Personalized treatment options for thyroid cancer: current perspectives

Abstract: Thyroid cancer is one of the most common endocrine malignancies, with increasing incidence all over the world. In spite of good prognosis for differentiated thyroid carcinoma, for an unknown reason, about 5–10% of the patients, the cancer will show aggressive behavior, develop metastasis, and be refractory to treatment strategies like radioactive iodine. Regarding the genetic information, each thyroid cancer patient can be considered as an individual unique one, with unique genetic information. Contrary to standard chemotherapy drugs, target therapy components aim at one or more definite molecular pathway on cancer cells, so their selection is underlying patient’s genetic information. Nowadays, several mutations and rearrangements including BRAF, VEGF receptors, RET, and RET/PTC, KDR, KIT, PDGFRA, CD274, and JAK2 are taken into account for the therapeutic components like larotrectinib (TRK inhibitor), vemurafenib, sunitinib, sorafenib, selumetinib, and axitinib. With the new concept of personalized treatment of thyroid cancer diagnoses, planning treatment, finding out how well treatment will work, and estimating a prognosis has changed for the better over the last decade.

Keywords: personalized medicine, target therapy, molecular testing

Introduction

The exact word of “personalized medicine” is defined for dividing people based on their genetic information in order to allocate different subgroups of treatment and predicted response efficacy, disease behavior or risk of the disease. Several terms are used for personalized medicine like personalized medicine, precision medicine, stratified medicine, and P4 medicine which are used for particular distinctions but same in principal. Personalized medicine emphasizes that clinicians are not facing the disease with an exact definition for all persons but are facing with individual patients with unique genetic information.

Personalized cancer medicine is a subgroup of personalized medicine in which a person’s genetic information support finding more effective strategies for prevention, screening, and treatment. The last decade of twentieth century is highlighted as the genomic age because high-throughput molecular technologies like next-generation sequencing (NGS), and gene expression microarrays provide a wide range of cancer genetic information. In fact in personalized cancer management approach, several attempts are done to identify the link between patients’ molecular characteristics and their survival or drug response. Genetic testing of cancer cells and normal cells aids clinicians make the treatment strategy more compatible with individual patient needs that may cause less side effects than standard options. Cancer personalized medicine is including...
of: (a) prediction of the chances to developing cancer and selecting screening strategies to lower the risk, (b) matching people with more effective treatments with less side effects, (c) predicting the risk of recurrence. The development and improvement of chemotherapy have revolutionized the cancer treatment, but there are still some patients fail to respond to the treatment. The secret of several efficacy for the same medication strategy is beneath to the genetic and epigenetic and is needed to be determined for a personalized cancer medicine approach for the “one-treatment-fits-all” mindset.5,6

Thyroid cancer is the most prevalent endocrine malignancy, and papillary thyroid carcinoma (PTC) incidence has increased over the past few decades due to improved diagnosis.7–10 Primary thyroid malignancies are mostly epithelial tumors that initiate from thyroid follicular cells with three main pathological types of carcinomas: PTC, follicular thyroid carcinoma (FTC), and anaplastic thyroid carcinoma (ATC) and poorly differentiated carcinoma (PDC). Another thyroid cancer which originates from thyroid parafollicular (C) cells is medullary thyroid carcinoma (MTC). As a result of well differentiation and indolent tumor growth in PTC and FTC, they are also known as differentiated thyroid cancer (DTC). PTC involves of 85–90%, FTC 5–10%, MTC about 5%, and ATC less than 2% of all thyroid cancer cases and their incidence continues to rise with age.11 Very recently it has been considered that some genetic mutations and polymorphism over DTC should be taken into the account of choosing the high efficacy treatment strategies.12 For example, some of these genetic alterations are BRAF mutation, vascular endothelial growth factor (VEGF) mutation,13 KDR (VEGFR2) mutation,14 KIT/PDGFRA mutation,15 PDGFRα promoter polymorphisms,16 Programmed death-ligand 1 (PD-L1) expression,17 and JAK2.18

Comprehensive data about thyroid cancer-genetics are provided by The Cancer Genome Atlas database which indicated to the mutations in either BRAF (specifically, BRAF-V600E) or RAS as the mitogen-activated protein kinase (MAPK) signaling pathway regulator, and novel driver gene EIF1AX change as the MAPK pathway intermediate.19

Using PM can help physicians to make a better decision for thyroid cancer patients treatment. In the current review, we are focusing on the current benefit of PM in thyroid cancer management and future perspective of PM in thyroid malignancies management.

Molecular characteristics of thyroid cancer

Several genetic changes are suggested as the driver genetic alterations with a central role in the triggering of thyrocytes to become malignant.20 The most important one is a specific mutation in the BRAF gene adenine at nucleotide position 1799 (T1799A) in exon 15th iamine trans conversion to, causing in an amino acid substitution at position 600 in BRAF, from a valine (V) to a glutamic acid (E) which is shown as the BRAF-V600E.21 BRAF is the intermediate of the MAPK pathway and transcription factors essential for cell growth, differentiation, proliferation, and survival.22 BRAF-V600E mutation happens in about 45% of sporadic PTCs, mostly in the aggressive subtypes, such as the tall-cell PTC.23 Another important common mutation in thyroid cancers is RAS mutation. Ras proteins are proto-oncogenes that are often altered in several human malignancies. They are coding by three genes: HRAS, KRAS, and NRAS which are GTPases responsible for proliferation and cell survival pathways. Point mutation at codons 12, 13, or 61 of RAS are linked to the uncontrolled cell proliferation and tumors formation.24 While RAS is the classic activator of the MAPK and PI3K–AKT pathways, RAS modification can specially stimulate the PI3K–AKT pathway in thyrocytes, as proposed by the link of RAS mutations with AKT phosphorylation in thyroid malignancies.25 In fact, the phosphoinositide 3-kinase–protein kinase B/AKT (PI3K-PKB/AKT) pathway is central signaling pathways of the developmental process. Its uncontrolled activation through numerous receptor tyrosine kinases (RTKs) alterations has resulted in aggressive cell proliferation during tumorigenesis, including thyroid carcinomas.26 The phosphatase and tensin homolog (PTEN) genetic and epigenetic alterations are established as the genetic changes that trigger the PI3K–AKT pathway and are the genetic basis for follicular thyroid cell tumor genesis in Cowden’s syndrome.27,28 Moreover, genetic alterations in exon 9 and 20 of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene can be responsible for coding the p110α catalytic subunit of PI3K and are reported several times in thyroid malignancies like FTC, PSC, and ATC.29,30 There are a list of other mutated genes in thyroid tumorigenesis like catenin (cadherin-associated protein), Tumor Protein P53 (TP53), isocitrate dehydrogenase 1 (IDH1), anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), Zinc and ring finger 3 (ZNRF3), and NADH dehydrogenase (ubiquinone) 1α subcomplex 13 (NDUFA13).31
In addition to point mutations some oncogenic gene amplifications, copy-number changes, and gene translocations are reported as the key driver genetic alterations in thyroid carcinogenesis. Copy-number changes are observed in genes encoding PI3K–AKT pathway members, including PIK3CA, PIK3CB, 3-phosphoinositide-dependent protein kinase 1 (PDPK1), AKT Serine/Threonine Kinase 1/2, IQ-motif-containing GTPase-activating protein 1 (IQGAP1). Copy-number gaining of oncogenes contributes to tumor formation because of higher protein expression resulting in constitutive activation of their downstream signaling pathway. These copy-number change can be seen alone or simultaneously with BRAFV600E. For example, IQGAP1 copy-number gain and BRAFV600E mutation are linked to the higher risk of recurrent PTC.\textsuperscript{34,36} Gene translocation more than gene amplification trigger oncogenic rearrangements in thyroid neoplasm. By way of illustration, there are more than ten types of RET–PTC translocation. The RET proto-oncogene with the chromosomal locus of 10q11.2 is responsible for coding a cell membrane RTK. In follicular cells, RET can be stimulated by fusion to other highly expressed genes and make a chimeric oncogene named RET/PTC (recombination of 3′end of RET and the 5′ portion of a recipient gene). By way of illustration, coiled-coil-containing gene 6 (CCDC6) in RET–PTC1 and nuclear receptor co-activator 4 (NCOA4) in RET–PTC3.\textsuperscript{37} Another prominent thyroid cancer-specific gene translocation which is happening in 60% of FTC and follicular variant of PTC, is the paired box 8 (PAX8)–peroxisome proliferator-activated receptor-γ (PPARG) fusion gene (PAX8–PPARG).\textsuperscript{38,39}

Contrary to genetic changes there are some epigenetic alterations like DNA methylation, histone modification, and microRNA that can change chromatin remolding and gene expression pattern of the thyroid epithelial cells (thyrocytes) with no change of the exact DNA sequence. These epigenetic modifications are important to recognize because can be the novel therapeutic targets for personalized thyroid cancer managements.\textsuperscript{40} Frequent promoter methylation of Ras Association Domain Family Member 1 (RASSF1) has been predominantly reported in thyroid malignancies.\textsuperscript{41–43} Some other candidate genes with aberrant promoter methylation have been highlighted in thyroid cancers including PTEN, Solute Carrier Family (SLC), DNA methyltransferases (DNMTs), O6-methylguanine DNA methyltransferase (MGMT), Thyroid-stimulating hormone receptor (TSHR), and E-cadherin.\textsuperscript{44–48}

MicroRNAs are small endogenous noncoding RNAs containing about 22 nucleotides that have role in silencing and post-transcriptional regulation of gene expression profile. Recent studies of thyroid cancer have indicated to several microRNAs deregulation as the key tumorigenesis elements with impact on impact cell differentiation, proliferation, and survival.\textsuperscript{49} Amongst, miR-146b and miR-222 persisted as distinguishing markers of PTC.\textsuperscript{49,50} MicroRNA-146b stimulates PI3K/AKT pathway and thyroid cancer progression by targeting PTEN.\textsuperscript{51}

**Current molecular test of thyroid nodules**

Nowadays discrimination of benign thyroid nodules from neoplastic one is done based Bethesda Histological and Immunohistological (IHC) tests and are essential diagnosis of malignancy between the benign and malignant counterpart’s tissues.\textsuperscript{52–55} System are for Reporting Thyroid Cytopathology (TBSRTC) and through fine needle aspiration biopsy and immunohistochemistry (IHC) reports.\textsuperscript{56–60} In spite of the fact that several IHC and cytopathological staining are recommended as the discriminative of benign and malignant markers, still some FNA results are not classified exactly as the benign or malignant resulting in an indeterminate diagnosis which are referred as the gray zone.\textsuperscript{60–62} Several molecular testsings are available for supporting the FNA result that is based on genetic and epigenetic profile of the patients.\textsuperscript{63} These tests are called AFIRMA GENE EXPRESSION CLASSIFIER (GEC), ThyGenX TEST, and ThyroSeq TEST.

- Afirma gene expression classifier (GEC) (Veracyte Inc, South San Francisco, California) is a microarray-based test for the RNA transcript (gene expression) of 167 genes.\textsuperscript{64,65} Non-determined samples of FNA or suspicious for Hürthle/follicular neoplasms are candidate of this test. In 2014, Veracyte suggested the Afirma Malignancy Classifiers (AMCs) support Afirma GEC and evaluate assess the risk of malignancy. The AMC tests are done over FNA samples carrying a suspicious diagnosis or a suspicious Afirma GEC result. The AMC profile is containing BRAFV600E gene more than genes expression of five genes include calcitonin-related polypeptide α (CALCA), carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), secretogranin III (SCG3), sodium channel voltage-gated type IX α (SCNG3), and pro-opiomelanocortin (POMC) gene.
subunit (SCN9A), and synaptotagmin IV (SYT4). The negative Afirma GEC result commanded as the significant reduction of thyroid surgical resection rate from 74% to 7.6% on cytological indeterminate nodules. Afirma XA includes the most common and emerging variants and fusions associated with thyroid carcinoma, such as variations of BRAF, Dicer1, Eif1ax, H/K/N Ras, Ret, Tp53, Tg, and Zfhx3 in addition to fusions of ALK, BRAF, Ntrk, Pax8, and Ret.

1. ThyGenX TEST/ThyraMIR is based on the NGS mutation detection panel of more than 100 genetic changes. ThyGenX TEST is made of point mutations (ALK, BRAF, Gnas, Hras, Kras, Nras, Pki3ca, PtEn, Ret, and Tert) and RNA panel and fusion (ALK, BRAF, NTRK, Pparg, Ret, Thada). Lately, Interspace Diagnostics has represented a new molecular test calling ThyraMIR in which ten different microRNAs (miRNAs) containing miR-29b-1-5p, miR-31-5p, miR-138-1-3p, miR-139-5p, miR-146b-5p, miR-155, miR-204-5p, miR-222-3p, miR-375, and miR-551b-3p are taken into the consideration. Nowadays, it is shown that combination of both ThyGenX and ThyraMIR has the sensitivity and specificity of 89% and 85%, respectively, with dabrafenib and the NPV and PPV were reported as 94% and 74%, respectively. (https://www.afirma.com/physicians/why-afirma/)

2. ThyroSeq TEST which is based on the high-throughput technique of NGS and fusion platform originally planned to target 12 key cancer genes with 284 mutational hot spots. Then in 2014, a new form of the test was presented as ThyroSeq v2 in which more extensive DNA changes (14 genes, including ≥1,000 mutations) and RNA variations (42 fusions, 16 genes for expression) were included. However, more than ThyroSeq, additional formats of NGS-based diagnosis molecular tests for thyroid nodules have been considered including Ion AmpliSeq to assess indeterminate FNA cytology of thyroid nodules. ThyroSeq test report is provided in a user-friendly format that states the probability of cancer in the patient’s nodule, suggests potential patient management, and also lists specific genomic alterations that are relevant to the individual patient (https://thyroseq.com/physicians/test-details/test-description).

Treatment strategies for thyroid cancers
 Several treatment options are available for thyroid cancer management including surgery as the chief treatment option in almost all thyroid cancer patients, except ATC cases. It can be lobectomy in which a part (one lobe) of the thyroid is removed or thyroidectomy as an operation that involves the surgical removal of all or part of the thyroid gland. However, on the occasion of the entire gland removal, it is named “total thyroidectomy” and on the occasion of almost all thyroid gland removal, it is named “subtotal thyroidectomy”. Subsequent treatment plan following thyroidectomy can be radioactive iodine [radioiodine] therapy. Thyroid cancer cases should receive daily thyroid hormone (levothyroxine) pills. Another treatment strategy is Radioactive Iodine (Radioiodine) Therapy in which radioactive iodine (RAI or I-131) is just absorbed by thyrocyte throughout the whole body. Therefore, RAI is delivered into the patient’s body in the form of fluid or tablet and aggregate in thyroid cells. The radiation will be able to abolish the malignant thyrocyte, with no harmful effect or any damage to the rest of the body. Following thyroidectomy, patients’ body will not be able to create the essential metabolic regulator hormone, thyroid hormone, so levothyroxine pills should be suggested.

The other treatment strategy for thyroid malignancies is external beam radiation (EBM) therapy in which high-energy emissions (or atoms) are used to remove tumor cells or cease their progress. Usually, this form of radiation therapy is not suggested in practice for (DTCs) patients’ who are defined as the good responder to RAI iodine. In fact, EBM is commonly practiced as the part of the treatment for MTC and ATC patients. More than that chemotherapy (chemo) is a treatment plan as the anti-cancer drugs that are injected into a vein or muscle, or are taken by mouth. Chemotherapy is a general therapy plan in which chemical components injected into the bloodstream and move throughout the whole body to find and destroy cancer cells. This therapeutic method is rarely beneficial for the most types of thyroid tumors. Therefore, chemotherapy is suggested with EBM therapy for ATC or occasionally is used for further advanced thyroid cancer patients who are no longer responded to other treatment strategies. Recently, scientists have initiated to improve new medications that
specially object the critical molecules responsible for tumor formation which is called “target therapy”.78

Dissimilar to general chemotherapy drugs, which attack cancer cells as the uncontrolled fast developing cells, target therapy drugs can aim at one or more specific molecular pathway on cancer cells. The list of some target therapy component with their target molecules is represented in Figure 1.

Vandetanib (Caprelsa) is for the treatment of aggressive and symptomatic MTC that is a specific drug in the form of 300 mg tablet is an oval-shaped, biconvex. Cabozantinib (Cometriq) is the medication used for MTC and a second line treatment for renal cell carcinoma. It is a small target therapy molecule that inhibits tyrosine kinases c-Met and VEGFR2 more than AXL and RET.79,80 In MTC patients, cabozantinib has been displayed to support break cancers from growing for about seven months longer than a sugar pill. Lenvatinib (Lenvima®) and sorafenib (Nexavar®) are two target therapy drugs for treating radioiodine-refractory differentiated thyroid cancer as the kinase inhibitors.81,82

**Personalized thyroid cancer treatment**

Personalized medicine is the novel strategy of patient care that conducts clinicians to choose treatments with the best efficacy based on a genetic understanding of their disease. NGS and array-based comparative genomic hybridization (array CGH) have assisted scientists to achieve high-throughput mutation screening and genome-wide copy-number analysis. Recent studies based on genetic analysis of thyroid tumors have brought several thinkable personalized treatment options for thyroid

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**Figure 1** Several small molecules are valid for thyroid cancer target therapies. These molecules can be categorized as the molecules targeting oncogenic kinases, signaling kinases, and vasculature and angiogenesis process. More than these molecules there are some other types of molecules which targeting epigenetic mechanisms (Fosbretabulin, Romidepsin, Celecoxib, Vorinostat, Valproic acid, Azacytidine, and Decitabine) or nuclear receptors.
cancer. A large-scale analysis was done by N. Pozdeyev and colleagues to define the genetic landscape of advanced differentiated and anaplastic thyroid cancer (ATC) and recognize genetic mutations of potential diagnostic, prognostic, and therapeutic implication. It was an updated schematic of thyroid cancer genetic evolution. An innovative aspect of medicine in which particular targeted therapy centered on specific targeted diagnostic tests called “Theranostics”. In fact, theranostics will provide a transition from conventional medicine to a contemporary personalized and precision medicine based on the genetic data. Radioiodine has the distinction of being the first theranostic agent and is a distinctive example of personalized medicine that has been used widely for the management of DTC. DTC has better thyroid cancer prognosis compared to other malignancies which can be the result of the successful treatment of unresectable distant metastasis by a therapeutic dose of 131I administration. However, about 65% of the patients with distant metastases finally become radioiodine-refractory disease. This radioiodine-refractory status is related to the sodium/iodide symporter (NIS) which is also identified as SLC NIS as the molecular target. Moreover, losing iodine avidity of DTC can be connected to the genetic and epigenetic alterations and MAPK and PI3K-AKT pathways signaling pathways. Some compounds like retinoic acid, PPARγ agonists, HDAC inhibitors (valproic acid and carbamazepine), PI3K/AKT inhibitors, and MEK/ERK inhibitors, have been recommended for NIS over-expression and have caused improved iodine uptake in both in vitro and in vivo studies of thyroid cancers. It was shown that Dabrafenib is the selective inhibitor of mutated forms of BRAF and can motivate radioiodine uptake in metastatic PTC BRAFV600E-mutant iodine-refractory patients. Higher efficacy of larotrectinib (LOXO-101) as a selective tropomyosin receptor kinase (TRK) inhibitor is suggested in neurotrophin receptors coding gene (NTRK) Fusion-Positive patients. Some molecular markers are indicators for the aggressive behavior of tumor associated with tumor dedifferentiation are including p53 (25–30%), PIK3CA (10–20%), CTNNB1 (10–20%), and AKT1 (5–10%). Mutation in the telomerase reverse transcriptase (TERT) promoter can be a marker of malignancy as well. TERT promoter mutations were reported in 7–22% of PTC and about 35% of FTC, were often found in concurrence with BRAF or RAS mutations. Distant metastatic to lung or bone disease happens in one-fifth of DTC patients and is the main reason for refractory to RAI. Innovative personalized based strategies for refractory thyroid cancer treatment are considered as the tyrosine kinase and small molecule inhibitors targeting iodine reuptake pathways. Amongst different therapeutic agent doxorubicins, motesanib, sunitinib, and sorafenib are non-specific tyrosine kinase inhibitors (TKIs), Vemurafenib is the inhibitor of BRAF V600E mutation and selumetinib is the selective MEK inhibitor and iodine reuptake inducer. TKIs non-specifically aim at pro-oncogenic kinases including VEGFR-1, VEGFR-2, EGFR, PDGFR, MET, FGFR, RAF, and RET. In a clinical trial Phase II, motesanib was submitted for patients with progressive DTC, 14% had a partial response and 35% had disease stability. Axitinib targeted the VEGF receptors and 30% partial response to axitinib was detected in a Phase II trial for patients with advanced or metastatic thyroid cancers. In order to evaluate the effectiveness of continuous dosing of sunitinib in patients with fluorodeoxyglucose positron emission tomography–avid, iodine-refractory well-differentiated thyroid carcinoma (WDTC) and MTC a Phase II clinical trial was done by L.L. Carr, and colleagues. One of the VEGF receptors, RET, and RET/PTC 1 and 3 targeting molecule is sunitinib, and the complete responses have been reported for patients with FDG-avid metastatic thyroid cancer.

Vemurafenib is a small molecular and specific inhibitor of BRAF V600E and the study of 51 papillary thyroid cancer patients between January 2011 and January 2013 showed antitumor activity in patients with progressive, BRAFV600E-positive papillary thyroid cancer refractory to radioactive iodine who had never been treated with a multi-kinase inhibitor. It was also suggested that specific genetic mutations in ATC, including amplifications of the KDR, KIT, and PDGFRα genes can increase the efficacy of treatment with lenvatinib. It was shown by Rothschild and his colleagues that lenvatinib has a reasonable clinical activity in unselected patients with RAI-refractory thyroid cancer and about two-third of patients showing clinical benefit and manageable toxicity.

More than that, some studies identified several genetic alterations as the vital determinant or for the development of personalized therapies for thyroid cancer. By way of illustration, the amplification of CD274, PDCD1LG2, JAK2, and DNA mismatch repair (MMR) deficiencies has been linked to the positive response to immune checkpoint inhibitors such as pembrolizumab and nivolumab. The evaluation of serum thyroglobulin (Tg) is currently...
employed to determine recurrence or persistence of the disease in DTC patients during the follow-up period after thyroidectomy or RAI therapy. Recently, Barbolosi and colleagues proposed a mathematical model to predict Tg kinetics, determine tumor doubling time under RAI treatment, and consequently categorize the patients into RAI-responding and non-responding groups. Although further investigations are required to determine the efficacy of these models for extensive clinical application, this novel field of research could eventually provide precise information on each individual patient and guide the physicians into more accurate and sophisticated decision-making. Furthermore, the application of RNAi agents such as small interfering RNA (siRNA) provides novel opportunities for the management of thyroid cancers with specific genetic mutations. Liu et al, introduced a novel near-infrared nanoplatform for systemic delivery of siRNA to treat ATC by targeting BRAF mutations which demonstrated a considerable down-regulation of BRAF protein expression, suppression of tumor growth, and reduced number of lung micrometastases in animal models of ATC with no notable adverse effects in the experimental group. In addition, in-vitro and in-vivo studies illustrated that knockdown of zinc-finger transcription factor SLUG by siRNA application could result in growth restraint of SW1736 ATC cells as well as increased sensitivity to doxorubicin administration.

Very recently liquid biopsy has presented a new non-invasive source for monitoring cancer-genetics in the blood. In several personalized thyroid cancer diagnosis and prognosis strategies, liquid biopsy is taken into consideration. Recently, in thyroid cancer, circulating nucleic acids and circulating tumor cells), and exosomes have brought new revolutionary insight to thyroid cancer personalized managements. In PTC patients, circulating microRNA profiles was suggested as potential biomarkers for cancer diagnosis.

**Conclusion**

In spite of the fact that thyroid cancers are commonly diagnosed with FNA test, there are some cytological results as the “indeterminate” or “Gray Zone”. Molecular profiling of FNAB cytology not only can improve diagnostic accuracy in the gray zone, but also support the thyroid cancer personalized treatment in a more favorable way. The connection of some genetic mutation and personalized refractory to treatment can improve prognostic consequence with much more optimized precision treatment strategies. Each thyroid cancer patient can be considered with regard to their genetic background to choose the exact therapeutic component.

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