

# Guest Editorial

## Molecular Targeted Drugs for Advanced Thyroid Cancer

Advanced thyroid carcinomas, which are difficult to control and are refractory to treatment, are sometimes encountered in the clinical setting. In recent years, molecular targeted drugs which inhibit various kinases involved in tumor growth or angiogenesis have been developed and have been demonstrated to exhibit efficacy against many carcinomas. Their usefulness has been explored in such malignancies as advanced, radioactive iodine (RAI), refractory differentiated thyroid cancer, local advanced or metastatic medullary thyroid and anaplastic carcinomas.

In tumor cells of thyroid cancer, variants of RAS and B-RAF that act downstream from RET or RTK, both being receptor tyrosine kinases (RTKs), occur frequently and abnormality in this serial signaling cascade contributes to tumor growth. Angiogenic factors secreted from tumors, such as vascular endothelial growth factor (VEGF), on the other hand, act upon vascular endothelial cells RKTs, i.e. vascular endothelial growth factor receptor (VEGF-R) and platelet-derived growth factor receptor (PDGF-R), to facilitate angiogenesis. Clinical trials of inhibitors of the kinases which interfere with growth signals in tumor cells or with angiogenic signals in vascular endothelial cells in patients with thyroid cancer are under way. The ongoing clinical trials for differentiated thyroid carcinoma include studies of sorafenib, which inhibits RAF, RET and VEGF-R,<sup>1-4</sup> a trial of axitinib, which is an inhibitor of VEGF-R, C-KIT and PDGF-R<sup>5</sup> trials of pazopanib, which is an inhibitor of VEGF-R and PDGF-R, and those of sunitinib, which is an inhibitor of E7080, VEGF-R, RET and PDGF-R. Further, vandetanib, which is an inhibitor of VEGF-R, RET and EGF-R, has proven to be promising in the treatment of medullary thyroid carcinoma.<sup>6</sup>

The toxicity (adverse reactions) of molecular targeted drugs differs slightly from that of the usual anticancer agents and primarily includes easy fatigability, hypertension, anorexia, diarrhea and skin disorders. This group of drugs basically requires to be given for a long term; eventually, dosage reduction or discontinuation becomes unavoidable because of adverse reactions, resulting in a substantial diminution of the antitumor effect. Since, elevation of the serum TSH level occurs with the use of kinase inhibitors, patients should be followed up by periodic checkups and may need to be administered an oral thyroid hormone preparation.

Various markers have been assessed for their efficacy in predicting antitumor responses. Biochemically, markers, such as VEGF and VEGF-R, are used. The diagnostic imaging modalities include fluorodeoxyglucose positron emission tomography (FDG-PET), magnetic resonance imaging (MRI), computerized tomography (CT) and ultrasonography (US). However, all of these measures have their limitations. Thyroglobulin (Tg) is useful for differentiated thyroid cancer but is liable to be affected by anti-Tg antibody as well as by changes in the serum thyroid stimulating hormone (TSH) level. It is widely recognized that serum calcitonin and carcinoembryonic antigen (CEA) serve as satisfactory markers in patients with medullary thyroid carcinoma.

## REFERENCES

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**Hiroshi E Takami**

Professor Emeritus and Visiting Professor  
Department of Surgery, Teikyo University, School of Medicine  
Scientific Advisor, Ito Hospital, Tokyo, Japan  
e-mail: h-takami@ito-hospital.jp