Chapter 9

Emerging Therapeutic Approaches for the Most Aggressive Epithelial Thyroid Cancers

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http://dx.doi.org/10.5772/64086

Abstract

The majority of epithelial thyroid carcinomas (TC) have a differentiated (DTC) histotype and include the papillary (PTC) and the follicular (FTC) TC which, ensuing dedifferentiation, generate the aggressive poorly differentiated (PDTC) and anaplastic (ATC) TC. Although derived from the same cell type, each TC shows specific histological features, biological behavior, and degree of differentiation because of different genetic alterations. Total thyroidectomy, followed by adjuvant therapy with ^{131}I, is the treatment of choice for most patients affected by DTC. The prognosis of DTC patients is favorable, with 10-year survival rate of nearly 90%. However, one third of them face the morbidity of disease recurrence and TC-related deaths. The worst outcomes are encountered in patients with PDTC and ATC. The latter, in particular, has a mean survival time of few months from the diagnosis, which is not influenced by current anticancer treatments. Following the progress made in the comprehension of the underlying molecular mechanisms deregulated in TC progression, novel therapeutic approaches have come to light. Here, we will attempt to review new targeted therapies, which are currently being exploited in preclinical and clinical studies, with tyrosine kinase inhibitors as well as with emerging inhibitors of mitotic kinases, in PDTC and ATC.

Keywords: thyroid carcinoma, therapy, tyrosine kinase inhibitors, mitotic kinases, aurora kinase inhibitors

1. Introduction

Thyroid cancer (TC) incidence has increased from about 5 new cases per 100,000 persons observed in the early 1990s to 15 new cases per 100,000 persons recorded in 2012 [1]. The reason of such increase resides essentially in the improved diagnostic ability to detect malignancy in small non-palpable thyroid nodules [2, 3]. Data from the Surveillance, Epidemiology, and End Results (SEER) program Cancer Statistics Review indicate that 62,450 new cases of TC are expected to be diagnosed in the US population in 2015 [1]. In addition, 1950 deaths related to TC are estimated to occur [1].

TC represents about 96% of all endocrine malignancies and one of the most frequent cancers in women [1]. Based on histological criteria and clinical behavior, TC are classified as well-differentiated TC (DTC), comprising the papillary (PTC) and follicular (FTC) TC and poorly differentiated TC (PDTC) and undifferentiated or anaplastic (ATC) TC. The PTC accounts for about 86% of all epithelial TC and has a propensity to spread via lymphatic vessels to local lymph nodes [4]. The FTC accounts for approximately 9% of all TC and is characterized by hematogenous spread producing lung and bone metastases [4]. The less differentiated and more aggressive PDTC and ATC, each of which accounts for 1–2% of all TC, develop from the dedifferentiation of DTC, according to the multistep model of thyroid carcinogenesis [4–6]. The latter is supported by the common observation of coexistence of DTC with PDTC or ATC bearing similar genetic alterations [7, 8]. The PDTC, included as a separate entity in the WHO classification of TC in 2004, is defined as a thyroglobulin-producing, non-follicular and non-papillary TC, having an intermediate clinical behavior between DTC and ATC and showing high-grade features such as widely infiltrative growth, necrosis, vascular invasion, and numerous mitotic figures [6, 9]. PDTC may show three different pathological subtypes including the solid, trabecular, and insular architectures [4]. The ATC appears as disseminated fleshy masses with areas of necrosis and hemorrhage. It is composed of undifferentiated cells negative for thyroglobulin and originating three morphological patterns: squamoid cells, pleomorphic giant cells, and spindle cells [4].

Total thyroidectomy followed by adjuvant therapy with ^{131}I is the treatment of choice for most patients affected by DTC [10]. Although the prognosis of these patients is favorable, with 10-year survival rate around 90%, nearly one third of them face the morbidity of disease recurrence and TC-related deaths [10]. The worst outcomes are usually observed in patients with PDTC and ATC, in which the reduced expression of the thyroid specific gene natrium/iodide symporter (NIS) renders ^{131}I treatment less effective [11–13]. In particular, patients affected by ATC have a dismal prognosis with a mean survival time of few months from the diagnosis [12]. These patients present with a rapidly growing thyroid mass and locoregional symptoms, which may include dyspnea, dysphagia, neck pain, hoarseness, and stroke [14]. Outcome of ATC patients is not, or only minimally, influenced by current anticancer treatments, including palliative surgery, when possible, chemotherapy (doxorubicin), and radiotherapy [12, 14]. In the majority of patients, death occurs following tumor airway obstruction [14]. Therefore, the identification of new therapeutic approaches capable of ameliorating the prognosis of PDTC and ATC patients is sorely needed.

http://dx.doi.org/10.5772/64086

2. Molecular alterations underlying thyroid cancer progression

Established risk factors for TC include radiation exposure, family history of TC, lymphocytic thyroiditis, reduced iodine intake, and female gender [15]. These risk factors are thought to induce genetic instability in thyrocytes through still poorly defined direct and indirect mechanisms [15]. Genomic instability, a hallmark of solid tumors including TC, is thought to represent the driving force responsible for acquisition by malignant cells of novel functional capabilities, including self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis [16–18]. In fact, the number and the frequency of chromosomal abnormalities observed during TC progression have been shown to increase from DTC to PDTC and ATC [18]. Genomic instability is also sustained by alterations in cell-cycle regulators, frequently encountered in TC [15]. In particular, a deregulated control of the G1/S transition, due either to an increased expression of promoting factors (cyclin D1 and E2F) or to the downregulation or presence of loss-of-function mutations of factors inhibiting the G1/S transition (retinoblastoma, p16INK4A, p21CIP1, p27KIP1, and p53), has been demonstrated in TC [15]. In addition, the aberrant expression of mitotic kinases, such as the polo-like kinase and the three members of the Aurora kinase family (Aurora-A, Aurora-B, and Aurora-C), regulating the G2/M phase transition and several mitotic processes (i.e., centrosome maturation, spindle formation, chromosome segregation, and cytokinesis), is held co-responsible for abnormal cell divisions and the establishment of aneuploid TC cells [19, 20].

The PTC are characterized by mutually exclusive activating somatic mutations of genes encoding proteins involved the MAPK (mitogen-activated protein kinase) signaling pathway [4, 21]. These include rearrangements of the RET (rearranged during transformation) (RET/PTC) and NTRK1 (neurotrophic tyrosine kinase receptor 1) genes and activating point mutations of the three RAS oncogenes (HRAS, KRAS, and NRAS) and BRAF [21]. All together these genetic alterations are held responsible for about 80% of all PTC. In addition, mutations of genes encoding key players of the phosphoinositide 3-kinase (PI3K) pathway, such as PTEN, PIK3CA, and AKT1, have been reported in PTC at lower frequencies [21].

Genetic alterations encountered in FTC include activating point mutations of RAS, present in about 45% of FTC; rearrangement of the paired-box gene 8 (PAX-8) with the peroxisome proliferator-activator receptor-γ (PAX8-PPARγ), observed in 35% of FTC; loss-of-function mutations of the tumor suppressor PTEN gene, encountered in about 10% of FTC; and activating mutations or amplification of the PI3KCA gene, encoding the catalytic subunit of the PI3K, present in about 10% of FTC [22, 23].

In agreement with the multistep model of thyroid carcinogenesis, some of the early genetic events characterizing DTC are also found in PDTC and ATC. In particular, RAS and BRAF gene mutations are found in approximately 35% and 15% of PDTC, respectively [4]. On the contrary, other early genetic alterations such as the rearrangements RET/PTCs and PAX8-PPARγ are very rarely found in PDTC and ATC suggesting that these oncogenes prevent tumor dedifferentiation. Progression of DTC to PDTC and ATC implies, however, tumor acquisition of novel genetic alterations, which are absent or present with low frequency in DTC

tissues. Among these are mutations of the tumor suppressor gene p53, thought to be a gatekeeper of TC progression from the indolent DTC to the aggressive PDTC and lethal ATC [24]. In fact, p53 mutations are rarely encountered in DTC (5–9% of cases), while they increase in the PDTC (17–38% of cases) and ATC (67–88% of cases) [15, 25, 26]. A similar trend regards the CTNNB1 gene, encoding the β-catenin, involved in cell adhesion and in the wingless (Wnt) signaling pathway [15]. In particular, CTNNB1 gene mutations are not found in DTC, while they are present in PDTC (25% of cases) and ATC (66% of cases) [27, 28]. Last but not least, the conversion of early-stage TC to more aggressive and invasive malignancies occurs through an epithelial-to-mesenchymal transition (EMT), which implies the loss of cell-cell contacts, remodeling of cytoskeleton, and the acquisition of a migratory phenotype [29, 30]. Reduced expression of E-cadherin and abnormal expression of integrins, Notch, MET, TGFβ, NF-kB, PI3K, TWIST1, matrix metalloproteinases, components of the urokinase plasminogen-activating system, and p21-activated kinase, all of them involved in the EMT, have been identified in TC progression [29–34].

3. Small-molecule inhibitors of protein kinases: a new hope for the treatment of the most aggressive thyroid cancers

As above mentioned, the identification of new therapeutic approaches able to improve the prognosis of PDTC and ATC patients is urgently required. Over the last decade, the advancements made in the comprehension of the molecular mechanisms underlying TC progression gave the opportunity to develop novel therapeutic approaches, based on small molecule inhibitors of tyrosine kinases and mitotic kinases, showing promising results in preclinical and clinical studies (**Table 1**) [19, 35, 36]. In the following paragraphs, the results of these studies will be reviewed.

Kinase inhibitors			
Drug	**Molecular target(s)**	**Status**	**References**
CLM3 and CLM29	RET, EGFR, and VEGFR	Preclinical	[43–47]
Sorafenib (Nexavar)	VEGFR-2, VEGFR-3, c-KIT, PDGFR, RET/PTC, Raf	Phase III	[48–52]
Vandetanib (ZD6474)	VEGFR-2, VEGFR-3, EGFR, and RET	Phase II	[53, 54]
Motesanib (AMG 706)	VEGFR, PDGFR, and c-KIT	Phase II	[55, 56]
Axitinib (AG-013736)	VEGFR, PDGFR-beta	Phase II	[57–61]
Sunitinib (SU011248)	VEGFR, PDGFR, and RET/PTC	Phase II	[62–68]
Cabozantinib (XL184)	VEGFR, C-MET, RET, c-KIT, FLT3, AXL, TRKB, and Tie-2	Phase I	[69–71]
Pazopanib (GW786034)	VEGFR, PDGFR, c-KIT, and Aurora-A kinase	Phase II	[72, 73, 108, 109]
Lenvatinib (E7080)	VEGFR, FGFRs PDGFRa, RET, and c-KIT	Phase II	[74–76]

Kinase inhibitors			
Drug	**Molecular target(s)**	**Status**	**References**
Vemurafenib (PLX4032)	BRAF	Phase II	[80]
CEP-32496	BRAF	Preclinical	[81]
Everolimus (RAD001)	mTORC1	Phase I	[82, 87]
MK-0457 (VX-680)	Aurora kinases	Preclinical	[101]
SNS-314	Aurora kinases	Preclinical	[102]
ZM447439	Aurora kinases	Preclinical	[103]
AZD1152	Aurora-B	Preclinical	[97, 104, 106]
MLN8054	Aurora-A	Preclinical	[105, 107]
MLN8237	Aurora-A	Preclinical	[106, 108]
BI 2536	Polo-like kinase 1	Preclinical	[110–112]
GSK461364A	Polo-like kinase 1	Preclinical	[113]

Table 1. New potential drugs for the treatment of aggressive epithelial thyroid cancer being exploited in preclinical and clinical studies.

3.1. Tyrosine kinase inhibitors

An increased knowledge of the molecular mechanisms involved in cancer has allowed the development of therapeutic agents that target specific pathways involved in the tumor growth

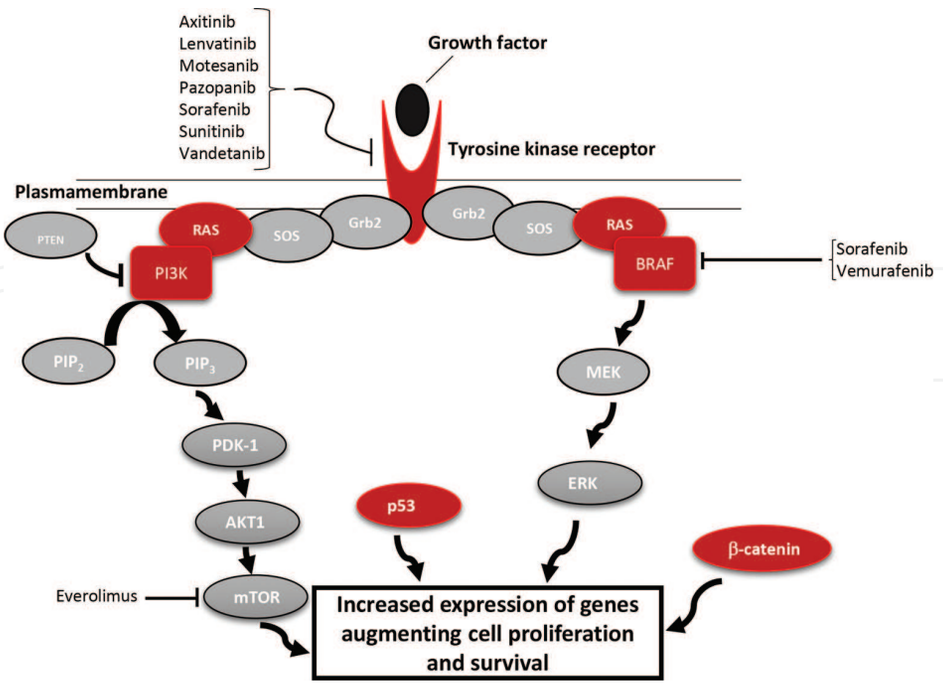

Figure 1. Molecular alterations (in red) involved in thyroid cancer progression and new targeted therapies being exploited in preclinical and clinical studies.

and progression, including RET, BRAF, RAS, epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) receptor (VEGFR), etc. [37] (**Figure 1** and **Table 1**). Among these, tyrosine kinase inhibitors (TKI) have come out as a new class of anticancer drugs [38]. TKI are small compounds that compete with the ATP-binding sites of the TK catalytic domains, affecting TK-dependent oncogenic pathways [39]. TKI act through the occupation of these sites inhibiting autophosphorylation and activation of TKs and preventing the activation of intracellular signaling cascades. These compounds can be specific to one or several homologous TKs [40]. However, a resistance to TKI treatment could occur when the inhibition of one kinase receptor is compensated by the activation of other TK pathways [41]. This suggests that the best way to approach cancer may be the simultaneous inhibition of multiple activated TKs [42].

3.1.1. RET pathway

The pyrazolo[3, 4-d]pyrimidine (PP) heterocyclic core is one of the most explored chemical templates, with a large spectrum of activity and active against RET. CLM3 and CLM29, pyrazolo[3, 4-d]pyrimidine derivatives with antiangiogenic activity, targeting RET, EGFR, and VEGFR, are capable of impairing the migration of dedifferentiated PTC (DePTC) cells [43–45]. Moreover, CLM3 and CLM29 exert antineoplastic activity in primary ATC cells [43, 46, 47].

3.1.2. Raf kinase pathway

Sorafenib is a bi-aryl urea multi-targeted TKI, with inhibitory activity against VEGFR-2 and 3, c-KIT, PDGFR, RET/PTC, Raf kinases, and the Raf/Mek/Erk pathway, able to induce apoptosis through downregulation of Mcl-1 [48, 49]. Sorafenib has been approved for the treatment of primary kidney cancer and advanced primary liver cancer. After several phase II trials, it has been conducted a multicenter double-blind randomized phase III study (DECISION trial), evaluating sorafenib versus placebo in advanced/metastatic radioactive iodine (RAI)-refractory DTC [50–52]. Patients in treatment with sorafenib showed a median progression-free survival (PFS) significantly longer (10.8 months) compared to those treated with placebo (5.8 months).

3.1.3. VEGF pathway

Vandetanib (ZD6474) is an orally active TKI with a good inhibitory activity on VEGFR-2 and also targeting VEGFR-3, EGFR, and RET kinases [53]. One hundred and forty-five patients with locally advanced/metastatic DTC, 72 of whom receiving vandetanib (300 mg/daily) and 73 placebo, were involved in a double-blind phase II study. Improved PFS were recorded in TKI-treated patients (11.1 months), compared to ones who received placebo (5.9 months), and partial response (PR) and stable disease (SD) were 8% and 57% in the former against 5% and 42% in the second group [54].

Motesanib diphosphate (AMG 706) is an ATP-competitive inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, and KIT. It was studied in several phase I and one phase II trials, where it was given orally 125 mg/day in patients with metastatic TC [55, 56]. The phase II trial was

http://dx.doi.org/10.5772/64086

conducted in 184 patients (93 DTC and 91 MTC) for 48 weeks. Among the DTC patients 57 were PTC (61%): PR was obtained in 14% of cases; SD was obtained in 35% for 24 weeks (or longer); serum thyroglobulin diminished with respect to the baseline in 81%; 7 patients (8%) had tumor progression, and median PFS was 40 weeks [56].

Axitinib (AG-013736) is an indazole derivative inhibitor of tyrosine kinase receptors with picomolar potency against VEGFR-1, VEGFR-2, and VEGFR-3 and nanomolar potency against PDGFR-beta [57–59]. In a phase II trial sixty patients with advanced TC (30 PTC, 15 FTC, and 11 MTC) were treated with axitinib (5 mg twice daily): 38% of patients obtained SD for at least 16 weeks, while 30% achieved PR [60]. Median PFS was 72.4 weeks (18.1 months). Fifty-two patients with metastatic or locally advanced MTC or DTC were involved in another phase II trial with axitinib (5 mg twice daily) [61]. The objective response rate (ORR) was 35% (18 PR), and SD was shown in 18 patients for more than 16 weeks. Median PFS was 16 months, and median overall survival was 27 months [61].

Sunitinib (SU011248), a multitarget TKI, inhibits selectively VEGFR-1, VEGFR-2, and VEGFR-3, PDGFR, c-KIT, and RET/PTC subtypes 1 and 3 [62]. It has been approved to treat gastrointestinal stromal tumor and clear-cell renal carcinoma, and it is now investigated in other human cancer types [63]. This TKI strongly inhibits the growth of the PTC-derived TPC1 cell line, bearing RET/PTC rearrangements [64]. However, indications emerged that clinical application of sunitinib should be directed by genotyping, since it inhibits RET/PTC- but not BRAF-mutated cells, as highlighted by another preclinical study in which the different inhibitory mechanisms of this drug against BRAF mutations or RET/PTC rearrangements were evaluated in cell lines or orthotopic TC mouse model [65]. In the largest open-label phase II trial performed to date, 28 patients with aggressive DTC and 7 with MTC were administered with sunitinib (37.5 mg) on continuous basis, showing a complete response (CR) in 3%, PR in 28%, and SD in 46% of cases [66]. Recently, several studies reported the efficacy of the therapy with sunitinib in progressive metastatic DTC patients [67]. Twenty-three patients were enrolled in a single center, nonrandomized, open-label, phase II clinical trial and treated with a starting daily, oral dose of 37.5 mg sunitinib. Six (26%) patients achieved a PR, and 13 (57%) had SD for a clinical benefit rate (PR + SD) of 83%. The overall median PFS was 241 days [68].

The oral multiple receptor kinase inhibitor cabozantinib (XL184) inhibits VEGFR-1, VEGFR-2, VEGFR-3, C-MET, RET, c-KIT, TRKB, AXL, FLT3, and Tie-2 [69, 70]. One phase I trial was recently carried out in a cohort of 15 patients with metastatic DTC who had failed standard radioactive iodine therapy [71]. Patients received cabozantinib with 140 mg free base (the same as 175 mg salt form) daily: PR was shown in 8/15 (53%), while SD in 6/15 (40%) [71].

Another VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, and c-KIT inhibitor is pazopanib (GW786034), approved for the treatment of renal cell carcinoma [72]. In a phase II trial, 37 patients with metastatic, rapidly progressive, and radioiodine-refractory DTC received pazopanib: a PR was achieved in 18 patients (49%) with 800 mg/day orally, but no CR were observed [73]. However, disease progression (PD) or clinical deterioration was ultimately observed in 27 of the 37 patients [73].

Lenvatinib (E7080) is an oral, multitarget TKI of the VEGFR-1, VEGFR-2, and VEGFR-3, FGFRs 1 to 4, PDGFR α, RET, and KIT [74]. After a phase II study, a randomized, double-blind, multicenter phase III study was carried out on lenvatinib (SELECT) in patients with progressive RAI-refractory TC, who randomly received the drug (261 patients, at a daily dose of 24 mg per day in 28-day cycles) or placebo (131 patients) [75, 76]. Median PFS was 18.3 months in the lenvatinib group and 3.6 months in the placebo one ($P < 0.001$). In the lenvatinib group, there were 4 CR and 165 PR, with a response rate of 64.8% *versus* 1.5% in the placebo group ($P < 0.001$).

3.1.4. BRAF inhibitors

BRAF is a serine-threonine kinase that mediates the signal transduction of the MAP/extracellular signal-regulated kinase (ERK) kinase (MEK)-ERK pathway, and it is a critical regulator of normal growth, differentiation, and oncogenic transformation (**Figure 1**). BRAF mutations are associated with lymph node metastases, extrathyroidal extension, tumor size, and multifocality in PTC [77, 78]. In addition, activation of BRAF significantly reduces NIS expression through the induction of robust TGFβ secretion. TGFβ, acting via Smad, was described as a potent repressor of NIS transcription through the functional antagonism of Smads and Pax8, a transcription factor essential for thyroid differentiation [79]. Although this mechanism is MEK-ERK independent, secreted TGFβ cooperates with MEK-ERK signaling in BRAF-induced cell migration, invasion of extracellular matrix, and EMT.

Vemurafenib (PLX4032), an oral analog of PLX 4720, inhibits BRAF and it is already approved for treatment of advanced melanoma. Safety and efficacy of vemurafenib in advanced PTC are currently under study in a phase II trial [80].

Another BRAF inhibitor having multi-kinase binding activity, CEP-32496, showed in vitro selective cellular cytotoxicity for BRAF(V600E) versus wild-type cells. Sustained tumor stasis and regressions were observed with oral administration (30–100 mg/kg twice daily) against $BRAF^{V600E}$ melanoma and colon carcinoma xenografts, with no adverse effect. Thus, it is expected to be effective in the treatment of BRAF-dependent malignancies, among which TC [81].

3.1.5. Mammalian target of rapamycin (mTOR) inhibitors

The mTOR is a serine/threonine kinase that nucleates at least two distinct multi-protein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), and acts through the phosphorylation of a number of proteins regulating protein synthesis, metabolism, and cell growth and survival [82, 83]. The mTOR is a major downstream effector of the PI3K/Akt pathway, involved in thyroid carcinogenesis. Activated mTOR is known to control protein synthesis through phosphorylation of the eukaryotic initiation factor 4E (eIF4E) binding protein 1 (4E-BP1) and release of active eIF4E, a key regulator of translation of gene products that participate in regulation of the cell cycle. In aggressive types of PTC and MTC cells, it was seen a strong activation of the mTOR signaling and overexpression of the initial factor eIF4E, whose levels were correlated with tumor aggressiveness [84].

http://dx.doi.org/10.5772/64086

Everolimus (RAD001) is an orally active rapalog (rapamycin analog) that inhibits mTORC1 upon binding FKBP12, a member of the FKBP family of immunophilins [85, 86]. The RAD001-FKBP12 complex interacts with the FKBP12 binding domain of mTOR and blocks the assembly of a functional TORC-1. Everolimus has been approved by FDA for the treatment of patients with advanced renal carcinoma and tested in vivo on MTC [87]. Fury et al. administered everolimus plus cisplatin in 30 patients with advanced solid tumors in a recent phase I study, seven of which had TC (5 DTC, 2 MTC). One patient with PTC completed 14 cycles and achieved SD [82].

3.2. Mitotic kinase inhibitors

The recognition that cell-cycle deregulation represents a hallmark of human cancers has led to the generation of several mitosis-based anticancer therapies [88]. Spindle microtubule-targeting agents (MTA) remain to date the most widely used and reliable antimitotic drugs for the treatment of several human cancers [89, 90]. MTA include microtubule-destabilizing agents, like vinca alkaloids, that inhibit microtubule polymerization and microtubule-stabilizing agents, like taxanes, that stimulate microtubule polymerization [89, 90]. A major limitation in the use of MTAs derives from the side effects observed on the microtubules of quiescent interphasic cells (i.e., neurotoxicity), by disrupting physiological processes such as vesicular trafficking, axonal transport, and cytoskeleton functions. Myeloid toxicity, resulting from the mitotic arrest of bone marrow cells, also occurs. This, along with the tumor cell resistance to MTAs, which appears in ATC, has prompted further research for the identification of new antimitotic drugs nontargeting the spindle microtubules [91].

The three members of the Aurora kinase family, Aurora-A, Aurora-B, and Aurora-C, and the polo-like kinase 1 (PLK1) are serine/threonine kinases playing a major role in the G2/M phase transition and in the regulation of several mitotic processes [19, 92]. Consistent with their role, the expression and activity of the Aurora kinases and PLK1 are low in the G0, G1, and S phases, rise in the late G2, and peak during the M phase [19, 93]. Aurora-A and PLK1 cooperate in the activation of the CDK1/cyclin B complex allowing the transition of the cell from the G2 to the M phase [19]. In addition, both Aurora-A and PLK1 are essential for centrosome maturation and bipolar spindle formation [19, 93]. Aurora-B, along with INCENP, Survivin, and Borealin, is a component of the chromosomal passenger complex (CPC), which localizes on the chromosome arms in prophase, concentrates in the inner centromere region from prometaphase to metaphase, then moves to the central spindle and cortex in anaphase, and remains in the midbody in telophase [19]. The CPC ensures accurate chromosome segregation by regulating chromosome structure, cohesin removal from the chromosomal arms, spindle formation, kinetochore assembly, correction of non-bipolar chromosome-microtubule connections, spindle assembly checkpoint, and cytokinesis [19]. Aurora-C, similarly to Aurora-B, takes part in the CPC, but it is mainly expressed in germ cells during spermatogenesis and oogenesis and in some cancer cell lines [94, 95]. Also PLK1 has been demonstrated to be involved in sister chromatid cohesion and formation of kinetochore-microtubule attachments, mitotic exit, and cytokinesis [93]. Therefore, in view of their important mitotic roles, aberrant expression

and/or function of Aurora kinases and PLK1 may lead to abnormal cell divisions with consequent generation of aneuploid cells.

An increased expression of all three Aurora kinases and PLK1 was shown in various cell lines originating from different epithelial TC histotypes, compared to normal thyrocytes, as well as in DTC and ATC tissues, compared to normal matched tissues [19, 20, 88, 96–98]. In addition, a study aimed to evaluate the gene expression profile in ATC, by means of tissue microarray and immunohistochemistry, identified the gene encoding Aurora-A as one of the most frequently and most strongly overexpressed in these tumors [99]. This is consistent with the observation that gain of chromosome 20q, where Aurora-A gene is located (20q13.2), is often encountered in ATC [100]. Based on these findings, the potential therapeutic value of Aurora kinases and PLK1 inhibition on the proliferation and growth of ATC cells has been evaluated in preclinical and clinical studies (**Table 1**).

Concerning the Aurora kinases, the in vitro effects of different small molecule pan-inhibitors, including the MK-0457 (VX-680), the SNS-314 mesylate, and the ZM447439, were investigated on proliferation, apoptosis, cell cycle, ploidy, and anchorage-independent growth of a panel of ATC-derived cell lines [101–103]. All these inhibitors were found to reduce proliferation of ATC cells in a time- and dose-dependent manner and to inhibit colony formation in soft agar. Cytofluorimetric analysis of cell cultures exposed to the Aurora inhibitors revealed an accumulation of tetra- and polyploid cells because of endoreplication events followed by activation of the apoptotic process [101–103]. Treated cells showed mitotic alterations consistent with Aurora kinase inhibition, including major spindle defects, inhibition of histone H3 phosphorylation, and cytokinesis failure [101–103]. Similar effects were obtained with the selective inhibition of either Aurora-A or Aurora-B [97, 104–106]. Suppression of Aurora-B expression by means of RNA interference, or of Aurora-B function by AZD1152, was demonstrated, in vivo and in vitro, to reduce growth and tumorigenicity of different ATC-derived cells [97, 104, 106]. In the same way, selective functional inhibition of Aurora-A by MLN8054 or MLN8237 was shown to inhibit cell proliferation and to induce cell-cycle arrest and apoptosis in a panel of ATC-derived cell lines [105, 106]. In xenograft experiments MLN8054 was found to reduce tumor volume by 86% [105]. Moreover, the combined treatment with MLN8054 and bortezomib, targeting the ubiquitin-proteasome system, showed additive effects on ATC-derived cell proliferation and apoptosis, compared to monotherapy [107]. It is worth to note that pazopanib, a TKI abovementioned, was found to potentiate the cytotoxic effects of paclitaxel in a preclinical study on ATC-derived cell lines in vitro and in vivo [108]. This effect of pazopanib was attributed to an unexpected off-target inhibition of Aurora-A. In fact, similar results were obtained when paclitaxel was combined with the selective Aurora-A inhibitor MLN8237. Remarkably, in the same study the authors showed that the combined administration of pazopanib and paclitaxel achieved a strong and long-lasting regression of lung metastasis in a single ATC patient [108]. However, while pazopanib was shown to have impressive therapeutic activity in patients affected by RAI-refractory PDTC, it was ineffective when tested in a phase II clinical trial on ATC patients [73, 109]. Although several of them had a transient disease regression, no Response Evaluation Criteria in Solid Tumors (RECIST) response was obtained [109].

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Regarding PLK1, different studies demonstrated that it could represent a valuable therapeutic target in PDTC and ATC [110–112]. The potential of PLK1 inhibition in cancer treatment was investigated by means of antisense oligonucleotides, small interfering (si) RNA, and small molecule inhibitors targeting either the N-terminal catalytic domain or the C-terminal polo-box (PB) domain, responsible for kinase subcellular localization [113]. In vitro experiments on a panel of ATC-derived cell lines showed that PLK1 inactivation by BI 2536, an ATP-competitive small molecule inhibitor, induced cell arrest in prometaphase with accumulation of cells with 4N DNA content and mitotic spindle aberrations [110]. ATC cells finally died, as evidenced by the increased levels of cleaved caspase-3 and apoptotic nuclear morphology [110]. In agreement with the results of this study, more recently a different PLK1 inhibitor, the GSK461364A, was reported to inhibit cell proliferation and to induce cell death in different PDTC- and ATC-derived cell lines, independent of the nature of their driver mutations [113]. Consistent with PLK1 inhibition, the drug was shown to induce a G2/M arrest, followed by apoptosis. GSK461364A was also effective in vivo, in an allograft model of ATC [113]. Taken together, these data suggest that PLK1 targeting is a promising and effective therapeutic approach against PDTC and ATC [113].

4. Conclusions

In spite of the generally good prognosis of patients affected by thyroid carcinomas, approximately 5% of them will develop metastatic disease not responsive to traditional therapies. New drugs have been developed following the increased knowledge of the molecular alterations occurring in thyroid carcinomas. Tyrosine kinase and mitotic kinase inhibitors are now emerging as new drugs for the therapy of aggressive thyroid cancers, capable of prolonging patients' median progression-free survival. So far, however, no significant improvement has been observed on overall patients' survival. It has also to bear in mind that side effects are common, limiting the dose and time of drug administration. Aims of a future development in this field will be the identification of new, more effective and safe compounds and tailoring of the new targeted therapies in each patient based on tumor-specific genetic background.

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