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REVIEW

Management of Progressive Radioiodine-Refractory Thyroid Carcinoma: Current Perspective

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Abstract: Patients with thyroid cancer (TC) usually have an excellent prognosis; however, 5–10% of them develop an advanced disease. The prognosis of this subgroup is still favourable if the lesions respond to radioactive iodine (RAI) treatment. Nearly two-third s of advanced TC patients become RAI-refractory (RAI-R), and their management is challenging. A multidisciplinary approach in the context of a tumour board is essential to define a personalized strategy. Systemic therapy is not always the best option. In case of slow neoplastic growth and low tumour burden, active surveillance may represent a valuable choice. Local approaches might be considered if the disease progression is limited to a single or few lesions, also in combination and during systemic therapy. Antiresorptive treatment may be started in presence of bone metastases. In case of rapid and/or symptomatic progression involving multiple lesions and/or organs, systemic therapy has to be considered, in absence of contraindications. The multi-kinase inhibitors (MKIs) lenvatinib and sorafenib are currently available as first-line treatment for advanced progressive RAI-R TC. Among second-line options, cabozantinib has been recently approved in RAI-R TC who progressed during MKIs targeting the vascular endothelial growth factor receptor (VEGFR). In the last few years, next-generation sequencing (NGS) assays have been increasingly employed, permitting identification of the genetic alterations harboured by TC, with a significant impact on patients' management. Novel selective targeted therapies have been introduced for the treatment of RAI-R TC in selected cases: REarranged during Transfection (RET) inhibitors (selpercatinib and pralsetinib) and Tropomyosin Receptor Kinase (TRK) inhibitors (larotrectinib and entrectinib) have recently expanded the panorama of the therapeutic options. Moreover, immune checkpoint inhibitors (ICIs) have shown promising results, and they are still under investigation.

Keywords: multidisciplinary tumour board, loco-regional treatment, multi-kinase inhibitor, selective RET inhibitor, selective TRK inhibitor, immunotherapy

Introduction

Thyroid cancer (TC) is the most common endocrine tumour, and differentiated TC (DTC) accounts for 85–95% of all TCs.[1] Although the majority of TC patients have an excellent prognosis, 5–10% of them develop an advanced disease. The prognosis of this subgroup is still favourable as long as the tumour maintains the ability to respond to radioactive iodine (RAI) treatment. However, 60–70% of patients with advanced TC become RAI-refractory (RAI-R). This event leads to a drop of the 10-year survival rate to less than 20%, with a mean life expectancy of 3–5 years.[2,3]

The loss of RAI sensitivity can be the consequence of an impairment of the normal mechanisms regulating iodide metabolism in TC cells. For example, their ability to concentrate RAI is reduced in case of low sodium iodide symporter (NIS) expression, which could be a consequence of the overactivation of the mitogen-activated protein kinase (MAPK) pathway, such as in case of BRAF-mutated TC.[4] Radiosensitivity can be lost especially in case of poorly differentiated histotypes, larger metastases, high ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake, and older age.[2]

According to recent guidelines and recommendations, RAI refractoriness may be defined in the absence of RAI uptake in all or in some lesions on a RAI scan, and/or in case of progression despite RAI uptake, and/or after having reached a cumulative RAI activity of 22.2 gigabecquerel (gBq).[3,5] However, many controversies regarding this definition

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still persist. The proposed criteria should be used to estimate the likelihood that a tumour will respond to RAI therapy, rather than to recommend RAI therapy or not. This implies the need of a multidisciplinary team in the patient-centred decision-making process.[5] In this review, we will focus on the salient points in the management of RAI-R TC, based on current evidence, with a look at future perspectives.

Characterization and Management of RAI-R TC Patients: How to Choose the Best Strategy

In all TC patients with persistent structural disease, it is recommended to achieve suppressed levels of thyroid-stimulating hormone (TSH) (<0.1 μIU/mL), in absence of contraindications.[6,7]

Multi-kinase inhibitors (MKIs) with anti-angiogenic activity have recently revolutionized the management of RAI-R TC. Sorafenib and lenvatinib have been approved as first-line systemic treatment in advanced and progressive disease by both the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA), thanks to the impressive results of phase 3 DECISION and SELECT trials, respectively.[8,9] The benefit of systemic therapies was confirmed also in real-life populations; when compared to registrative trials, progression-free survival (PFS) seemed to be less favourable, likely due to the different patient characteristics.[10,11]

However, MKI therapy is not always the most suitable option for all RAI-R TC patients. In some cases, a watchful waiting strategy can be safely adopted instead of a systemic treatment. In selected subjects, loco-regional treatments can be performed, alone or in combination with MKI.[3,6,12] Both the expected survival benefit and the potential toxicity of a targeted therapy in each single patient must be considered when planning the best strategy. On the basis of data deriving from post hoc analyses of phase 3 trials and retrospective evaluations, some authors have even proposed a scoring system which integrate multiple factors in order to identify patients potentially eligible to MKI therapy.[13] In general, several aspects should be considered in the selection of the most appropriate strategy in case of advanced RAI-R TC, including clinical, biochemical, and morpho-functional data, together with patient preferences, according to a personalized approach.

Radiological Imaging

A periodic radiological assessment is essential to identify the ideal timing for the MKI start in RAI-R TC patients. Contrast-enhanced computed tomography (CT) can be scheduled at 3-, 6-, or 12-month intervals, on a clinical judgment basis.[14] As in clinical trials, Response Evaluation Criteria in Solid Tumours (RECIST) are commonly applied also in real-life practice to identify target lesions and determine the disease status.[15]

Both the neoplastic growth velocity and the tumour burden should be carefully evaluated.

According to the international guidelines regarding RAI-R TC patients, a wait-and-see approach can be adopted in case of slowly progressive disease. Conversely, a rapid enlargement of the lesions should orient towards the start of MKI treatment.[3,6,12]

In patients with lung metastases, the tumour-volume doubling time (TV-DT) has been proposed as a useful tool to distinguish subjects with a more aggressive disease. Instead of considering the variation of neoplastic lesions in a single diameter, TV-DT reflects the volume change of lesions over time; it can be easily calculated using the Kuma Hospital calculator (https://www.kuma-h.or.jp/english/about/doubling-time-progression-calculator). According to a retrospective evaluation, patients with a TV-DT ≤1 year had a worse prognosis in comparison to cases with longer TV-DT. In this subgroup, a significant benefit was preliminarily observed with the use of MKI therapy, suggesting the utility of this parameter in the identification of patients that should be addressed to systemic treatment.[16]

Tumour burden might play a role in orienting toward the MKI treatment. According to a post hoc analysis of the SELECT trial, lenvatinib-treated patients with a smaller tumour size at baseline (defined as the sum of the longest dimensions of measurable target lesions) showed a better overall survival (OS): the adjusted hazard ratio (HR) was 0.55 (95% CI 0.35–0.88) in case of baseline tumour size ≤40 mm versus >40 mm.[17] These data are consistent with a previous post hoc evaluation of the same phase 3 trial: significant survival prolongation was observed in MKI-treated patients with baseline lung metastases ≥1.0 cm versus placebo, despite the high rate of crossover; in both the treated and the untreated arms, median OS was shorter in patients with larger lung metastases (≥2 cm) versus patients with lung metastases of ≥1 cm.[18] Overall, these results suggest that the effect of targeted therapy may be greater when the tumour burden is

lower. Conversely, delaying the start of MKI therapy in patients with a high tumour load may negatively affect the patients' prognosis.[19]

Nuclear Medicine Imaging

Functional evaluation by ^{18}F-FDG positron emission tomography (PET)/CT can be employed in combination with morphological imaging techniques to select the cases with a more aggressive disease requiring intensive treatments. ^{18}F-FDG PET/CT showed good sensitivity and specificity for the detection of lesions in DTC patients with negative ^{131}I whole-body scan (WBS) and high serum thyroglobulin (Tg) levels, providing a whole-body assessment that is extremely useful for disease staging. Moreover, it offers additional data on tumour biology and gives prognostic information, since DTC patients with PET-positive neoplastic lesions showed a significantly worse survival in comparison to patients without increased glucose uptake.[20] The pre-administration of recombinant human TSH (rhTSH) does not seem to provide significant additional information for the decision-making process.[21]

Biochemical Parameters

Serum Tg level on l-thyroxine therapy and its trend over time can provide valuable additional information: Tg values generally correlate with tumour burden, and Tg doubling time (Tg-DT) <1 year can predict rapid disease progression and poor prognosis.[22] Nevertheless, this marker cannot be considered reliable in the presence of elevated anti-thyroglobulin antibodies (TgAbs) levels. Moreover, Tg levels might not reflect the tumour load in aggressive poorly differentiated TCs (PDTCs) that lose the ability to synthesize and/or secrete Tg.[23] Therefore, the isolated increase of Tg should not lead to the start of a MKI in the absence of evident structural disease progression.

Tumour-related inflammation and host immune response have been shown to play a pivotal role in cancer progression in several malignancies. Among biochemical data, the neutrophil-to-lymphocyte ratio (NLR) has been recently proposed as a parameter to be evaluated in RAI-R TC patients who are candidates for systemic treatment. NLR is defined as the ratio between the number of absolute neutrophil and absolute lymphocyte counts; it reflects the antitumoral immunity status and has a prognostic role in several solid tumours. In metastatic RAI-R TC patients, subjects with a NLR >3 before the start of MKI had a significantly worse survival than cases with NLR ≤3, also in a post hoc analysis of the SELECT trial.[24] Since patients with higher NLR appeared to have a more aggressive disease, an intensive management might be useful.[25]

Recently, the prognostic role of the Controlling Nutritional Status (CONUT) score, an immuno-nutritional screening tool based on serum albumin, total cholesterol, and lymphocyte count, has been retrospectively evaluated in patients with advanced TKI-related TCs. It was observed that both PFS and OS were better in patients with CONUT score <3 than in those with CONUT score ≥3 before the start of MKI therapy.[26]

Clinical Parameters

A careful clinical evaluation is always recommended during the periodical follow-up visits. Commonly, patients' clinical conditions are worst in real-life settings when compared to registrative clinical trials. To ensure a safe and effective use of MKI, a multidisciplinary approach should constitute the standard of care.

The presence of comorbidities or contraindications to treatments must be taken into account.[3,6,12] A special attention should be reserved to tumour-related symptoms, which generally orient toward a more aggressive strategy. In selected cases, additional diagnostics procedures may be useful to assess the local neoplastic extension and the associated imminent risk of complications. In a post hoc analysis of the DECISION trial, sorafenib demonstrated prolonged PFS in both asymptomatic and symptomatic treated patients compared with those treated with placebo.[27] However, data from studies specifically focused on the relationship between tumour-related symptoms and response to MKI are lacking.

Performance status (PS) should be assessed by Eastern Cooperative Oncology Group (ECOG) scale or Karnofsky's index, in order to describe a patient's level of functioning. ECOG PS (0 versus ≥1) resulted in a prognostic factor for PFS and OS in a retrospective analysis of the SELECT trial in lenvatinib-treated patients.[24] Other important aspects to take into consideration are the nutritional status and the body composition. In TC patients, malnutrition is common and is caused by a compromised intake or assimilation of nutrients due to the cancer itself, but potentially worsened by MKI treatment. Malnutrition can be accompanied by weight loss and sarcopenia, characterized by loss of skeletal muscle

mass. The association between sarcopenia and treatment outcomes of MKIs in metastatic TC has been retrospectively investigated, resulting in an independent prognostic factor for PFS at multivariate analysis.[28] Moreover, a retrospective exploratory analysis of data from the DECISION trial has been performed to assess the relationship between MKI therapy, risk of toxicity, and presence of sarcopenia: even if no significant association was found between sarcopenia and MKI dose modification due to adverse events (AEs), an effect of sorafenib on muscle mass was observed.[29] Alterations in body composition were observed also in TC patients during lenvatinib treatment.[30]

Overall, a nutritional screening before starting MKI and during follow-up seems essential to guarantee a safe start and a better tolerance to treatments and improve patients' prognosis.[31] Multimodal prehabilitation programmes have been introduced in the management of several solid tumours, including TC.[32] Cancer prehabilitation includes the identification and the optimization of care of pre-existing comorbidities, nutritional counselling, physical exercise programme, and psychological support, aiming to improve the patient's functional capacity with targeted interventions before the start of a treatment.[33]

Genetic Profile

TC initiation is commonly driven by mutually exclusive mutations of genes belonging to the MAPK and phosphatidylinositol 3-kinase (PI3K) pathways (eg $BRAF^{V600E}$, RAS). In TC progression, the loss of differentiation is associated to the increased mutational burden due to accumulation of additional mutations (eg, TP53, TERT).[1,34]

The understanding of the molecular mechanisms underlying thyroid tumorigenesis has led to the identification of potential targets for systemic therapies more selective than MKIs, including REarranged during Transfection (RET) inhibitors or Tropomyosin Receptor Kinase (TRK) inhibitors, which have recently shown impressive results also in RAI-R TC patients.[35]

In recent years, next-generation sequencing (NGS) assays have been increasingly employed, allowing the simultaneous analysis of several genomic alterations by using targeted sequencing panels. This new technology can easily identify the genetic alterations harboured by TC, both point mutations of proto-oncogenes and chromosomal rearrangements, with a significant impact on the management and outcome in the RAI-R TC setting.[36]

Loco-Regional Approaches

In RAI-R TC patients, the use of loco-regional treatments (LRTs) before the start of systemic therapies might be considered in case of oligometastatic and/or oligoprogressive disease, aiming to obtain local control and relief of symptoms. The rationale behind this approach lies in the significant impact of MKI therapies on patients' well-being, which induces the clinician to choose the systemic treatment only in case of symptomatic and/or multimetastatic, progressive TC.[3,12]

In selected cases, LRTs can be employed alone or in combination with systemic therapies according to a multimodal strategy, mainly for treating single or few progressive and/or symptomatic lesions, while the remaining localizations are effectively controlled by MKI treatment.[3] In these cases, a transient interruption of MKI has to be considered before the planned LRTs, taking into account the type of intervention and the half-life of the drug.[37]

In general, LRTs must be performed by expert teams after multidisciplinary tumour board agreement, since a cautious selection of the candidates is mandatory.

Surgery has a primary role in the management of local cervical relapse, especially in the paratracheal soft tissues, given the associated increased risk of invasion of vital structures. The involvement of the aerodigestive tract should always be excluded through endoscopy in patients with loco-regional relapse and, if present, must be treated, especially in case of symptomatic obstruction and/or significant risk of bleeding and other local complications. In case of recurrent cervical lesions not amenable to surgery, other available treatment methods include external beam radiotherapy (EBRT).[3,12] Both surgical and EBRT approaches to locally invasive lesions constitute risk factors for tracheo-esophageal fistula formation during MKI treatment for advanced RAI-R TC. Therefore, the occurrence of this rare but potentially life-threatening AE should be carefully taken into account in case of local treatment for aerodigestive infiltration and subsequent MKI treatment.[38]

A surgical approach might be employed in case of bone metastases (BMs) too, especially for spinal lesions with impending fracture risk, pain, or instability.[39] Complete resection of BMs showed a possible survival benefit in selected cases, according to some authors, particularly in case of younger age, good PS, and oligometastatic disease.[40] In the palliative setting, surgical intervention maintains a role in treating symptomatic lesions and preventing skeletal-related events (SREs), such as pathological fracture and spinal cord compression.[39]

In RAI-R TC patients, also metastases in other sites could be surgically treated, including liver or brain lesions. The metastatic involvement of these two organs usually occurs in case of very advanced and plurimetastatic disease; therefore, patients are often ineligible for a surgical intervention with radical intent.[12] A possible survival benefit deriving from the surgical approach was observed in a small retrospective cohort. However, the rarity of these types of metastases and the limited quality of the studies do not allow definitive recommendations to be made.[41,42]

Although RAI-R TC is not particularly sensitive to radiation, EBRT is frequently employed in the advanced metastatic setting to slow down the growth rate of the neoplastic lesions. This technique can be used for a wide range of distant metastases.[3] In case of brain metastasis, the approach differs on the basis of the number and localization of lesions. Whole-brain RT is mainly employed for managing multiple and diffuse lesions. Newer procedures, such as stereotactic EBRT, allow the physician to treat smaller lesions in a more precise way, limiting the damage to the surrounding healthy tissue, since they are able to deliver higher doses of radiation to the target lesion.[43] The high rate of response, the safety, and the low risk of local relapse associated with stereotactic EBRT have recently been demonstrated for brain metastases from DTC, especially in patients with good PS and low brain metastatic burden.[44] By using robotic arms and a target tracking system, radiosurgical systems like GammaKnife and CyberKnife allow a large number of lesions in virtually every organ to be treated with stereotactic EBRT.[45,46]

EBRT is also frequently employed in the treatment of BMs, especially in patients not amenable to surgical intervention, and it is particularly effective for the reduction of pain.[47] The typical fractionated scheme usually contemplates 20 Gray (Gy) given in 5 fractions or 30 Gy in 10 fractions; generally, the onset of the therapeutic effect is not immediate after the end of the RT cycle, unless a single dose of 8 Gy is employed. Despite its effectiveness and the low percentage of related AEs, EBRT might be associated with a significant risk of vertebral fractures, particularly in case of osteolytic lesions, high radiation doses, or previous pathologic fractures. A prophylactic stabilization could prevent this complication and, therefore, should be considered prior to EBRT treatment.[39] The real clinical impact of EBRT for RAI-R TC patients still needs to be established, also taking into account the non-significant effect on survival shown in a recent multicentre real-life experience.[48]

Percutaneous interventional techniques (PITs) are increasingly used for treating neoplastic lesions as an alternative to surgery approach. Being less invasive, they offer the possibility to treat patients with worse PS and more advanced disease. PITs could be employed in order to postpone the need of systemic therapy, but also alongside MKI treatment, to optimize disease control. They can also be effectively combined with other TLRs.[3]

Specific guidelines about the use of PITs in DTC have been recently published.[49] Embolization PITs (trans-arterial embolization, TAE; trans-arterial chemoembolization, TACE; trans-arterial radioembolization, TARE) can be employed in case of diffuse metastatic liver involvement. They have been demonstrated to be effective in cases of low metastatic liver burden (<30% of hepatic involvement) and lesions ≤3 cm.[3,50] They might also play a role in the treatment of BMs, mainly in the pre-surgical phase with the aim of significantly reducing the vascularization and the subsequent risk of intraoperative bleeding.[39]

Ablative PITs (radiofrequency ablation, RFA; microwave ablation, MWA; ethanol ablation; cryoablation) can be applied to local relapses or lymph node metastases as an alternative to surgical intervention or EBRT.[49] Liver metastases can also be treated with ablative techniques, which are especially indicated for single or few lesions far from the hilum and the main bile ducts, given the risk of bile duct fibrosis.[50] When ablative PITs are employed in BMs, a subsequent consolidative technique is indicated to prevent a secondary fracture if the lesion is in a weight-bearing site. Cementoplasty can be performed in the treatment of osteolytic BMs, both alone and in association with ablative PITs or other TLRs, with the aim of ameliorating the bone segment stability and achieving pain relief.[39]

Literature regarding both embolization and ablative PITs in the treatment of RAI-R TC lesions is very limited. Moreover, precise indications for the different procedures and the optimal treatment sequence are still not known. Further studies are needed to explore the role of these approaches in the advanced TC setting.

Bone-Modifying Agents (BMAs)

In DTC patients, bone is the second most common site for distant metastases and the spine is the site where almost half of BMs are likely to occur.[51,52] BMs derive more frequently (7–28%) from follicular TC or PDTC than from papillary TC (1–7%); they are mainly osteolytic and associated with a worse overall prognosis than lung metastases.[53–55] More than 20% BMs from TC are RAI-R.[2] Patients with BMs must face a significantly reduced PS and quality of life (QoL), sometimes with intractable pain and/or neurological symptoms.[56,57] The occurrence of at least one SRE has been reported in up to 78% of patients with BMs, ultimately leading to an increase in mortality.[58]

BMAs have a crucial role in the clinical management of BMs, since they can prevent or treat damage from BMs in cancer patients by inhibiting osteoclast bone resorption.[59] Among them, the most widely used are the bisphosphonate (BP) zoledronic acid (ZA) and the fully human monoclonal antibody against receptor activator of nuclear factor-κB ligand (RANKL) denosumab (DEN). Both ZA and DEN showed efficacy in reducing SRE in solid tumours, including breast and prostate cancer.[60–63] A greater efficacy of DEN versus ZA was suggested by a meta-analysis; however, a more recent study showed only a non-inferiority of DEN compared to ZA in preventing SREs.[64,65]

Regarding BMA-related AEs, osteonecrosis of the jaw (ONJ) is a potentially serious but also rare complication common to ZA and DEN; in prospective clinical trials the rate of this complication was 1–2%, with a slightly increased risk shown with DEN versus BPs, although not statistically significant, and a higher frequency in patients with malignancies and during chemotherapy or head and neck EBRT.[66,67]

Other AEs common to ZA and DEN are hypocalcemia, with higher rates among DEN users, and the extremely rare atypical femoral fractures.[62,63,68,69] Risks specifically related to the use of ZA are nephrotoxicity and acute phase reactions, while a peculiar DEN-related AE is the rebound-associated increase in vertebral fractures after drug discontinuation.[70–72]

In order to reduce BMA toxicity, based on data deriving from studies in other solid tumours, it has been suggested to limit the cumulative dose of the drug, scheduling longer intervals between administrations.[73–75] The non-inferiority of a 12-week interval of ZA administration in comparison to 4-week interval in preventing SRE has been demonstrated; similar data for DEN are still preliminary.[76,77] In the recent ESMO guidelines, the 12-week schedule is suggested only for BPs, but not for DEN.[12]

Overall, the studies aiming to explore the effects of BMAs in patients with TC-BMs are scanty and mainly retrospective; a significant reduction in SREs was reported in studies including ZA-treated patients.[78–80] Robust data on the effects of DEN in this TC setting are lacking. Moreover, no conclusive data on the effect of BMA on OS in RAI-R TC have been reported.

The concomitant use of BMA and anti-angiogenic agents, including lenvatinib, has been reported to increase the risk of ONJ.[81,82] The data on the concomitant use of DEN and lenvatinib in RAI-R TC patients are scarce, but a clinical trial aiming to assess the outcomes on the combined use of lenvatinib plus DEN is ongoing.[83]

Although recommended by current clinical guidelines, the combined use of BMAs and MKIs requires special caution in real-life practice. The risk of ONJ during treatments with BMAs and/or TKIs can be reduced by preventive measures, such as careful oral examination including radiographic assessments, maintenance of a proper oral hygiene, and completion of dental treatments before the start of BMAs. Especially in high-risk subjects, regular dental examinations during systemic treatments are advisable.[84]

MKI Approved for RAI-R TC

Efficacy

Both lenvatinib and sorafenib were demonstrated to prolong PFS compared with placebo in the randomized phase 3 trials which included RAI-R TC patients (Table 1). Radiological evidence of disease progression within 13–14 months was

Table 1 Main Data from Registration Trial Data of the MKIs Approved for RAI-R DTC

Drug	Sorafenib	Lenvatinib	Cabozantinib
Molecular targets	VEGFR1-3, c-Kit, PDGFR, RET, RAF	VEGFR1-3, c-Kit, PDGFR, RET, FGFR	VEGFR1-2, c-Kit, RET, MET, FLT3, AXL
Phase 3 trial **- Patient (n°)** **- Randomization**	DECISION[8] 417 1:1	SELECT[9] 392 2:1	COSMIC-311[94] 187 2:1
Eligible population	RAI-R, locally advanced or metastatic, progressive DTC	RAI-R, locally advanced or metastatic, progressive DTC	RAI-R, locally advanced or metastatic DTC, with progression after at least one VEGF-targeted therapy
Starting drug dosage (mg)	400 b.i.d.	24	60
Median PFS (months) **Median OS (months)**	10.8 41.5	18.3 Not reached	Not reached NA
ORR (%) **DCR (%)**	12.2 54.1	64.8 87.7	9 43
Mean dose (mg)	651	17.2	42
Most frequent all-grades AEs (%)	PPES (76.3) Diarrhoea (68.6) Alopecia (67.1) Rash (50.2) Fatigue (49.8) Weight loss (46.9) Hypertension (40.6) Decreased appetite (31.9) Mucositis (23.2)	Hypertension (67.8) Diarrhoea (59.4) Fatigue (59) Decreased appetite (50.2) Weight loss (46.4) Nausea (41) Stomatitis (35.6) PPES (31.8) Proteinuria (31)	Diarrhoea (51) PPES (45) Hypertension (28) Fatigue (27) Increased ALT (24) Nausea (24) Increased AST (23) Decreased appetite (23) Weight loss (19)
Patients (%) with: **- Treatment interruptions** **- Dose reductions** **- Drug withdrawals**	 66.2 64.3 18.8	 82.4 67.8 14.2	 NA 56 5

Abbreviations: DTC, differentiated thyroid cancer; FGFR, fibroblast growth factor receptor; FLT3, fms-like tyrosine kinase 3; NA, not available; PDGFR, platelet-derived growth factor receptor; PPES, palmar-plantar erythrodysesthesia syndrome; RAI-R, radioiodine-refractory; RET, REarranged during Transfection; VEGFR, vascular endothelial growth factor receptor.

included among the inclusion criteria of both phase 3 trials, while the inclusion of MKI pre-treated patients was allowed only in the SELECT trial. Therefore, there is no solid evidence to support the efficacy or safety of sorafenib treatment following lenvatinib therapy. Since no head-to-head comparison of the two agents has been performed, the best sequence of MKIs with anti-angiogenic activity cannot be defined on the basis of the currently available data.[35]

Drug efficacy was observed both in MKI-naïve and pre-treated patient for lenvatinib.[9] Among responders, the most evident tumour shrinkage commonly occurred in the first weeks of treatment[85] and responses were durable and clinically meaningful, with a prolonged median PFS of 33.1 months.[86] Concurrently, a serum Tg reduction is usually observed, even if the drop in Tg levels might be detected after MKI initiation also in the absence of lesion shrinkage.[87]

PFS benefit occurred independently from sex, histotype, baseline Tg levels, or the detection of BRAF or RAS genetic alterations both in the DECISION and in the SELECT trials.[3] Conversely, the drug's activity was different according to the site of disease metastases. For lenvatinib, a shorter duration of response was observed in the presence of brain and liver metastases.[86] Moreover, the mean maximum tumour shrinkage was smaller for BMs than in lymph nodes, lung, or liver.[85]

There are no available data showing a clear OS benefit, although the crossover design of the phase 3 studies has to be considered in the data interpretation.[8,9] According to a post hoc analysis of the SELECT trial, median OS was

significantly longer in the lenvatinib than in the placebo arm in the subgroup of patients aged >65 years (HR 0.53, 95% CI 0.31−0.91).[88] It can be speculated that lenvatinib might provide clinical benefit especially in older subjects and that treatment delay can affect their survival outcomes. On the other hand, the cancer was less aggressive in younger people in comparison to older patients, as reflected by the different median OS in the placebo-treated groups (not reached in patients aged ≤65 years versus 18.4 months in adults aged >65 years).[19]

The effect of MKI treatment on RAI-R TC is commonly assessed by morphological evaluations with whole-body CT scan with intravenous contrast medium, using RECIST criteria. Recently, the role of ^{18}F-FDG PET/CT assessment during MKI therapy according to Positron Emission Tomography Response Criteria in Solid Tumours (PERCIST) was explored also in the RAI-R TC setting. It was observed that the first ^{18}F-FDG PET/CT scan evaluation performed after 4 weeks of treatment can predict the long-term morphologic response to lenvatinib therapy and the impact of the MKI on survival, with longer OS in patients showing a metabolic response. This information might orient the clinician toward an earlier discontinuation of the drug in some patients when a poor metabolic response is detected, for instance in case of intolerable lenvatinib-related AEs.[89] Therefore, a multiparametric approach involving both morphological and metabolic data might be advisable in evaluating the tumour response during MKIs.[23]

Real-life data confirmed the clinical benefit observed in clinical trials, but also revealed a reduced efficacy in comparison to the phase 3 studies, which normally include a more selected population.[90]

Outside the registrative trials, the initial dosage of MKI is commonly chosen on an individualized basis, sometimes preferring an initial lower dose in case of poor PS and/or presence of several comorbidities. A recent randomized clinical study compared the effects of two different starting daily doses of lenvatinib (24 mg versus 18 mg). It observed a comparable safety profile, but greater efficacy in terms of objective response rate (ORR, 57.3% vs 40.3%) in case of higher starting dose, supporting the use of the approved starting dose, when possible.[91]

In case of progressive disease defined by RECIST criteria, the continuation of the MKI in sorafenib-treated patients was shown to reduce the lesion growth progression when compared to the drug interruption.[92] Moreover, in subjects with advanced metastatic TC who experience PD after initial response to the MKI, a successful MKI rechallenge was anecdotically reported both for sorafenib and lenvatinib, as in other solid tumours.[93] Therefore, it is generally advisable to maintain the systemic treatment until an alternative anticancer therapy is available and can be prescribed.

The switch to another MKI must be considered in case of unequivocal progression. Among second-line treatments, cabozantinib has been recently approved by the FDA and the EMA in RAI-R TC who progressed during MKIs targeting the vascular endothelial growth factor receptor (VEGFR), on the basis of a phase 3 trial (COSMIC-311). In the first 100 randomly assigned patients, the ORR was 15% in the treated-arm vs 0% in the placebo arm (p=0.028); cabozantinib showed significant improvement in PFS over placebo (median not reached versus 1.9 months).[94]

Tolerability

Several AEs might occur during MKI treatment even during the early phases of therapy, including AEs of grade ≥3 according to the Common Terminology Criteria for Adverse Events.[95] The toxic profile was significantly higher in older patients, at least for lenvatinib.[88] In lenvatinib-treated patients, it was observed that the onset of specific drug toxicity was significantly associated with improved outcomes.

For instance, treatment-emergent hypertension may be predictive for MKI efficacy.[96] Moreover, diarrhoea was associated with better OS in multivariate analyses.[97] Beside the most common toxicities registered during the phase 3 trial (Table 1), other AEs were observed in the real-life setting.[98,99]

The high rate of AEs reduces the treatment compliance, frequently leading to treatment interruptions or dose reductions, which has a negative effect on treatment efficacy. Not surprisingly, a post hoc analysis of the SELECT trial revealed that lower mean dose intensities and longer drug interruptions reduced the clinical benefit derived from the treatment.[100] Therefore, careful monitoring and proper management of the drug toxicity are essential to improve the adherence to these lifelong treatments.[19] Both clinicians and patients should be aware of the drug toxic profile, and they must know how to handle the most frequent AEs, since most of them can be effectively managed with symptomatic therapies, avoiding or reducing the treatment schedule adjustments.[32,38] Medical therapy must be discontinued in case of unacceptable toxicity or if the patient requests to stop treatment.[3,12]

Health-related quality of life (HRQoL) data regarding treatment with sorafenib were recorded during the DECISION trial; mild reductions in HRQoL were reported in MKI-treated patients compared to the placebo arm.[101] Conversely, no QoL information is available from the SELECT study. An exploratory prospective analysis in the real-life setting showed a decrease of self-perceived QoL during the first months of therapy with lenvatinib; nevertheless, patients' well-being seemed not to be worsened by the cumulative toxicity of the drug and QoL was restored over time, probably as a result of therapy optimization.[102] In another study, no significant differences were observed before and during the first months of treatment. A minor improvement of the general health was found, the emotional and the cognitive status accompanied by a slight worsening of the physical role and social functioning.[103] However, these data need to be confirmed with further research.

Selective NTRK and RET Inhibitors

In the era of personalized medicine, novel selective targeted therapies have been introduced also for the treatment of RAI-R TC, based on the molecular signature of the tumour. In particular, these second-generation kinase inhibitors (KIs) belong to two categories: RET inhibitors (selpercatinib and pralsetinib) and TRK inhibitors (larotrectinib and entrectinib).[4,35]

The crucial difference between these new drugs and MKIs lies in their different mechanism of action: by targeting several kinases in addition to RET (in particular VEGFR), MKIs are responsible for many AEs that often limit their tolerability and, consequently, the entity and the duration of the disease response. The higher target selectivity of the new generation of KIs determines a better safety profile, making such therapies more manageable and tolerable.

RET fusions are uncommon in DTC subtypes other than PTC. Even in this subgroup, only 10–30% harboured RET rearrangements, with higher frequencies in children and adolescents and in radiation-induced PTC.[104] NTRK fusions are also rare and especially found in PTC histotype; these alterations are more common in children than in adults (up to 26% vs 6% of cases).[4,105]

Selpercatinib inhibits with high potency different RET alterations, both point mutations and fusions, regardless of the RET fusion partner (CCDC186, ERC1, KTN1, RUFY3). FDA and EMA approved this drug for the treatment of RET fusion-positive advanced RAI-R TC with an accelerated approval in consideration of the excellent results highlighted in the multicohort phase 1–2 trial (LIBRETTO-001).[106] In pre-treated RET fusion-positive TC, selpercatinib showed high rates of ORR (79%) and 1-year PFS of 64%; in those who had not received prior treatment (other than RAI, when appropriate), the ORR was 100%. Drug-related AEs were mainly of grade 1–2; only 2% of patients had to permanently discontinue the drug due to toxicity, while dosage interruptions were necessary in 42% of cases. Regarding the indication in this specific setting, there are some differences between countries: in the United States the drug can be used in patients aged ≥12 years with advanced RET fusion-positive RAI-R TC who require systemic therapy, while in Europe it can be used only in adults who have been previously treated with an approved MKI.[35]

Pralsetinib, another RET inhibitor, showed a similar efficacy and toxicity profile and analogue rates of patients requiring dose reduction and treatment discontinuation. Based on the results of a phase 1–2 study (ARROW), the drug is FDA-approved with the same requirements specified for selpercatinib.[35,107]

Larotrectinib is a highly selective inhibitor of TRKA, TRKB, and TRKC, while entrectinib also inhibits anaplastic lymphoma kinase (ALK) and ROS1, and has the peculiarity of crossing the blood–brain barrier.[108] Based on the results of phase 1/2 clinical trials, both TRK inhibitors are FDA and EMA-approved for the treatment of adult and pediatric patients (≥12 years for entrectinib) affected by locally advanced or metastatic solid tumours that harbour a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion.[109,110]

A recently published pooled analysis from three phase 1/2 clinical trials highlighted a rapid disease control with a very favourable safety profile in patients with TRK fusion-positive TC treated with larotrectinib. AEs were mostly of grade 1 and 2; only 7% of patients experienced an AE leading to a dose reduction, while no patients had to permanently discontinue treatment due to AEs.[111] A pooled analysis evaluating entrectinib demonstrated a similar favourable toxicity profile with a lower ORR, although the smaller number of patients with TC did not allow an adequate comparison.[112]

As already mentioned, in light of these data a genetic test (preferably NGS analysis) should be considered if a systemic therapy is planned.[35] Some, although limited, data show the possible emergence of resistant clones during

treatment with selective inhibitors, with progression not responsive to subsequent highly selective lines of therapy.[113] Moreover, there are no real-life data regarding second-generation KIs available in the literature at the moment.

Redifferentiation Therapies

Given the pathophysiology of RAI refractoriness, the possibility of reinducing NIS expression with the aim of restoring RAI avidity has been investigated.[114] MAPK pathway inhibitors showed efficacy in inducing redifferentiation of RAI-R TC cells. Selumetinib, a MEK inhibitor, increased RAI avidity in 12 out of 20 patients with RAI-R TC, allowing 8 patients to be treated with RAI.[115] Seven of these patients showed a partial response, although no data regarding duration of response are available. The efficacy of vemurafenib and dabrafenib (both BRAF inhibitors) in restoring RAI avidity has been studied in BRAF-mutated RAI-R TC patients, with similar results.[116–118] However, it was noticed that BRAF-mutated TC showed worse response to redifferentiation therapies,[115] assuming the need of a stronger MAPK pathway inhibition in those patients, obtained by combining a BRAF- and a MEK-inhibitor.[119–122] The short-term schedule of these therapies (4–8 weeks in the majority of trials) could induce significantly lower toxicity in comparison with long-term MKI treatment, also reducing the economic burden of therapy.[114] Albeit redifferentiation therapy seems promising, data regarding their clinical benefit are still preliminary and large trials are lacking.

Immunotherapy

The expression of programmed cell death ligand 1 (PD-L1) in the tumour microenvironment and its binding to its main receptor (PD-1), expressed by activated T lymphocytes, has been shown to contribute to solid tumour proliferation. The complex PD-L1/PD-1 is an immune checkpoint inhibiting the signalling pathways involved in T-cell proliferation, survival, and cytotoxic activity. Therefore, blocking the interaction between PD-L1 and PD-1 is a key therapeutic target in avoiding and escaping immune responses and a promising target for many tumours. Definitively, immune checkpoint inhibitors (ICIs) are being used increasingly for several malignancies. However, the clinical use of neutralizing monoclonal antibodies to immune checkpoint molecules for advanced TC has been limited to date.

A large proportion of anaplastic thyroid carcinoma (ATC) and a subset of advanced DTC and PDTC express PD-L1 on the tumour cell surface, providing the rationale for treatment with ICIs.[123] These tumours are diffusely infiltrated with T-lymphocytes bearing PD-1 receptor, pointing to a high immunogenic environment targetable with ICIs.[124,125] A high PD-L1 expression in TC cells seems to be associated with a more aggressive tumour behaviour, suggesting that elicitation of the PD-1/PD-L1 axis influences tumour evasion process.[126,127]

Since PD-L1 is more frequently found in ATC and PDTC, most preliminary evidence to date concerns these aggressive cancers. Collectively, preliminary studies with ICIs as salvage therapy at TC progression have shown conflicting results.

Among DTC patients, pembrolizumab, a monoclonal antibody against the PD-1 receptor, showed promising results in terms of clinical responses and overall survival in a phase 1b proof-of-concept non-randomized study performed in subjects progressing on standard therapies.[128]

Good results in terms of prolonged response were confirmed by Dierks et al, who retrospectively analysed six patients with metastatic ATC and two patients with PDTC treated by combining lenvatinib and pembrolizumab as front-line therapy after chemotherapy failure. A PR/complete response (CR) was observed in 75% of all the group within 16 months of treatment. In this cohort, combined treatment was well tolerated even in the elderly patients with a higher ECOG.[129]

To date, several clinical trials on immunotherapy for DTC/PDTC are ongoing (Table 2). Furthermore, preclinical studies are exploring many other modalities of immunotherapy (eg cytokines and interleukins, cancer vaccines, and chimeric antigen receptor/CAR T cell therapy) for potential application for TC.[127]

Indeed, several critical issues on the correct use of ICIs for the treatment of advanced TC still remain, and many questions are still unanswered, such as the existence of predictive criteria of response, the opportunity to use them in combination with MKIs, or their place in the treatment algorithm. The upfront combination of immunotherapy and MKIs might be much more effective and better tolerated than using these drugs sequentially, for instance.[129] Moreover, the role of tumour markers (such as PD-L1 expression and the tumour mutational burden) for treatment decisions remains to be established. Last but not least, the combination of MKIs and immunotherapy may be associated with AEs for which patients need close monitoring.[128,130]

Table 2 Ongoing Active Clinical Trials with Immunotherapy Enrolling Patients with DTC and PDTC

Study Number	Treatments	Thyroid Cancer Type	Phase	Status	Estimated Study Completion Date
NCT03215095	Durvalumab and radioiodine	DTC/PDTC	1	Active, not recruiting	July 2023
NCT03360890	Pembrolizumab and docetaxel	DTC/PDTC	2	Recruiting	September 2022
NCT03246958	Nivolumab and ipilimumab	DTC/PDTC/MTC/ATC	2	Active, not recruiting	March 2025
NCT02973997	Lenvatinib and pembrolizumab	DTC	2	Active, not recruiting	September 2024
NCT04061980	Binimetinib, encorafenib, and nivolumab	DTC	2	Recruiting	August 2024
NCT04171622	Lenvatinib and pembrolizumab	DTC/PDTC/ATC	2	Not yet recruiting	August 2022
NCT03181100	Atezolizumab, bevacizumab, cobimetinib, nab-paclitaxel, paclitaxel, and vemurafenib	PDTC/ATC	2	Recruiting	July 2023
NCT04514484	Cabozantinib and nivolumab	DTC/MTC	1	Recruiting	November 2025
NCT04802876	Spartalizumab	DTC/PDTC/MTC/ATC	2	Recruiting	December 2024
NCT01552434	Bevacizumab and temsirolimus ± valproic acid or cetuximab	DTC/PDTC/MTC/ATC	1	Active, not recruiting	March 2022
NCT03866382	Nivolumab, ipilimumab, and cabozantinib	DTC/PDTC/MTC/ATC	2	Recruiting	February 2023
NCT02834013	Nivolumab, ipilimumab	DTC/PDTC/MTC/ATC	2	Recruiting	October 2023
NCT04524884	Surufatinib and toripalimab	DTC/PDTC/MTC/ATC	2	Not yet recruiting	September 2022
NCT04521348	Multiple TKI combined with anti-PD-1 antibody	DTC/MTC/ATC	2	Recruiting	June 2023
NCT03753919	Durvalumab and tremelimumab	DTC/PDTC/MTC/ATC	2	Recruiting	December 2022

Note: https://www.clinicaltrials.gov.

Abbreviations: DTC, differentiated thyroid cancer; PDTC, poorly differentiated thyroid cancer; MTC, medullary thyroid cancer; ATC, anaplastic thyroid cancer; TKI, tyrosine kinase inhibitors; PD-1, programmed cell death receptor 1.

Conclusions

The management of progressive RAI-R TC is challenging, and several factors have to be carefully evaluated; undoubtedly, a multidisciplinary approach in the context of a tumour board should constitute the standard of care. Taking into account the frequent AEs of MKI treatments and their potential negative impact on the patients' QoL, systemic therapy is not always the best choice. Active surveillance, together with l-thyroxine suppressive therapy, may represent a valuable strategy in case of low tumour burden and slow neoplastic growth. Local treatments, such as surgery, EBRT, and percutaneous LRTs, might be considered if the disease progression is limited to a single or few lesions, also in combination and during systemic therapy. For patients with BMs, antiresorptive therapies may play a role in the disease management. Systemic therapy should be started in case of rapid and/or symptomatic progression involving multiple lesions and/or organs, in absence of contraindications, especially when refraining from systemic treatment would lead to considerable harms. The MKIs lenvatinib and sorafenib are currently approved as first-line treatment for advanced progressive RAI-R TC. In the last few years, other alternatives have become available for RAI-R TC in selected cases: cabozantinib, selpercatinib, pralsetinib, larotrectinib, and entrectinib have recently expanded the panorama of the therapeutic options in case of disease progression during systemic treatment. In this context, also ICIs have shown

preliminary promising results, and they are still under investigation. A personalized multimodal approach, including a genetically guided treatment, will be the clinical challenge for the next years.

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