A new appraisal of iodine refractory thyroid cancer

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Abstract

Thyroid cancer incidence is increasing all over the world – mostly due to an increase in the detection of small tumors that were previously undetected. A small percentage of these tumors lose the ability to uptake and/or to respond to radioiodine (RAI) therapy, especially in metastatic patients. There are several new therapeutic options that have emerged in the last 5 years to treat RAI refractory thyroid cancer patients, however, it is very important to properly identify RAI refractory patients and to clarify those appropriate for these treatments. In this review, we discuss the RAI refractory definitions and the criteria that have been suggested based on RAI uptake in the post therapy scan, as well as the response after RAI therapy and the possible molecular mechanisms involved in this process. We offer a review of the therapeutic options available at the moment and the therapeutic considerations based on a patient’s individualized personal characteristics, primary tumor histology, tumor burden and location and velocity of lesion growth.

Introduction

In 2012, ~300 000 new cases of thyroid cancer were estimated worldwide and ~40 000 deaths from its cause (http://globocan.iarc.fr/Pages/fact_sheets_population.aspx, accessed on 10th August 2015). The 10-year survival rates in patients with differentiated thyroid cancer (DTC) are considered excellent, ranging from 80 to 95%; on the higher end are those patients with papillary thyroid cancer (PTC) with 93–95% survival, while cases of follicular carcinoma are a little lower, ranging between 80 and 85%. (Hundahl et al. 1998, Links et al. 2005). However, there is a small group of patients that may have 10-year survival rates as low as 47%, such as in the cases of follicular carcinoma and stage IV distant metastasis (based on the TNM classification of malignant tumors (TNM) from the American Joint Commission on Cancer (AJCC)/Union for International Cancer Control (UICC); Jonklaas et al. 2006). In fact, between 7 and 23% of thyroid cases develop into distant metastases and from those around 60% become iodine refractory during follow-up (Anderson et al. 2013, Brose et al. 2014).

In many malignancies, the risk of recurrence and the risk of disease-specific mortality are closely linked. In thyroid cancer, this is often not the case and it is common to have patients at a high risk of recurrence but who have a very low disease-specific mortality (e.g., young patients with well-DTC; Mazzaferri & Kloos 2001). In these young thyroid cancer patients, staging systems developed to predict disease-specific mortality might inaccurately
predict the risk of recurrence. On the other hand, patients who were initially at intermediate or low risk of recurrence, according to the American Thyroid Association (ATA) guidelines (Cooper et al. 2009), but remain with structural disease after 6–24 months of initial therapy can have the initial risk of recurrence doubled or tripled in some cases (Vaisman et al. 2011). This is especially important in patients with metastatic disease that becomes iodine refractory during follow-up. Some studies have already shown that the overall survival of this subgroup of patients can be significantly lower in comparison to patients who had some iodine uptake (10% vs 29–92% in 10 years respectively; Durante et al. 2006). In the last 5 years, a significant amount of research has been dedicated to better identify these patients and to find alternatives to radioiodine (RAI) treatment that can increase overall survival, progression-free survival, and improved quality of life.

The aim of this review is to discuss the molecular mechanisms that may be involved in iodine refractivity, the clinical criteria used to classify a patient as no longer a candidate for iodine therapy due to resistance to treatment and the management of these patients.

Molecular mechanisms of iodine refractivity

In the case of DTC, the detection of cancer relapse by whole body scanning and treatment of the cervical remnant, locoregional, and distant metastasis with RAI is possible due to the residual ability of tumor cells to accumulate iodine. The effectiveness of RAI therapy depends on both the radiation dose delivered to the tumor tissue and the iodine concentrating ability of the cells (Carvalho & Ferreira 2007).

The importance of the sodium iodide symporter (NIS) for the diagnosis and treatment of thyroid diseases has raised a series of questions regarding the mechanisms underlying not only the control of NIS expression but also the regulation of its function in the plasma membrane. In thyroid cells, iodide transport through NIS is stimulated by thyrotropin (TSH) and inhibited by the well-known classic competitive inhibitors thiocyanate (SCN⁻) and perchlorate (ClO₄⁻) (Dai et al. 1996, Smanik et al. 1996, Eskandari et al. 1997, Dohan et al. 2001, 2003). Apart from these classic mechanisms of NIS regulation, in more recent years other intracellular pathways that modulate NIS expression have been described in thyrocytes (Zaballos et al. 2008, De Souza et al. 2010, Andrade et al. 2011). Interestingly, these novel pathways have been shown to be activated during thyroid cancer progression (Faustino et al. 2012, Phay & Ringel 2013, Vidal et al. 2013).

Although DTC retains most of the biochemical properties that are typical of normal thyroid follicular cells, a variety of abnormalities have been demonstrated. Malignant tumors show up as hypofunctioning areas on thyroid scintigraphy, indicating that the loss of iodide uptake ability is hallmark of thyroid carcinogenesis. In fact, several previous studies reported a lower expression of NIS mRNA in samples of thyroid carcinomas compared to normal tissues (Smanik et al. 1997, Arturi et al. 1998, Lazar et al. 1999, Ringel et al. 2001), which could be responsible for the thyroid’s inability to concentrate iodine; however, immunohistochemistry studies demonstrated that NIS is actually overexpressed in some thyroid cancer samples. In fact, some data showed that NIS localization is predominantly intracellular in some tumors, suggesting that abrogated targeting of NIS to the plasma membrane could explain the decreased iodide uptake ability (Saito et al. 1998, Dohan et al. 2001).

TSH stimulates iodide accumulation by positively regulating NIS expression at the protein and mRNA levels via the cAMP pathway (Doahan et al. 2003). In cells responding normally to TSH, NIS is active and inserted at the basolateral membrane of thyrocytes; though upon TSH withdrawal, NIS protein half-life decreases from 5 to 3 days, and it is suggested that the protein translocates from the plasma membrane to intracellular compartments (Riedel et al. 2001), which was also reported in some thyroid cancers (Doahan et al. 2001).

The mechanisms regulating the subcellular distribution of NIS and its function have only been partially elucidated. Our group has recently demonstrated that NIS protein content is acutely down regulated in the absence of TSH by the stimulation of the energy sensor AMP-activated protein kinase (AMPK) pathway, leading to NIS lysosomal degradation (Andrade et al. 2011, Cazarin et al. 2014) and that the expression and activity of AMPK is increased in PTCs (Vidal et al. 2013). These novel findings highlight the possible role of AMPK in thyroid cancer control and NIS regulation.

In thyrocytes, the phosphatidylinositol-3-kinase (PI3K) pathway has been shown to hold a central role in controlling both cell proliferation and differentiation and has been reported to be activated during thyroid cancer progression (Phay & Ringel 2013). Activated in thyrocytes by many growth factors such as insulin/insulin-like growth factor 1, hepatocyte growth factor, or epidermal growth factor (Kimura et al. 2001), the activation of PI3K leads to Akt phosphorylation and NIS down regulation in thyrocytes (Zaballos et al. 2008). It thus follows that it might also be involved in the NIS dysfunction in cancer cells.
Noteworthy, the serine–threonine protein kinase mammalian target of rapamycin (mTOR) is a critical regulator of cellular metabolism, growth, and proliferation. These processes contribute to tumor formation, and many cancers are characterized by aberrant activation of mTOR. Although activating mutations in mTOR itself have not been identified, activation of the mTOR pathway is prevalent in thyroid cancer (Faustino et al. 2012). The prototypic mechanism of mTOR regulation in cells is through the activation of the PI3K/Akt pathway, yet it is important to note that mTOR receives input from multiple signaling pathways. In 2010, we showed that mTOR activation led to decreased NIS expression in thyrocytes (De Souza et al. 2010), which in thyroid cancers would likely be involved in NIS down regulation in tumor cells.

The BRAFV600E mutation is frequent in RAI refractory and fluorodeoxyglucose (FDG)–positron emission tomography (PET) positive recurrent metastatic tumors, and this mutation is associated with a lower NIS expression and lower radioactive iodine uptake, both in vitro and in vivo (Ricarte-Filho et al. 2009, Chakravarty et al. 2011). These findings allowed the design of the Selumetinib (MEK inhibitor) study (Ho et al. 2013) and the development of trials with BRAF inhibitors (vemurafenib and dabrafenib) (Dadu et al. 2015, Rothenberg et al. 2015). However, thyroid tumor cells bearing the BRAFV600E over express neuregulin 1 and the human epidermal growth factor receptor 3 (HER3) signaling pathway when treated with RAF or MEK inhibitors, a phenomenon that leads to drug resistance (Montero-Conde et al. 2013). Thus, the association of MEK or RAF inhibitors with the HER3 inhibitor lapatinib or the anti-HER3 MAB might be a valuable therapeutic approach. Future studies are needed to determine the possible clinical benefit of these associations.

The crucial role of RAI therapy for thyroid carcinomas stimulated the search for drugs that could also enhance functional NIS expression in tumors and, in turn, iodine accumulation, such as retinoic acid (Coelho et al. 2005) and more recently mTOR, BRAF, and MEK inhibitors (Ho et al. 2013, Plantinga et al. 2014, Rothenberg et al. 2015). These drugs that inhibit the intracellular kinases responsible for both tumor progression and NIS disappearance benefit the patient by both tumor stabilization and RAI treatment, with the internal radiation killing tumor cells resistant to the kinase inhibitors. This strategy could be more effective in the control of advanced thyroid cancer by decreasing the appearance of tumor lesions resistant to drugs.

Thyroid cancer research continues to explore the interplay among the intracellular pathways involved in cancer progression, drug resistance and NIS regulation to improve the benefit garnered from RAI treatment.

**Clinical criteria of RAI refractivity**

The most recent guidelines (Tuttle et al. 2014) and studies (Xing et al. 2013, Brose et al. 2014, Schlumberger et al. 2015) for the management of thyroid cancer defined iodine refractory tumors as tumors that show no uptake in the post therapy scan after RAI therapy; patients with more than one metastatic lesion with at least one target lesion not showing uptake of RAI in the post therapy scan; patients whose tumors have structurally progressed shortly after RAI therapy despite having uptake in the post therapy scan (12–16 months after treatment); and patients submitted to an accumulated 600 mCi or more (or 22.3 GBq) of RAI with no sign of remission.

However, it is important to explore the clinical data that support this definition and the reason for not giving additional RAI for this subset of patients.

**Tumors with no uptake of RAI in all lesions or in at least one target lesion in the post therapy scan**

Around two-thirds of known metastatic lesions seen in cross-section imaging studies will lose the ability to uptake RAI; thus it seems reasonable to assume that RAI is no longer an option to treat these cases. Some recent studies have also found that progression-free survival rates in patients with a negative diagnostic scan and known metastatic disease (seen in other image modalities) are not benefited by empiric doses of RAI (Sabra et al. 2012).

It is important to note that the therapy and/or the scan be performed in the proper conditions without iodine contamination and/or inadequate TSH elevation. A combination of a low-iodine diet (<50 mg iodine/day) and a modified diuretic program increases the RAI uptake and retention in tumor tissue (Ma et al. 2005). Urinary iodine levels can take up to 2 months to normalize depending on the iodine overload (Nimmons et al. 2013). Even when properly prepared, RAI uptake can be heterogeneous both in different lesions and within the same metastatic lesion. Studies performed with 124I PET/computed tomography (CT) were able to show this pattern of uptake. If one lesion does not concentrate iodine well enough, a minimum of cytotoxic absorbed activity will not be achieved when RAI is administered and, thus, the standard treatment is unlikely to work (Ho et al. 2013).

Negative post therapy scans can result from improper preparation of the patient (Leger et al. 1998), iodine
contrast used for CT, high iodine content diet or the use of medication that has iodine in its composition, such as amiodarone. In cases in which iodine contamination is suspected, serum and urinary iodine should be measured and a whole body scan (WBS) should be repeated 4-6 weeks after an iodine-depletion regimen is considered. The other important issue regarding proper preparation for iodine treatment and/or scan is the serum TSH levels. It is established that TSH levels should be ≥ 30 mIU/l at the time of RAI administration (Guimaraes & DeGroot 1996). This can be achieved by levothyroxine replacement withdrawal (so-called endogenous hypothyroidism) or by the administration of recombinant human TSH (Meier et al. 1994).

Tumors that structurally progressed shortly after RAI therapy despite having uptake in the post therapy scan (12–16 months after treatment)

It is widely accepted that the peak of $^{131}$I therapy action is between 6 and 12 months with most ablated patients having no evidence of disease or demonstrating some response to this therapy in this time frame (Comtois et al. 1993). Even in cases in which prolonged action of RAI was suggested, the first 6-12 months after therapy, there is some response detected and continues to improve over-time (Carhill & Vassilopoulou-Sellin 2012, Vaisman et al. 2012). Thus, it is well within reason that patients who show structurally progressive metastatic disease within the first 16 months after RAI therapy should be considered as non-responders and classified as RAI refractory, ruling out RAI as a therapeutic option (Tuttle et al. 2014).

600 mCi (or 22.3 GBq) or more of RAI as cumulative activity with no response

RAI therapy had been thought to be innocuous for many years in the past. As the follow-up of these patients became longer and physicians found the expected adverse effects reported more frequent, this notion has been reconsidered. Several studies agree that most side effects are dependent on the given activity of RAI and that high activities are more likely to cause side effects, specially salivary and lacrimal dysfunction (Grewal et al. 2009, Almeida et al. 2011, Mallick et al. 2012, Schlumberger et al. 2012, Rosario & Calzolari 2013). Some studies also suggested that high RAI administration activities could be associated with the appearance of a second primary tumor in the long term (Rubino et al. 2003, Iyer et al. 2012) and that this risk becomes significant for cumulative activity of more than 600 mCi (or 22 GBq) (Rubino et al. 2003). Durante et al. (2006) further showed that patients who would achieve a complete response (meaning no more evidence of disease after RAI therapy) needed no more than 600 mCi cumulative activity and the administration of more than this should be considered on an individual basis. Currently, most guidelines reflect these findings and recommend that activities over 600 mCi should be avoided, and when there is no response or progression at this activity, an alternative therapy to RAI should be considered (Tuttle et al. 2014).

Useful test and markers to predict iodine refractory in clinical practice

There are several staging systems designed to predict cancer-specific mortality and some to predict recurrence. The more aggressive tumors usually occur in older people with locally invasive tumors at presentation and with distant metastasis (Byar et al. 1979, Cady & Rossi 1988, Degroot et al. 1990, Hay et al. 1993, Shaha et al. 1995, Cooper et al. 2009, Sobin et al. 2009). In clinical practice, there are some useful tools that can help predict who is likely to become RAI refractory during the follow-up, especially when combined with the classic prognostic factors (Table 1).

The role of $^{18}$F-FDG–PET/CT

FDG–PET/CT is an important diagnostic and prognostic imaging modality for many malignancies. Its use has been extensively studied in thyroid malignancies over the last decade. Guidelines suggest that the FDG–PET/CT may be useful in patients who, after initial therapy, continue with high serum levels of thyroglobulin (Tg) or show an increasing Tg trend with all cross-sectional imaging results negative (Cooper et al. 2009, Rosário et al. 2013, Tuttle et al. 2014). While having a high sensitivity (ranging from

| Table 1 Clinical factors to predict RAI refractory at early evaluation |
|---|---|
| **Patients characteristics** | **Older age (> 40 years)** |
| Tumor characteristics and clinical presentation Images | Aggressive histology, local invasion, and presence of metastases |
| Markers | FDG–PET/CT, $^{18}$F-fluorodeoxyglucose–positron emission tomography–computed tomography; Tg, thyroglobulin |

FGD–PET/CT, $^{18}$F-fluorodeoxyglucose–positron emission tomography–computed tomography; Tg, thyroglobulin.
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85 to 100%), its specificity is low (around 75%) and is dependent on the tumor burden (Kuba et al. 2007, Leboulleux et al. 2007).

More recently, FDG–PET/CT has been used for a prognostic purpose. Wang et al. (2001) showed that patients with tumor lesions that were positive on FDG–PET/CT were less likely to respond to high doses of RAI. The same group went on to show that metastatic patients with a positive FDG–PET/CT had a worse prognosis than those with a negative scan, independent of the RAI avidity (Robbins et al. 2006). This so-called flip–flop phenomenon describes the condition of when the tumor is no longer able to uptake iodine or this uptake is low and lesions are FDG-avid due to intense glucose uptake and metabolism. These tumors tend to be larger, more invasive (Esteva et al. 2009) and with more aggressive histology (Rivera et al. 2008) and have a higher prevalence of mutations such as BRAF, HRAS, and NRAS compared with FDG-negative tumors (Ricarte-Filho et al. 2009). Nowadays, FDG–PET/CT is considered a useful tool to predict RAI refractory.

The molecular mechanisms involved in the metabolic shift that leads to higher glucose uptake by tumor cells are poorly defined. Recently, we described that the AMPK plays an important physiological role in the thyroid gland by regulating uptake of both iodide and glucose (Andrade et al. 2011, 2012). In fact, AMPK activation in the normal thyrocyte induces a dramatic reduction of iodide uptake that is accompanied by a higher glucose uptake and glycolytic pathway utilization. Until now, few studies have analyzed the AMPK pathway in thyroid cells, but recent studies report that metformin treatment induces thyroid tumor cell apoptosis (Chen et al. 2012, Han et al. 2015, Plesws et al. 2015); however, interestingly, the expression and activity of AMPK has been shown to increase in PTC (Vidal et al. 2013).

Histology

PTC is the most common histologic type of thyroid cancer all over the world, corresponding to 80–85% of all cases (Sherman & Gillenwater 2003, Lastra et al. 2014). While this tumor has a very good prognosis with an overall survival rate above 95% for small intra-thyroidal tumors (Siegel et al. 2013), some rare variants of PTC can be more aggressive and also more likely to be RAI refractory. The tall-cell variant of PTC is the most common aggressive variant. This variant has been reported to have a more aggressive genetic profile (such as BRAF and TERT mutations) associated with RAI refractory and worse prognosis (Liu et al. 2013). Other aggressive variants of PTC include columnar-cell, diffuse sclerosing, solid, HOB-nail, and the widely invasive follicular variant. These seem to have a worse prognosis due to their genetic profile, aggressive initial presentation and lack of response to RAI therapy (Lastra et al. 2014, Omur & Baran 2014).

Tg doubling time

Tg is a cornerstone in thyroid cancer management and follow-up. This marker is used to determine remission (when TSH is suppressed or not) and also to diagnose the persistence of the disease despite therapy. Recently, some authors have proposed that its rate of increase, i.e., the doubling time, could be useful to identify those more likely to develop new metastasis despite RAI or die from the disease. Miyachi et al. showed that patients with a Tg doubling time of <1 year were more likely to have local recurrence, develop new metastatic lesions and die from the disease even when treated with RAI. Patients with positive Tg antibodies were excluded from this analysis (Miyachi et al. 2011).

Therapeutic approach

Overall survival rates are known to be lower in patients with RAI refractory disease. With RAI no longer a therapeutic modality for this group, follow-up should address not only the right time to start other therapies but also which therapy to offer in each case. A complete remission is often extremely unlikely to happen in these cases, therefore careful consideration should be made for real benefits vs side effects as many therapies will have a basic palliative purpose.

Active surveillance

Despite being RAI refractory, some patients will have stable metastatic disease for several years even without additional therapy (Vaisman et al. 2011). Two important factors influence this treatment decision: tumor burden and rate of progression. Tumors with <1–2 cm or low tumor burden, in most cases, should be followed actively without additional therapy (Cooper et al. 2009). Several studies suggest that small (<1 cm) metastatic lymph nodes and also thyroid bed nodules can be safely followed for years with ultrasound (Rondeau et al. 2011, Guy et al. 2014, Urken et al. 2014, Tufano et al. 2015). Small soft tissue metastasis can also be followed with cross-sectional images. Depending on the site, some stable and/or very slow progressive lesions (i.e., no progression within
12–16 months) can also be actively followed, with the exception of when a lesion is located near important structures and is likely to become symptomatic even with a very small growth rate (Tuttle et al. 2014).

## Localized therapy

Localized therapy should be considered when there is only one metastatic site and/or there are only a few progressive lesions. Surgery is still the best therapeutic option when feasible for metastatic lesions. Another option that can be used alone or in combination with other treatment modalities (such as surgery or systemic therapy) is external beam radiation, commonly used with bone and CNS metastasis (Tuttle et al. 2010).

Other therapeutic modalities also can play a role in this scenario. Embolization and radiofrequency ablation has been described for liver (Fromigue et al. 2006, Wertenbroek et al. 2008), bone (Hoffmann et al. 2008) and some other soft tissue metastasis with local disease control.

## Systemic therapy

The most difficult challenge nowadays is to properly select patients for systemic therapy. A large number of molecules are being tested, most of which are tyrosine kinase inhibitors (TKIs). The main goal of these molecules, until now, is to stop progression, though in some cases lesion shrinkage (20–30%) has also been seen (Capdevila et al. 2012). Unfortunately, studies have not yet shown an improved overall survival in these cases, mainly because all of the studies allowed patients to crossover to the drug arm once they documented progression. They did, however, prove that this approach could significantly improve progression-free survival rates when compared to placebo (Brose et al. 2014, Schlumberger et al. 2015).

As mentioned earlier, the life expectancy for this group is significantly lower with symptoms usually appearing in an advanced stage of the disease, and although these drugs offer new options, they often carry a profile of innumerable side effects that can have a large impact on quality of life (Brose et al. 2014). It is this point in which the paradox lies and a considerate analysis of the risks and benefits should be weighed.

Most authors agree that the candidates for these therapies are symptomatic patients with large tumor burdens, a rapidly progressive disease (within 12–16 months) and/or a high risk of local complications (Schlumberger et al. 2014). The Federal Drug Administration (FDA) has recently approved some of these drugs to be considered for treatment with this group of patients (Table 2).

### Future perspectives

An exciting emerging field in thyroid cancer research is TKIs that are able to enhance iodine uptake and make RAI a more effective therapy. In this case, patients previously considered RAI refractory due to poor response could be again treated with RAI. Currently, this is not yet available outside of clinical trials (Ho et al. 2013). Some promising ongoing phase II trials with new drugs for first and second line use (such as BRAF inhibitors, including dabrafenib, vemurafenib, or nintedanib, which is a triple angiogenesis inhibitor that inhibits receptors of VEGF, FGF, and PDGF) or combining drugs that act in different pathways (such as sorafenib plus temsirolimus) (http://www.clinicaltrial.gov, accessed on 10th August 2015) may add new concepts to the ideal approach of iodine refractory thyroid cancer patients. In this case, two tumor growth pathways would be inhibited but with greater side effects.
Most recently, other potential therapeutic targets involved in cell cycle, apoptosis, and activation of proliferation pathways are being tested such as heat shock protein 90 inhibitor, MABs against HER, microtubule destabilizing agents, and proteasome inhibitors among others (http://www.clinicaltrial.gov, accessed on 10th August 2015). Probably, in the future, some of these will be added to the therapeutic options, associated with other drugs that are currently available today.

Closing remarks

There has been an increasing interest in thyroid cancer shown by the large number of recent published papers regarding RAI refractory thyroid cancer patients. These patients represent the minority of thyroid cancer patients seen in clinical practice; however, they need to be properly identified and treated as their mortality is much higher and they require more intensive care.

It is important to note that while patients are classified as RAI refractory, meaning RAI is not a therapeutic option anymore, a great number will remain stable with no need for additional therapy, using the so-called active surveillance approach.

The greatest challenge remaining is to balance the decision to start therapy with an appropriate evaluation of the clinical benefit it will offer. The two major factors – initial size and location of the target lesion – need to be taken into account along with the pace of growth when considering whether it is best treated with local treatments such as surgery or external beam radiation, or systemic therapy with oral agents or if it is best to continue to observe (Fig. 1).

Declaration of interest

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