A “new/old method” for TSH stimulation: could a third way to prepare DTC patients for ^{131}I remnant ablation possibly exist?

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A growing body of evidence supported the possibility to prepare patients affected by differentiated thyroid cancer (DTC) at low and/or intermediate risk with recombinant human thyroid-stimulating hormone (rhTSH) for radioiodine remnant ablation (RRA) [1]. Thus, patients' quality of life can be improved and the radiation exposure of patients can be reduced at the same time [2–5]. The efficacy of this type of preparation was recently confirmed by two randomized trials [6, 7] in low-risk DTC patients reporting the same rate of remnant ablation patients pretreated with rhTSH and those with 4–6 weeks of thyroid hormone withdrawal (THW). The novel 2015 American Thyroid Association (ATA) guidelines confirmed that exogenous TSH may replace THW for achieving remnant ablation, based on evidence of superior short-term quality of life, non-inferiority of remnant ablation efficacy and lack of a consistent difference in long-term outcome [1]. The principal limitation of this stimulation method seems to be related [8] to the high cost of rhTSH, which is not necessarily balanced by the reduction of hospitalization or sick days.

However, beyond rhTSH stimulation, only weak recommendations, supported by low-quality evidence, are given concerning the optimum endogenous TSH level needed for an optimal ablation rate and long-term outcome [1]. In this context it is easy to understand how the correct levothyroxine

withdrawal interval before radioactive iodine (RAI) therapy has still not been established. The TSH level >30 mU/l, generally adopted in preparation for RRA therapy and usually reached after 4–6 weeks of LT_4 withdrawal, is a never proven dogma for which more attempts at evaluation should be conducted. In fact, even though endogenous TSH levels >30 mU/l are recommended before radioiodine administration in almost all clinical guidelines, only one paper in the literature supports this statement [9]. In addition, this study was published in 1977 when, in general, large thyroid remnants were much more likely after thyroidectomy: as a consequence results indicated that a low endogenous TSH was an indicator of incomplete surgery rather than an insufficient physiologic stimulus for ^{131}I uptake.

In this setting DTC patient preparation with a shorter time of THW (e.g. 2–3 weeks) and lower levels of TSH should be tested to know whether an effective and efficient endogenous TSH stimulation is possible without important reduction of the quality of life. At the moment only one study [10] showed that in about 80 % of DTC patients a TSH level >30 mU/l may be reached from TSH suppression if levothyroxine was withdrawn for 3 weeks. This observation opened the door to shorter hormone withdrawal but of course did not clarify whether patients with TSH levels <30 mU/l may effectively reach remnant ablation or not.

In the present issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Vrachimis and colleagues [11] present the results of a two-centre study about the relevance of endogenous TSH levels at the time of RAI therapy. They retrospectively evaluated 1,873 DTC patients without distant metastases, scheduled for ablative postsurgical RAI therapy, who discontinued levothyroxine 4–6 weeks before ^{131}I administration. No patients presented excessive ^{131}I remnant uptake (>10 %) on the ^{131}I uptake test performed before ablation. They found that 275 patients did not achieve a proper

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TSH level (i.e. $\text{TSH} < 30 \text{ mU/l}$). They compared these patients with the other 1,598 in terms of ablation success, recurrence-free survival rates and DTC-specific survival. Surprisingly, in contrast with current recommendations, no influence of TSH levels was observed, neither in univariate nor in multivariate analysis, on postoperative ^{131}I ablation success rates, recurrence-free survival rates and DTC-specific survival rates. Serum Tg levels were higher in patients with a $\text{TSH} < 30 \text{ mU/l}$, suggesting that thyroid remnant size is a factor influencing TSH, but no differences were found in terms of ablation success and outcomes in this subgroup. In particular, focusing our attention on the ablation rate, they found a similar rate of ablation success in each of the nine groups in which they divided patients according to function of TSH levels (e.g. TSH level ranging from 0 to 10 mU/l in the first group and $> 80 \text{ mU/l}$ in the last group). Patients who presented a $\text{TSH} < 10 \text{ mU/l}$ had a similar ablation success rate as those with $\text{TSH} > 80 \text{ mU/l}$. On the other hand, the authors confirmed that established risk factors such as age, tumour dimension and lymph node metastases influenced the ablation rate and the DTC outcome.

This study from Vrachimis and colleagues has several strengths:

Firstly, they demonstrated for the first time that a comparatively low TSH peak at the time of ablation did not directly affect ^{131}I remnant ablation. Indeed, only one paper showed similar findings reporting a high ablation rate after a single administration of 3.7 GBq of radioiodine in DTC patients previously treated by lobectomy alone despite a mean TSH level of 15 mU/l [12].

Secondly, this study was conducted on a large DTC population including a relatively high number of DTC patients at intermediate risk. This population well represents the clinical context in which most physicians outside of a few selected dedicated cancer centres are involved in everyday clinical practice.

Thirdly, from a statistical point of view, both univariate and multivariate logistic analyses were conducted including all the principal prognostic factors considered in DTC patients.

Overall, these data are of practical importance as patients presenting with TSH levels $< 30 \text{ mU/l}$ several weeks after thyroidectomy in the light of these data can receive ^{131}I ablation without the need for prolongation of the LT_4 withdrawal phase or additional injection of rhTSH without compromising ablation effectivity or long-term prognosis.

In addition, the data reported by Vrachimis and colleagues may support the very interesting theory concerning the endogenous TSH stimulation proposed in the 2009 ATA guidelines and called “area under the curve hypothesis” [13]. This hypothesis states that the sodium-iodide symporter (NIS) stimulation is not only related to the TSH peak achieved but is also strictly related to the TSH level over time. In other words, a low but prolonged TSH stimulation may be comparable with

one shorter but more intense. In this context very interesting opportunities are opening up and new strategies for ^{131}I remnant ablation seem to be attainable. On the one hand, 1–3 weeks of THW could be proposed instead of the currently accepted standard of 3–4 weeks [1]. This intense but short TSH stimulation might be sufficient to properly increase the NIS activity and iodine uptake. On the other hand, a proper NIS activation might be achieved after a longer period of weak TSH stimulation through an incomplete levothyroxine substitution. Both these strategies might imply a significant reduction of related hypothyroidism symptoms, thus improving the quality of life of DTC patients.

Indeed, some limitations should be mentioned. Ablation effectiveness was assessed by serum Tg measurement without any imaging (i.e. ultrasound, radioiodine whole-body scan) due to well-illustrated technical limitations. A stimulated Tg $< 1 \mu\text{g/l}$ generally indicates that no large amounts of thyroid tissue are present. However, in clinical practice, patients with clear disease foci or significant thyroid remnants but undetectable serum Tg levels despite negative TgAb test results are occasionally encountered [14]. Different preparation modalities (i.e. rhTSH, THW with or without T_3 replacement) and the burden of residual functioning thyroid tissue may affect the stimulated Tg level at restaging [15]. Thus, it may be argued that likely some patients were falsely classified as ablated or not-ablated, respectively, based on stimulated Tg levels alone [16]. Even of more importance, the present results were obtained in DTC patients without metastases when undergoing RRA and only a very low number of recurrences and DTC-related deaths were found during long-term follow-up. Additionally, conventional clinical determinants independently predict recurrence-free and DTC-specific survival, confirming that a good prognosis is inherent to the tumour biology rather than to the TSH level at radioiodine ablation in patients with a low-risk profile after surgery.

In conclusion, thus far two main ways to prepare patients for RRA have been well defined, including either a relatively long period of potentially debilitating THW (3–4 weeks) or a quick but expensive exogenous stimulation with rhTSH [1]. These methods work very well and are supported by many years of clinical experience. However, in the case of elderly DTC patients presenting TSH levels $< 30 \text{ mU/l}$ at the time of RRA, the possibility to proceed with the administration of ^{131}I therapy without extra rhTSH stimulation should not be neglected. Indeed, even in younger patients it seems that the currently accepted dogma that TSH levels should mandatorily exceed 30 mU/l should be taken with a grain of salt at the very least.

In addition, this study, beyond any intrinsic limitations of retrospective studies, recognizes the possibility to test a “third way” to prepare DTC patients for RRA, which could indeed result in an endogenous stimulation which neither has the side effects of currently used withdrawal protocols nor the high costs associated with rhTSH, thus representing

the “best of both worlds”. Indeed, it would be very interesting to test the preparation of low- or intermediate-risk DTC patients with ultrashort THW periods (e.g. 1–2 weeks) against both a strategy of a longer period of low endogenous TSH stimulation induced by suboptimal thyroid hormone replacement and against the current de facto standard TSH stimulation strategies in a randomized trial. Thus, potentially both patients’ quality of life and significant amounts of money can be spared.

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