SHORT COMMUNICATION

Clinical utility of BRAF and pTERT mutations in precision management of papillary thyroid cancer

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ABSTRACT

Papillary thyroid cancer is the most prevalent and indolent thyroid cancer, but still, around 20% of cases will develop regional recurrence or distant metastasis. Isolated or coexistent BRAF V600E and telomerase reverse transcriptase promotor (pTERT) mutations in thyroid cancer are associated with poor clinical outcomes. The prior knowledge of BRAF V600E and pTERT mutation may help to identify the cases that may recur or become refractory to standard radioactive iodine treatment. Such cases could be treated initially with complete disease eradication through extensive surgery followed by maximum permissible high-dose radioactive I-131 ablation and vigilant follow-up. Conventional risk assessment coupled with genotype-based risk assessment can help in the precise management of aggressive thyroid cancers.

Keywords: BRAF, TERT, thyroid cancer, precision management, molecular.

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Introduction

Thyroid cancer is considered indolent cancer but still, around 20% of cases will develop regional recurrence or distant metastasis [1]. BRAF V600E is the most prevalent mutation in papillary thyroid cancer (PTC) (40%-80%) and the risk of structural disease recurrence is around 28% [2,3]. However, isolated BRAF V600E mutation cannot be used as an independent prognostic biomarker for risk stratification as it loses significance after adjustment with other clinicopathological prognostic factors. Rather it could be used to identify the most aggressive phenotype within an assigned risk group [4].

Telomerase Reverse Transcriptase Promotor (pTERT) mutations have emerged as a potential marker for prognostication and management in thyroid cancers [5]. The prevalence of pTERT mutations in differentiated thyroid cancer (DTC) is about 11% and they are more common in poorly differentiated thyroid carcinoma and anaplastic thyroid cancer (40%-43%) [6]. These mutations are associated with disease aggressiveness and decrease 10-year survival in DTC (66% *vs.* 99%) [7]. The risk of structural disease recurrence is about 47.5% after initial treatment which leads to increased mortality [8]. American Thyroid Association guidelines 2015 have included pTERT mutations as an independent prognostic factor for high-risk groups in PTC >1 cm [9].

pTERT mutations can exist alone or in combination with BRAF V600E. The prevalence of concomitant BRAF and pTERT mutations in PTC is around 7.7% [10]. The risk of recurrence increases to 68% in cases harboring a genetic duet of BRAF V600E and pTERT mutation [8]. Coexistent BRAF V600E and pTERT mutations are a strong predictor of recurrence, radioactive iodine (RAI) avidity loss, and mortality; and can be used effectively for the management and prognostication of thyroid cancer. In clinical trials, BRAF V600E mutation alone has demonstrated a sensitivity of 84.2% and specificity of 94.4% to predict loss of RAI avidity and can be used as an independent RAI avidity biomarker in primary lesions[11,12]. Remarkably, sensitivity increases to 97.4% for RAI avidity loss in cases harboring genetic duet of BRAF V600E and pTERT mutations[13]. Genetic biomarkers could be placed in the following order to signify their prognostic importance:

pTERT + BRAF V600E > pTERT > BRAF V600E [14].

Clinical utility of BRAF and pTERT mutation

The use of genetic biomarkers is not indiscriminative, rather it should be used cautiously.

Molecular markers as "Tiebreaker" for risk stratification

Genetic information can play a "Third Umpire Role" when a clinician doubts conventional clinicopathological risk assessment for treatment planning of thyroid cancer [15].

Value of negative prognostic test (BRAF + pTERT)

BRAF V600E and pTERT mutations in thyroid cancer are associated with poor clinical outcomes [16]. In the absence of BRAF and pTERT mutations, cancer-specific mortality in PTC is around 0.6% which increases to 22.7% when BRAF and pTERT mutations are coexistent [17]. In this context, the high negative predictive value of the molecular test for poor prognosis of PTC makes the negative test equally valuable.

Molecular markers in the management of clinically aggressive DTC

BRAF V600E and pTERT mutations are also gaining importance in the management of clinically aggressive DTC having an extrathyroidal extension, lymph node, and distant metastasis. As the risk of recurrence is high in these cases, therefore they are treated aggressively in surgical and nuclear medicine premises. Despite the aggressive approach, response to treatment is not uniform and a significant number of cases experience disease recurrence [18]. TERT mutations alone or in combination with BRAF V600E are associated with increased mortality, disease aggressiveness, and reduced RAI avidity [17]. The prior knowledge of BRAF V600E and pTERT mutation may help to identify the cases that may recur or become refractory to standard treatment. Such cases could be treated initially with complete disease eradication through extensive surgery followed by maximum permissible high-dose RAI ablation and vigilant follow-up.

Molecular markers in the management of solitary intra-thyroidal PTC (SI-PTC)

BRAF and TERT mutations analysis may help in decision-making to carry out lobectomy versus total thyroidectomy in SI-PTC. The risk of recurrence in mutant SI-PTC with size >2 cm is around 20%-30% as compared to 2%-3% in wild-type matched size SI-PTC. Remarkably, the risk of recurrence stays the same (2%-3%) for wild-type SI-PTC >4 cm. The mutant SI-PTC of size 2-4 cm constitutes 8.3% of total cases that need to be treated aggressively with total thyroidectomy [19]. All cases with SI-PTC having a size <2 cm could be managed safely with lobectomy irrespective of genetic status. It is also reasonable to carry out lobectomy in wild-type SI-PTC >4 cm. In this way, the vast majority of SI-PTC cases could be treated with lobectomy alone using molecular status [15].

Molecular markers in the management of papillary thyroid microcarcinoma (PTMC)

Although surgical treatment of clinically aggressive PTMC is widely accepted, however, there is debate on surgical treatment versus non-surgical active surveillance in clinically low-risk PTMC [20]. There is no reliable clinical feature that can differentiate the fraction of PTMC destined to be aggressive. Molecular biomarkers like BRAF and TERT may be helpful to isolate aggressive PTMC phenotype. Active surveillance seems to be a reasonable option in clinically low–risk PTMC with a wild-type molecular profile. The presence of BRAF or pTERT mutations alone or in combination warrants cautious long-term surveillance and may require surgical intervention [21,22]. The presence of BRAF mutations confers a growth advantage to cells and may drive PTMC to grow to the size of PTC. The growing PTMC nodules (>3 mm change) that could trigger surgery otherwise could be kept under surveillance with BRAF wild-type PTMC. The growing PTMC-carrying genetic duet of BRAF V600E and pTERT mutations are more likely to be aggressive and could be managed by total thyroidectomy [15].

Molecular markers in the early appraisal of radioiodine refractory thyroid cancer

BRAF V600E mutations reduce the expression of sodium-iodide symporter (NIS) via HDAC8 and DNMT3 genes-mediated epigenetic changes [23,24]. It further enhances the expression of mutated TERT through FOS-activated GA-binding protein subunit beta (GABPB)/GABPB complex formation [25]. Though TERT-expressed cells achieve immortality, their membrane becomes too fragile to hold NIS after successive cell division due to the production of reactive oxygen species. The cells become poorly differentiated and refractory to RAI. The presence of BRAF V600E mutation reduces the expression of NIS and increases the expression of mutated pTERT leading to synergism in the working of both genes [26]. The presence of BRAFV600 mutations can be used as an independent RAI avidity marker in PTC. The genetic duet of BRAF and pTERT mutations predicts RAI avidity loss with an almost sensitivity of 97.4%. The early appraisal of refractory status may help to eliminate the disease completely on the surgical floor followed by high-dose RAI ablation before the cell achieves more refractory genetic signatures [4,17].

Molecular markers for selection of kinase inhibitors

The use of tyrosine kinase inhibitors in thyroid cancer is not curative, rather its purpose is to achieve progression-free survival. Currently, lenvatinib and sorafenib (pan kinase receptor inhibitor) are recommended as first-line treatment options either in advanced or metastatic RAI-refractory

DTC *irrespective of genetic status.* However, Lenvatinib is considered superior to sorafenib due to better progression-free survival and disease control rate [27,28]. Cabozantinib is a recently approved 2nd line multi-kinase receptor inhibitor in patients unresponsive or intolerable to sorafenib or lenvatinib [29]. The prolonged use of multi kinase inhibitors (MKI), is associated with cost toxicity and adverse events. Recently Food and Drug Administration has also granted accelerated approval to dabrafenib and trametinib in BRAF V600E mutated metastatic solid tumors having no alternative option [30].

Re-differentiation therapies- back to basics

The current focus is on the development of re-differentiation therapies that might interrupt or delay the use of MKIs. Selumetinib (MEK inhibitor) has shown unsatisfactory results to induce re-differentiation in BRAFV600 mutated phenotype [31]. The double inhibition of the mitogen-activated protein kinase (MAPK) signaling pathway with trametinib (MEK inhibitor) and Dabrafenib in this group is more effective to induce re-differentiation as appeared in preliminary small series clinical trials. In the case of BRAF wild-type disease, re-differentiation with MEK inhibitors alone might be sufficient [32]. The induction of re-differentiation by BRAF V600 mutation-specific inhibitors (dabrafenib and vemurafenib) in the BRAF-mutated group followed by radioiodine treatment has also shown promising results [33,34]. Large studies in the future are needed to compare the re-differentiation efficacy of dabrafinib alone or dabrafinib + trametinib in BRAF V600E mutated group.

A number of clinical trials are underway to check the efficacy and safety of drugs targeting the MAPK signaling pathways to better define re-differentiation therapies for RAI-R thyroid cancers. In the next 5 years, we might see re-differentiation therapies and subsequent RAI treatment prior to MKIs as an effective option if proven successful.

Currently, the success of re-differentiation therapies is limited to partial response or stable disease and partial response is approximately 22% (5%-50%) across different studies [32-37]. We might need to explore the potential negative role of other genetic biomarkers (like pTERT)-hindering the incorporation of radioiodine into cell membranes that might improve our selection of patients. In addition, answers regarding the time of re-differentiation therapy, duration of MKIs, RAI dose, patient selection pre-requisites and overall survival are still awaited.

Conclusion

- All apparently clinically aggressive DTC should be tested for BRAF V600E and pTERT mutations preferably prior to surgery or immediately after surgery to isolate the most aggressive or RAI refractory phenotype out of the group. That will help to complete disease eradication at an early stage.
- All SI-PTC of size >2 cm should be tested for BRAF and TERT mutations to decide between lobectomy or total thyroidectomy.
- All growing PTMC should be tested when one is indecisive between active surveillance or lobectomy
- A negative BRAF + pTERT mutations test is equally valuable and important for prognostication.
- Conventional risk assessment followed by genotype-based risk assessment can help in the precision management of aggressive thyroid cancer.
- Genotype-guided MAPK inhibition has the potential to decide on re-differentiation therapies for unresectable RAI-R thyroid cancer and to delay MKI treatment.

List of Abbreviations

BRAF	RAS activated fibroblast (isoform B)
DTC	Differentiated thyroid cancer
FOS	Fos proto-oncogene, AP-1 transcription factor subunit
HDAC8	Histone deacetylase 8
MEK	Mitogen-activated extracellular kinase
MKI	Multi kinase inhibitor
NIS	Sodium iodine symporter
PTC	Papillary thyroid cancer
pTERT	Promotor of telomerase reverse transcriptase
PTMC	Papillary thyroid microcarcinoma
RAI	Radioactive iodine
SI-PTC	Solitary intra thyroidal PTC

Conflict of interest

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