
</tr>
<tr>
<td>EGFR</td>
<td>ATC</td>
<td>76</td>
</tr>
<tr>
<td>MET</td>
<td>MTC</td>
<td>77</td>
</tr>
<tr>
<td>p53</td>
<td>ATC, MTC</td>
<td>44, 78</td>
</tr>
<tr>
<td>PI3K</td>
<td>ATC, MTC</td>
<td>79, 80</td>
</tr>
<tr>
<td>mTOR</td>
<td>ATC, MTC</td>
<td>60, 81</td>
</tr>
<tr>
<td>Histone deacetylase</td>
<td>ATC, MTC</td>
<td>82, 83</td>
</tr>
<tr>
<td>PDGFR</td>
<td>MTC</td>
<td>51</td>
</tr>
<tr>
<td>CABL</td>
<td>ATC</td>
<td>51</td>
</tr>
<tr>
<td>Proteasome</td>
<td>ATC, MTC</td>
<td>47</td>
</tr>
<tr>
<td>PPARγ</td>
<td>ATC</td>
<td>84</td>
</tr>
<tr>
<td>RET</td>
<td>MTC</td>
<td>85</td>
</tr>
<tr>
<td>BRAF</td>
<td>ATC</td>
<td>48</td>
</tr>
</tbody>
</table>

ATC = anaplastic thyroid cancer; EGFR = epidermal growth factor-receptor; IGF-R = insulin-like growth factor receptor-1; MTC = medullary thyroid cancer; mTOR = mammalian target of rapamycin; PDGFR = platelet-derived growth factor receptor; PI3K = phosphoinositide 3-kinase; PPARγ = peroxisome proliferator-activated receptor gamma; VEGF = vascular endothelial growth factor.

above 45–50 Gy should be administered in order to achieve tumour control. A retrospective analysis of patients treated at MD Anderson revealed no differences in toxicity between intensity modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy (SDRT).

By increasing the local tumour control rate, distant metastasis become a more important determinant of OS. Consequently, systemic chemotherapy is frequently used to reduce that risk. Doxorubicin either alone or in combination with cisplatin results in usually short-term remissions in 20–30 %. Newer drugs like paclitaxel induce higher remission rates up to 53 %. It is unclear, however, if the use of chemotherapy in this setting translates into prolonged survival.

Long-term survival in ATC was only observed in patients who were treated with a combined approach using surgery, radiation and chemotherapy. However, the optimal sequence of the available treatment modalities is still a matter of debate. In several studies surgery is used as first line treatment in resectable cases, followed by either radiation or radiochemotherapy. In more recent studies neoadjuvant radiation or radiochemotherapy preceding surgery and with increased dose from <30 Gy to hyperfractionated doses between 45 and 60 Gy was investigated. These studies also showed that complete local tumour resection with this multimodality approach is a strong predictor for long term survival. Pre-operative radiation or radiochemotherapy might be advantageous, since it may enhance operability. In addition, surgical biopsy or attempted resection might delay the initiation of further local therapy due to poor wound healing which also favours pre-operative radiation or radiochemotherapy. However, randomised, prospective clinical trials would be necessary to finally clarify the question of the optimal sequence of multimodality treatment.

Molecular Targets in Thyroid Cancer

Targeted agents, focused on inhibition of molecular pathways, are expanding treatment options for patients with a broad spectrum of tumours. Advancing knowledge of the molecular pathogenesis of thyroid cancer and the precise characterisation of potential molecular targets for therapy has led to an increasing number of targeted drugs that are currently being explored in thyroid cancer in vitro and in vivo (Figure 2 and Tables 1–3). As a result of intense research, several agents have been and are currently being investigated in clinical trials and some of them demonstrate significant activity (see Table 3). Most of these drugs are tyrosine kinase inhibitors (TKIs) and one of the best explored in MTC, vemurafenib, was recently approved by the FDA on the basis of the positive results of a randomised placebo-controlled Phase III trial.

Potential Targets in Medullary Thyroid Cancer

Activating mutations of the RET proto-oncogene are strongly associated with MTC and found in up to 98 % of hereditary and 35–50 % of sporadic forms of MTC, respectively. A variety of mutational hotspots of the RET gene with tumourigenic potential were described. Mutated RET provides mitogenic and survival signals and some specific activating point mutations like M918T appear to be strong negative prognostic indicators for metastasis free survival and OS. Thus it is logical to target RET as a key driving element of MTC.

In familial MTC, loss of heterozygosity in the von Hippel-Lindau (VHL) disease tumour suppressor locus at the somatic level has been described and might be associated with progression of MTC. Furthermore, chromosomal imbalance with partial or complete loss of chromosome 3 resulting in a reduced or complete loss of VHL protein expression is reported in MTC. Both events in turn may result in increased expression of the hypoxia-inducible factor I which promotes tumour angiogenesis by overexpression of vascular endothelial growth factor (VEGF). In this context, increased VEGF expression was reported by Cap et al in MTC specimens which provides the rationale for a VEGF-targeted treatment approach.

Activation of c-Met triggers tumour growth and angiogenesis and recent data suggest that c-Met is
overexpressed in MTC. Therefore, targeting c-Met might be another attractive therapeutic strategy in MTC. In studies in rodents showed that predispersing factors for the development of MTC are mutations in pRB, p53, PTEN, and the cyclin dependent inhibitors p27 and p18 expanding the range of possible targets significantly. Further pre-clinical evidence suggest a potential role of the RAS-RAF-ERK, PI3K-AKT, NF-

\gamma (PPAR-\gamma) as additional target in ATC. A variety of further molecular alterations have been reported in ATC. However, these need to be investigated further or are not amenable to pharmacological targeting. For a comprehensive overview on further molecular alterations in ATC see amongst others the review by Smallridge et al.10

### Molecular Treatment in Medullary Thyroid Cancer

Multiple clinical trials were conducted or are still ongoing to explore the value of molecular treatment in thyroid cancer. Most of these studies include merely a few patients with MTC and only a limited number of trials focussed on MTC. The majority of clinical trials were conducted with TKIs which have RET and/or the VEGF-system as one of their major targets (see Table 2). In several of these Phase II and Phase III studies the therapeutic agents exerted a considerable amount of partial responses and a large proportion of prolonged disease stabilisation (see Table 3). Interestingly, activity in MTC was observed not exclusively for agents with designated RET inhibitory activity but also for TKIs without RET inhibitory capacity. This suggests that besides targeting RET other targets like the VEGF system are clinically relevant targets for the treatment of MTC.

In the first large-scale randomised, placebo-controlled Phase III study in MTC, vandetanib met the primary study objective and significantly prolonged the PFS. At present, no final data are available yet since the survival data are still maturing and median PFS is not reached at 24-month follow-up. However, the available data were sufficient for the FDA to grant approval to vandetanib as an orphan drug for the treatment of metastatic or progressive inestable MTC in April 2011.

Other multi TKIs like sorafenib, axitinib or sunitinib were tested in Phase II trials in thyroid cancer including cases with MTC. Overall, these drugs induced remissions and led to stable disease at a similar rate as vandetanib in MTC (see Table 3).

In contrast, two studies evaluating the activity of imatinib, an oral TKI of BCR-Abl and KIT, reported no objective response and only a few patients achieved disease stability. Three patients discontinued the
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Table 3: Summary of Clinical Data in Anaplastic Thyroid Cancer and Medullary Thyroid Cancer

<table>
<thead>
<tr>
<th>Compound</th>
<th>Histology</th>
<th>Patients</th>
<th>CR/PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>ATC, MTC</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>MTC</td>
<td>15</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Sorafenib plus tipifarnib</td>
<td>MTC</td>
<td>-</td>
<td>16</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Axitinib</td>
<td>ATC, MTC</td>
<td>2</td>
<td>11</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>MTC</td>
<td>-</td>
<td>15</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Imatinib</td>
<td>MTC</td>
<td>-</td>
<td>15</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Fosbretabulin</td>
<td>ATC</td>
<td>18</td>
<td>-</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Fosbretabulin plus Paclita</td>
<td>ATC</td>
<td>75</td>
<td>-</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>MTC</td>
<td>-</td>
<td>30</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>ATC, MTC</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Motesanib</td>
<td>MTC</td>
<td>-</td>
<td>91</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>XL184</td>
<td>MTC</td>
<td>-</td>
<td>37</td>
<td>14</td>
<td>-</td>
</tr>
</tbody>
</table>

*1 patient not evaluable, only patients from Arm B; **8 patients not evaluable; % patients indeterminate; NA patients not available; ATC = anaplastic thyroid cancer; Carbo = carboplatin; SD = stable disease.*

therapy due to toxicity and dose reductions were required in additional four cases. Schlumberger et al. conducted a trial in MTC patients with the multi TKI motesanib. Although this drug targets both the VEGF-axis and the RET tyrosine kinase, partial tumour responses were observed in only two per cent of patients and disease stabilisation in 48 % lasting more than 24 weeks.57

The combined MET, RET and VEGFR2 inhibitor cabozantinib (XL184) exerted meaningful activity in a recent Phase I study including 37 patients with MTC. Twenty-nine per cent confirmed PR and 41 % disease stabilisation lasting for more than six months prompted the launch of the current randomised Phase III study in MTC.61

Response data from a recent Phase I trial of lenvatinib (E7080) prompted the launch of a Phase II study in patients with MTC and refractory DTC.62 Aberrant activation of PIK3/AKT-pathway and mTOR was recently reported in MTC. Based on these data a Phase II study evaluating the activity of everolimus in different types of thyroid cancer including MTC was launched.63

From the molecular biology perspective, targeting of different pathways active in thyroid cancer might further increase therapeutic activity. In particular, data from melanoma trials suggested that pathway switching in cancer cells might contribute to resistance to TKI. In order to overcome this phenomenon combined application of drugs targeting different pathways gained attention. In MTC, a first trial was conducted combining sorafenib and the farnesyltransferase inhibitor tipifarnib with a partial remission rate of 38 % and disease stabilisation exceeding six months of 31 %.58

Molecular Treatment in Anaplastic Thyroid Cancer

Beside a considerable number of agents in pre-clinical research an increasing number of targeted agents have been explored in ATC. Beyond the most promising class of drugs are TKIs and vascular disrupting agents.

Markedly increased vascularisation and elevated VEGF levels are commonly found in thyroid cancer. VEGF levels appear to correlate with the aggressiveness of the disease providing the rationale for the clinical evaluation of agents directed at vascularisation in ATC. Based on promising results from a Phase I trial, the vascular disrupting agent fosbretabulin was investigated in a Phase II study in 18 patients with ATC as a single agent. There was no objective response but some disease stabilisation (see Table 3).64 Based on reported synergy of fosfotretabulin and chemotherapy in pre-clinical studies, a Phase II study assessing the combination of fosbretabulin with a regimen of paclitaxel and carboplatin was initiated. Of the 80 patients included, 75 received therapy. A median survival time of 5.2 months was reported for the combination arm opposed to four months for the standard arm. With a relative reduction in the risk of death by 35 % the one year survival was 27 % in the combination arm versus 9 % in the standard arm.65

In a recent Phase II study by Cohen et al. exploring the activity of the TKI axitinib in thyroid cancer, two patients with ATC were included. Axitinib exerted activity in all histological subtypes including one patient with ATC which experienced a partial remission.66 In a Phase II study, Nagaiah et al. explored the activity of the broad spectrum TKI sorafenib in 15 patients with ATC.67 Overall, a disease control rate of approximately 40 % was observed including two partial responses (see Table 3). However, time to progression and median OS were not encouraging with 1.9 and 3.5 months respectively. Despite the short PFS and median OS reported, the one year survival was 25 % after treatment initiation.68 Following initial reports of relatively high response rates of sorafenib observed by Nagaiah, other studies reported more discouraging results.69

In thyroid cancer, inhibition of tumour-related angiogenesis and BRAF inhibition are of potential therapeutic value and thus it is unclear, whether the observed benefit of the VEGFR1-3 and BRAF-inhibitor sorafenib treatment is related to inhibition of BRAF-kinase or disruption of angiogenesis. In fact, particularly BRAF V600E mutation is associated with higher rate of lymph node metastases and higher TNM stage as well as increased VEGF-expression.69 This would favour a combined VEGF and BRAF inhibitory approach particularly for patients with proven BRAF V600E mutation.

The BCR-ABL and PDGFR inhibitor imatinib is commonly known for its activity in chronic myeloid leukaemia (CML) and gastrointestinal stromal tumour (GIST). Intrigued by the reported overexpression of PDGFR and cABL in ATC, Ha et al. launched a Phase II study of imatinib in ATC. They reported a promising activity with 2/8 evaluable patients showing a PR
**Targeted Drugs in the Treatment of Advanced Medullary and Anaplastic Thyroid Cancer**

and 4/8 achieving stable disease. Further studies to explore the activity of imatinib in ATC seem to be warranted.

PPAR-γ is a member of a superfamily of nuclear hormone receptors, which were recently found to be overexpressed in ATC cell lines. Based on promising activity data from preclinical research a Phase I/II clinical trial was launched to evaluate the activity of the combination of paclitaxel and the oral PPAR-γ agonist CS7017. Preliminary data published by Smiridges et al suggested potential activity of the combination of CS7017 and paclitaxel.

Histone deacetylase inhibitors induce hyperacetylation of histones which results in cellular differentiation, cell cycle arrest and apoptosis. This could result in synergistic interaction between cytotoxic agents like doxorubicin and histone deacetylase inhibitors in ATC.

**Conclusion**

Despite tremendous research the treatment of advanced and metastatic medullary and anaplastic thyroid cancer hasn’t significantly improved until recently.

While there was no active systemic treatment option for metastatic MTC in the past, the introduction of targeted agents clearly improved the prognosis of patients shown in several recent clinical trials, which is highlighted by the FDA approval of vantetibab for the treatment of advanced or metastatic MTC in 2011. Research is continuing and new targeted treatment strategies were recently explored with overall promising results. Particularly to either overcome primary resistance or to override a ‘pathway switching’, combinations of drugs targeting different key pathways in MTC will potentially further improve the overall cancer related prognosis of MTC patients.

Despite significant progress in decoding the molecular biology of thyroid cancer the outcome of ATC is still dismal. Aggressive multimodal locoregional treatment reduced the rate of local relapse, however due to the lack of active systemic treatment regimens patients die of metastatic disease. New molecular targeted agents are currently in clinical evaluation with partially promising results. Particularly vascular targeting agents like fosfotarabulin proved in combination with conventional chemotherapy in one of the largest clinical trials in ATC ever a significant improvement in one-year survival.

With the new therapeutic agents new challenges arise. Based on their therapeutic principle the new agents often affect tumour vitality more rapidly without then inducing significant tumour shrinkage, if at all. Therefore new diagnostic techniques beyond RECIST have to be validated in order to measure activity. These could be more functional measurements like perfusions or changes in tracer accumulation in PET-CT scans.

From the patient perspective, these patients have to be convinced that a long lasting tumour stabilisation is often of higher value than a tumour shrinkage of short duration.

The emerging therapies in thyroid cancer raise new hopes for patients with MTC and ATC. The approval of vantetibab has set the basis to change practice in MTC. Further clinical research is necessary particular in ATC to improve prognosis. Besides approaching new targets like aurora kinases or specific BRAF mutations, targeting the vascular systems definitively warrants further clinical research based on recently published data.

For all involved in thyroid cancer research and treatment it is an inspiring time and it is clear that we indeed are witnessing a new era in the treatment of thyroid cancer.
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