Minireview Article

The effect of molecular markers in advanced thyroid cancers

Abstract

Introduction

Molecular markers play an important role in the diagnosis, prognosis and treatment of thyroid cancers, as in many types of cancer.

Our aim in this study is to investigate the effect of molecular markers in the follow-up and treatment of advanced thyroid cancers.

For this purpose, the results obtained in recent articles investigating molecular markers in the follow-up and treatment of advanced thyroid cancers were evaluated and new findings were presented.

Conclusion

According to the results of our study, molecular markers have very important effects in the treatment of advanced thyroid cancers. It can already be said that future studies on this subject will further increase the treatment possibilities and prolong survival in advanced thyroid cancers.

Keywords: molecular markers, advanced thyroid cancer.

Introduction

In today's world, molecular markers (MM) are in every field of medicine. As a result of numerous studies on this subject, it is increasingly involved in the diagnosis, follow-up and treatment of diseases, and accordingly, the lifespan of human beings is prolonged.

Many studies have demonstrated the importance of MM in the diagnosis, screening tests and follow-up of cancers[1,2,3]. New methods have been proposed with noninvasive MMs in the diagnosis and follow-up of TC[1], and new algorithms have been developed[4].

In a review study by Prete et al., it was stated that MMs play an important role in diagnosis risk assessment and targeted therapy as a result of studies on genetic characteristics of TCs in recent years[5]. A new genetic molecular profile of medullary thyroid cancers (MTC) has been revealed according to their role in RET mutations. Accordingly, it has been stated that important innovations have emerged in clinical applications. Micro RNAs have an important place in the pathogenesis of TCs. In a study by Ghafouri et al., the role of micro RNAs in the pathogenesis of TCs was examined, and it was stated that whether the tumor is malignant or not with noninvasive serum MM tests can easily be determined, and that there are microRNAs that are effective in TC-related MAPK and RET gene pathways[6]. It has been emphasized that some mRNAs have proven therapeutic effects in TC xenograft models.

In a review study by Nylen et al., it was emphasized that MM should be taken as a guide in the follow-up of TC[7]

In a review study by Sandhub et al. on cancer MMs, it was stated that the cause of cancer was molecular changes caused by specific mutations, and their importance in early diagnosis and targeted therapy was emphasized. In addition, it has been reported that BRAF and RAS point mutations, RET/PTC and PAX8/peroxisome-proliferator activated receptor γ rearrengements are found in papillary and follicular cancers, which are the most common types of TC [8].

In a study by Kyriakopoulos et al., the effects of histopathological, immunohistochemical, genetic and MMs on diagnosis and treatment in neuroendocrine tumors were investigated, and it was reported that targeted drugs such as Everolimus and sunitunib were developed in this way[9]. In a review study conducted by Ullmann et al., although less aggressive treatment methods are recommended for differentiated thyroid cancers (DTC) according to ATA criteria, there may be an increase in recurrence and death rates, therefore, a different follow-up and treatment is required in these cases.Therefore, it has been reported that a different follow-up and treatment should be continued in these cases[10]. It has been stated that by determining the molecular genetic and epigenetic structure of the tumor, targeted therapy such as tyrosine kinase inhibitors (TKI) may be more effective in these cases.

In a study conducted by Bible et al., it was reported that in advanced stage TCs, survival can be prolonged in patients with anticancer immunotherapy when the molecular structure of the tumor is determined[11].

In a study by Naoum et al., it was stated that 15-20% of DTCs, 30% MTCs and almost all of anaplastic thyroid cancers (ATC) are resistant to treatment after surgery[12]. in radioactive iodine (RAI) resistant DTC cases in chemotherapy; Sorafenib and Lenvatinib are the most commonly used advanced treatment methods in MTCs. Most importantly, it has been determined that there are dynamic immune activities in the microenvironment of the tumor, and cancer immunotherapy to be performed in addition to chemotherapy can prevent this molecular escape. Apart from the MAPK pathway; the clinical importance of the PI3K pathway, ALK translocations and HER2/3 receptors in the treatment of advanced TCs was discussed and the role of immunotherapy was presented.

In a study by Dunn et al., it was shown that when a BRAF mutant is detected in RAI-resistant TCs, molecular redifferentiation of the tumor can be achieved with Vemurafenib and RAI uptake can be increased [13]. Thyroglobulin values in 4 of 10 RAI-resistant patients treated with vemurafenib after treatment decreased from an average of 30.6 to 1.0 ng/ml.

Buffet et al., in a study they conducted, as a MM in TCs with BRAF mutations; they reported that DUSP5 and DUSP6 are 2 extracellular signal-regulated kinase (ERK)-specific phosphatases that show increased activation of MAPK signaling[14]. According to the results obtained in the study, especially in BRAFV600 papillary thyroid cancer (PTC) cell line models, it was stated that DUSP5 and DUSP6 have protumorogenic properties and MMs showing the activation of the MAPK pathway.

In a study by Pozdeyev et al., they determined genetic landscaping in 779 advanced stage DTC and ATC and performed genetic analyzes to reveal their potential prognostic and therapeutic importance[15]. They found the most genetic changes in ATCs and more in Pediatric PTCs than in other cancer types. In these cases, DNA mismatch repair failure and increased APOBECH cytidine deaminase activity were detected, together with high mutational density. In ATCs, CDKN2A CDKN2B mutations, CCNE1 amplifications, KDR, KIT and PDGFRA gene kinase amplifications to the receptor tyrosine, immune evation amplification of CD274, PDCD1LG2 and JAK2 genes, activation of point mutations in small GTPase RAC1 were observed.In a study by Untch et al., in HRAS-driven poorly differentiated and ATC mice, they tried treatment with FT1Tipifarnib,although they provided tumor regression and prolongation of survival, early and late resistance emerged after treatment[16]. Although RAS - MAPK signal adaptive reactivation with selective RTK inhibitors (such as EGFR, FGFR) was ineffective in vivo in these cases, positive results were obtained with the combination of MEK inhibitor AZD6244 and tipifarnib.

In a study conducted by Priya et al. on the follow-up and treatment of MTC cases with distant metastases, it was reported that positive results were obtained with Vandetanib and cabozantinib for effective targeted therapy in the molecular pathway of the tumor, and it was also effective in targeted radionuclide therapy as an alternative method[17].In a review study

by Schmidbauer et al. emphasized the importance of tyrosine kinase inhibitors in the treatment of advanced DTCs[18].In a study by Beadnell et al., c-SRC was stated to be a key mediator and therapeutic target in TCs, and MAPK pathway activation was increased, probably by b-RAF and c-RAF dimerization, in 4 different cell cultures with 30-fold more acquired Src inhibitor dasatinib resistance, It has been reported that MEK1/2 and ERK1/2 inhibitors combined are more effective in induction of apoptosis and inhibition of growth [19].In a study by Allegri et al. on the effect of nutraceuticals on ATC cell lines, the anti-cancer effect of curcumin was demonstrated in mRNA analyzes [20]. After curcumin treatment, hsa-miR-221, hsa-miR-222, hsa-miR-21 There was a significant reduction in hsa-miR-146b levels.

Gene fusions, which play an important role in cancer pathogenesis, may have prognostic and therapeutic importance in TCs. In a study by Yakushina et al., gene fusions can be found between 1 - 80% depending on the type in TCs, new gene fusions are detected in TCs with massive sequencing technologies (MST) and their detailed characteristics are revealed (RET fusions, NTRK fusions, BRAF fusions ,ALK fusions, PAX8/PPARG fusions] have been reported to inhibit some fusions with targeted therapies[21].In a study by Moon et al., it was reported that the co-existence of BRAFV600E and TERT Promoter mutations in cases with poor clinical results in PTCs creates a synergistic effect and the analysis of these molecules in PTC cases is important in the prognostic and therapeutic approach [22].In a study by Liu et al., it was emphasized that co-detection of BRAFV600E and TERT promoter mutations is a very effective method to predict a decrease in RAI uptake in relapsed PTC cases[23].

In a study by Lombargo et al., it was reported that there is an increase in the expression of hTERT mRNAs in ATCs, hTERT promoting mutations are common, and the effects of anti-hTERT siRNA-loaded nanoparticles on growth blocking in ATC xenografts were investigated[24]. According to the results obtained in the study, it was stated that such anti-TERT nanoparticle treatment in ATCs could be effective.

Conclusion

According to the results of our study, MMs have very important effects in the treatment of advanced TCs. It can already be said that future studies on this subject will further increase the treatment possibilities and prolong survival in advanced TCs.

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