Targeted therapy in refractory thyroid cancer

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The large majority (>85%) of patients with differentiated thyroid carcinoma (DTC) and many (40%) patients with medullary thyroid carcinoma (MTC) can be cured, others may survive for decades despite persistent disease, and few patients with advanced disease may require novel therapeutic modalities [1,2]. Very few patients with anaplastic carcinoma survive over one year. These refractory thyroid cancer patients are rare, with an estimated annual incidence in France of 350 cases that is stable with time, including 200 patients with DTC, 50 with MTC and 100 patients with anaplastic thyroid carcinoma. In most patients, an initiating carcinogenic event can be found and molecular targeted therapy can be given with a scientific rationale. Patients with progressive thyroid cancer should preferably be included in prospective trials, and even phase I trials that are testing the newest therapies should be considered for these patients, as these protocols may allow early identification of possibly effective drugs.

Although response criteria in these contemporary trials differ markedly from those evaluating cytotoxic chemotherapy, anti-tumour efficacy of these agents in MTC patients is likely to be much greater than that of earlier chemotherapies (ORR < 20% with chemotherapy using 5FU-DTIC) [3]. Tumour response rates are similar in lymph nodes, and lung, liver and bone metastases, and were similar in patients with smaller or larger tumour masses. Serum calcitonin and CEA levels decreased during treatment in most patients, and this indicates an inhibition of the RET kinase, but it may be not paralleled by a decrease in tumour volume. Comparison of the outcome among these compounds is at the present time not possible. Toxicity was significant. Benefits demonstrated with vandetanib in a randomised phase III trial on both ORR (44% with long lasting responses) and PFS (>30.5 months in the treatment arm (median not reached) versus 19.3 months in the placebo arm) counterbalance toxic effects and justify its use in MTC patients with progressive or symptomatic disease and those with large tumour burden [4]. Vandetanib is available in France within the framework of an Autorisation Temporaire d'Utilisation (ATU) and has been labelled in the USA by the FDA. Results of the ongoing phase III trial with XL-184 are expected to confirm promising results obtained in the phase I trial in which 29% of 35 patients had a confirmed partial tumour response. There is apparently no cross resistance between drugs. Drugs used up to now have similar mechanisms of action, all being anti-angiogenic and some (including vandetanib and XL-184) targeting the RET tyrosine kinase. The relative role of the inhibition of each target or of their combined inhibition is currently unknown, but because axitinib and pazopanib are thought to be only anti-angiogenic drugs, responses suggest that the anti-angiogenic effects of these compounds might play an important role. Also, responses to vandetanib or XL-184 have been observed in patients without *RET* mutation. Even among patients with an *RET* mutation, tumour responses were partial and were observed in only a fraction of patients. This may indicate that targeting RET may not be sufficient in all MTC patients. Future studies should explore the interest in effective inhibition of the MAPkinase pathway downstream of the RET kinase, and of other pathways such as the PI3K-AKT-mTOR pathway, and search for other relevant targets that may indicate the use of other drugs. Toxicities of the drugs used in these patients led to dose reduction in 11–73% of patients and to drug withdrawal in 7–25%. There were no unexpected toxicities with long-term treatment.

In DTC patients, refractory disease is defined by the presence of at least one tumour focus without any uptake of radioiodine, or by progressive disease following radioiodine treatment or by persistent disease after six treatments with radioiodine [5–7]. Among these cancers, histology (papillary and variants, follicular and poorly differentiated) and genetic defects may differ. Anti-tumour efficacy of these agents is likely to be greater than that of earlier chemotherapies, with partial responses observed in 8–32% of patients and long-term stable disease in at least another half. Comparison of the outcome among these compounds is at the present time not

possible, but the response rates recently reported with pazopanib and E7080 (around 50%) seem higher than in previous reports. It also appears that efficacy may differ among histological subtypes, but further studies are needed to correlate drug efficacy with the genetic defect present in the tumour. Only results of phase II trials have been reported; a phase III trial (sorafenib vs. placebo) is ongoing and at least two phase III trials (with either pazopanib or E7080 vs. placebo) will be activated in 2011, as well as several phase II trials. Also, the stability of response and patterns of relapse have not been well characterised. Drugs used up to now have similar mechanisms of action, all being anti-angiogenic and some targeting the kinases in the MAPkinase pathway. Tumour responses were partial and transient and were observed in only a fraction of patients. This may indicate that future studies should use drugs targeted to already known abnormalities (such as an inhibitor of the BRAF kinase in patients with a papillary thyroid carcinoma harbouring the mutated *BRAF*), and search for other relevant targets. However, there was no significant unexpected toxicity, and the dose of l-thyroxine treatment had to be increased in the majority of patients.

Given the commercial availability of sorafenib and sunitinib, these agents have entered into clinical use for those patients with progressive, refractory disease who are not suitable candidates for clinical trials.

Finally, trials should be performed in patients with anaplastic thyroid carcinoma, using drugs directed against angiogenesis or other targets.

Further trials should also search in MTC and DTC patients for other treatment modalities, including combination or sequential treatment. Recent trials have shown that inclusion of the expected number of thyroid cancer patients to reach statistically significant conclusions is possible in a limited period of time, and this may be further improved by networks such as the French TUTHYREF network and organisations such as the Endocrine taskforce of the EORTC.

Conflict of interest statement

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