Advances in pharmacotherapy for advanced thyroid cancer of follicular origin (PTC, FTC). New approved drugs and future therapies.

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Abstract

Introduction. The most common altered signaling via found in aggressive iodine-refractory Thyroid cancer derived from follicular cells (RAI-TC) are RTK, MAPK, PI3K, WNT, BRAF, RAS, RET, and TP53. Tyrosine Kinase Inhibitors (TKI) are multi-kinase inhibitors able to act against different pathways, that elicit an anti-neoplastic activity. The aim of this paper is to review recent novel molecular therapies of RAI-TC.

Areas covered. Recently, sorafenib and lenvatinib, have been approved for the treatment of aggressive RAI-TC. Other studies are evaluating vandetanib and selumetinib in RAI-TC. Furthermore, preliminary studies have evaluated dabrafenib, and vemurafenib in BRAF mutated RAI-TC patients to re-induce 131-iodine uptake. The interplay between cells of the immune system and cancer cells can be altered by immune checkpoints inhibitors. The expression of PDL1 in RAI-TC was related to tumor recurrence and poor survival. Several clinical trials are investigating a combination of different therapies, such as lenvatinib and pembrolizumab.

Expert opinion. Mechanisms of resistance to TKIs inhibitors can be of intrinsic or acquired origin. An acquired resistance to lenvatinib, or sorafenib can be due to upregulation of FGFR, therefore anti-FGFR agents are evaluated. A new strategy is to combine TKIs with immunotherapy. Several studies are evaluating lenvatinib and pembrolizumab in RAI-TC patients.

Keywords: thyroid cancer, tyrosine kinase inhibitors, lenvatinib, sorafenib, immune-therapy.

1. Introduction

Thyroid cancer (TC) is the most frequent diagnosed endocrine tumor, with an incidence and

mortality that is increasing worldwide [1,2].

The US Surveillance, Epidemiology, and End Results (SEER) demonstrated that an increase of TC-related mortality has actually occurred in the last 2 decades, especially for advanced tumours. **Therefore, the nature of TC is changing becoming more frequent. Discordant results have been found in different countries about the TC related mortality that it is increased in some and decrease in others [1,3].**

The causes of TC increase are due to environmental issues, such as the exposure to radiation or pollution, nutritional issues, viral infection [4]

A high risk of TC is observed among those workers exposed to chemical contamination, as suggested by occupational studies. Moreover, thyroid-disrupting activity has emerged for a broad set of anthropogenic chemicals, such as polychlorinated biphenyls, heavy metals, dioxins, bisphenols [1].

In addition, the use of neck ultrasound (US) and fine-needle aspiration (FNA) allows a more accurate diagnosis with the detection of smaller cancer [5,6].

The most common histologic TC type is the differentiated TC (DTC), deriving from thyroid follicular cells, that embraces papillary TC (PTC), accounting 90% of cases, follicular TC (FTC), and Hürthle cells TC. Anaplastic TC (ATC) derives from thyrocytes, and is the most aggressive of all TC, with the lowest incidence; accounting for 1-2% of all thyroid cancers worldwide [2,7,8]. Poorly differentiated TC (PDTC) accounts for about 2-15% of TC, and it has an aggressiveness intermediate between PTC/FTC and ATC [9].

The overall mortality is low for most of TCs, excluding ATC that is the cause of more than 50% of annual death for TC.

SEER-9 data reported an incidence-based mortality increased of TC during the period 1994-2013, with an average of 1.1% (95% CI, 0.6% to 1.6%). According to the histologic type, the annual increase in incidence-based mortality rates was restricted to PTC [1.7% (95% CI, 0.6% to 2.9%)] [3]. Almost 90% of ATC patients die within 6 months after the diagnosis. This high mortality is

caused because of the fast growth rate of ATC, for its resistance to the classic cancer therapies, and also because this type of tumor is often diagnosed in advanced stage [9-11].

DTC patients are treated with different types of surgery, such as lobectomy or total/near-total thyroidectomy, associated or not with lymph node dissection, according to tumor characteristics; e.g size, extrathyroidal extension, and metastases. Patients with low-risk PTCs, and with small tumor and stable size over time, can avoid surgery and can be actively followed by US [12,13]. Patients defined at high-risk (in presence of persistent/recurrent TC, and/or with radioiodine (RAI)-up-taking metastases), and patients with intermediate risk (for persistent-recurrent TC) at follow-up will be submitted to RAI therapy after total thyroidectomy [12,13].

The follow up of patients foresees to perform US and thyroid-stimulating hormone (TSH)-stimulated thyroglobulin (Tg) for the first year (every three-six months), with subsequent intervals on the basis of initial risk assessment, in order to assess the presence of a possible persistent/recurrent disease [14-16].

However, the life expectancy is normal for the majority of DTC subjects [17] with metastases at the diagnosis found in approximately 5% of DTC patients. Tumor recurrence in lymph nodes or thyroid bed occurs in around 15% of patients, and this leads to a decrease in the survival at 10-years from 70% to 50% [18,19].

During DTC progression thyroid cells can lose the ability to uptake the iodide becoming refractory to RAI [17-19]. Metastatic TC (without RAI uptake) are associated with bad prognosis; actually the five-year survival is lower than 10% [13].

In case of metastatic aggressive DTC despite the treatment with RAI and TSH-suppressive thyroid hormone [20], other types of intervention (such as surgery, chemotherapy, external beam radiation therapy) had a palliative role with significant side effects and uncertain result on prolongation of survival [21].

Significant progresses have been achieved in the comprehension of the pathways that are involved in the TC growth, and new molecules targeting these aberrant signaling pathways can aid in

overcoming resistance to standard cancer therapy.

The aim of this paper is to review recent novel molecular therapies of aggressive DTC derived from follicular cells.

2. ***Thyroid cancer and molecular pathways dys-regulation***

The most common altered signaling via found in TC are the receptor tyrosine kinase (RTK), mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3K), and Wingless/Integrated (WNT) pathways [12,22]. Mutations in murine sarcoma viral oncogene homolog B (BRAF), rat sarcoma RAS, and RET (rearranged-during-transfection)/PTC rearrangements are mostly found in DTC; mutations in TP53 (tumor protein p53) in PDTC and ATC [23].

2.1 BRAF mutations in TC

The main oncogenic BRAF mutation is that in exon 15 resulting in a V600E substitution (valine replaced by glutamic acid) in BRAF protein. The nucleotide sequence around this codon in the *BRAF* gene is highly susceptible to alterations and change of the electrically neutral V600 to an electrically charged amino acid, such as to 600E, leading to the BRAF kinase activation despite the state of the amino acids in the vicinity [27]. BRAF kinase activity is then markedly activated against different targets, e.g. MAPK and extracellular signal-regulated kinase (ERK).

$BRAF^{V600E}$ mutation is mostly found in PTC classic and tall cell variants (45%), and in ATC (25%); it is related to tumor aggressiveness and to a bad prognosis [2, 24-26]. According to the Thyroid Cancer Genome Atlas (TCGA), $BRAF^{V600E}$ represents the most common driver mutational event involved in PTC [27-30].

The oncogenic role of $BRAF^{V600E}$ in TC pathogenesis has been investigated in animal model. It is found that a thyroid-specific expression of $BRAF^{V600E}$ induces goiter and invasive PTC. This

mirrors the phenotype of BRAF-positive PTCs in humans underlining the key role for this oncogene in its pathogenesis [28].

$BRAF^{V600E}$ mutation was related to a decreased or absent expression of different genes, such as those encoding the sodium-iodide symporter, the TSH receptor, the thyroperoxidase and the Tg, and the pendrin gene (SLC26A4) [31,32].

Moreover, several studies showed the association of mutated BRAF PTC with different clinico-pathological conditions with a negative prognostic impact, such as lymph node metastases, extra-thyroidal extension and advanced disease stage [33,34].

A recent multicenter study highlighted the clinical implications of BRAF status in the clinical decision-making. Two thousand six hundred thirty-eight PTC subjects were retrospectively analyzed for the mortality risk associated with lymph node metastasis. They found that the BRAF status may differentiate the risk status; in particular among those with conventional PTC in which lymph node metastases were not linked to an increase of mortality risk in wild-type BRAF patients, but the risk was strongly increased in BRAF-mutant patients [35].

2.2 ***RAS mutations in TC***

The *RAS* genes (*H-RAS*, *K-RAS*, and *N-RAS*) encode highly related G-proteins that are placed at the inner surface of the cell membrane and are involved in the intracellular transduction of signals of tyrosine kinase and G-protein-coupled receptors [36].

On average *RAS* genes mutations are detected in 30-45 % FTC, 30-45 % follicular variant PTC (FVPTC), 20-40 % PDTC, 10–20 % ATC, and rarely classical PTC. *RAS* mutations are also found in 20–25 % benign follicular thyroid adenoma [37].

The TCGA study identified RAS mutations in 12.7% of the PTC cohort. The most frequently found alteration is that involving the codon 61 of NRAS [30]. However, RAS mutations are also found in

follicular adenoma [38]. RAS mutations were associated with a negative prognostic effect [39-41]. It is thought that RAS mutations may worsening TC prognosis by stimulating the passage from a well-differentiated cancer to a less differentiated type [42]. Moreover, the de-differentiate effect has been sustained by the chromosome instability due to mutant RAS [29, 43].

RAS and BRAF mutations were mutually exclusive in differentiated PTC, therefore Ras mutation can independently cause PTC [44,45].

2.3 RET rearrangements in TC

The RET proto-oncogene is located at chromosome 10q11.2 and encodes a cell membrane RTK [46].

In some PTCs, the tyrosine kinase domain of RET is fused with an heterologous gene that provides the promoter and the 50-coding region [46]. The chimeric RET/PTC protein obtained by the recombination is able of auto-activation, through dimerization and auto-phosphorylation, independently from the presence of a ligand, this is the cause of its oncogenic activity [47,48].

There are several lines of evidence pointing to RET/PTC as a driving event in thyroid carcinogenesis [48-51]. RET/ PTC is specifically associated with the classic subtype of PTC [50]. However, the TCGA data found RET/PTC as a primary genetic event in only 6.8% of the PTC cohort [30]. Because of the apparently weak association of the mutation with clinical outcome, RET/PTC is not currently used in the stratification of PTC [29].

2.4 Vascular Endothelial Growth Factor (VEGF) and epidermal growth factor receptor (EGFR) in TC

VEGF-A is released by tumor and activates both the angiogenesis process through the VEGFR2

receptor displayed by blood endothelial cells, as well as the lympho-angiogenesis through the involvement of VEGFR3 on lymphatic endothelial cells [2,52,53]. Also the immune cells of the tumor microenvironment (TME) contribute to the angiogenesis with the production of VEGF-C and VEGF-D [54]. The transcriptional factor hypoxia inducible factor-1 alpha (HIF1α) is upregulated by intra-tumoral hypoxia and by growth factor signaling pathways (i.e., PI3K/AKT and MAPK), and induces VEGF-A activation. HIF1α is principally expressed in ATC cells and its target MET oncogene is up-regulated in the majority of TC allowing cell motility, angiogenesis, invasion, and metastasis [21].

An increased expression of VEGF and VEGFR-2 is present in DTC, contributing to the progression of the tumor and to its aggressiveness; the VEGF overexpression in PTC has been associated to local and distant metastases [55,56].

Analysis of germline VEGF-A SNPs could empower a prognostic approach to DTC as investigated by a multicenter, retrospective, observational study. The Authors found that VEGF-A SNPs is a promising tool for prognostic stratification of DTC, also thanks because it is a stable and easily accessible prognostic marker in non-advanced DTC [57].

EGFR protein (of the ErbB family of receptors) misregulation, amplifications, or mutations are found in about 30% of epithelial carcinoma. EGFR is overexpressed in ATC and is associated to TC progression and invasiveness [58].

2.5 Telomerase reverse transcriptase (TERT) promoter mutations in TC

Telomerase activity is up-regulated in about 80-90% of malignant cancers; while is not present in normal thyrocytes. The two TERT promoter mutations linked to carcinogenesis are a C-to-T substitution (C1,295,228 T) and a C-to-A substitution (C1,295,250A) [59].

Genetic alterations of TERT promoter predicted poor clinical outcome [29]. Therefore, the prognostic effect of TERT mutation has been categorized as dramatic, even more than of the $BRAF^{V600E}$ oncogene.

Nevertheless, several papers analyzed both TERT promoter and BRAF mutation raising discordant opinion [60,61]. It has been shown that the prognostic effect associated to TERT promoter mutations disappeared when BRAF mutation occurred separately; therefore, the co-existence with BRAF mutation is necessary for promoting tumor aggressiveness [29].

2.6 Anaplastic lymphoma kinase (ALK), Tropomyosin receptor kinases (TRK) and ROS1

A minor subset of PTCs reported NTRK1/3, ALK, and ROS1 translocations [62].

The TRK family of neurotrophin RTK are encoded by genes NTRK1, NTRK2, and NTRK3, whose fusion has been observed in different pediatric and adult malignancies, including PTC, PDTC and ATC. The encoded fused oncoprotein is constitutively active, leading to the activation of downstream pro-oncogenic pathways MAPK, PI3K/AKT and phospholipase C (PLC-γ) [63,64].

ALK is a transmembrane tyrosine kinase that once activated triggers multiple downstream signaling pathways, such as MAPK, PI3K/AKT and JAK/STAT. ALK gene activations due to different genetic alterations are found in PDTCs, ATCs, and less frequently in PTCs. These alterations are related with disease progression and aggressiveness [65].

A constitutive activation of the tyrosine kinase could be also due to genetic rearrangements of ROS1 gene [66].

3. Preclinical studies

Different preclinical in vitro studies have been carried out aiming at investigating the therapeutic potential of new drugs inhibiting the RTK/BRAF/MAPK/ERK and PI3K/AKT/mTOR pathways.

The MEK inhibitor PD0325901 has been evaluated in thyroid cancer cells. This drug showed inhibitory effects on thyroid cancer cells, some of which appeared to be genotype-selective. Therefore, the inhibition of MEK may be therapeutically effective for TC, in particular if the PI3K

and NF-kB pathways are also inhibited [67]. Another MEK inhibitor, RDEA119, has been evaluated alone and with temsirolimus (mTOR inhibitor) in TC cell lines. The anti-tumorigenic effect of both drugs is higher in those cells harboring other genetic alterations in the MAP kinase and PI3K/Akt pathways. These findings supported the important therapeutic potential of RDEA119 and its synergism with temsirolimus in TC [68].

A novel Akt inhibitor, MK2206, was tested on TC cells with respect to the genotypes of the PI3K/Akt pathway. The Authors found a genetic selectivity of MK2206 in inhibiting TC cells by targeting the PI3K/Akt pathway [69].

4. Tyrosine Kinase Inhibitors as therapy of aggressive DTC

Tyrosine Kinase Inhibitors (TKI) are multikinase inhibitors able to act against different pathways, that are involved in the growth and dissemination of the tumor (angiogenesis, invasiveness, local and distant spread) [70].

4.1 Sorafenib

Sorafenib exerts its antitumoral effects by inhibiting RAF, VEGFR2, Platelet-Derived Growth Factor Receptor (PDGFR), VEGFR3, RET, and KIT kinases. Its effects have been observed in preclinical models of cancer xenograft (breast cancer, colon, and non-small-cell lung) as well as in *in-vitro studies* with TPC1 (RET/PTC1 mutation) and TT (C634W RET mutation) cell lines [71-73].

The FDA approved the use of sorafenib for metastatic DTC, renal and hepatocellular carcinoma; it is assumed *per os* (twice daily at a maximum dosage of 400 mg) and it is usually well tolerated.

The clinically relevant antitumor activity of sorafenib was highlighted by a phase II trial in patients with metastatic, iodine-refractory TC (RAI-TC). Thirty patients received sorafenib (400 mg bid/die) for about 27 weeks. The therapy was interrupted by six of them because the appearance of adverse events (AEs); in order to monitor the toxicities the dose was reduced in almost half of the patients

(47%) [74]. They showed a high percentage of partial response (PR) + stable disease (SD) (77%), and median progression-free survival (PFS) was of 21 months [74].

The efficacy of sorafenib was assessed by different studies, that includes metastatic RAI-refractory TC patients [75-77].

Despite sorafenib is generally well tolerated, fatal AEs were registered in a longitudinal, retrospective study with 17 subjects having progressive RAI-TC [78]. Dose reduction or a transitory interruption of the therapy occurred because of the manifestations of three cases of severe bleeding and two of cardiac arrests. Low performance in PFS (9 months) and overall survival (OS) (10 months) were obtained in comparison to other studies; probably because of the worse condition of the enrolled patients from the beginning of the study. The best responses were found in patients with lymph node or lung metastases. The radiological response was correlated with basal Tg and Tg response to therapy. The dosage of Tg, at baseline and in response to treatment, could be aid in the prediction of clinical outcome. Non-responding patients could be rapidly identified by an early fluorodeoxyglucose-positron emission tomography (FDG-PET) [78].

A double-blinded, randomized phase III trial (DECISION) demonstrated the effectiveness of sorafenib in RAI-TC [79]. 417 subjects with RAI-TC, of whom 207 received sorafenib (800 mg daily) and 210 placebo, were studied. PFS was higher in the “sorafenib group” than in the “placebo group” (10.8 months and 5.8 months, respectively). A PFS improvement occurred in all subgroups, without difference in the relation to the mutation status. The 98.6% of subjects of the “sorafenib group” had AEs [79].

A combined treatment of sorafenib (200 mg twice daily *per os*) plus temsirolimus (25 mg weekly) was investigated in a phase II study with 36 patients having RAI-TC. The combination of these drugs was effective overall in TC patients who had no prior treatment with respect to those treated with sorafenib alone. Activity is also observed in patients who received a prior treatment with sorafenib [80].

A recent meta-analysis explored sorafenib in RAI-refractory DTC subjects by evaluating fifteen appropriate studies and 636 patients [81]. It was found an improved PFS in patients treated with sorafenib, with respect to placebo. Twenty-six% of patients reached a PR and 44% SD [81].

4.2 Lenvatinib

Lenvatinib is another mTKI, that received the FDA and EMA approval for the treatment of RAI-TC. It acts against fibroblast growth factor receptor (FGFR)1, -2, -3, -4, PDGFRβ, VEGFR1, -2, -3, RET, and KIT kinases [82,83].

The activity of lenvatinib has been shown by *in vivo* studies in xenografts of different TC cells (DTC, and ATC) in nude mice, showing anti-angiogenic effects [84]. Also**,** *in vitro* studies showed its anti-neoplastic effect, it is actually able to inhibit proliferation and to increase apoptosis of ATC cells (primary and continuous); in addition it can decrease the expression of VEGF-A and microvessel density and can inhibit tumor growth in xenograft model of ATC cells [85].

Fifty-eight patients with advanced RAI-TC, that had progressed in the former 12 months were included in a phase II trial [86]. The subjects received lenvatinib (24 mg once daily) in 28-day cycles. Patients had an objective response rate (ORR) of 50%, and only PRs were shown, after about 14 months of follow-up. The median: a) time to relapse (TTR) was 3.6 months; b) PFS was 12.6 months; c) response duration was 12.7 months. The 17 subjects who have previously received an anti-VEGF therapy reached an ORR of 59%. The tumor response is related to higher PFS [86].

A phase III double-blinded, randomized trial, investigated lenvatinib in 261 patients having RAI-TC, in comparison to 131 patients who received placebo [87]. 24 mg of lenvatinib were daily administered in a 28-day cycle and those DTC patients who progressed during the placebo therapy were allowed to assume open-label lenvatinib. Median PFS of patients treated with lenvatinib was significantly longer (18,3 months) with respect to those who received placebo (3.6 months). In the lenvatinib group, patients had a response rate of 64.8% vs. 1.5% of the placebo group; 165 had PR and 4 CR, while OS was not attained. Therapy was interrupted because of the appearance of AEs in

14.2% of patients in treatment with lenvatinib and in 2.3% of patients following a placebo therapy; 6/20 deaths were associated to lenvatinib. Therefore, lenvatinib appeared to significantly improve PFS, such as response rate in these patients, however it is also associated with significant AEs [87].

Lenvatinib was evaluated in a subgroup of Japanese DTC patients who took part in the phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) trial [88]. The outcome was evaluated in relation to those of the SELECT population (n=261, lenvatinib; n=131, placebo). In the subgroup analysis were included 30 subjects who received lenvatinib and 10 placebo; the achieved outcomes of median PFS and OS were comparable for both groups, while the ORR was of 63.3% for lenvatinib and 0% for placebo. No difference arose about safety of lenvatinib between the Japanese patients and the total SELECT population, albeit higher incidence of hypertension was reported. In this subgroup there were more dose reductions, however less discontinuations due to AEs. The Authors found that lenvatinib had similar clinical results in Japanese patients with RAI-TC, in comparison to the SELECT population [88].

The tumor size changes due to lenvatinib were investigated by a phase III, randomized, double-blinded, SELECT trial [89]. In the analysis were involved the responders to therapy (n=169) according to their complete response (CR) or PR; and 76/92 among the non-responders, who had at least one post-baseline tumor evaluation. A median maximum percentage change in tumor size of -42.9% was shown by patients treated with lenvatinib (responders, -51.9%; non-responders, -20.2%). Changes in the tumor size were markedly visible at an initially evaluation, afterwards the change decreased constantly. According to these findings tumor size changes are of an initial rapid decline, followed subsequently by a slower, but continuous shrinkage [89].

The anti-neoplastic effect of lenvatinb in RAI-TC, and also its promising efficacy in ATC, was recently showed by a phase II trial. Lenvatinib (24 mg once daily) was administered to 51 patients with RAI-TC, ATC. RAI-TC patients had a median PFS of 25.8 months; while for those with ATC was of 7.4 months [90].

Recently was performed a multicenter study with 43 RAI-TC patients treated with lenvatinib (as first, or second-line therapy after treatment with sorafenib) for 14 months (median) [91], with a follow up of 16 months (median). Based on the experienced AEs the lenvatinib was reduced to 10 mg (median). The OS was not reached, while the median PFS was of 21.8 months, and the disease control rate (DCR) was 97.7%, with the first objective response (OR) at 3.8 months. PFS was not associated with a previous sorafenib therapy, type of metastases, or sustainable dose. PFS was associated with the tumor growth slope before and after the therapy, and with Tg doubling time, but tumor volume doubling time, evaluated before or after lenvatinib, did not impact PFS. These results suggest that lower dose of lenvatinib correlated with a lower rate of severe AEs with no changes of the effectiveness in these patients [91].

5. Comparison of Sorafenib and Lenvatinib in RAI-TC

The criteria to define a RAI-TC are: a) presence of one or more metastatic measurable lesions not up-taking 131-I **at post therapy whole body scan**; b) presence of measurable metastatic lesions up-taking 131-I, but in progression within 6-12 months after radioiodine administration; c) progression of RAI-TC after administration of a cumulative dose of I-131 > 600 mCi [92,93].

Sorafenib and lenvatinib are actually recommended for RAI-TC treatment, however we are still far from a structured therapeutic algorithm [94].

The most frequent treatment-related toxicities induced by sorafenib are diarrhea, fatigue, hand-foot skin reaction and hypertension. Most of these AEs are mild to moderate and manageable to varying degrees; however, cardiovascular events might lead to death [95].

The most commonly reported grade 3 AEs in patients treated with lenvatinib are hypertension (41.8%), diarrhea (8%), fatigue (9.2%), decreased appetite (5.4%), decreased weight (9.6%) nausea (2.3%), stomatitis, (4.2%). In addition other AEs events that include, skin toxicities (including palmar-plantar erythema, and rash) and cardiovascular AEs are of clinical relevance to the care of

patients receiving lenvatinib [96]. The tolerability of sorafenib, and lenvatinib appears low, even under the ideal conditions of clinical trials [97].

A proper sequence of administration is not available because the lack of a direct comparison between drugs. However, phase III trials showed milder toxicity for sorafenib, that could be preferred in presence of cardiovascular morbidities. Moreover, lenvatinib showed efficacy in TKIs pre-treated patients, and for this reason could be used as second-line treatment [94].

6. Thyroid cancer resistance to therapies and new therapy strategies

The survival rate at 10 year for patients with RAI-TC is of only 10 %. This poor prognosis is also due to the impairment of the NIS. This symporter placed on the basolateral surface of the thyroid follicular cells has an important role in mediating the iodide transport into follicular cells. The radioactive iodine follows the same road, therefore if NIS is loss or down-regulated because of genetic alteration of the RTK/BRAF/MAPK/ERK and PI3K/AKT/mTOR pathways is thought to be a candidate to radioiodine refractory TC [98,99].

$BRAF^{V600E}$ mutant TC are characterized by a high risk of both relapse and poor outcomes, because BRAF activating mutations alter genes involved in iodine metabolism causing a more aggressive tumorigenesis and thyroid cell dedifferentiation. BRAF and MEK inhibitors were investigated against RAI-TC. A study investigated the MEK1/2 inhibitor selumetinib (75 mg/twice daily) in 20 patients with RAI-TC [100]. RAI uptake increased in 12 out of 20 patients after therapy. RAI treatment was done in eight out of 12 patients, three of whom achieved SD, and five PR.

Another study investigated dabrafenib, a selective BRAF inhibitor, in 10 patients with $BRAF^{V600E}$ mutated PTC [101]. It is able to re-induce RAI uptake in 6/10 patients, with two PRs and four SD at three-months post RAI.

Vemurafenib, another BRAF inhibitor, has been evaluated in 12 BRAF mutated TC patients [102]. Four out of ten evaluable subjects were ^{124}I responders on vemurafenib and received a ^{131}I

treatment; tumor regressions occurred at 6 months. An increased thyroid gene expression and RAI uptake occurred with the vemurafenib inhibition of the MAPK pathway, as revealed by tumor biopsies. Two days after ^{131}I treatment the therapy with vemurafenib was interrupted giving the possibility of RAI treatment [102].

Mechanisms of resistance to BRAF inhibitors can be of intrinsic or acquired origin [103]. The inhibition of apoptosis through the B-Cell CLL/Lymphoma 2 (BCL2) pathway confers an intrinsic resistance to BRAF inhibitors. A preclinical model [104] showed a resistance of TC cells to vemurafenib; these cells harbour a copy number gain of myeloid cell leukemia 1 as well as a loss of cyclin-dependent kinase inhibitor 2A. Sensitivity was improved by the combination of vemurafenib with obatoclax, a BCL2 inhibitor [104].

Intrinsic resistance is also the results of mutations in $BRAF^{V600E}$ and PI3KCA. Therefore, an effective strategy could be treating with MAPK inhibitors plus drugs such everolimus, that target PI3K/AKT/mTOR pathway [105].

Everolimus (10 mg, daily) efficacy was tested in a phase II clinical trial involving 28 subjects with locally advanced or metastatic RAI-TC and 7 with ATC; the median follow-up duration was of 38 months. Outcomes were: SD in 65% of subjects, no PR or CR; 58% had SD for more than 24 weeks. The subjects experienced a mild toxicity in line with the known side effect profile [106]. Secondary mutations in the MAPK pathway, such as acquisition of NRAS Q61K [107,108], or KRAS G12V [108], lead to acquired resistance to BRAF inhibitors. Hence, interesting potential treatment options will be combining or replacing MEK inhibitors, with novel MAPK inhibitors such as KRAS or ERK inhibitors. As regard the VEGFR inhibitors such as lenvatinib, or sorafenib, an acquired resistance can be due the up-regulation of FGFR; therefore, anti-FGFR agents could be useful in this setting [109].

A phase 2 trial evaluated vandetanib, a TKI, in 145 patients with advanced RAI-TC. Patients under

therapy with vandetanib showed a longer PFS of 11.1 months with respect to the placebo group of 5.9 months [110].

A double-blind, placebo-controlled phase 3 study (VERIFY, NCT01876784) [111] is ongoing, testing vandetanib in advanced RAI-TC. The most frequent AEs related to vandetanib are nausea, hypertension, diarrhea, rash, asthenia, fatigue, and QT interval prolongation [111].

Drugs acting against TRK kinases are under investigation, such as larotrectinib (active against all TRK kinases) and entrectinib (active against all TRK kinases + ROS1 and ALK).

Larotrectinib received the FDA and EMA approval for the treatment of adult and pediatric patients with TRK fusion cancer. Its efficacy and good safety profile was shown in patients with advanced TRK fusion TC [64,112]. Moreover, it was able to restore radioiodine avidity in PTC-pediatric patients, with an inhibition of tumor growth [65,113]

Entrectinib had the FDA approval in 2019, and was designed to target brain metastases or primary brain cancers with NTRK 1/2/3, ROS1, or ALK fusions [64]. A durable and significant responses was observed in patients with NTRK fusion-positive solid tumors [65,114].

7. Immunotherapy for aggressive DTC

The tumor microenvironment contributes to cancer progression and to the response to therapy; then it is a potential therapeutic target [12].

The interaction between the immune system cells and tumor cells can be altered by immune checkpoints inhibitors, acting against programmed cell death protein 1 (PD1) and its ligand-PDL-1, or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [115,116]. A meta-analysis showed an

association between the PDL1 expression in TC and tumor recurrence or poor survival [117].

According to the Cancer Genome Atlas database higher level of PD-L1 mRNA was related to extrathyroidal invasion, lymph node metastases, and shorter disease-specific survival [118].

However, because of a low mutation burden DTC is poorly immunogenic, some studies revealed a relatively poor response to immunotherapy with checkpoint inhibitors in DTC [119,120]. Several clinical trials are testing combined treatments in solid tumors, including TC, aiming to improve immunotherapy effectiveness.

High mutation burden is present in de-differentiated tumors, such as widely invasive Hürthle cell cancer and ATC; therefore these types of tumors may benefit of these therapies [121,122].

8. Combined treatments

A new strategy is to combine TKIs with immunotherapy. A prolonged tumor control, thanks to the treatment with target therapy plus immunotherapy, has been depicted by different case series of TC, also in RAI-TC who have progressed on prior targeted therapy [123,124].

Lenvatinib (24 mg/kg daily) plus pembrolizumab (200 mg every 3 weeks) were administered to 8 patients with metastatic ATC or DTC. No significant grade 3 or 4 toxicities were registered, and 4 patients achieved a PR, 2 SD, 1 a CR and 1 expired from PD [125].

A multicenter phase II trial evaluated lenvatinib and pembrolizumab in 30 RAI-TC patients. 18 of 30 patients (62%) had a PR, and 10 had SD, and the clinical benefit rate (ORR +SD) was 97%. [126]. Several clinical trials for RAI-TC are ongoing (such as for Metastatic DTC: NCT03732495, Lenvatinib + Denosumab; NCT03099356 Cyclophosphamide + Sirolimus; NCT03753919

Durvalumab + Tremelimumab) [98].

9. Ongoing clinical trials in TC

The mTKI have allowed to improve PFS and to prolong the responses. However, some issues need to be addressed, such as what type of drug to be used as first option; possible drug resistance; AEs of long-lasting treatment that could affect the quality of life; tumor resistance [127]. These issues could be overcome through a personalized therapy, by precisely selecting which patients to treat with novel targeted therapies by considering these factors. A close monitoring of the appearance of AEs and of the quality of the life should be taking in account prior to start the therapy. RAI-refractory diseases are more likely a result of specific molecular profiles [128,129]. Most of the patients have asymptomatic, slowly progressive disease, also in the presence of distant metastases. In patients with RAI-refractory disease if the symptoms are limited to a single site can be effectively treated with surgery, thermal ablation, or external beam radiotherapy, according to the site of the lesion and local expertise. The treatment with TKIs should be took in account when disease progression involves multiple sites in subjects having target lesions >1-2 cm in diameter [130]. Despite the several AEs associated to TKIs, the improved knowledge of the risk factors for these adverse effects, as well as the improved experience in the use of these drugs are likely to improve their tolerance [131,132]. Specific inhibitors selumetinib [100] and dabrafenib [101] (BRAF inhibitor) showed to improve RAI uptake by RAI-refractory tumor tissues. Also, immunotherapy seems to be a promising approach to TC, alone or in combination with other drugs. However, these drugs have yet to be approved.

A new therapeutic approach to assess the response to TKIs could be performing *in vitro* tests with TC cells obtained directly from each patient. *In vitro* drug test screening with human primary tumor cells mirror an *in vivo* clinical response with a positive predictive value of 60%, and negative predictive value of 90% [133,134].

Moreover, FNA could be a via to obtain primary TC cell, instead of surgery, that can be used for *in vitro* study to investigate their sensitivity to several chemotherapies [134-139].

The enrollment of subject with RAI-TC in clinical trials, should be encouraged to better evaluate the clinical outcomes, and to increase the medical knowledge in the field [111].

10. Future directions

The current RAI-TC treatment options are scarcely. Therefore, the importance of new studies investigating targeted therapies is necessary. A crucial point is the definition of patient inclusion and exclusion criteria, and the selection of appropriate outcome measures.

Important issues may be encountered with the definitions of I-131 refractory disease, differentiation between progressive and indolent disease, and primary and secondary outcome variables. Moreover, among patients having a progressive disease, it is important to select those who may obtain a benefit from a TKI, from those who need a watchful waiting.

RECIST criteria are used by most of the studies involving RAI-TC patients, aiming at identifying targeted and other antineoplastic approaches. Nevertheless, there are limitations associated with this morphologic assessment (e.g., necrosis and edema) [140].

At present, the effectiveness of sorafenib and lenvatinib in RAI-TC are evident. Additional studies of these and other new compounds will investigate different dosing regimens and combinations with other kinase inhibitors, such as mTOR inhibitors, or combination with immune checkpoints inhibitors [141].

11. Conclusion

The traditional treatment of aggressive RAI-TC by surgery, levothyroxine [142], radiotherapy

ablation (etc.) is not associated with a real and important improvement of survival and quality of life in these patients.

Recent studies have evaluated the importance of molecular genetics in the identification of the more aggressive types of RAI-TC. The most common altered signaling via found are RTK, MAPK, PI3K, WNT, BRAF, RAS, RET, TP53, in RAI-TC.

Tyrosine Kinase Inhibitors (TKI) are multikinase inhibitors able to act against different pathways, that are involved in the growth and dissemination of the tumor (angiogenesis, invasiveness, local and distant spread).

Recently, sorafenib and lenvatinib (that improve PFS), have been approved for the treatment of aggressive RAI-TC. Hand-foot syndrome, diarrhoea, hypertension and fatigue are some of the most common registered AEs.

BRAF and MEK inhibitors were investigated against RAI-TC. Preliminary studies have evaluated dabrafenib, and vemurafenib (selective BRAF inhibitors) in BRAF mutated TC patients to re-induce 131-iodine uptake.

Mechanisms of resistance to TKIs inhibitors can be of intrinsic or acquired origin. As regard the VEGFR inhibitors such as lenvatinib, sorafenib, an acquired resistance can be due the upregulation of FGFR, therefore anti-FGFR agents may have application in this setting.

The interaction between the immune system cells and tumor cells can be altered by immune checkpoints inhibitors (PD1, PDL-1, CTLA-4) [115, 116]. The expression of PDL1 in TC was related to tumor recurrence and poor survival. However, because of a low mutation burden DTC is poorly immunogenic; some studies revealed a relatively poor response to immunotherapy with checkpoint inhibitors in DTC [119,120].

A new strategy is to combine TKIs with immunotherapy. Several studies are evaluating lenvatinib

and pembrolizumab in RAI-TC patients.

The enrollment of subject with RAI-TC in clinical trials should be encouraged to better evaluate the clinical outcomes, and to increase the medical knowledge in the field [111].

12. Expert Opinion

The traditional treatment of aggressive RAI-TC by surgery, radiotherapy ablation (etc.) is not associated with a real and important improvement of survival and quality of life in these patients.

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Recently, sorafenib and lenvatinib (that improve PFS), have been approved for the treatment of aggressive RAI-TC.

Sorafenib and lenvatinib are actually recommended for RAI-TC treatment, however we are still far from a structured therapeutic algorithm [94].

The criteria to define a RAI-TC are: a) presence of one or more metastatic measurable lesions not up-taking 131-I **at post therapy whole body scan**; b) presence of measurable metastatic lesions up-taking 131-I, but in progression within 6-12 months after radioiodine administration; c) progression of RAI-TC after administration of a cumulative dose of I-131 > 600 mCi [92,93].

A recent meta-analysis explored sorafenib in 636 RAI-TC subjects [81]. It was found an improved PFS in patients treated with sorafenib, with respect to placebo. Twenty-six% of patients reached a

PR and 44% SD. Hand-foot syndrome, diarrhoea and fatigue are some of the most common registered AEs.

Lenvatinib has been evaluated in RAI-TC patients in many studies, showing a significant increase of the median PFS, and the DCR. PFS was associated with the tumor growth slope before and after the therapy. Tumor size changes were of an initial rapid decline, followed subsequently by a slower, but continuous shrinkage [89].

The most frequent treatment-related toxicities induced by sorafenib are diarrhea, fatigue, hand-foot skin reaction and hypertension [95].

The most commonly reported grade 3 AEs in patients treated with lenvatinib are hypertension, diarrhea, fatigue, decreased weight, stomatitis. Most of these AEs are mild to moderate and manageable to varying degrees; however, cardiovascular events might lead to death [95].

The tolerability of sorafenib, and lenvatinib appears low, even under the ideal conditions of clinical trials [97].

Usually the appearance of grade 3 AEs is managed by a reduction of the dosage of the drugs, that in most of the cases can lead to the amelioration, or the disappearance of the AEs themselves, permitting to continue the therapy.

A proper sequence of administration is not available because the lack of a direct comparison between drugs. However, phase III trials showed milder toxicity for sorafenib, that could be preferred in presence of cardiovascular morbidities. Moreover, lenvatinib showed efficacy in TKIs pre-treated patients, and for this reason could be used as second-line treatment [94].

Mechanisms of resistance to TKIs inhibitors can be of intrinsic or acquired origin. As regard the VEGFR inhibitors such as lenvatinib, sorafenib, an acquired resistance can be due the upregulation of FGFR, therefore anti-FGFR agents could be useful in this setting.

New studies are evaluating vandetanib, in patients with advanced RAI-TC. Patients under therapy

with vandetanib showed a longer PFS of 11.1 months with respect to the placebo group of 5.9 months.

BRAF and MEK inhibitors were investigated against RAI-TC. Preliminary studies have evaluated dabrafenib, and vemurafenib (selective BRAF inhibitors) in BRAF mutated TC patients to re-induce 131-iodine uptake. Intrinsic resistance can be the results of mutations in $BRAF^{V600E}$ and PI3KCA. Therefore, treating with MAPK inhibitors plus drugs such everolimus, that target PI3K/AKT/mTOR pathway, may be an effective strategy [105].

The interplay between cells of the immune system and cancer cells can be altered by immune checkpoints inhibitors (PD1, PDL-1, CTLA-4) [115, 116]. A meta-analysis showed that the expression of PDL1 in TC was related to tumor recurrence and poor survival [117]. According to the Cancer Genome Atlas database higher level of PD-L1 mRNA was related to extrathyroidal invasion, lymph node metastases, and shorter disease-specific survival [118]. However, because of a low mutation burden DTC is poorly immunogenic; some studies revealed a relatively poor response to immunotherapy with checkpoint inhibitors in DTC [107, 120].

A new strategy is to combine TKIs with immunotherapy. Several studies are evaluating lenvatinib and pembrolizumab in RAI-TC patients. Moreover, other clinical trials for RAI-TC are ongoing (such as for Metastatic DTC: NCT03732495, Lenvatinib + Denosumab; NCT03099356 Cyclophosphamide + Sirolimus; NCT03753919 Durvalumab + Tremelimumab) [98].

The enrollment of subject with RAI-TC in clinical trials, should be encouraged to better evaluate the clinical outcomes, and to increase the medical knowledge in the field [111].

Highlights

1) The most common altered signaling via found in more aggressive types of RAI-TC are RTK, MAPK, PI3K, WNT, BRAF, RAS, RET, TP53.

2) Tyrosine Kinase Inhibitors are multikinase inhibitors able to act against different pathways, that are involved in the growth and dissemination of the tumor (angiogenesis, invasiveness, local and distant spread).

3) Recently sorafenib and lenvatinib (that improve PFS) have been approved for the treatment of aggressive RAI-TC.

4) Preliminary studies have evaluated dabrafenib, and vemurafenib (selective BRAF inhibitors) in BRAF mutated TC patients to re-induce 131-iodine uptake.

5) The interplay between cells of the immune system and cancer cells can be altered by immune checkpoints inhibitors (PD1, PDL-1, CTLA-4). The expression of PDL1 in TC was related to tumor recurrence and poor survival. Recent studies revealed a relatively poor response to immunotherapy with checkpoint inhibitors in DTC.

6) A new strategy is to combine TKIs with immunotherapy. Several studies are evaluating lenvatinib and pembrolizumab in RAI-TC patients.

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The Authors report no conflicts of interest

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