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Review-Derleme

New advances in the diagnosis, medical management and follow-up of medullary thyroid cancer

Medüller tiroid kanserinin tanı, takip ve medikal tedavisindeki yeni gelişmeler

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Abstract

Medullary thyroid cancer (MTC), which behaves more aggressively than the other well-differentiated thyroid cancers of follicular cell origin, accounts for 10% of all thyroid cancer-related deaths. Most MTCs are sporadic however approximately 25% is hereditary as part of the multiple endocrine neoplasia syndrome type 2 (MEN 2a and 2b). Both sporadic and inherited forms of MTC have a propensity for lymphatic and distant metastasis. The primary treatment of MTC is total thyroidectomy and removal of all neoplastic tissues present in the neck. After surgical treatment, measurements of serum calcitonin and carcinoembryonic antigen are of paramount importance in the postoperative follow-up since these markers reflect the presence of persistent or recurrent disease. Systemic chemotherapy with dacarbazine, 5-fluorouracil and doxorubicin, either alone or in combination, has shown very limited efficacy, producing only partial responses in the range of 10-20% and of short duration. Although current treatment options for patients with metastatic and refractory MTC are limited, recent advances in molecular oncology have fostered the invention of novel small molecules which target specific pathways which are thought to be essential in the MTC carcinogenesis. Several kinase inhibitors are currently under evaluation and preliminary results are promising.

Keywords: Medullary thyroid cancer, thyrosine kinase inhibitors

Özet

Medüller Tiroid Kanseri (MTC) folikül hücrelerinden kaynaklanan iyi diferansiye tiroid kanserlerinden daha agresif seyreder ve tiroid hastalıklarına bağlı oluşan ölümlerin yaklaşık %10'unu oluşturur. MTC'rinin çoğu sporadik olarak ortaya çıkar fakat %25'i MEN Tip 2'nin bir parçası olarak herediter olabilir. MTC'nin her 2 formunda da lenf nodu metastazı ve uzak metastaz görülebilir. Hem sporadik hem de herediter formun primer tedavisi total tiroidektomi ve boyundaki tümör dokusunun tamamının çıkarılmasıdır. Total tiroidektomi sonrası serum CT (kalsitonin) ve CEA ölçümü MTC hastaların operasyon sonrası takibinde önemlidir çünkü bu belirteçlerdeki artış persistan veya rekürren hastalık olduğunu düşündürür. Dakarbazin, 5-florourasil ve doksorubisinle (tek veya kombinasyon şeklinde) sistemik kemoterapinin etkisi oldukça sınırlıdır, kısmi cevap %10-20 arasındadır ve kısa sürelidir. Metastatik veya rekürren MTC hastalarında günümüzde tedavi seçenekleri sınırlı olmasına rağmen moleküler onkolojideki son ilerlemeler MTC tümör oluşumunda önemli olduğu düşünülen spesifik yolaklara yönelik küçük moleküllerin gelişimini hızlandırmıştır. Bazı kinaz inhibitörleri MTC'lerinde denenmektedir ve ön sonuçlar ümit vericidir.

Anahtar sözcükler: Medüller tiroid kanseri, tirozin kinaz inhibitörleri

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Medullary thyroid cancer

Medullary thyroid cancer (MTC) is a relatively rare neuroendocrine tumor which arises from the calcitonin-secreting parafollicular C cells of the thyroid gland. MTC accounts for 5-10% of thyroid malignancies and secretes calcitonin (CT) and carcinoembryogenic antigen (CEA) in large amounts [1, 2]. Local and/or distant metastasis may be present in up to 50% of patients at intial presentation. Sporadic variant is the most common form with a rate of 65-75%. This form does not have mutations in the germline RET proto-oncogenes however in 25% of the cases it arises from a single parafollicular cell (monoclonal origin) or occurs de novo secondary to unexplained mechanisms which lead to single or multiple somatic mutations in the RET proto-oncogene [2-4]. Unlike the sporadic form, hereditary MTC is associated with RET proto-oncogene germline mutations and is more common in patients younger than 20 years of age. Similar to the sporadic variant, hereditary MTC has a propensity for lymphatic and distant metastasis, including the mediastinal lymph nodes, liver, bone and lungs with a high morbidity and mortality. Hereditary MTC occurs as a part of the multiple endocrinal neoplasia 2 (MEN2) syndrome. Identification of MTC is very important in children with MEN2b due to the risk of metastatic disease in the early years of life. MTC associated with MEN2b is described as the most aggresive form. Lymph node metastasis is common in the early years of life, with distant metastasis occuring in the second decade. In patients with metastatic disease, death usually occurs in the third or fourth decade [4-7]. In MEN2a syndrome, the prevalance of MTC is low prior to age 10 however it increases with age. In these patients, hyperpigmented pruritic lesions, known as ‘‘notalgia’,’can be detected on the shoulders and the back [8]. Since RET proto-oncogene mutations are identified in 4-10% of patients with sporadic disease, these cases might have a hereditary component. For this reason, analysis of RET proto-oncogene should be performed in sporadic MTC patients, and if a mutation is detected, all first-degree relatives should also be screened with genetic analysis [9]. Although controversy exists about the timing of prophylactic thyroidectomy in RET mutation carriers who have a family history of MEN2, prophylactic thyroidectomy is recommended in children with MEN2A at the age of around 5 years. Since MTC in MEN2b behaves more aggresively, thyroidectomy should be performed within six months after birth [10].

Preoperative evaluation

Once the diagnosis of MTC is made, patients should be first evaluated for the extent of the disease and the presence of any comorbid conditions such as hyperparathyroidism and pheochromocytoma. Preoperatively, neck ultrasonography should be performed in all patients. In patients with lymph node metastasis or elevated CT levels (>400pg/mL), the neck, thorax and liver should be evaluated with either computed tomography or magnetic resonance imaging [4]. While bilateral or multicentric tumor involvement is found in 30% of the sporadic cases, this approximates 100% in the hereditary cases. After total thyroidectomy, patients should be given thyroxin replacement therapy keeping in mind that TSH suppression is not necessary and maintaining the TSH level within the normal range is sufficient.

Follow-up

MTC derives from the neural crest cells which form part of the amine precursor uptake and decarboxylation (APUD) system. Therefore this tumor also synthesizes a number of neuroendocrine markers such as chromogranin-A, neuron spesific enolase and serotonin in addition to CT and CEA [11]. CT is an important follow-up marker. Since the half life of CT is more than 30 hr, measurements of this marker should be performed 2-3 months

after surgery depending on the preoperative serum levels [4]. CT levels, determined by immunoradiometric assay (IRMA), less than 10 pg/mL is regarded as normal [12]. It is important to note that the CT levels may also be elevated in about 15% of the patients with certain conditions such as advanced kidney failure, autoimmune thyroid diseases, follicular cancers, chronic hypercalcemia, hypergastrinemia and pulmonary or pancreatic neuroendocrine tumors. In addition to this, basal CT levels may be normal in some patients with minimal C-cell disease but increases after provocative tests [8]. Pentagastrin-induced CT secretion is a widely used provocative test [13]. In the morning of an overnight fasting, pentagastrin 0.5µg/kg diluted in 5 mL serum saline is administered in 3 minutes when patient is in the supine position. CT measurements are performed 3 and 5 minutes before and after the injection. The peak levels are obtained within 3 minutes in most patients. This test is contraindicated in pregnant patients and in patients with asthma, coronary heart disease, severe hypertension or duodenal ulcer. The adverse effects of this test are dizziness, tachycardia, bradycardia, nausea and substernal discomfort. Pentagastrin-stimulated CT levels are less than 10 pg/mL in 80% of the patients and less than 50 pg/mL in the remaning 20%. The unmeasurably low levels of basal CT during the postoperative period is a strong indicator for the complete remission of the disease. However, remission should be confirmed with the procovative test by demonstrating unmeasurable or no elevation of CT levels. No further imaging is necessary after the confirmation of remission is made. CT levels should be measured every 6 months for the first 2 years and then once every year. On the other hand, measurable basal or provocative test-induced CT levels imply the persistence of the disease and the imaging modalities may not detect the disease unless the CT level is greater than 150 pg/mL [14]. In such cases, the cervical region should be carefully investigated with ultrasonography since local cervical metastasis is common [4]. Distant metastasis is very rare in these cases. In the presence of suspicious lymph node metastasis, fine needle aspiration biopsy and CT measurements in the aspirate should be performed in order to confirm the diagnosis [8]. For the screening and follow-up of patients, omeprazole-based tests may also be used to increase CT secretion [15]. The omeprazol-based test is easy to perform and more advantageous than the pentagastrin stimulation test as it does not cause complications, including retrosternal discomfort, nausea, vomitting, metallic taste, abdominal cramps, esophageal spasm and tachycardia. Today, curative treatment of MTC can be achieved with complete surgical resection if the diease is confined to the neck. Nevertheless, complete resection can be very difficult. Most MTC patients present with a palpable thyroid nodule and ipsilateral (80%) or contralateral lymph node metastasis (40%) or distant metastasis to the liver, bone or lungs. The most appropriate surgical procedure for the localised MTC is total thyroidectomy and central (level VI and VII) and bilateral (level II and V) lymph node dissection. Curative surgery is difficult when CT level is less than 5 pg/mL and the complete cure can be achieved in 25% of selected patients [1-4, 16]. Total thyroidectomy with central and bilateral neck dissection is also the procedure of choice in patients with local metastatic disease. Many difficulties exist in the management of patients with incomplete resection and metastatic disease. Many theraupetic agents have been suggested and tested. However, MTC is characterized by slow growth even in the presence of metastasis. Since chemotherapy generally shows its direct effect on rapidly growing cancer cells, it is difficult to develop a chemotherapeutic agent for this slow-growing tumor [2, 4, 16]. Radiotherapy is used to provide palliation for localized bone metastasis or mediastinal or extensive neck lesions. Although radiotherapy has been shown to be effective in preventing and controlling the cervical and mediastinal complications of MTC, no evidence exists that it prolongs life [2]. There is still no effective treatment for the persistant or recurrent MTC. Chemotherapeutic agents such as dacarbazine, fluorourasil ve doxorubicin provide partial and short-term response in 10-20% of patients. They neither produce complete remission nor have positive effect on survival. Dacarbazine-based chemotherapy can be used if there is no other treatment option for these cases [2, 4, 16].

New advances in the medical therapy

Thyrosine kinase inhibitors (TKIs) are small molecules which bind to adenosine triphosphate binding sites. Occupation of these sites by TKIs inhibits autophosphorylation of thyrosine kinase and its activation which eventually inhibits further activation of the intracellular pathways. Kinase inhibitors are the most studied agents in phase II studies and the results of these studies show the potential of TKIs (motesanib, vandetanib, XL184, sorafenib, sunitinib, axitinib) for possible clinical use. Most TKIs also inhibit vascular endothelial growth factor receptors (VEGFRs). Being a very vascular tumor, MTC expresses large amounts of VEGFRs therefore the use of VEGFR inhibitors may provide an effective targeted therapy [1-4, 16-19]. Vandetanib (Zactima) is a selective inhibitor of VEGFR-2 and less commonly EGFR. Vandetanib inhibits the VEGF-mediated endothelial cell migration and proliferation. Reportedly, vandetanib 300 mg/day stabilized the disease in 9 of 30 patients with hereditary metastatic MTC, produced partial response in 6 and reduced CT level by more than 50% within 6 weeks in 9 patients [20]. Vandetanib 100 mg/day provided partial response in 3 (16%) out of 19 patients with advanced MTC, stabilized the disease in 10 patients (53%) within 24 weeks (cumulative response, 68%), reduced CT and CEA levels by more than 50% in 3 (16%) and 1 (%5) out of 19 patients, respectively [21]. The side effects of this drug are diarrhea, nausea, skin rash, fatigue, hypertension and asymptomatic QTc prolongation, but fortunately these side efects are less common with low doses [20, 21]. In a recent phase III trial (ZETA trial), vandetanib 300 mg and placebo were given to 231 and 100 MTC patients, respectively and all patients were followed up for 90 months. According to the results of this trial, the rate of disease stabilization was significantly higher in the vandetanib group than the placebo group and partial responses were observed in 45% (104 patients) and 13% (13 patients) in the Vandetanib and placebo groups, respectively. Reduction in CT and CEA levels were observed in 69% and 52% of the patients, respectively. The drug had to be discontinued in 12% of the patients due to its side-effects [22]. Motesanib is a multikinase inhibitor which targets VEGF, platelet derived growth factor and Kit receptors. It has antiangiogenic and direct antitumor activities. In a phase II trial including 83 patients, motesanib treatment resulted in reduction of tumor burden in more than 80% of the patients within 32 weeks [23]. In another study which included 91 patients who received motesanib, 2% of patients achieved objective response and 48% had durable stable disease however 30% of patients required a higher L-thyroxine dosage. The most common treatment-related adverse events were diarrhea, hypertension, fatigue, dizziness, nausea, vomiting and headache [24]. Axitinib is a potent VEGFR-1, 2 and 3 inhibitor. It does not cause RET inhibition. In a study which included 11 patients with grade 4 MTC, axitinib treatment resulted in partial response in 2 patients (%20), and stable disease in 5 patients (%50). The side affects were hypertension and proteinuria [25]. XL-184 is a multikinase inhibitor which targets RET and VEGFR. XL-184 produced partial response in 55% of the 22 patients with advanced MTC. A phase III trial has recently been initiated [26]. TKIs such as sunitinib and sorafenib have been approved for the treatment of renal cell cancer. Treatment with sunitinib which is a RET and VEGFR inhibitor has also been shown to induce partial response in 13% of the patients with refractory MTC and stable disease in 83%. The side effects are fatigue, palmar-plantar erythrodysesthesia, neutropenia and hypertension [27]. Sorafenib is a VEGFR-2 and 3, RET, serine kinase and BRAF inhibitor. No sufficent evidence exists to support its use in MTC. In one study, imatinib (Glivec) has been shown to be ineffective in 15 patients with advanced MTC [28] and in another study, it provided disease stabilization in only one out of 9 patients for 12 months [29]. Gefitinib ve erlotinib are EGFR inhibitors. Although they are more commonly used in the treatment of differantiated thyroid cancers, the recent discovery of EGFR overexpression by MTC has led to the iniatiation of the studies on these agents for MTC [30]. Targeted treatment with angiogenesis, kinase inhibitors and inhibition of RET mutation phosphorylation appears to be very promising for the treatment of MTC patients. Having a partial response and maintenance of disease stability are generally achievable with the kinase inhibitors.

Another expectation for RET inhibitors is to decrease the serum CT levels by inhibition of gene expression without reducing the tumor size. Lack of complete response and improvement on patient survival during treatment imply the aggressiveness of advanced MTC. A major problem in interpreting the effectiveness of TKIs is due to the fact that few patients were included in the related studies and the results of these studies are reported as ''abstract'' presentations. Somatostatin analogues have been used in the treatment of advanced MTC. However, they are reported to be ineffective in terms of tumor regression, recurrence rates, survival and mortality [31]. Nevertheless, these agents could be alternative to anticholinergics for the management of diarrhea in patients with metastatic MTC [32]. There are studies which have focused on 131I-CEAradioimmunotherapy and IL-12 gene transfer. In less radiosensitive tumors, tumor tissue uptake can be enhanced by ''pretargeting''. In a study, 29 patients with advanced MTC received an anti-CEA specific monoclonal antibody, followed 4 days later by a 131I-labeled bivalent hapten. When compared with controls, overall survival was significantly longer in treated patients with high risk (110 vs 61 months). However, severe side effects were observed; thrombocytopenia in 17% of patients, neutropenia in 15% and myelodysplastic syndrome in 3%. Therefore, treatment with these agents reported to be less attractive in patients with MTC [33]. IL-12 plays a central role in the activation of antitumor immune response. Systemic injection of recombinant IL-12 is not appropriate because of its toxicity. Recent data indicates that intratumoral injection of IL-12 in patients with cervical squamous cell cancer enhances natural killer cell activity and immunuologic response, which in turn induce tumor elimination. Thus, IL-12-based immunotherapy seems very promising for the future [34]. Bortezomib inhibits a chymotyripsin-like activity in the 26S proteasome, which leads to cell-cycle arrest and apoptosis. This drug has been approved for the treatment of multiple myeloma. Also, it induces apoptosis in MTC cells and sensitizes thyroid carcinoma cells to doxorubicin. Bortezomib is recommended for the treatment of patients with MTC but it has not been applied in clinical use [35]. Another potential ''targetted'' therapy for MTC would be the use of inhibitors of glycogen synthase kinase-3β (GSK-3β) which is an important regulator of cell proliferation and survival. Lithium is a GSK-3β inhibitor and is currently being investigated in phase II clinical trials [36]. Also, a phase I study which investigates the Raf-1/mitogen-regulated extracellular kinase (MEK)/extracellular regulated kinase (ERK) signaling pathway is being conducted. Valproic acid and suberoylanilide hydroxamic acid (SAHA) which are known as histone deacetylase (HDAC) inhibitors are strong activators of the Notch-1 (a transmembrane receptor) and these agents have been defined as epigenetic cancer drugs for MTC. HDAC inhibitors activates the apoptosis-related genes. Activation of Notch-1 induces cellular differentiation and apoptosis in MTC cells. The efficacy of valproic acid in patients with MTC is being investigated [36]. Vorinostat (SAHA) has been tested in 3 patients and found to be ineffective [37]. Capecitabine, a derivative of doxifluridine carbamate, is converted to 5-fluorouracil. Selective activation of this drug in the target tumor tissue reduces its systemic toxicity. It can be used in 5-fluorouracil resistant cases. Treatment with capecitabine in patients with metastatic MTC has been shown to result in disease stabilization and reduction of CT and CEA levels by 80% [38, 39]. This drug is commonly used in patients with metastatic breast cancer and it is belived that it has a promising future in the treatment of MTC. Diarrhea and hand-foot syndrome are the most common side effets [16]. Indomethacin is a nonselective cyclooxygenase inhibitor. It exerts its effects through a mechanism not involving the reduction of intracellular prostaglandins, possibly extenuating the S-phase proggresion via inhibition of the Rb protein expression. It has been reported that treatment with indomethacin only (3x50 mg/day) in three patients with metastatic MCT resulted in disappearance of the tumor on imaging studies in one patient, regression of the tumor mass, metastases and reduction of CT levels in another and no response in one patient [16]. Further studies are required in order to investigate the effects of this drug on MTC. While rofecoxib which is a cyclooxygenase inhibitor-2 has been demonstrated to sensitize the MTC cells to doxorubicin in vitro [40], celecoxib, a similar cyclooxygenase

inhibitor-2, has shown no effect on metastatic MTC [41]. Treatment with the four cardiac hormones in pharmacologic doses (atrial natriuretic peptide, vessel dilator, long-acting natriuretic peptide and kaliuretic peptide) has indicated that these hormones have potent anticancer effects in cell cultures. Therefore, ANP derivatives can be used if the MTC cells have natriuretic receptors [42]. ‘‘Cautleya gracilis’’is a high-altitude tropical ginger native to the eastern Himalayas during monsoon season. Interestingly, the extract of this plant has shown anticancer activity in both MTC cell lines and severely immunocompromized MTC-transplanted mice. The prominent feature of the extract of this plant is the disruption of the globular cell structure of the MTC, which in turn destroys most MTC cells. The effective components of this extract and its toxicity should be investigated first before it is used on clinical grounds [43].

In conclusion, there is still no effective medication available for the treatment of MTC. To investigate the role of many TKIs in advanced MTC, phase II trials are still continuing and some of the trials are at the phase III stage. It has been demonstrated that TKIs provide disease stabilization and improve quality of life with relatively few side-effects. Also, radioimmunotherapy seems promising for the treatment of MTC patients with bone metastases. However, the primary expectation of these studies is the discovery of a method or medication which can induce complete remission of MTC and improved patient survival.

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