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Review Article

Real world use of T3 to alleviate symptoms of hypothyroidism during preparation of radioactive iodine ablation: experts' viewpoint

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ABSTRACT

Thyroid carcinoma is a common endocrine malignancy with most of the cases being diagnosed as differentiated thyroid cancer. Thyroidectomy is the cornerstone of treatment for thyroid carcinoma. Adjuvant therapy with radioactive iodine after surgical resection of all known primary tumor tissue and metastatic foci is advocated. The preparation for radioactive iodine ablation requires elevation of thyroid stimulating hormone to 30 mIU/l for ensuring uptake of I-131 by thyroid follicular cells. In the Indian setting, there are specific challenges in preparation for radioactive iodine ablation including the high cost of recombinant TSH injection which may preclude its use in most patients. The practical approach adopted by Indian endocrinologists, endocrine surgeons and nuclear medicine physicians in the preparation of post-thyroidectomy thyroid cancer patients for radioactive iodine ablation in the real-world setting needs to elaborated and chronicled for providing guidance specific for the constraints encountered in the Indian scenario. Thyroid hormone withdrawal is affected by cessation of levothyroxine for 4 weeks prior to radioactive iodine ablation leading to profound hypothyroidism. This can be addressed by appropriate use of liothyronine (LT3) to substitute levothyroxine after its withdrawal. LT3 administration of 20 mcg twice or thrice a day (40 to 60 mcg/day in divided doses) is the best practice during THW. The duration of LT3 replacement following cessation of levothyroxine, is for 2-3 weeks and then 10-14 days off LT3. These practices are corroborated by evidence from literature and recommendations from guidelines elucidating the use of liothyronine during the period of thyroid hormone withdrawal.

Keywords: Thyroid hormone withdrawal, Liothyronine, Levothyroxine, Hypothyroidism, Differentiated thyroid cancer, Radioactive iodine ablation

INTRODUCTION

Thyroid carcinoma is a common endocrine malignancy.[1] More than 90% of diagnosed thyroid cancers are differentiated thyroid cancer (DTC).[2,3] An increasing incidence of DTC has been reported globally over the past decade owing to better screening and testing facilities. The long-term prognosis is excellent in about 70-80% of these patients.[4] Thyroidectomy is the cornerstone of treatment for thyroid carcinoma.[1] Adjuvant therapy with radioactive iodine (I-131) after surgical resection of all known primary tumor tissue and metastatic foci is advocated. I-131 helps to destroy subclinical microscopic tumor deposits provides remnant ablation, decreases local recurrence, improves survival in patients with local recurrence and improves the condition of patients with bone metastases.[4] Among the factors which affect the success of I-131 are a relative deficiency of iodine and the presence of high thyroid stimulating hormone (TSH) level (>30 mIU/l) ensuring that I-131 is driven into thyrocytes and/or DTC cells. Follow up studies to evaluate presence of thyroid cancer recommend serial monitoring of serum thyroglobulin and radioactive iodine (RAI) imaging.[4] The American Thyroid Association has defined three groups of patients with different risk of recurrence: high risk (>20%), intermediate risk (5–20%) and low risk (<5%). In the current era of

precision medicine, the use of post-surgical radioactive iodine ablation may be tailored according to a risk-based approach. The decision for postoperative RAI therapy should be taken based on initial prognostic indicators for thyroid cancer related death and recurrence.[4]

The use of I-131 therapy as an adjuvant treatment or treatment of known disease is indicated in the high-risk group. In this setting, high activities (≥3700 MBq) of radioiodine are preferred over low activities. In the intermediate-risk category, RAI therapy may be indicated according to individual risk factors. In low-risk patients, RAI therapy should be based on individual risk modifiers. Patients with biopsy proven lymph node metastases and/or unstimulated post-operative serum Tg values above an institutional cut-off (e.g. >2 ng/ml) should be considered for RAI.

The greatest benefit of post-operative I-131 therapy may be expected in patients with advanced age, with aggressive histology, increasing volume of nodal disease, extranodal extension of the tumor, multiple N1 and/ or lymph node metastases outside the central neck compartment.[5,6] Higher ablation rates have been observed with higher activities of I-131 in patients with large thyroid remnants, but similar rates of successful remnant ablation have been reported using activities ranging from 1110 to 3700 MBq of I-131.[4]

Prior to RAI therapy, some groups advocate preparation of the patients with a low-iodine diet (LID) of ≤50 µg/day of iodine for 1–2 weeks and recommend avoiding excessive iodine exposure (i.v. contrast agent, amiodarone or any other iodine-containing drugs). This may facilitate remnant ablation. However, there are no studies to define a clear cut-off over which iodine interference may actually occur.[5-9]

The preparation of the patient for RAI includes thyroid hormone withdrawal commonly by effecting LT-4 cessation. This leads to an increase in endogenous TSH secretion to levels sufficient to induce significant RAI uptake in thyroid cells. However, this results in profound hypothyroidism and has an adverse effect on quality of life.

Several methods have been proposed for thyroid hormone withdrawal, two possible approaches are used, (i) switch from L-T4 to triiodothyronine (L-T3) for 2–3 weeks (3, 4) and then stop L-T3 for 2 weeks, or (ii) stop L-T4 for 3–4 weeks without switching to L-T3. An alternative approach proposed is induction of a less prominent hypothyroidism by reducing L-T4 to half the original dose.

An alternative method of preparation for RAI therapy entails the i.m. administration of exogenous recombinant human TSH (rhTSH) 0.9 mg on 2 consecutive days with RAI administration on the day of the second rhTSH injection.[4,10-14] The practical approach adopted by Indian endocrinologists, endocrine surgeons and nuclear medicine physicians in the preparation of post-thyroidectomy thyroid cancer patients for radioactive iodine ablation in the real-world setting needs to be chronicled and discussed for providing guidance specific for Indian clinical challenges. To understand the treatment approach for preparation of adjuvant therapy with radioactive iodine ablation post thyroidectomy for thyroid cancer. To understand best practices of thyroid hormone withdrawal in Indian setting.

A panel of nine experts from the field of endocrinology, endocrine surgery and nuclear medicine from diverse regions of India, with considerable experience in treating thyroid cancer, were invited to participate in a discussion on their approach to preparation for RAI in the real-world setting. Prior to the meeting, a literature review was done using the medline database.

The key words used for the search were thyroid cancer, I-131, RAI, thyroid hormone withdrawal. The findings of the literature review were used to present current evidence and guidelines-based recommendations to the expert group for discussion and comparison with their real-world practices. Insights from the discussion emerging from the meeting were chronicled and a manuscript of the real-world approach for preparation for radioactive iodine ablation was drafted.

INSIGHTS FROM THE DISCUSSION OF INDIAN EXPERTS REGARDING THEIR APPROACH TO PREPARATION FOR RADIOACTIVE IODINE ABLATION

Radioactive iodine ablation post-thyroidectomy for thyroid cancer

The number of thyroidectomies performed by the endocrine surgeons varied from 100 to 400 thyroidectomies per year. The panelists opined that 50-80% of thyroidectomies are indicated for DTC. Post-thyroidectomy, the patients are put on a low iodine diet and checked for radioactive iodine uptake on scan.[4]

More than 90% of the cases show radioactive iodine uptake and are posted for radioactive iodine ablation with the only exception being tumors <1 cm in size and and minimally invasive follicular carcinomas up to 4 cm in size. When the risk stratification including staging of the tumor is done, it is important to perform a whole-body scan along with a stimulated serum thyroglobulin testing to determine the dose of RAI required for ablation.[3,4]

After thyroidectomy, risk stratification is followed by RAI ablation using a dose of about 30 millicurie for residual disease and 100-150 millicurie for nodal metastasis. The dose of I131 for systemic metastasis is 150-200 millicurie and that for bony metastasis is approximately 200millicurie. After the appropriate dose of RAI is determined, ablation is performed. The panel concurred that in most of the institutes, over 80% of post-thyroidectomy cases are followed up with RAI ablation.[4]

Preparation of the patient for RAI ablation: real world challenges in the Indian setting

The preparation for RAI ablation includes low iodine diet for 2 weeks and thyroid hormone withdrawal for endogenous TSH production ensuring TSH level of 30m IU/l and above. All the panelists agreed that recombinant TSH injection may not be affordable for most Indian patients, hence it is prudent to perform thyroid hormone withdrawal (THW) instead.

The majority of patients are prepared by THW rather than the recombinant TSH injection approach. The panel agreed that TSH level >30 mIU/l is required for adequate RAI uptake to ensure effective ablation. The duration of LT4 cessation required for TSH elevation of 30m IU/l is 4 weeks.[4] Extending the duration of levothyroxine cessation beyond 4 weeks is not required.

Role of liothyronine in thyroid hormone withdrawal

As it may not be economically feasible to use recombinant TSH injection for the majority of Indian patients in the real-world setting, as an alternative, thyroid hormone withdrawal is performed in a large proportion of patients. LT4 is withdrawn for a period of 4 weeks. The degree of increase in TSH and the time required for the same is highly variable with a few patients demonstrating TSH levels of 100 mIU/l in 2 weeks and others attaining 30-40 mIU/l in 4 weeks of LT4 cessation.

The patient's experience of hypothyroidism varies with a few patients with TSH levels of 100 mIU/l or higher not complaining of symptoms of hypothyroidism. Conversely, there is a subset of patients who complain of profound symptoms of hypothyroidism even with relatively milder elevated TSH levels of 10-15 mIU/l. This subset of patients would potentially benefit from LT3 substitution for LT4 in the first 2 weeks of THW.

LT3 substitution is especially critical in cases with stable cardiac disease or renal complications where profound hypothyroidism can lead to difficulty in management of the comorbid conditions. Most patients have good outcomes with LT3 substitution during THW especially for patients in high precision jobs. LT3 substitution alleviates symptoms of hypothyroidism in these patients and leads to considerable improvement in their quality of life. However, in case of patients with unstable cardiac disease or arrhythmia, recombinant TSH is preferred rather than LT3 regimen due to the risk of worsening cardiac symptoms.[15]

Dosing and duration of LT3 used for LT4 substitution during thyroid hormone withdrawal

The point of contact with the patient post-thyroidectomy, for review of the histopathology report is appropriate for withdrawal of LT4 and simultaneously LT3 is initiated, to alleviate the symptoms of hypothyroidism. The panel agreed that the pharmacodynamically equivalent dose of LT3 for substitution is one-third of the LT4 dose which was administered post-thyroidectomy, as the potency of LT3 is three times that of LT4. Broadly the common practice included administration of LT3 in a dose of 20 mcg twice or thrice a day i.e., 40-60 mcg/day to patients for a period of 2-3 weeks.

Another approach followed is LT3 in the dose 10 mcg TID i.e., 30 mcg/day for a period of 2-3 weeks post cessation of LT4. The experts opine that majority of Indian patients have been noted to tolerate 40-60 mcg/day of LT3 well.

The consensus amongst the panelists was that LT3 administration of 20 mcg twice or thrice a day (40 to 60 mcg/day in divided doses) is the best practice during THW. LT3 is preferably given in divided doses i.e., twice or thrice a day rather than once a day to minimize fluctuations in serum T3 levels.[16]

The most common approach involves LT3 administration in the first 2-3 weeks followed by LT3 cessation for 10-14 days. The experts noted that a minimum of 10 days of LT3 withdrawal results in the required TSH levels for effective RAI ablation. The panel agreed that LT3 can be administered for 2-3 weeks followed by 10-14 days of LT3 withdrawal prior to RAI ablation for ensuring TSH levels>30 mIU/l.

Improvement in quality of life on LT3 substitution during THW

Symptoms of hypothyroidism such as brain fog, fatigue and weight gain can be alleviated by LT3 substitution during THW, resulting in improvement in quality of life.17 Compared to the LT4 withdrawal approach, almost all patients subjectively feel better on LT3 substitution. When LT3 is not substituted, patients frequently complain of brain fog, fatigue and weight gain of about 2-3 kg.

Most patients are highly sensitive to these symptoms of hypothyroidism and would prefer to avoid them by substituting LT3 during THW. The panelists concurred that invariably most of the patients feel better on LT3 substitution underscoring that LT3 substitution results in alleviation of hypothyroid symptoms.[17] However, this was not quantified by any scale measuring quality of life in the real-world setting.

Efficacy of radioactive iodine ablation following T3 use in thyroid hormone withdrawal

The studies cited in ETA guidelines demonstrate comparable efficacy for the three approaches to TSH elevation (LT4 withdrawal/ LT4 withdrawal with LT3 substitution followed by complete withdrawal/ recombinant TSH injection) with respect to ablation success.[18] The panelists were in consensus that LT3 substitution during thyroid hormone withdrawal followed by RAI therapy results in effective ablation.[18]

GUIDANCE FROM LITERATURE AND GUIDELINES ON T3 IN THYROID HORMONE WITHDRAWAL

Tumor biology varies from patient to patient, necessitating a tailored approach for every patient. The treatment protocol is accordingly personalized. The ETA 2022 consensus statement on thyroid cancer management state that LT4 cessation of 4 weeks is required, but in clinical practice, the period of LT4 withdrawal depends on the completeness of surgical resection achieved by the surgeon.[18]

If there is remnant thyroid tissue after thyroidectomy, then the period of LT4 withdrawal would be longer whereas in the case of complete resection, the period of LT4 withdrawal needed could be shorter than the stipulated 4 weeks in the guidelines. The panel concurred that LT3 substitution as one of the approaches during THW is elucidated in established guidelines on management of thyroid cancer such as European Thyroid Association 2022 guideline and American Thyroid Association 2015 guideline.[18,19] The details of LT4 withdrawal and LT3 therapy are personalized considering patient characteristics and limitations.

CONCLUSION

Thyroid hormone withdrawal as preparation for RAI ablation may be preferably done by liothyronine substitution of levothyroxine to alleviate symptoms of profound hypothyroidism. LT3 administration of 20 mcg twice or thrice a day (40 to 60 mcg/day in divided doses) is the best practice during THW. The duration of LT3 replacement following cessation of levothyroxine, is for 2-3 weeks and then 10-14 days off LT3, to effectively reduce the duration of profound hypothyroidism before radioactive iodine ablation.

The considerably higher cost of recombinant TSH injection when compared to the cost incurred in thyroid hormone withdrawal is an impediment in Indian settings. Clinical experience of Indian experts in the field of endocrinology, endocrine surgery and nuclear medicine corroborates the place of LT3 in alleviating symptoms of hypothyroidism during the challenging period of LT4 cessation prior to radioactive iodine ablation.

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