Thyroid Cancers: Surgery and Therapies

Subjects: Oncology

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Differentiated thyroid cancers (DTC) are commonly and successfully treated with total thyroidectomy plus/minus radioiodine therapy (RAI). Medullary thyroid cancer (MTC) is only treated with surgery but only intrathyroidal tumors are cured. The worst prognosis is for anaplastic (ATC) and poorly differentiated thyroid cancer (PDTC). Whenever a local or metastatic advanced disease is present, other treatments are required, varying from local to systemic therapies. In the last decade, the efficacy of the targeted therapies and, in particular, tyrosine kinase inhibitors (TKIs) has been demonstrated.

differentiated thyroid cancer | medullary thyroid cancer | targeted therapy | tyrosine kinase inhibitors | sorafenib | lenvatinib | vandetanib | cabozantinib | selpercatinib | pralsetinib

1. Introduction

Thyroid cancer (TC) is the most common endocrine neoplasia and represents approximately 2.9% of all new cancer cases in the United States each year [1]. In the last three decades, the incidence rate of TC has continuously increased all over the world and, although it was mainly attributed to an increased detection rate of small tumors, a real increase of TC was also identified as demonstrated by an increase of larger tumors too [2]. In this review, we discuss the different types of current and future systemic therapies that can be used in different types of advanced and metastatic TC. A brief description of the different histotypes of TC and signaling pathways is required to better understand the different types of targeted therapies available.

2. Differentiated Thyroid Cancer

Differentiated thyroid cancer (DTC) is the most frequent tumor type, representing > 90% of all TC [3]. It originates from follicular cells and includes the three main subtypes: papillary (PTC), follicular (FTC), and Hürthle cell carcinoma (HTC). Despite the overall survival (OS) rate being 98.3% at 5 years for the majority of cases [1], local recurrence (thyroid bed or cervical lymph nodes) occurs in about 20% of patients and distant metastasis in approximately 10%, lungs being the most common site of metastases (50%) followed by bone (25%) [4]. In one third of advanced DTC, the metastatic lesions lose the ability to take up iodine (RAI-refractory DTC) with subsequently no efficacy of radioiodine with ^{131}I (RAI) and decrease of OS rate (less than 10% at 10 years) [5]. As well as RAI-refractoriness, the stage of neoplastic disease at diagnosis can also predict mortality. In particular,

according to the 8th Edition of the American Joint Committee on Cancer TNM classification [6], an excellent prognosis is reported for stage I and II of DTC with an overall disease-specific survival of >75% to 95% at 10 years that falls to 60% to <50% for stage III and IV, respectively.

Poorly differentiated thyroid cancer (PDTC) is a heterogeneous group that includes those TCs that, according to the Turin classification, lose the papillary nuclear features and have a solid, insular, or trabecular growth pattern with an increased number of mitoses and necrosis [7][8]. PDTC in respect with other DTCs has a higher risk of persistence/recurrence both in the neck and at distant localization (lung, liver, bone, and brain) and a higher mortality [9][10].

According to the most recent guidelines [11], the gold standard of treatment for DTC and PDTC is represented by surgery (total or near-total thyroidectomy). Before cervical surgery, an accurate ultrasound evaluation of neck and mediastinum should be performed in all patients to identify lymphadenopathy that should be surgically removed simultaneously with the thyroid. Patients with intermediate or high risk of recurrent disease or with distant metastases should be treated with a subsequent ^{131}I therapy and thyroid stimulating hormone (TSH) suppressive therapy [11].

For patients with metastatic DTC that progresses despite standard therapies, systemic cytotoxic chemotherapy has been evaluated both in phase 2 and retrospective studies but, to date, there is no role for its routinary use. Doxorubicin (recommended dosage: 60–75 mg/m^2 every 3 weeks) remains the single most effective and approved cytotoxic chemotherapy for the treatment of RAI-refractory DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease but it should be used only when cases are not manageable with other approaches. Nowadays, as described in following paragraphs, targeted therapies able to inhibit abnormal activated tyrosine kinases (TKI) represent the systemic therapies that should be used as first line in metastatic TCs.

Regarding adjuvant neck/thyroid bed/locoregional external beam radiation (EBRT), its application in DTC/PDTC patients remains controversial and, according to the literature, there is no role for routine adjuvant EBRT to the neck in DTC patients, especially when an initial complete surgical removal of the tumor is achieved. However, EBRT should be considered for those patients undergoing multiple and frequent neck re-operations for palliation of locoregional recurrences and, in some cases of bone metastases especially to control the pain that is frequently associated with these lesions. [12][13].

Recently, several studies have reported the efficacy of other localized treatments with thermal (radiofrequency or cryo-) ablation [14][15], ethanol ablation [16][17], or chemo-embolization [18] on single/few metastases or on locoregional persistence/recurrence of neoplastic disease. These kinds of treatments can be offered to those patients with high risk for surgery, those who refuse to undergo repeated surgeries, and those with oligometastatic but progressing disease. The possibility of performing these localized treatments should always be taken into consideration before the initiation of systemic treatment [11].

3. Anaplastic Thyroid Cancer

Anaplastic thyroid carcinoma (ATC) represents about 1% of all TC and is the most aggressive thyroid tumor, accounting for the majority of all TC death [19]. The ATC is a rare undifferentiated form of TC, unable to take up ^{131}I and with no chance of cure [19][20]. It is associated with a rapid and lethal progression, especially at a local level. At the time of diagnosis, 30–40% of patients have locoregional metastases and/or vocal cord paralysis and 70% have direct invasion of local tissue including the trachea, muscle, esophagus, and larynx. Distant metastasis usually appears in those patients receiving aggressive treatments and can involve multiple sites including the lungs (50–80%), bone, skin, and brain (6–12%) [21]. Median survival time in ATC patients is approximately 5–6 months, and only 10–15% of patients survive 2 years after presentation [19][21]. Due to this fatal outcome, TNM classification of the American Joint Committee on Cancer provides only stage IV for this tumor, which can be subdivided into IVA when the tumor is confined to the thyroid, IVB when the tumor is present beyond the thyroid gland but confined in the neck, and IVC when distant metastases are present.

The initial management of ATC should include the evaluation of airways' stability to establish whether an immediate intervention is necessary, and the evaluation of full resectability (R0) of primary tumor, since the only debulking of the cancer does not improve the patient's outcome. Therefore, surgery should be of first choice when a full resection of tumor can be obtained and when no distant metastases are identified. About 2 to 4 weeks after surgery, chemoradiation should be offered to the patient, while unresectable ATC should be treated directly with radiation therapy (> 60 Gy on primary tumor) and adjuvant chemotherapy. Standard cytotoxic chemotherapy includes taxane, platinum-based drugs, and doxorubicin [22].

The same approach (radiation therapy and chemotherapy without local surgery) should also be offered to those patients with small-volume metastases while systemic therapies with or without palliative radiation therapy should be considered in patients with large-volume metastases. Nowadays, only specific TKI can be used in restricted subgroups of ATC with specific molecular alterations such as *BRAF*^{V600E} mutations, *RET* or *TRK* fusions as discussed below.

4. Medullary Thyroid Cancer

Medullary thyroid cancer (MTC) originates from neural crest C cells and represents 4% of all TC. The biological behavior of MTC is more severe than that of DTC: the 10-years survival rate is approximately 50% and can be lower in patients with advanced disease at diagnosis [23]. Distant metastases are observed at presentation in 7–23% of MTC patients and are the main cause of MTC-related death. Total thyroidectomy and central compartment neck dissection is the primary surgical treatment and the only curative one for localized MTC. When a widespread regional or metastatic disease is present, repeated surgeries are not associated with a higher cure rate, and less aggressive procedures should be considered. In these cases, whenever possible, according to the extension and the sites of the disease, a local treatment should be preferred while systemic therapy should be used when the disease becomes multimetastatic and rapidly progressive [24][25]. EBRT is indicated to improve the local control of disease in case of local recurrence or locoregional lymph node metastases or as palliative therapy to reduce pain

from bone metastases or to treat brain metastases [25]. Radiofrequency thermo-ablation is frequently applicable to bone, liver, and lung to treat single metastases or a single progressive and symptomatic one in the context of a stable disease [26][27]. Another quite new and promising local treatment is the conventional transarterial chemoembolization (TACE) or radioembolization (TARE) commonly used in some advanced cases of liver metastatic disease, especially when liver metastases are smaller than 3 cm and the liver involvement is less than 30% [28]. Among systemic therapy, chemotherapy shows no clinical durable advantages and benefits in MTC and for this reason is no longer indicated [25]. Over the years, several types of radionuclides have been studied for the treatment of MTC, based on its neuroendocrine origin, but despite the decrease of its serum marker (i.e., calcitonin (CT)), no results have been obtained in terms of reduction of size and number of metastatic lesions [29]. Recently, promising results have been shown for the peptide receptor radionuclide therapy using 177Lu-labeled or 90Y-labeled somatostatin analogues, but it is limited to MTC cases with significant somatostatin receptors expression [30].

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