Targeted therapy in radioiodine refractory thyroid cancer

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The majority of differentiated thyroid carcinomas (DTCs) of follicular cell origin are cured with adequate surgical management and radioiodine therapy. Other thyroid malignancies such as medullary thyroid carcinoma (MTC) or poorly differentiated thyroid carcinomas frequently metastasize, precluding patients from a curative resection. Therapeutic options for these patients include additional surgery for resectable lesions, external radiotherapy and chemotherapy. The results of this approach are usually disappointing and the use of novel therapeutic approaches is needed. The outstanding progress in the molecular basis of thyroid carcinoma offered the tool for the development of new drugs, mainly tyrosine-kinase inhibitors and inhibitors of proangiogenic factors, which are currently in phase II or III clinical trials with promising results (the so-called targeted therapy). This review will summarize the most relevant achievements in the field and will discuss the limit and perspective of the new compounds.

KEY WORDS: Thyroid neoplasms - Oncogenes - Protein-tyrosine kinases.

While accounting for only 1% of solid malignancies, thyroid carcinoma is the most common malignancy of the endocrine system and is the human malignancy showing the largest increase in incidence. This increase is likely due to better detection as suggested by the finding that most of the new cases are small, intrathyroidal tumors, fortuitously discovered at neck ultrasonography. The majority are well-differentiated thyroid carcinomas (DTCs) of follicular cell origin that are cured with adequate surgical management and radioiodine therapy. However, some thyroid malignancies such as medullary thyroid carcinoma (MTC) or poorly differentiated thyroid carcinomas frequently metastasize, precluding patients from a curative resection. Therapeutic options for these patients include thyroid-stimulating hormone (TSH) suppressive therapy and radioiodine administration provided that the tumoral cells retain a functional sodium-iodide symporter (NIS) gene in DTC patients, surgery for resectable lesions, and external radiotherapy in selected cases. All of these therapies are rarely curative but may be effective in reducing the tumoral burden, improving the quality of life and stabilizing the disease, even for many years. When the above strategies fail and the disease progresses, systemic therapy with anti-neoplastic drugs is proposed. In general, the available experience has been disappointing, showing that the response rate is very low (below 20%), short lasting, and associated with high degree of toxicity. Thus, new therapeutic approaches are needed.

The molecular basis of DTC, MTC, and anaplastic thyroid cancer are well characterized and the critical genetic pathways involved in the development of specific tumor histotypes have been elucidated. Most of them act through the RTK-RAS-RAF-MAPK pathway.
or the phosphatidylinositol 3-kinase (PI3K)-Akt pathway, and all of them confer constitutive activation to the transformed cells. In addition, mutations of tumor suppressor genes have been discovered and associated with progression toward a more aggressive phenotype. As in several other human malignancies, the knowledge of the molecular alterations has prompted the search for new agents able to inhibit the function of specific oncoproteins, aiming to shut down the uncontrolled growth of neoplastic cells and, hopefully, have less toxicity in normal cells, the so called “targeted therapy”. In thyroid cancer several molecules have been developed, blocking the RTK-MAPK and the PI3K-AKT pathways, those activated by RET-PTC, RAS, and BRAF mutations. In addition, some experimental drugs are not restricted to one single protein, but are also direct against non thyroid-specific genes that play a critical role in tumor cell growth and metastasis, such as angiogenesis regulatory genes. Of the identified proangiogenic factors, vascular endothelial growth factor (VEGF) is key, binding to two tyrosine kinases receptor, VEGF receptor (VEGFR)-1 and VEGFR-2 that also trigger MAPK signalling. In papillary thyroid cancer, the intensity of VEGF expression correlates with a higher risk of metastasis and recurrence, and a shorter disease-free survival. Inhibiting VEGFR blocks the growth of the tumor's endothelial cells, and moreover inhibiting EGFR may deprive the tumor of one important growth factor sustaining an aggressive phenotype. After extensive in vitro experiments showing that several compounds are effective, some are currently being tested in phase I-II-III clinical trials.

**Results of clinical trials**

Motesanib diphosphate (AMG 706; Amgen, Thousand Oaks, CA), is a small molecule targeting several tyrosine kinases (Table I). After promising results in a phase I study involving patients with advanced solid malignancies, a multicenter, open-label phase II trial was conducted in patients with advanced or metastatic differentiated and medullary thyroid cancer.

A total of 184 subjects was enrolled and receiving motesanib, starting at 125 mg daily: among 93 patients with DTC, partial response was confirmed in 14% and stable disease was achieved in 67%. Progression free survival lasted more than 24 weeks in 35% of these patients.

Pennell et al. conducted a phase II open-label trial using Gefitinib (Iressa; AstraZeneca, London, UK) a small molecule inhibitor of the EGFR tyrosine kinase. The drug has been effective in the treatment of non-small cell lung cancer, where an activating mutation of the EGFR gene is present. Although, EGFR mutations have been found in a small proportion of papillary thyroid cancer, EGFR is highly expressed in normal and malignant thyroid tissue, and its expression has been associated with a more aggressive phenotype in papillary thyroid cancer. Based on this rationale the authors treated 27 patients with locally advanced or metastatic thyroid cancer of different histotypes, including papillary, follicular, medullary, and Hurthle cell carcinomas. The drug was given orally at a dosage of 250 mg once daily. Among the 25 patients available for evaluation no objective responses were observed, although tumor reduction, that did not meet the criteria for partial response, was achieved in 32% of them. In addition, stabilization of the disease was obtained in 46%, 24%, and 12% of these patients after 3, 6, and 12 months of treatment, respectively. The authors interpreted these results as modest but still suggestive of a biological effect of the drug.

Axitinib (AG-013736, Pfizer), a selective inhibitor of VEGF receptors, PDGFR-β and c-KIT, was evaluated...
in a single arm study 11 of 60 subjects with advanced thyroid cancer, principally with papillary histology (30/60, 50%). Stable disease and partial response was observed in 23 patients (38%) and 18 patients (30%) respectively. Thirty-two patients discontinued treatment primarily because of lack of efficacy (10/32, 17%), adverse events (8/32, 13%) and in 23 patients the dose was reduced because of adverse events, principally fatigue, hematuria and diarrhea.

Sorafenib (Nexavar, Bayer) was tested in phase II trials 12, 13 in a total of 71 patients with advanced or metastatic thyroid cancer at a dosage of 400 mg orally twice daily. Among them, partial responses lasting at least 18 months were obtained in 13 patients (18%) and had stable disease lasting more than 14 weeks was observed in 39 patients (55%). Considering these promising results, a clinical phase III trial has been planned in a large group of patients with locally advanced/metastatic radioiodine-refractory differentiated thyroid cancer.

Sunitinib (Sutent, Pfizer) has inhibitory activity against RET, VEGFR and PDGFR. In a phase II trial 14 the drug was tested in 43 subjects (37 DTC, 6 MTC) with a treatment schedule of 50 mg once daily, four weeks on and two weeks off. Among 31 evaluable DTC patients who completed 2 cycles, partial responses were observed in 13%, stable disease in 68% and disease progression in 10%. In MTC patients stable disease was recorded in 83% and disease progression in 17%. In another phase II trial, 15 sunitinib was administered under a continuous dose regimen (37.5 mg orally, once a day): 33 patients were enrolled (26 DTC, 7 MTC) and 29 of them were evaluable. With a median time on study of 7.5 months, complete response was achieved in 7% (2/29), partial response in 25% (8/29), and stable disease in 48% (14/29). The cumulative rate of disease control (SD+PR+CR) at 3 months was 83%.

Of 91 patients with MTC treated with motesanib, two (2%) had confirmed partial response, 81% had stable disease (48% durable ≥24 weeks) and 76% experienced a decrease from baseline in target lesion measurement. Median progression-free survival was 48 weeks.16

Vandetanib (ZD 6474, Zactima; AstraZeneca) is a small molecule with potent inhibitory effect on VEGFR-2, EGFR, and RET. When tested in two open-label phase II clinical trials in metastatic hereditary MTC the first 17 with a dose of 300 mg and the second with 100 mg,18 vandetanib induced partial responses in 20% and 10% of the patients respectively and prolonged stable disease in 30% and 31%, respectively. A 50% reduction in serum calcitonin levels was observed in 63%.

XL184 is an oral, small-molecule inhibitor of several receptors and, in addition, it has inhibitor effects on C-MET, which is highly expressed in DTC and MTC.19-21 Only preliminary results from a phase I trial are available in patients with MTC. Among 34 patients with measurable disease, 14 (41%) achieved partial response (9 confirmed, 26%) and the disease control rate (PR +SD+3 months) was 84%. Moreover, most patients obtained a reduction in plasma calcitonin and carcino-embryonic antigen levels.22 The drug was generally well tolerated. A phase III trial in patients with MTC, comparing XL184 with placebo is currently ongoing.

Side effects

Although all the above compounds have shown promising clinical results their effectiveness is hampered by the association with a variety of toxic effects. Diarrhea, nausea, vomiting, fatigue, alopecia are the most common adverse events associated with the drugs, but only rarely they reach grade 3 or 4 toxicity, those in which the treatment needs to be discontinued.

Hematologic complications have also been reported: grade 3 or 4 neutropenia, thrombocytopenia, lymphopenia, anaemia and other hematologic toxicities require a dose reduction.

Patients assuming tyrosine-kinase inhibitor have a significant risk of developing hypertension (with incidence ranging 16-50%). The phenomenon may be directly related to the inhibitory effect on the VEGF receptor. Possible mechanisms include impaired angiogenesis leading to a decrease in the density of micro vessels (a process known as rarefaction), endothelial dysfunction associated with a decrease in nitric-oxide production and an increase in oxidative stress, or changes in neurohormonal factors or the renin-angiotensin-aldosterone system.23 Early detection and effective management of hypertension may allow for safer use of these drugs.

Asymptomatic QTc prolongation and cardiac toxicity are common adverse requiring periodical monitoring of cardiac function.

Skin toxicity typically occurs after 3-4 weeks of
treatment in more than 50% of patient. A number of different skin changes may be observed, including hand-foot syndrome, changes in hair colour, skin rash, dry skin, skin discoloration, acral erythema, folliculitis, and it is reported with almost all drugs.

Folliculitis occurs in 43-85% of patient and experimental models have shown that the blockage of EGFR profoundly increases chemokine expression in keratinocytes, leading to skin inflammations. The most clinically significant skin toxicity is the hand-foot syndrome and palmar-plantar erythrodysesthesia, which occur in 9-62% of patients receiving sorafenib or sunitinib. Hand-foot syndrome presents as painful symmetric erythematous and oedematous areas on the palms and soles, commonly preceded or accompanied by paresthesias, tingling or numbness. The exact pathogenesis of this type of hand-foot syndrome is still unknown, but evidence suggest that may be due to the direct anti-VEGFR or anti-PDGFR effects of the drugs on dermal endothelial cells. Management strategies for hand-foot syndrome include dose reduction or treatment interruption until improvement of symptoms. Although fastidious for the patients, the appearance of side effects, particularly skin toxicity and hair loss, are associated with significant tumor response.

Several tyrosine-kinase inhibitor can induce hypothyroidism. In patients treated for non-thyroidal malignancies, who have a normal thyroid gland, hypothyroidism may be the result of a destructive thyroiditis through follicular-cell apoptosis. In thyroid cancer patients, who have been treated with total thyroidectomy and are on thyroid hormone replacement therapy, hypothyroidism may be due to an alteration in the absorption or metabolism of l-thyroxine. In this case the dose of l-thyroxine must be increased and regular monitoring of the thyroid function is warranted.

In contrast to conventional chemotherapy, which is given only over a defined period of time, targeted therapy is a chronic, continuous treatment that may be given over a prolonged period of time, sometimes years, thus the understanding and possibly the prevention or treatment of side effects is critical to ensure a good quality of life.

### Table II.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Stable disease (%)</th>
<th>Stable disease &gt;24 weeks (%)</th>
<th>Partial response (%)</th>
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* hMTC: hereditary MTC.
advanced. For this reason the selection criteria for clinical trials have to include patients who demonstrate measurable disease progression within a set interval before enrolment. This is an essential component of the Response Evaluation Criteria in Solid Tumors (RECIST). RECIST criteria allow objective and standardized analysis of the results, and eliminate the need for a placebo treated group.26

All together based on the preliminary results of clinical trials we can summarize that partial response is observed in 2-29% of the patients and disease stabilization in another 40-81% (Table II). An important aspect is that no cross resistance has still been observed to various drugs and this could have a clinical impact due to the possibility to change from a compound to another in the hope of a clinical benefit to the patient, also because so far no comparative study between different drugs has been performed.

Many issues still need to be resolved. Among them we must consider "efficacy, specificity, cytostatic versus cytotoxic effect, compensatory pathways, resistance, and factors related to stem cells as the most important. The need for efficacy and specificity is self-evident. The drug must target a mutated protein or a protein downstream from that protein in a manner sufficient to block or substantially attenuate signal transmission. This prerequisite is relatively easy to ascertain by initial cell culture, in vitro, and animal studies. Unfortunately, targeted therapies are generally cytostatic and not cytotoxic. This is a problem since it requires treatment to be continued on a life-long basis. This may be satisfactory if the drug has low toxicity and is well tolerated. In addition, however, there is usually a high risk that "resting" neoplastic cells will develop compensatory pathways, often by acquiring other mutations. Accordingly, researchers are very aware of the need to develop second-line drugs that have to be administered as a "cocktail" to inhibit several pathways. Another serious limitation of current targeted therapies is that they are probably not effective against cancer stem cells, a continuous reservoir for new tumour growth.26

In conclusion, clinical trials offer promise for suffering patients, but even if some drugs prove efficacious, the time required to approve and bring them to clinical practice is always too long. In addition, future studies should be designed not only based on the clinical features of the tumors but also on their molecular phenotype.

References


