

New treatment opportunities for patients with advanced and/or metastatic thyroid cancer

According to the RARECAREnet definition [1], thyroid carcinomas (TCs) are rare malignant tumors being their crude incidence rate in Europe of 5.07/100,000/year (CI 95% 5.03-5.10). TCs included three different tumor types: i) differentiated thyroid carcinoma (DTC), which derives from the follicular thyroid cells including papillary (PTC) and follicular carcinomas (FTC) and their variants ii) medullary thyroid carcinoma (MTC) originating from the parafollicular C cell and considered a neuroendocrine carcinoma, and iii) anaplastic thyroid carcinoma (ATC). This latter has an epithelial origin and may evolve from a pre-existing DTC (most commonly papillary phenotype) or originate *de novo*.

Surgery (emi- or total thyroidectomy) is the standard of care in each histotype, combined with radioactive iodine (RAI) only in high-risk DTC cases. Prognosis is related to the histotype: better in case of DTC (5-yr relative survival 91-96%) and MTC (5-yr relative survival 88%) while definitely worse for ATC (5-yr relative survival 14%) [2]. Outcome drops down dramatically at the appearance of distant metastases and in case of RAI-resistant DTC, being 30% at 5 years for these latter subjects [3] and 40% at 10 years for MTC patients [4].

Except RAI for DTC patients, no other effective treatment was available for patients with relapsed and/or metastatic TC since few years ago. Doxorubicin was approved on 1974 and since that date no new drugs have been approved. The presence of several genetic aberrations both in DTC and in MTC such as gene rearrangements (*RET/PTC*; *PAX8-PPAR γ* ; *RET/NTRK1*; etc.) and mutations (*RET M918T*; *BRAFV600E*; *RAS*; etc.) paves the way to test new compounds as multi-tyrosine kinase inhibitors (TKIs). Moreover, TCs are characterized by a high intrinsic vascularization and VEGFR is tailored by most of TKIs under evaluation in TCs.

In the last 10 years, several compounds have been investigated (e.g. motesanib, sunitinib, axitinib, pazopanib), most within phase II while only some of them in phase III trials. This is the case of sorafenib [5] and lenvatinib in RAI-resistant DTC [6] and vandetanib [7] and cabozantinib in MTC [8]. Primary aim was met in each trial, demonstrating a significant advantage in progression-free survival in the treatment arm in comparison with placebo although no conclusive data on overall survival have been published yet. Based on these trials, all latter 4 drugs were approved for patients with relapsed and/or metastatic TCs by the international regulatory agencies as Food and Drug Administration and European Medicine Agencies: vandetanib was the first approved drug on 2011, followed by cabozantinib (2012), sorafenib (2013) and lenvatinib

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(2015). The authorization of these agents addressed a dramatic unmet need for patients with relapsed and/or metastatic RAI-resistant DTC and MTC, representing a real therapeutic innovation in this setting of patients.

Although these drugs are currently authorized in many countries, reimbursement is not provided by all the national health systems, so the treatment options for these patients remain still scant. For example, in Italy sorafenib and cabozantinib are currently approved but not reimbursed while lenvatinib and vandetanib are the only therapeutic option for RAI-resistant DTC and MTC patients, respectively. Some issues need to be still addressed. For example, how to reduce the toxicities burden that currently involves the majority of treated patients as well as the lack of a clear benefit in terms of overall survival. Even if a significant survival improvement has been recently reported within two subgroups of patients: subjects with RAI-resistant DTC older than 65 years on lenvatinib [9] and patients with metastatic MTC carrying *RET*M918T mutation on cabozantinib [10].

Moreover, some questions about the efficacy are still open: which type of patients could get a real benefit from these drugs? When is the right moment to start a TKIs? The approved dose is the right one? Some trials are already ongoing to try to address these questions. Unfortunately, despite the major developments of the last years in the field of genetic profile and therapeutic management in TCs, no progress has been done in ATC that still remains a neglected disease with a very dismal prognosis.

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Conflicts of Interest

LDL acted as consultant or advisory board member for the EISAI; LL acted as consultant or advisory board member for the following companies: EISAI and Bayer.

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