Commentary

A Logical levothyroxine dose Individualization: Optimization Approach at discharge from Radioiodine therapy ward and during follow-up in patients of Differentiated Thyroid Carcinoma: Balancing the Risk based strategy and the practical issues and challenges: Experience and Views of a large volume referral centre in India

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ABSTRACT

In this communication, the authors discuss the issue of individualization of thyrotropin suppressive therapy in differentiated thyroid carcinoma (DTC) patients and share their views with respect to optimizing the dose of levothyroxine (LT) prescription both during discharge from radioiodine therapy ward and during follow-up. The changing management paradigm at our Institute during post-thyroidectomy period and during the preparation for radioiodine scan is also briefly highlighted. Five factors can be identified as important determinants for the dose individualization approach: (1) Persistence or absence of metastatic disease, (2) the risk characteristics of the patient and the tumor (3) patient's clinical profile, symptomatology, and contraindications (4) the feasibility to ensure a proper thyroid stimulating hormone TSH suppression level (depends on patient's socio-economic and educational background, the connectivity with the local physician and his expertise) (5) time period elapsed since initial diagnosis. While discussing each individual case scenario, the authors, based upon their experience in one of the busiest thyroid cancer referral centers in the country, discuss certain unaddressed points in the current guideline recommendations, deviations made and some challenges toward employing them into practice, which could be situation and center specific. In addition to these, the value of clinical examination, patient profile and detailed enquiry about clinical symptomatology by the attending physician in each follow-up visit cannot be overemphasized. According to the authors, this aspect, quite important for dose determination in an individual, is relatively underrepresented in the present guidelines. It would also be worthwhile to follow a conservative approach (till clear data emerges) in patients who have characteristics of "high-risk" disease, but are clinically and biochemically disease free, if no medical contraindications exist and patient tolerates the suppressive therapy well. This would be particularly applicable in the presence of aggressive histopathological variants, where, in the event of recurrence/metastasis, the disease demonstrates adverse prognosis and higher incidence of radioiodine refractoriness. At the end, certain important and noteworthy concepts pertaining to LT prescription that has definitive practical implications for the suppressive therapy in DTC patients are described.

Keywords: Differentiated thyroid carcinoma, levothyroxine, thyroid stimulating hormone TSH suppression, thyrotropin-suppressive therapy

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INTRODUCTION

The clinical management of differentiated thyroid carcinoma (DTC) is undergoing a transition in the recent years. From a more aggressive approach for all patients, the trend is to risk stratify and individualize the treatment according to the disease characteristics. Truly, DTC is a heterogeneous disease

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with a wide spectrum and hence there has been an endeavor by various guidelines[1,2] and practitioners to address this more succinctly in practice. However, several areas in the decision making steps are not clear at this moment due to the lack of reliable data and the suggested liberal approach have been, at least in part, based upon the personal experience of the practitioners. The practice at this juncture, thus, is varied across the world, especially at the decision steps where solid scientific data is unavailable.

Levothyroxine (LT) suppressive therapy has been one of the mainstays of management of DTC, and the implications of which extends beyond the aims of avoiding hypothyroidism. By several authorities, this has been considered an important step not only in those who have a persistent metastatic disease, but also those who are apparently disease free, where this measure aids in minimizing the risk of recurrence. In the recent years, a risk based strategy has been emphasized in the management of DTC. The concept of risk based management approach in DTC has been extended toward this aspect too: The guidelines calls for a more liberal approach with regard to the level of thyroid stimulating hormone TSH suppression in various patient population groups. There have been certain subtle differences in recommendations made by the various guidelines (viz. American Thyroid Association [ATA], European Thyroid Association [ETA] and the National Comprehensive Cancer Network) based upon the belief and experience of practitioners and hence are being adopted in various centers across the world to a varying extent. In addition, there are certain practical hurdles toward employing them into a routine that are situation, country and center specific. The Head and Neck Surgery Unit of Tata Memorial Hospital and the Radiation Medicine Center functions represent the busiest thyroid cancer management center in the country. In this editorial, we discuss our own views with respect to optimizing the dose of LT prescription both during discharge from radioiodine therapy ward and during follow-up in this group of patients and how a logical balance can be kept to obtain the best results.

In a high volume referral center like ours, the patients belong to a very diverse background with an access to medical expertise that is very widely heterogeneous. It is not infrequent in our practice to encounter patients who after returning from our care had consulted the local physician in the interim period for a general medical problem where his serum TSH level was interpreted abnormal and the LT dose was reduced toward replacement intent irrespective of the disease status and risk. These were corrected in the follow-up visits of these patients.

THE DETERMINANTS FOR DOSE INDIVIDUALIZATION

According to our experience, considerations should be made on the following five domains while advocating TSH suppressive therapy: (1) Persistence or absence of metastatic disease (2) the risk characteristics of the patient and the tumor (3) patient's clinical profile, symptomatology, and contraindications (4) the feasibility to ensure a proper TSH suppression level (depends on patient's socio-economic and educational background, the connectivity with the local physician and his expertise) (5) time elapsed since initial diagnosis and follow-up duration. Taking the aforementioned 5 factors, we suggest a logical model of LT dose optimization-individualization approach either in the initial years or in the subsequent period thereafter. While discussing each individual case scenario, we also make reference to the ATA or ETA guidelines and make mention especially where we have to make some deviation from the standard guidelines based upon our practical experience in a large population base.

1. Group A: In patients who have persistent metastatic disease there is almost uniform agreement about maintaining the serum TSH level below 0.1 mU/L for an indefinite period. How much LT should be prescribed during discharge from the radioiodine therapy ward to achieve this level? Our institute's practice has gradually shifted over the last 5 years from a rigid approach of prescribing LT 300mcg/day to 200mcg/day. This is presently the prescribed LT dose during discharge from our radioiodine therapy ward. This is based upon our experience that the latter dose is usually sufficient to maintain the serum TSH level at the desired level in this subgroup of patients; very rarely a dose increase has been required. In a randomly selected population of 156 patients of DTC taken equally from 3 independently functioning physicians, more than 2/3rd patients (n = 104) on follow-up were on a dose that was lower than 300 mcg dose and had a TSH that was below 0.1 mU/L (unpublished data). Amongst the various dosages (100/125/150/200/250/300), the largest population belonged to the 200 mcg/day group. In another retrospective analysis of 100 DTC patients (unpublished data) who were on 200 mcg/day, only eight were found to be symptomatic of hyperthyroid features (compared to 52% with 300 mcg suppressive dose). Thus, we concluded that this could be the prescribed dose while discharging the patients from the therapy ward and subsequently do the individualization of the dose on an individual case basis according to the risk stratification. In our overall experience in a large number of patients with long clinical follow-up, at this dose, (i) the symptoms related to thyrotoxicosis are substantially less and (ii) the adverse effects of subclinical thyrotoxicosis secondary to TSH suppression are also minimal. A further reduction of the dose is required only occasionally, in elderly patients and those with known cardiac disease where further fine tuning of the dose is undertaken to achieve the level with minimum LT dose. One practical determining factor for prescribing 200 mcg/day (and not lower) in a referral center like ours (where majority of the patients hail from outstation and far-off and remote places) is the feasibility (non) to undertake a rigorous dose titration in an individual patient, which heavily depends on the patient's socio-economic and educational background, the connectivity with the local physician and his expertise and understanding of the disease. Certainly, in this subgroup

of DTC patients, it is imperative not to take the risk of fine-tuning the dose and hence 200 mcg/day remains the preferred dose during discharge to be on the safer side.

2. Group B: In patients who have characteristics of "high-risk" disease, but are clinically and biochemically disease free continued suppression of TSH has been suggested in both ATA and ETA guidelines. ATA specifies at maintaining the serum TSH levels of 0.1-0.5 mU/L for initial 5-10 years, whereas the ETA suggests the need for TSH suppression for 3-5 years (though not specific on the degree of TSH suppression, it presumably indicates a serum TSH ≤0.1 mU/L). In our Institute, we do advocate TSH suppression rigorously in this group of patients, akin to that of Group A, especially in the initial 5 years (or even the subsequent 5 years). Certain factors would be important in this respect:
    i. Firstly as has been mentioned in ATA guidelines, the "appropriate degree of TSH suppression by LT4 is still unknown" as there have not been any reliable prospective data on this yet. Furthermore, the guidelines also cite major studies[3-6] that demonstrate the importance of thyrotropin suppression in preventing recurrence and adverse clinical events and that the degree of TSH suppression being an important determinant for this effect,[3] especially in high-risk disease. Conversely, there have been cites of studies that show the degree of TSH suppression is less important compared to other factors such as disease stage, patient age, and I-131 therapy.[7] In the presence of conflicting reports and multiple studies indicating the value of higher TSH suppression, the authors feel it would be judicious to advocate higher degree of TSH suppression in this group till significant data emerges otherwise. A particularly important specific with regard to the tumor in this scenario relates to aggressive histopathology of the primary such as tall cell, columnar cell, diffuse sclerosing, solid/trabecular, and insular variants all of which in the event of recurrence/metastasis demonstrate adverse prognosis and frequently develop radioiodine refractory disease. Similar concern exists for Hurtle cell carcinoma of thyroid as well. Taking into account their aggressive disease biology, a tighter control of TSH may be deemed appropriate in the presence of the aggressive histological variants.
    ii. Secondly, from a practical and clinical standpoint, the difference of LT dose required to maintain a serum TSH value between 0.1 and 0.5 or below 0.1 will be usually by an increase of 25 μg/day, whose clinical significance is uncertain or presumably minimal. In our view, the patients' clinical profile, symptomatology, and examination findings could play an important role in determining the level of TSH suppression wherein elderly patients and those with known cardiac disease or those who are symptomatic could be advocated a less aggressive approach.
3. Group C: Patients with low risk of recurrence and disease free status: After ensuring successful ablation, this group of patients could be put on a dose that would keep the serum TSH in the low normal range. Both guidelines are quite similar in this group; the only point of difference is the definition of the "low-normal" range. The ATA advocates 0.3-2 mU/L, whereas ETA guidelines define this as 0.5-1.0 mU/L. While this is quite logical, the authors suggest adoption of an individualized approach in the initial 5 years based upon two factors: (i) The clinical profile of the patient including age and (ii) the feasibility to ensure a proper TSH suppression level in coordination with the local physician. As the interval crosses the 5-year threshold a more liberal approach could be employed.
4. Group D. In the event of reporting pregnancy or a female patient planning for conception: Several of our thyroid cancer patients, after an adequate interval following I-131 therapy, had a successful pregnancy and delivery of healthy off springs. We also have a good experience of patients with metastatic disease (especially pulmonary metastases with good prognostic features), following successful disease control with multiple I-131 therapies, had given birth to healthy children. Pregnancy or conception is one situation where there is uniform agreement about adopting a liberal approach with regard to TSH suppression. A risk based dose individualization is suggested in this case scenario: (i) Those who are at lower risk and are disease free for sufficient time: The TSH value could be safely kept between 2 mU/L and 3 mU/L (the median value that is thought to be ideal during the pregnancy) for the entire period of pregnancy (ii) for those has persistent disease and harboring high-risk disease (which of course is relatively rare to encounter), the ETA approach of maintaining serum TSH around 0.1 mU/L should be employed.
5. Thyroid cancer in the pediatric age group: The guidelines do not make any specific mention about the pediatric thyroid cancer patients. It is imperative that the approach would be similar to that of adults and would be based upon risk stratification, but here the LT prescription could be more rigidly guided by the serum TSH level.
6. In patients with neck nodal recurrences: The patients with neck nodal recurrences form another group where the role and extent of adequate TSH suppression is less defined. This is a subgroup which is encountered in a practical scenario, but the present guidelines have not made any separate categorization or recommendation on this. In a referral center like ours, neck nodal recurrence has been observed, though uncommonly, soon or rarely after years of disease free period. No specific mention has been made in the present guidelines for this specific subgroup, where the disease biology could be intermediate between the extremes. Recognizing that these patients are at increased risk of future recurrences, it would be worthwhile to advocate TSH suppression rigorously (TSH ≤ 0.1 mU/L) in this group of patients if there is no clinical contraindication, especially in the initial 5 years (where the chance of recurrence is relatively higher).

IMPORTANT AND NOTEWORTHY CONCEPTS PERTAINING TO LT PRESCRIPTION AND THEIR PRACTICAL IMPLICATIONS FOR THE TREATING PHYSICIAN

Certain important and interesting aspects of LT therapy is worth mentioning in this context: (a) the recommended dose of LT4 (per body weight) for hypothyroidism reduces with increasing age. The daily recommended replacement dose per kg body weight (i) for the 1-5 years age group is 5-6 mcg/kg/day, (ii) for the 6-12 years 4-5 mcg/kg/day, (iii) for more than 12 years is 1.7 mcg/kg/day, (iv) for the adult population, 1.6 mcg/kg/day;[8] however, the appropriate dosage would vary to a certain extent among patients depending upon the duration and severity of the hypothyroidism and the presence of other associated medical disorders. The fact of reducing the requirement of LT with increasing age could be extrapolated and may have relevance for the suppressive therapy as well for DTC patients. While adopting the individualization protocol, this should be kept in mind by the treating physician. (b) The start (or restart) of LT4 following radioiodine scan or therapy (undertaken with withdrawal protocol) should be gradual with weekly increments; this has particular relevance for elderly patients and those who have associated cardiovascular ailments. (c) It is usually recommended that levothyroxin be taken in the morning, 30 min before eating. Other medications containing iron (ferrous sulfate forms a ferric-thyroxine complex) or calcium supplements (calcium carbonate is known to form an insoluble chelate with LT) should be avoided (it is recommended to keep a gap of at least 4 h apart from these agents) as they can interfere with absorption of the thyroxine sodium. The preferred single dose of LT4 is in direct contrast to the divided dose regimen of LT3. LT3 is usually available as 25 mcg tablets and is started in weekly increments following stoppage of LT4 5 weeks before the radioiodine scan, administered in the initial 3 weeks and stopped 2 weeks before the radioiodine scan date. We find a scheme with interval LT3 medication (while preparing a patient for radiodiodine scan) quite gratifying, more comfortable for patients and is economically acceptable for our patients, many of whom are in the low-middle class socio-economic background. Indigenous production of LT3 tablets in India and more wide availability of this agent across the country would be beneficial to many DTC patients.

CONCLUSION

Individualized approach in the management of DTC based upon disease risk stratification is certainly an attractive approach that continues to be a "work in progress." Beyond doubt, the practice of appropriate individualization of LT dose in DTC patients is the need of the hour. The individualization approach of thyrotropin suppression though advocated by the guidelines has unclear points that require be scientifically exploring and clarifying to evolve a sound management protocol.

REFERENCES

1. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, *et al.* Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
2. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W, *et al.* European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803.
3. Pujol P, Daures JP, Nsakala N, Baldet L, Bringer J, Jaffiol C. Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. J Clin Endocrinol Metab 1996;81:4318-23.
4. McGriff NJ, Csako G, Gourgiotis L, Lori C G, Pucino F, Sarlis NJ. Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer. Ann Med 2002;34:554-64.
5. Hovens GC, Stokkel MP, Kievit J, Corssmit EP, Pereira AM, Romijn JA, *et al.* Associations of serum thyrotropin concentrations with recurrence and death in differentiated thyroid cancer. J Clin Endocrinol Metab 2007;92:2610-5.
6. Jonklaas J, Sarlis NJ, Litofsky D, Ain KB, Bigos ST, Brierley JD, *et al.* Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 2006;16:1229-42.
7. Cooper DS, Specker B, Ho M, Sperling M, Ladenson PW, Ross DS, *et al.* Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: Results from the National Thyroid Cancer Treatment Cooperative Registry. Thyroid 1998;8:737-44.
8. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, *et al.* Clinical practice guidelines for hypothyroidism in adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid 2012;22:1200-35.

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