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On-levothyroxine measurement of thyroglobulin is not a reliable test for the follow-up of patients at high risk for remnant/recurrent differentiated thyroid carcinoma

Monitorowanie stężenia tyreoglobuliny w trakcie terapii lewotyroksyną u chorych na zróżnicowanego raka tarczycy nie jest wiarygodną metodą wykrywania nawrotu choroby

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Abstract

Introduction: At present the most widely accepted tool for follow-up management of differentiated thyroid cancer (DTC) patients is serum thyroglobulin (Tg) measurement. It is not uncommon for the serum Tg level to be measured while the patient is taking thyroid hormones (on-treatment Tg measurement). The purpose of the study was to evaluate the accuracy of on-treatment measurement of serum Tg in detecting remnant/recurrent or metastatic disease in high-risk DTC patients.

Material and methods: We retrospectively analysed the medical records of 26 high-risk DTC patients and compared the on-treatment and off-treatment Tg levels of these patients. All patients were anti-Tg negative. Using off-treatment measurement of Tg as the gold standard, the results of on-treatment measurement of Tg in the diagnosis of remnant/recurrent disease were analysed for sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV).

Results: The median serum Tg level under thyroid hormone suppressive therapy (on-treatment Tg) was 16.5 ng/ml and after withdrawal of thyroid hormone suppressive therapy (off-treatment Tg) was 95.0 ng/ml (*P* value = 0.001). In 6 patients (23%) the on-treatment Tg level missed the recurrence of the disease. Regarding the off-treatment Tg as the gold standard, the sensitivity, specificity, PPV and NPV of the on-treatment Tg measurement were 72.7%, 100%, 100%, and 40% respectively.

Conclusion: Normal serum Tg level without TSH-stimulation (on-treatment) is not diagnostically reliable in the follow-up of DTC patients with a high probability of residual/recurrent or metastatic disease.

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Key words: *thyroid cancer, serum thyroglobulin, levothyroxine, recurrence*

Streszczenie

Wstęp: Obecnie najszerzej akceptowanym narzędziem używanym w badaniach kontrolnych u chorych ze zróżnicowanym rakiem tarczycy jest pomiar osoczowego stężenia tyreoglobuliny (Tg). Nierzadko zdarza się, iż pomiary stężenia Tg odbywają się, gdy chory jednocześnie przyjmuje preparaty hormonów tarczycowych. Celem niniejszego badania była ocena przydatności pomiaru osoczowego stężenia Tg w trakcie stosowania hormonów tarczycy w wykrywaniu choroby resztkowej/nawrotowej lub obecności przerzutów u chorych z wysokim ryzykiem wznowy zróżnicowanego raka tarczycy.

Materiały i metody: Retrospektywnej analizie poddano dokumentację medyczną 26 pacjentów obciążonych dużym ryzykiem wystąpienia zróżnicowanego raka tarczycy. Porównano wartości pomiarów osoczowego stężenia Tg odpowiednio w trakcie stosowania hormonów tarczycy oraz po ich odstawieniu. U wszystkich badanych wykluczono obecność przeciwciał przeciwko Tg. Przyjmując pomiary stężenia Tg w okresie odstawienia hormonów tarczycy jako „złoty standard”,

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przeanalizowano (ustalając czułość, specyficzność oraz dodatnią i ujemną wartość predylekcyjną) wyniki oznaczeń stężenia Tg podczas przyjmowania hormonów tarczycy pod kątem diagnostyki resztkowej/nawrotowej choroby.
Wyniki: Średnie osoczowe stężenie Tg w warunkach stosowania terapii supresyjnej za pomocą podawanych egzogennych hormonów tarczycy wynosiło 16,5 ng/ml, natomiast po zaprzestaniu stosowania tyroksyny — 95,0 ng/ml (wartość p = 0,001). U 6 chorych (23%) przyjmujących hormony tarczycy stężenie Tg nie potwierdzało wznowy procesu nowotworowego. Przy założeniu, że pomiary stężenia Tg w okresie odstawienia hormonalnych preparatów tarczycy stanowią „złoty standard", czułość, specyficzność, dodatnia i ujemna wartość predylekcyjna wynosiły odpowiednio: 72,7%, 100%, 100% i 40%.
Wnioski: Monitorowanie stężenia Tg w trakcie terapii tyroksyną nie jest wiarygodną metodą w wykrywaniu wznowy choroby u chorych na zróżnicowanego raka tarczycy.

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Słowa kluczowe: *rak tarczycy, tyreoglobulina w surowicy, lewotyroksyna, wznowa*

Introduction

Differentiated thyroid carcinomas (DTC) are the most common malignancies of the endocrine system [1] and with current strategies most patients will achieve a definitive cure and have a normal quality of life. Current treatments, including total thyroidectomy and ablation therapy with radio-iodine [1], have had quite remarkable successes in completely eradicating the disease. This progress in treatment as well as the fairly well-differentiated character of these malignancies has led to relatively long survival and good prognosis. Although this is both pleasant and inspiring for patients, it indicates the need for long-term follow-up [2] in order for appropriate treatment to be applied promptly on the appearance of any sign of recurrence or residual disease with the aim of eradicating it.

At present the most widely accepted strategy for the follow-up management of DTC patients consists of whole-body ^{131}I scanning (WBS) and serum thyroglobulin (Tg) measurements [3]. Previous researches have shown that the sensitivity of serum Tg is satisfactory while the thyroid-stimulating hormone (TSH) level is high and in this situation it can be used as an appropriate test for the follow-up of patients and as a reliable screening test to assess disease recurrence [1, 4–10]. The use of high-quality serum Tg measurements can significantly improve the cost-effective management of this disease by identifying low-risk patients in whom periodic radio-iodine scans or therapy may be deferred in favour of serial serum Tg monitoring. Nevertheless, a rising TSH level requires thyroid hormone withdrawal for about 3 to 4 weeks (off-treatment measurement of Tg) or administration of recombinant human TSH (rhTSH), each of which will pose some problems.

First, the withdrawal of the hormone, assumed to be the gold standard, subjects patients to the symptoms and complications of hypothyroidism, which is not pleasant for the patient [5] and theoretically also results in an increased risk of recurrence [5]. Apart from this, rhTSH is not available everywhere (as is the case in our country) and is also somewhat expensive. Finally, the use of Tg measurement under rhTSH-stimulation has not been accepted generally as a sensitive and reliable test. These problems have led to the follow-up of these patients frequently being done by Tg measurement, while TSH is inhibited (on-treatment) [2, 4, 5].

The purpose of our study was to assess the efficacy of on-treatment Tg measurement and to determine its efficacy in detecting recurrent/persistent disease in those DTC patients who have a high risk of recurrence and residual disease.

Material and methods

We performed a large retrospective review of the medical records of patients suffering from DTC who were assessed, followed and treated for papillary or follicular thyroid carcinomas (DTC) in our Nuclear Medicine Ward between 1995 and 2005. Of this population only those were included in the study who had a history of total thyroidectomy and radio-iodine ablation therapy for DTC and who had subsequently, during the course of follow-up, developed high levels of Tg with negative WBS. These patients were regarded as a high-risk sub-group for remnant/recurrent disease and selected for final analysis. Six months after radio-iodine treatment for elevated Tg and negative WBS the results of Tg measurement in two TSH suppression and TSH elevation states were recorded and compared with each other. Only those patients in whom all three tests, namely TSH, Tg and anti-Tg, in both on-treatment and off-treatment states, had been performed in the ward's own laboratory were entered for analysis.

In all cases treatment with levothyroxine had been stopped 4–6 weeks before the Tg measurement and diagnostic whole-body scanning, and these two diagnostic tests were performed 2 weeks after discontinuation

of a 2-week course of liothyronine consumption. The serum levels of TSH and anti-Tg antibody were measured by IRMA (RADIM/Italy) and the Tg tests was measured by the RIA method (CIS Bio international, France). A serum Tg level of more than 1ng/ml was considered positive [9, 11], while tests for anti-Tg antibodies were negative in all patients (titer < 1:100).

With the off-treatment measurement of Tg as the gold standard, the results of the on-treatment measurement of Tg in diagnosis of remnant/recurrent disease were analysed for sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV). SPSS for the Windows software package (Release 11.5.0, SPSS Inc, Chicago, IL) was used for statistical analysis. Serum Tg levels before and after withdrawal of thyroid hormone were compared by using the sign test for all patients. When more than one post-withdrawal Tg was available, the lowest value was used. A ***P*** value of 0.05 or less was considered significant.

Results

Complete data was obtained for a total of 26 patients, 10 men and 16 women with a mean age of 42.3 yr ± ± 17.4 years, and therefore these were accepted for final analysis. Twenty-three patients had papillary and three had follicular thyroid cancer. The mean interval between on-treatment Tg measurement and off-treatment Tg measurement was 36.2 ± 4.6 days, above 27 and below 46 days in all patients. At the time of the off-treatment Tg measurement the mean serum TSH level was 46.8 mIU/litre (median: 41.9 mIU/litre), and all patients had a serum TSH level above 35 mIU/litre. The mean serum TSH level at the time of on-treatment measurement of Tg was 0.6 mIU/litre (median: 0.4 mIU/ /litre) and in all patients was below 1.4 mIU/litre.

The median serum Tg level under thyroid hormone suppressive therapy (on-treatment Tg) was 16.5 ng/ml (range 0.2–210). After withdrawal of thyroid hormone suppressive therapy the median Tg (off-treatment Tg) was 95.0 ng/ml (range 1.5–470). The difference was statistically significant (***P*** value = 0.001). The ratio of the off-treatment Tg to on-treatment Tg was 11.4 ± 14.4 (range 1.95 to 51.2). Mean values are expressed in Figure 1 (on-treatment mean Tg level: 39.1, off-treatment mean Tg level: 158.1).

In general, the on-treatment Tg level missed the recurrence of the disease in 6 patients (23%). In fact, regarding the off-treatment Tg as the gold standard, the sensitivity, specificity, PPV and NPV of the on-treatment Tg measurements were 72.7%, 100%, 100%, and 40% respectively.

Discussion

Measurement of serum thyroglobulin has been recognised as a sensitive and valuable tool for screening residual/recurrent disease in patients previously treated by thyroidectomy and radio-iodine ablation therapy. In fact, after total thyroidectomy and radio-iodine remnant ablation serum Tg should be undetectable where there is complete remission. As mentioned earlier, it is not infrequent for the serum Tg level to be measured while the patient is on treatment with thyroid hormone and TSH is suppressed [2, 4, 5, 9, 12]. However, today on-treatment Tg measurement is considered to be insufficient and Tg measurement under TSH elevation (after withdrawal of the thyroid hormone over 4–6 weeks or under recombinant TSH intramuscularly) is thought to be the most reliable indicator for persistent or recurrent disease. The rationale for the use of TSH stimulation is the well-documented appreciable percentage of patients having false-negative Tg measurements during levothyroxine treatment when no TSH stimulation is employed: 20% of patients with lymph node metastases and 5% of patients with distant metastases but normal plain radiographs [5, 8].

However, as mentioned earlier, the withdrawal of the hormone subjects patients to the symptoms and complications of hypothyroidism. A non-randomised French multicentre study found a mean 13.7 days of missed work per follow-up with levothyroxine withdrawal in patients working outside the home (J Lecle're, Satellite Symposium Presentation at the European Association of Nuclear Medicine Congress, Paris, France, 3 September 2000) [5]. The corresponding data from a German tertiary referral centre were 11 days missed with levothyroxine withdrawal (Luster M, Felbinger R,

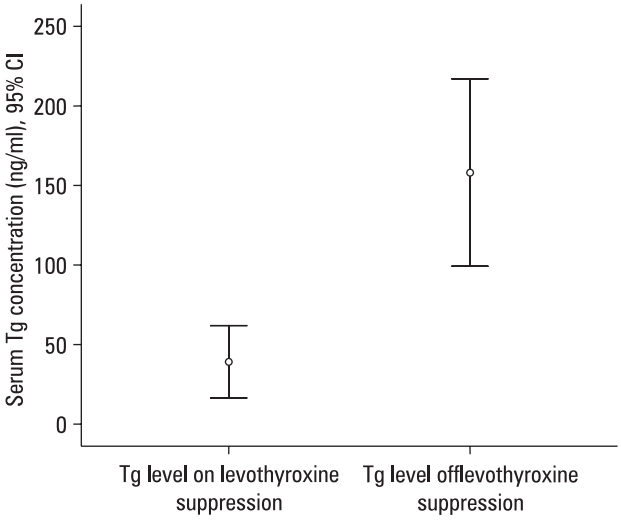

Figure 1. *The difference between mean on-treatment and off-treatment Tg levels is statistically significant*

Rycina 1. *Statystycznie istotne różnice między średnimi wartościami osoczowych stężeń Tg w okresie otrzymywania i nieotrzymywania preparatów hormonów tarczycy*

Dietlein M & Reiners C, unpublished observation) [5]. Hence several authors have also used the on-treatment Tg levels as their screening tool and mentioned that DTC patients who have an undetectable serum Tg on thyroid hormone therapy (a TSH-suppressed measurement of Tg) in the absence of Tg-antibody interference are considered to be at low risk for residual/recurrent disease [2, 4, 5, 9, 12]; the same approach is widely used in current clinical practice.

There have also been a few trials to reduce the need for TSH elevation and therefore decrease the incidence of symptomatology of severe hypothyroidism in the follow-up of patients with DTC. Guimaraes and DeGroot emphasised that this severe hypothyroidism produces fatigue, weight gain, depression, inability to carry out usual activities and occasionally significant illness. They compared the efficacy of inducing moderate hypothyroidism by cutting replacement therapy by half to the standard method and reported that a reduction in the thyroxine replacement dosage to half the usual amount allowed sufficient elevation of TSH for the measurement of Tg levels after 5 weeks in most patients [13].

Despite these reports our study findings indicate that on-treatment measurement of Tg is not reliable for all cases. In fact the measurement of serum Tg under thyroid hormone replacement therapy is not a sensitive and reliable screening tool, at least in those patients who are at high risk of recurrent/residual disease. In our study this approach (on-treatment measurement of Tg) missed 6 patients who actually needed further treatment and on the basis of its results 23% of patients missed the opportunity of receiving further therapeutic interventions. Indeed a sensitivity of ~73% is not acceptable for an ideal screening test. Our study findings are also in agreement with Eustatia-Rutten et al. [6], who previously stated that the best accuracy of Tg-guided follow-up in patients treated for differentiated thyroid carcinoma is obtained if Tg testing is performed while off levothyroxine treatment. This fact was also previously mentioned in nuclear medicine literature: the sensitivity of Tg is much higher under TSH elevation > 30 mU/I (98%) than under TSH-suppressive thyroid hormone therapy (80%) [14]. In a large multicentre trial that included 30 patients with ^{131}I uptake outside the thyroid bed an elevated Tg level (> 2 ng/ml) was detected in only 80% of those taking thyroid hormone but was found in 100% of patients given rhTSH or who had experienced withdrawal of thyroid hormone [15]. It is generally reported that only 90% of patients with metastasis have an elevated Tg level during thyroid hormone therapy [16]. Mazzaferri et al. have also emphasised that an undetectable serum Tg measured during thyroid hormone suppression of TSH is often misleading [10]. These authors noted that 21% of patients who had no clinical evidence of tumours with baseline on-treatment serum Tg levels (usually below 1 micro g/litre) showed, in response to recombinant human TSH (rhTSH), a rise in serum Tg to more than 2 micro g/litre.

Our study also shows that the mean level of serum Tg will increase more than eleven-fold following thyroid hormone withdrawal. The same finding was previously reported by Schlumberger et al. [5] and these authors noted that TSH stimulation will increase serum Tg values by about ten-fold over baseline levels. As explained earlier by Spencer et al. [9], serum Tg levels principally integrate three variables: the mass of thyroid tissue present (benign or neoplastic), the degree of thyrotropin (TSH) receptor stimulation and a tumour's intrinsic ability to synthesise and secrete Tg. It should be emphasised that serum Tg measurements should be interpreted relative to the TSH status of the patient. When TSH is low, basal serum Tg may be undetectable and TSH elevation (via rhTSH injection or thyroid hormone withdrawal) may be needed to increase serum Tg into the measurable range. The proportionate Tg response to rhTSH (rhTSH-stimulated Tg/basal Tg) is an index of the tumour's sensitivity to TSH. Normal thyroid remnant and well-differentiated thyroid tumours display a greater (> 10-fold) serum Tg response to TSH stimulation than less well-differentiated tumours (< 3-fold) [9].

Zakavi et al. [17] also reported that serum Tg increment after thyroid hormone discontinuation seems to be a better predictor of tumour recurrence, although a minimal Tg increment may not be a specific marker. Fifty-five patients with DTC treated with thyroidectomy and ^{131}I were enrolled. Serum Tg levels increased > or = 1 ng/ml in 25 patients after discontinuation of levothyroxine. Of these, 17 patients had metastatic disease or a detectable thyroid remnant. Of 16 patients with unchanged serum Tg levels (–1 < Delta Tg < +1), three had a thyroid remnant or metastases. In 14 patients with Tg decrement (Delta < or = –1) only two had a thyroid remnant. The positive predictive value for a Tg increment of more than 1, 2 and 5 ng/ml was 68%, 77.2% and 88.9% respectively. The authors concluded that DeltaTg is a more reliable indicator of remnant disease than on-treatment Tg or even off-treatment Tg levels [17].

Conclusion

Normal serum thyroglobulin level without on-treatment of thyroid-stimulating hormone is not diagnostically reliable in the follow-up of differentiated thyroid cancer patients with a high probability of residual/recurrent or metastatic disease.

Authors' contributions

MS and AG participated in the design of the study and supervised the study progress. AG, SJ, AT, JA and SM performed the data collection. AG and SA participated in the statistical analysis and drafted the manuscript. All authors read and approved the final manuscript.

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