Precision Medicine Approach to Anaplastic Thyroid Cancer: Advances in Targeted Drug Therapy Based on Specific Signaling Pathways

Hilda Samimi[1], Parviz Fallah[2], Alireza Naderi Sohi[3], Rezvan Tavakoli[4], Mahmood Naderi[5], Masoud Soleimani[6], Bagher Larijani[1,7], and Vahid Haghpanah[1]

[1] *Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Department of Laboratory Sciences, Faculty of Allied Medicine, Alborz University of Medical Sciences, Karaj, Iran*

[3] *Department of Nanotechnology and Tissue Engineering, Stem Cell Technology Research Center, Tehran, Iran*

[4] *Department of Molecular Biology and Genetic Engineering, Stem Cell Technology Research Center, Tehran, Iran*

[5] *Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran*

[6] *Department of Hematology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran*

[7] *Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract- Personalized medicine is a set of diagnostic, prognostic and therapeutic approaches in which medical interventions are carried out based on individual patient characteristics. As life expectancy increases in developed and developing countries, the incidence of diseases such as cancer goes up among people in the community. Cancer is a disease that the response to treatment varies from one person to another and also it is costly for individuals, families, and society. Among thyroid cancers, anaplastic thyroid carcinoma (ATC) is the most aggressive, lethal and unresponsive form of the disease. Unfortunately, current drugs are not targetable, and therefore they have restricted role in ATC treatment. Consequently, mortality of this cancer, despite advances in the field of diagnosis and treatment, is one of the most important challenges in medicine. Cellular, molecular and genetic evidences play an important role in finding more effective diagnostic and therapeutic approaches. Review of these evidences confirms the application of personalized medicine in cancer treatment including ATC. A growing body of evidence has elucidated that cellular and molecular mechanisms of cancer would pave the way for defining new biomarkers for targeted therapy, taking into account individual differences. It should be noted that this approach requires further progress in the fields of basic sciences, pharmacogenetics and drug design. An overview of the most important aspects in individualized anaplastic thyroid cancer treatment will be discussed in this review.

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Introduction

Personalized medicine is a set of diagnostic, prognostic and therapeutic approaches in which medical interventions are carried out based on individual patient characteristics (1). Although this branch of science is thousands of years old and dates back to the time of Hippocrates only in recent years, coinciding with the mapping of the human genome in 2003, has expanded in all medical fields (2,3). Actually, in this approach individuals' genetic codes determine the treatment strategy. Completion of the Human Genome Project (HGP) revealed that about 99.9% of the human genome sequence is the same among people, but there is a 0.1% difference showed genetic variants that determine person's risk of disease, severity and how an individual's response to treatment (4,5). Therefore, due to genetic differences between people and without taking into account environmental factors, it is clear that one drug cannot have the same result for everyone (6). Thus to improve the quality of treatment and health care, people's genetic profile should be considered. With this approach, the term

Corresponding Author: V. Haghpanah
Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 88220037, Fax: +98 21 88220052, E-mail address: v.haghpanah@gmail.com

of "Personalized Medicine" entered the science (7).

As life expectancy increases in developed and developing countries, the incidence of diseases such as cancer goes up among people in the community. One of the most important potential applications of personalized medicine is in the field of prevention and treatment of cancer (8). In general, cancer is a heterogeneous disease, and consequently, its incidence, metastasis and patients' response to treatment are different (9). Anaplastic Thyroid Carcinoma (ATC) or Undifferentiated Thyroid Cancer (UTC) represents about 2-5% of cases and clinically appears as a mass with rapid growth. ATC can affect patients at any age group; however maximum incidence has been reported between 60 to 80 years of age. The disease occurs in women 3 times more than men (10). In half of the cases, ATC occurs following a long-term history of goiter, thyroid adenoma and papillary or follicular carcinoma (11). Among all thyroid neoplasms, the clinical course of ATC has the worst prognosis. A combination of surgery, chemotherapy, and radiotherapy are routinely applied for the treatment of the disease with a low rate of success (12,13). Since chemotherapy is not targetable, these compounds are not effective against ATC. Therefore, mortality of this cancer, despite advances in the field of diagnosis and treatment is one of the most important challenges in medicine (14). Targeted cancer drugs inhibit the growth and spread of tumor by interfering with the function of molecules with a role in cancer (15,16). This study aims at showing the molecular complexity of ATC and highlighting appropriate targeted therapies.

This review is based on searches of PubMed, Google Scholar, ClinicalTrials.gov (17), MedChemExpress (18) and Selleckchem (19) databases using the terms "personalized medicine", "target therapy", "signaling pathway", "cancer stem cell", "pharmacogenetics" associated with the terms "thyroid cancers" and "anaplastic thyroid cancer" to identify relevant literature for the survey. While the search was restricted to articles published in English, we did not eliminate the results according to the time of their publication. Since ATC is a rare disease in populations, most previous researches were performed on cell line models, inevitably resulting in retrieving data mostly according to this type of experiment in the current review.

Cellular and molecular heterogeneity of ATC

The baseline threshold for genomic complexity in ATC is higher than other types of thyroid malignancies even when we ignore the alterations resulted from epigenetic changes and gene expression (20-22). Actually, the summarized genetic alterations in Table 1 and tissue-specific gene expression in Table 2 vividly highlight the degree of genomic and transcriptomic heterogeneity. These aforementioned points are important because drug's effectiveness cannot be generalized to all patients. In personalized medicine, a person's genome is compared with the consensus reference genome to choose the most effective therapeutic strategy on the basis of obtained information. In this approach, the drug effectiveness is already predicted, and the most appropriate medication with the most effective dose is applied to the patients (23).

Apart from genomic and transcriptomic alterations, it is critical to take into account the cellular nature of Cancer Stem Cells (CSCs) as the origin of ATC (36-38). While it is expected to have the same specific cancer stem cell gene pattern in these cells due to the stemness state we practically observe the heterogeneous pattern of cancer stem cell gene expression on the cells (Table 3). Hence, personalized medicine should be based on systemic inspection of data for the best results.

Signaling pathway inhibitors and CSCs

The majority of genetic alterations in ATC tumorigenesis act through two signaling pathways including PI3K/Akt/mTOR and RAF/MEK/ERK pathways. The function of these pathways is a common and important mechanism in the development and progression of cancer (41-43). It is now increasingly becoming clear that PI3K/Akt/mTOR signaling pathway is involved in thyroid tumorigenesis, particularly in ATC (44,45). This pathway is an important regulator of cell cycle progression, apoptosis, sodium/iodide symporter (NIS) expression and self-renewal. RAF/MEK/ERK signaling pathway is also involved in drug resistance, metastasis, angiogenesis, differentiation, apoptosis and cell cycle progression (35,46,47). The increase in genetic, cellular and molecular knowledge about the carcinogenesis process has introduced new drugs with the targeted-therapy application. These drugs are multi-target and affect many cancer stem cell signaling pathways. In this way, the risk of adverse drug reactions (ADRs) and side effects is reduced. On the other hand, it can also be unique due to patient genetic variations (48). Therefore, one of the options for ATC therapy would be to use drugs that could be effective with respect to an individual's genetic profile (23,49-51). For instance, knowing the underlying mechanisms of NIS could be beneficial for the immunotherapy of the disease. A number of available targeted drugs that act on PI3K/Akt/mTOR and RAF/MEK/ERK pathways

Table 1. Genetic alterations of anaplastic thyroid cancer cell lines

Gene	Cell line																				
	8505c	SW1736	Cal-62	T235	T238	Uhth-104	ACT-1	HTh74	KAT18	TTAT	FRO81-2	HTh7	C643	BHT101	KTC-2	OCUT-1	OCUT-2	OCUT-3	OCUT-4	OCUT-5	OCUT-6
EGFR	-/+	-						+					+				+				
H-RAS	-/+	-						+	-				+								
K-RAS	-							-	-				-								
N-RAS	-						+	-	-			+	-								+
BRAF	+	+	-			+	-	-	-	-	-/+	-	-			+	+	+	+	+	
PTEN	-	-											+								
THRB	-							+					+								
mTOR	-	-											+								
PI3KCA	-							-					-			-/+	+	-	-	-	-
PIK3CB	-	+											-								
PIK3CG	-	+											-								
PIK3R1	+	-											-								
PIK3R2	+	+											+								
P53	+	+						-					+	+		-	-	-	-	-	-
MET	-	+											-								
AKT*												+									
Reference	(28,29, 31, 32, 34)	(27-29, 32, 33)	(28, 29)	(28, 29)	(28, 29)	(28, 29)	(24, 28, 29)	(28, 29, 31)	(28, 29, 33)	(28, 29)	(28, 29)	(26, 28, 29, 33)	(24, 26, 27, 29-31)	(28-30)	(27-29)	(24-27)	(24, 25)	(24, 25)	(24, 25)	(24, 25)	(24, 25)

The asterisk sign (*) indicates that the type of alteration is a gain of Copy Number Variation (CNV). All the other genes have Single Nucleotide mutations. BRAF: v-raf murine sarcoma viral oncogene homolog B1, EGFR: epidermal growth factor receptor, RAS: rat sarcoma, PI3KCA: phosphoinositide 3-kinase catalytic alpha subunit, PIK3CB: phosphoinositide 3-kinase catalytic beta subunit, PIK3CG: phosphoinositide 3-kinase catalytic gamma subunit, PIK3R1: phosphoinositide 3-kinase regulatory subunit 1, PIK3R2: phosphoinositide 3-kinase regulatory subunit 2, PTEN: phosphatase/tensin homologue, THRB: thyroid hormone receptor beta, mTOR: mammalian

and also signaling pathways involved in CSCs are listed in Table 4.

Table 2. Expression survey of thyroid-specific genes in anaplastic thyroid cancer cell lines

Gene	Cell line																			
	8505c	SW1736	Cal-62	T235	T238	Uhth-104	ACT-1	HTh74	KAT18	TTAT	FRO81-2	HTh7	C643	BHT101	KTC-2	OCUT-1	OCUT-2	OCUT-3	OCUT-4	OCUT-5	OCUT-6
TSH-R	-							-					-			-	-	-	-	-	-
PAX8	-/+	+	+	+	+	+	+	+/-	+/-	+/-	+/-	-	-/+	-	-	+	+	+	+	+	+[a]
NIS	-	-											-								
TPO	-							-					-			-	-	-	-	-	-
Tg	-	+						-					-			-	-	-	-	-	-
THOX1	-																				
THOX2	-																				
TTF-1	+	-/+	-	-	-	+	+	-/+	-/+	-	-	-	-/+	-	-				+	+	
TTF2	-																				
Reference	(28, 29, 31)	(28, 29, 35)	(28, 29)	(28, 29)	(28, 29)	(28, 29)	(28, 29)	(28, 29)	(28, 29)	(28, 29)	(28, 29)	(28, 29)	(28, 29, 31, 35)	(28, 29)	(28, 29)	(25)	(25)	(25)	(25)	(25)	(25)

[a] pax8 mRNA (-), pax8 protein (+)
TSHR: thyroid stimulating hormone receptor, NIS: sodium/iodide symporter, TPO: thyroid proxidase, THOX1: thyroid oxidase 1, THOX2: thyroid oxidase 2, Tg: thyroglobulin, TTF-1: thyroid transcription factor 1, TTF-2: thyroid transcription factor 2, Pax8: paired box 8.

Table 3. Phenotypic survey of CSC markers in anaplastic thyroid cancer cell lines

CSC characteristics	Cell line				
	8505c	SW1736	ACT-1	C643	KTC-2
ABCG2		+		+	t
Oct-4		+		+	
ALDH	-		+		+
SOX2		+		+	
Nestin		-		-	
CD13	-		+		+
CD15	-		-		-
CD44	+		+		+
CD90	-		+		+
CD17	-		+		-
CD133	-	+	-	+	-
CD166	+		+		+
CD326	-		+		-
Tumor formation	+		+		-
Colony formation	+		+		-
References	(39)	(35, 40)	(39)	(35, 40)	(39)

ABCG2: ATP-binding cassette sub-family G, Oct4: octamer-binding transcription factor 4, SOX2: SRY-box containing gene 2, ALDH: aldehyde dehydrogenase.

Table 4. Summary of important signaling pathways inhibitors in ATC therapy*

PI3K/Akt/mTOR Pathway	Compound	Target	IC_{50}
PI3K inhibitor	LY294002	PI3Kα/δ/β	0.5 μM, 0.57 μM, 0.97 μM, respectively.
	BKM120	p110 α/β/δ/γ	52 nM, 166 nM, 116 nM, 262 nM, respectively.
	SAR245408	PI3Kα/δ/γ	39 nM, 36 nM, 23 nM, respectively.
	GDC-0980	PI3Kα/β/δ/γ	5 nM, 27 nM, 7 nM, 14 nM, respectively.
	CH5132799	PI3Kα	14 nM
mTOR inhibitor	Torin 1	mTORC1/2	2 nM, 10 nM respectively.
	KU-0063794	mTORC1/2	10 nM
	Palomid 529	mTORC1/2	
	WYE-687	mTORC1/pS6K, mTORC2/P-AKT	7 nM
	WAY-600	mTORC1/pS6K, mTORC2/P-AKT	9 nM
Dual PI3K/mTOR inhibitor	BEZ-235	p110α/γ/δ/β, mTOR (p70S6K)	4 nM, 5 nM, 7 nM, 75 nM, 6 nM, respectively.
	GSK-2126458	P110α/β/γ/δ, mTORC1/2	0.019 nM, 0.13 nM, 0.024 nM, 0.06 nM and 0.18 nM, 0.3 nM, respectively.
	PF-04691502	PI3Kα/β/δ/γ, mTOR	1.8 nM, 2.1 nM, 1.6 nM, 1.9 nM and 16 nM, respectively.
	PKI-587	PI3Kα/γ, mTOR	0.4 nM, 5.4 nM and 1.6 nM, respectively.
	PKI-402	PI3Kα/β/γ/δ, mTOR	2 nM, 7 nM, 16 nM, 14 nM and 3 nM, espectively.
Akt inhibitor	MK-2206 2HCl	Akt1/2/3	8 nM, 12 nM, 65 nM, respectively.
	Perifosine	Akt	4.7 μM
	GSK690693	Akt1/2/3	2 nM, 13 nM, 9 nM, respectively.
	GDC-0068	Akt1/2/3	5 nM, 18 nM, 8 nM, respectively.
	AT7867	Akt1/2/3, p70S6K/PKA, AGC kinase family	32 nM, 17 nM, 47 nM and 85 nM, 20 nM, respectively.
RAF/MEK/ERK Pathway			
RAF inhibitor	PLX4032	B-RAF (V600E)	31 nM
	GDC-0879	B-RAF	0.13 nM

Continuance of Table 4.

	PLX4720	B-RAF (V600E),c-Raf-1(Y340D and Y341D), B-RAF	13 nM
	Dabrafenib	B-RAF (V600)	0.8 nM
	AZ628	B-RAF, B-RAF (V600E), C-RAF-1	105 nM, 34 nM and 29 nM, respectively.
MEK inhibitor	trametinib	MEK1/2	0.92 nM, 1.8 nM, respectively.
	PD 184352	MEK1/2	17 nM
	Pimasertib	MEK1/2	0.005-2 μM
	AZD8330	MEK 1/2	7 nM
	PD318088	MEK1/2	
ERK inhibitor	SCH772984	ERK1/2	4 nM and 1 nM, respectively.
Stem Cell Pathways			
TGFβ inhibitor	LY2157299	TGFβ receptor I	56 nM
	SB 525334	TGFβ receptor I	14.3 nM
	LY2109761	TGF-β receptor type I/II	38 nM and 300 nM, respectively.
	Pirfenidone	TGF-β production	
	GW788388	ALK5, TGF-β receptor type I/II	18 nM
Wnt inhibitor	ICG-001	Wnt/β-catenin/TCF	3 μM
	IWP-2	Wnt secretion	27 nM
	IWR-1	Wnt pathway	180 nM
	KY02111	Wnt pathway	
	Wnt-C59	Wnt3A	74 pM
Noth inhibitor	RO4929097	γ-secretase	4 nM
	LY450139	γ-secretase, Aβ42, Aβ40, Aβ38	10.9 nM, 12.1 nM, 12.0 nM and 14.1 nM, respectively.
	YO-01027	γ-secretase, APPL	2.6 nM and 2.9 nM, respectively.
	LY-411575	γ-secretase	0.078 nM and 0.39 nM, respectively.
	LY2811376	β-secretase	239 nM-249 nM
Hedgehog inhibitor	GDC-0449	hedgehog	3 nM
	LDE225	Smoothened, Hedgehog signaling	1.3 nM (mouse) and 2.5 nM (human), respectively.
	LY2940680	Smoothened, Hedgehog signaling	
	PF-5274857	Smoothened, Hedgehog signaling	5.8 nM and 4.6 nM, respectively.
	SANT-1	Smoothened receptor, Smoothened agonist	1.2 nM and 20 nM, respectively.

* The sources of data are http://clinicaltrials.gov (17), http://medchemexpress.com (18) and http://selleckchem.com (19).

The impact of anti-cancer drugs is measured based on the fact that all cancer cells are equally dangerous. Most of these drugs only target non-CSCs and consequently they merely shrink the size of the tumor while being of little benefits to patients in long-term (52). CSCs constitute approximately 0.1% of all tumor cells, have limited ability to reproduce and have little contribution to a tumor diameter. Even though, these cells have an important role in relapse and resistance to chemotherapy and radiotherapy (53). Pharmacogenetics is a new branch of science which examines the individuals' potential response to different drugs and thus provides a fertile ground for answers to questions about people's different reactions to a variety of treatments (54,55). Hence, this knowledge can assist us in developing specific targets for ATC therapy. However, this knowledge suffers from the objection of putting less attention on the role of CSCs (56). Characteristics of CSCs originate from specific signaling pathways including Wnt, TGFβ, Notch and Hedgehog (57). It is thought that these cells could be potential targets for the anti-cancer drug in ATC targeted therapy (58). Reaching this goal requires strategies for true identification and isolation of CSCs because specific markers for these cells have not been reported yet (39). Preclinical and pharmacokinetic data have shown that chemotherapy that targets both CSCs and cancer cells reduces the risk of drug resistance and relapse by decreasing the number of CSCs.

Challenges

Personalized medicine has been gradually becoming more common in medicine and seems to be one of the most important medical fields in the future. Nevertheless, its use potentially poses serious

challenges in data privacy for patients mainly due to revealing the patient's susceptibilities to different types of diseases according to genome sequencing data (1). Hence, considering ethical concerns are highly crucial. The other concern is the high volume and validity of whole genome sequencing (WGS) as well as whole exome sequencing (WES) data which necessitate the use of upgraded software and appropriate infrastructures (6). Personalized medicine in cancer treatment as an efficient approach is based on individual patient characteristics. However, so far its clinical application is limited only to a few genes that due to the heterogeneous nature of cancer require further progress in the field (55). This problem would be more complicated when we consider the heterogeneity of ATC cell lines as the basis of our current knowledge from ATC (37). Also, in order to achieve more effective treatment strategies and prevent drug resistance and relapse, personalized medicine needs to progress so that it is able to identify CSCs for their effective targeting (59).

Future prospects

Personalized medicine has opened a new horizon for cancer treatment. However, for its practical application, we still need further progress in the field of basic sciences, pharmacogenetics and drug design. Researchers have been always looking for new ways for efficient diagnosis and treatment of cancer so as to reduce cost and side effects in patients. In recent years, methods of cancer therapy have been gradually changing from conventional therapy with toxic and nonspecific chemicals to smart and effective use of targeted therapy. The importance of personalized medicine in ATC therapy is related to its deep discrimination of disease nature. This allows oncologists to be aware of cancer's molecular stage even before the onset of clinical symptoms, and, consequently, appropriate treatment can be applied. Actually, in individualized medicine, the treatment policy could be tailored according to a patient's background information which in turn would result in reducing treatment cost, side effects, drug resistance and risk of failure. Personalized medicine can also be effective in the management of ATC patients and the prevention and early intervention, especially for high-risk people (14,23,48). To pave the way for personalized medicine, human specimens are an invaluable source of data for biomodeling of diagnostic systems. Hence, the establishment of standardized biobanking would be the basis for facilitated data mining (10).

Conclusion

Various types of genetic variations cause a difference in human genomes between individuals. To appoint the best strategy for ATC treatment, personalized medicine uses different data types such as a patient's genetics and clinical background to elucidate the molecular basis of the disease. This approach will inevitably reduce patients' cost due to prescribing appropriate dose and ruling out ineffective medication options. In practice, it is compulsory to pay more attention to CSCs as the origin of ATC in pharmacogenetics studies in order to improve the quality of personalized medicine. Notably, the practical application of personalized medicine is still in its infancy and therefore performing well-designed randomized clinical trials will make a solid ground for its future expansion. Collectively, to achieve these goals, a widespread and systemic collaboration between biologists and clinicians is essential to ultimately create a breakthrough in targeted therapy and personalized medicine of ATC.

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