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Editor's page

The right drug for the right patient at the right time with the right test in differentiated thyroid cancer (DTC)

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ABSTRACT

Thanks to the identification of crucial molecular pathways, the therapeutic landscape for advanced differentiated thyroid tumors (DTCs) has significantly improved during the last ten years. The therapeutic scenario has been greatly impacted by the discovery of mutually exclusive gene changes in the MAPK and PI3K/AKT pathways, such as *RET* or *NTRK* fusions and pathogenic mutations of the *BRAF* and *RAS* genes. Indeed, multi-kinase inhibitors and selective inhibitors have demonstrated outstanding efficacy for radioactive iodine-refractory (RAI-R) drug treatment, with overall response rates reaching up to 86%. Thus, for RAI-R DTCs, routine molecular testing for actionable gene alterations is now essential, for choosing the right therapy for the right patient.
Additionally, tumor genotyping also allows to identify a subset of patients with worse prognosis disease, which may deserve a tailored clinical management. Thus, the right test should also include non-driver *TERT*, *TP53*, *PIK3CA*, and other mutations of aggressiveness, with the aim of a molecular-based risk stratification. Therefore, tumor genotyping should be considered in the diagnostic work-up of metastatic DTC patients or with highly aggressive histological features, in order to give the right drug for the right patient at the right time.

Introduction

The vast majority of differentiated thyroid cancers (DTC) have an excellent prognosis, but about 5–10 % of cases develop metastatic disease, whose prognosis is affected by the maintenance of iodine sensitivity. Radioactive iodine (RAI) refractoriness is standard recognized as the lack of RAI uptake metastatic lesions or when the structural progression of disease occurs within 6–12 months after the last RAI administration [1]. It occurs in less than 5% of all metastatic DTC patients, about 4–5 new cases/year/million and it is associated with poor prognosis, with a 10-year survival of only 10% [1].

Nevertheless, in the last ten years, systemic treatment of advanced DTC has undergone a marked revolution, since the advent of multikinase inhibitors first and then of agnostic selective inhibitors [2–7]. This has been possible due to growing advances in the knowledge of molecular mechanisms underlying tumorigenesis of DTC, leading to the identification of a wide spectrum of gene alterations of established therapeutical meaning. Indeed, most of the DTCs are featured by mutually exclusive gene alterations involving the MAPK pathway and phosphatidylinositol-3 kinase (PI3K)/AKT pathway, including point mutations of *BRAF* and *RAS* genes or gene fusions involving *RET* and *NTRK* [8–10]. Exactly thanks to both these rearrangements, detectable in about 10 % of cases, the therapeutic scenario of radioactive iodide refractory (RAI-R) DTC has been enriched with new strategies, such as NTRK-inhibitors and RET-inhibitors, with impressive overall response rates (ORR) of 86% and 79%, respectively [5–7].

Therefore, routine molecular testing for actionable gene alterations is now strongly recommended for all RAI-R DTC, because it determines an unquestionable therapeutic opportunity [11,12]. Thus, the first key message we would point out once again is that the right drug for the right patient is made by a prompt tumor genotyping that covers all actionable gene fusions.

Besides this already worldwide recognized as a milestone in the era of agnostic therapies and precision oncology, we would also emphasize another clinical relevance of tumor genotyping of all advanced DTC, that is its role in identifying that subset of patients with more aggressive disease and predicting RAI-R development. To date, the definition of RAI-R DTC is still based on clinical evolution and iodine uptake pattern, and the timing of considering systemic treatment has been in the past reserved only for those patients with symptomatic disease, disease that threatens vital structures or clinically significant disease rapidly progressive [2,13]. However, applying this approach to all DTC patients may delay the start of effective therapies, with a negative impact on long-term overall survival. Indeed, real-world data have shown that systemic treatment is generally started later than the trial population, with more advanced disease and worse clinical conditions, affecting drug compliance and effect [14–16]. One year after the approval of lenvatinib for RAI-resistant-progressive DTC patients, retrospective French data reported an overall response rate (ORR) of 31% and median progression-free survival (PFS) of 10 months [14]. In a smaller series of patients within the Swiss Named Patient Program ORR was 31% and a median PFS of 7.2 months [15]. Analogously, in the Italian experience among patients in the lenvatinib compassionate use program, ORR was 36% and median PFS 10.8 months [16]. In all three realities, patients'

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clinical characteristics overlapped and outcomes were clearly inferior to those reported in the SELECT trial (ORR 64% and median PFS of 18 months) [4].

Therefore, an emerging unmet clinical need is exactly to determine which DTC patients are being or becoming RAI-R, in order to personalize their management. For this purpose, some multivariable prediction models of RAI-R-disease, based on clinic-pathological features including age, N-stage at diagnosis, vascular invasion, metastatic presentation and site of recurrences, and pre-operative thyroglobulin levels, have been assessed [17–20]. To date, several risk calculators are available, as TNM (Tumor, Nodes, Metastasis), MACIS (Metastases, Age, Completeness of resection, Invasion, Size), AGES (Age, Grade, Extent, Size), AMES (Age, Metastases, Extent, Size), EORTC (European Organization for Research and Treatment of Cancer), and ATA (American Thyroid Association) risk. However, to date, the ATA risk is the only one used in clinical practice for the evaluation of recurrence risk, while the others are predictive for patients' survival.

Tumor genotyping, especially the coexistence of *TERT* promoter mutations, has been also recognized as an indicator of more aggressive disease in terms of risk of recurrence, disease persistence, and RAI-R development [21–29]. Accordingly, also some prediction models including molecular profiling have been investigated [19,24,30,31]. More recently, *TERT* promoter, *TP53, PIK3CA* mutations, and other genetic alterations belonging to polyclonal evolutions to poorly differentiated and anaplastic thyroid cancer, both as single events or as co-mutations have been found to be correlated with RAI refractoriness and time to RAI development, suggesting that a molecular risk stratification may serve as a valuable tool for both prognosticating clinical outcomes and directing precision-based therapeutic management [32,33].

Therefore, the second key message we would point out is that the right drug for the right patient could be given at the right time once again by a prompt tumor genotyping of all metastatic DTC patients or with highly aggressive histological features, with the aim of molecular-based risk stratification.

Since at least *TERT* promoter, *TP53, PIK3CA,* and other aggressiveness-related mutations play a relevant role in prognostic DTC patients' stratification, the third key message we would point out is that the right drug for the right patient at the right time could be given once again by a prompt tumor genotyping with the right test. A multi-gene panel including not only all Single Nucleotide Variants (SNVs) / small indel of thyroid driver genes (*BRAF*, *KRAS*, *NRAS*, *HRAS*) but also all aggressiveness mutations should be performed for better risk stratification of all DTC patients [34]. In the absence of variants in the driver genes or in the presence of aggressiveness mutations only, an RNA-based Next-Generation Sequencing (NGS) panel for gene fusions should be adopted, with a time–cost-saving sequential approach.

To conclude, tumor genotyping should be considered in the diagnostic work-up of all metastatic DTCs with highly aggressive histological features, not only for the identification of actionable gene alterations but as well as an additional prognostic tool, which could be useful for a better and tailored clinical management of all patients [Fig. 1].

CRediT authorship contribution statement

Dario de Biase: Writing – review & editing, Methodology, Data curation, Conceptualization. **Andrea Repaci:** Writing – review & editing, Data curation, Conceptualization. **Maria Concetta Nigro:** Writing – review & editing, Investigation. **Thais Maloberti:** Writing – review & editing, Investigation. **Francesca Carosi:** Writing – review & editing, Investigation. **Maria A. Pantaleo:** Writing – review & editing. **Giovanni Tallini:** Writing – review & editing. **Margherita Nannini:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

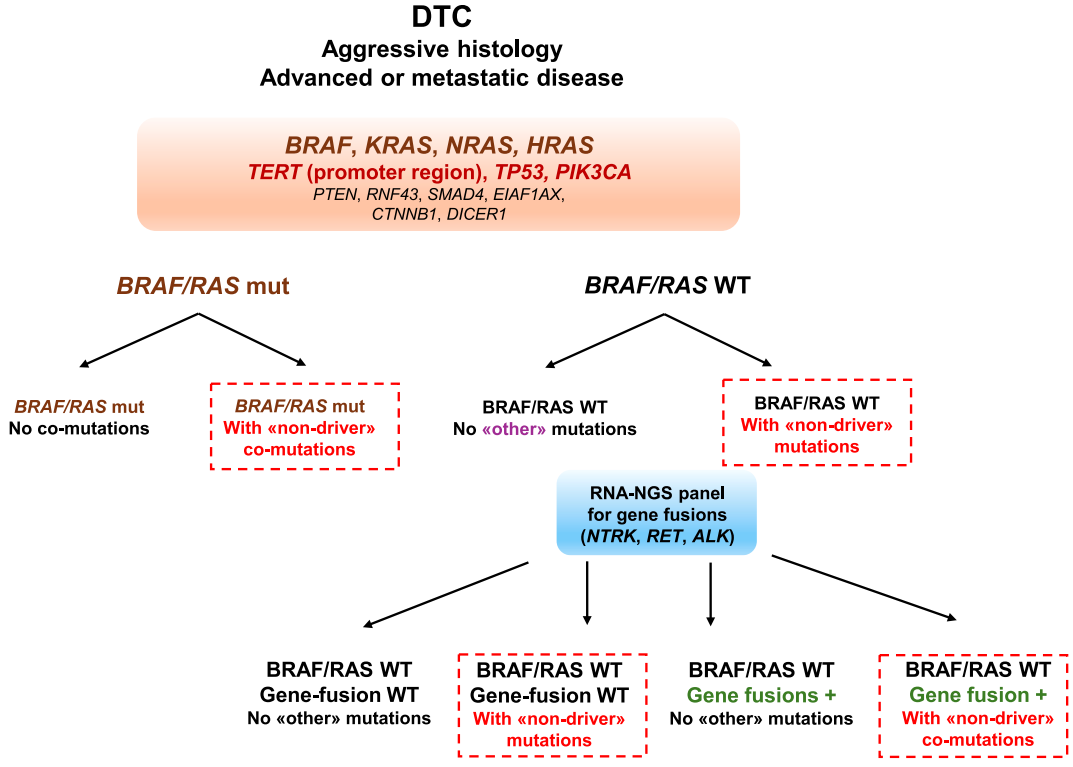

Fig. 1. Tumor genotyping in differentiated thyroid cancer (DTC).

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