Case Report

30 mCi exploratory scan for two-step dosimetric ^{131}I therapy in differentiated thyroid cancer patients: A novel approach and case report

ABSTRACT

Differentiated thyroid cancer patients with significantly elevated or rapidly rising serum thyroglobulin (Tg) levels and negative diagnostic radioiodine scans (DxScan) often present a therapeutic dilemma in deciding whether or not to administer an ^{131}I treatment. In this report, we describe a novel two-step approach of a 30 mCi ^{131}I exploratory scan before a dosimetric ^{131}I therapy to help "un-blind" the treating physician of the benefit/risk ratio of a further "blind" ^{131}I treatment. A 51-year-old man presented with rising Tg levels, a negative DxScan, and a history of widely metastatic follicular thyroid cancer. He had undergone total thyroidectomy, remnant ablation with 3.8 GBq (103.5 mCi) of ^{131}I, Gammaknife®, and treatment with 12.1 GBq (326 mCi) of ^{131}I for multiple metastases. However, at 19 months after the treatments, his Tg levels continued to rise, and scans demonstrated no evidence of radioiodine-avid metastatic disease. In anticipation of a "blind" ^{131}I treatment, the medical team and the patient opted for a 30 mCi exploratory scan. The total dosimetrically guided prescribed activity (DGPA) was decided based on the whole-body dosimetry. The patient was first given 30 mCi of ^{131}I, and the exploratory scan was performed 22 h later, which demonstrated ^{131}I uptake in the left lung, left humeral head, T10, and right proximal thigh muscle. Based on the positive exploratory scan, the remainder of the DGPA was administered within several hours after the scan. On the post-DGPA treatment scan performed at 5–7 days, the lesions seen on the ~ 22 h exploratory scan were confirmed, and an additional lesion was observed in the left kidney. The 30 mCi exploratory scan suggested the potential for a response in the radioiodine-avid lesions despite a negative diagnostic scan. This method allows ^{131}I treatment to be administered to patients who may have a greater potential for a therapeutic response while avoiding unwarranted side effects in those patients with nonavid disease.

Keywords: ^{131}I treatment, 30 mCi exploratory scan, differentiated thyroid cancer, dosimetry, negative diagnostic scan, positive thyroglobulin

INTRODUCTION

The management of differentiated thyroid cancer (DTC) patients who have positive serum thyroglobulin (Tg) levels and negative diagnostic radioiodine scans (DxScan) is problematic.[1] The treating physician does not know whether or not a metastasis will take up radioiodine that will result in a significant therapeutic effect, and hence the physician is "blind" to the benefit/risk ratio. In these patients, one option is to administer a "blind" ^{131}I therapy, which may result in no beneficial effect with the potential for significant side effects; however, the alternative is to not administer a "blind" ^{131}I therapy, which may eliminate a potential therapeutic treatment for that patient.

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The 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Thyroid Cancer recommends that a "blind" ^{131}I treatment may be considered based on the levels of serum Tg ≥10 ng/ml.[2] However, no reliable method is available to help determine *a priori* whether or not a patient may benefit from a "blind" ^{131}I treatment other than actually administering the ^{131}I treatment itself and subsequently observing a posttherapy scan (TxScan) to assess the degree of uptake. In order to better differentiate radioiodine-avid versus nonavid disease, we propose a 30 mCi exploratory scan before a dosimetric ^{131}I therapy as a novel empiric approach, which may help "un-blind" the treating physician. This might allow ^{131}I treatment in more patients who could benefit from a therapeutic effect while eliminating the side effects of a "blind" ^{131}I treatment in patients who have little or no potential benefit. This approach may be of interest in patients who are being considered for larger activities of ^{131}I, typically determined by dosimetry.

Methodology of the 30 mCi ^{131}I exploratory scan

A patient who has DTC, significantly elevated or rising Tg levels, and negative DxScan is informed of the risks and benefits of the various options of no treatment (e.g., active surveillance), focal treatment of structural disease, a "blind" ^{131}I treatment, a 30 mCi ^{131}I exploratory scan, and systemic therapy. If the patient and referring physician agree to the empirical option of a 30 mCi ^{131}I exploratory scan, then the preparation and performance of the exploratory scan is as follows.

The patient maintains a low-iodine diet for at least 10–14 days with adequate iodine depletion assessed by the measurement of urinary iodine-to-creatinine ratio at the end of the period of low-iodine diet. The patient is prepared with either thyroid hormone withdrawal or injections of recombinant human thyroid-stimulating hormone (rhTSH). Subsequently, whole-body dosimetry is performed with 74 MBq (2 mCi) of ^{131}I.[3,4] Based on the dosimetrically calculated maximum tolerated activity (MTA) and patient history, the medical team and the patient agree upon a dosimetrically guided prescribed activity (DGPA) for the patient's possible ^{131}I treatment. The patient is then orally administered 1.11 GBq (30 mCi) of the total ^{131}I DGPA. Twenty-four to 36 h later, anterior and posterior whole-body images, anterior and posterior spot images of the neck and chest, and anterior pinhole collimator images of the thyroid bed are obtained. If necessary, single-photon emission computed tomography (SPECT) is performed. Appropriate radiation precautions for a prescribed activity of 1.11 GBq (30 mCi) are followed. The specifics of performing these scans and the radiation safety precautions have been previously discussed in more detail by Van Nostrand and Atkins[5] and Vetter and Glenn,[6] respectively. The images are promptly reviewed by the nuclear medicine physician. If the images are positive for DTC metastasis, then a decision whether or not to administer the remainder of the DGPA is taken. If the images are negative for functioning metastasis, then no further ^{131}I is administered. Regardless of whether the patient received only 1.11 GBq (30 mCi) or the total DGPA, a TxScan is performed 5–7 days later.

The ^{131}I activity of 1.11 GBq (30 mCi) was chosen because it used to be the highest ^{131}I activity allowed for outpatient procedures by the United States Nuclear Regulatory Commission.[7] This activity amount would be reasonable to choose because it would allow most imaging facilities to do the 30 mCi exploratory scan as an outpatient procedure without any further radiation safety forms that had to be completed by the patient and/or additional approval through a radiation safety committee or department.

CASE REPORT

A 51-year-old man presented to the clinic with rising Tg levels, a negative DxScan, and a history of widely metastatic follicular thyroid cancer. Previously, he underwent total thyroidectomy with no lymph node dissection and remnant ablation with 3.8 GBq (103.5 mCi) of ^{131}I for a 7.4 cm well-differentiated minimally invasive follicular carcinoma with no other aggressive features. At 9 months after ^{131}I therapy, his suppressed Tg was 0.8 ng/ml (TSH not available; TgAb negative). Fourteen months later, he was found to have multiple bilateral pulmonary and liver, renal, and brain metastases with a Tg of 31 ng/ml while on thyroxine. The brain metastases were treated with Gammaknife®, and the other metastases were treated with 12.1 GBq (326 mCi) of ^{131}I. The ^{131}I TxScan showed radioiodine-avid bilateral pulmonary metastases, right-lobe hepatic metastases, and left humerus and right iliac crest bone metastases. For 12 months, the suppressed Tg was stable between 5.2 and 6.0 ng/ml.

However, at 14 and 19 months after the treatment, the suppressed Tg had risen from 29 ng/ml (TSH 0.64 mIU/L) to 160 ng/ml (TSH 1.01 mIU/L), and the stimulated Tg was 327 ng/ml (TSH 81 mIU/L) at 19 months. An ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) scan showed new lesions in the left side of T10 and left suprascapular muscle. A rhTSH stimulated 74 MBq (2 mCi) ^{131}I DxScan, with TSH 80.74 mIU/L and urinary iodine-to-creatinine ratio 38.7 mg/g, demonstrated no evidence of radioiodine-avid metastatic disease [Figure 1], and a "blind" treatment was considered.

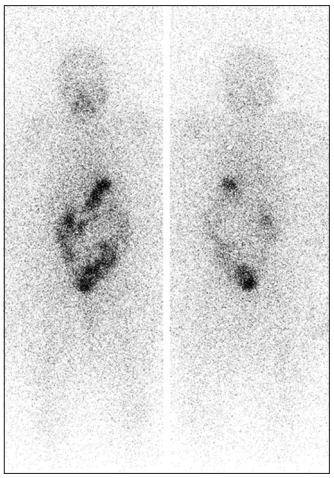

Figure 1: Negative diagnostic ^{131}I scan. The thyrogen-stimulated 74 MBq (2 mCi) ^{131}I diagnostic radioiodine scans imaged at 48 h demonstrated no evidence of radioiodine-avid metastatic disease. Thyroid-stimulating hormone stimulation was adequate at thyroid-stimulating hormone 80.74 mIU/L, and low-iodine diet decreased urinary iodine-to-creatinine ratio to 38.7 μg/g

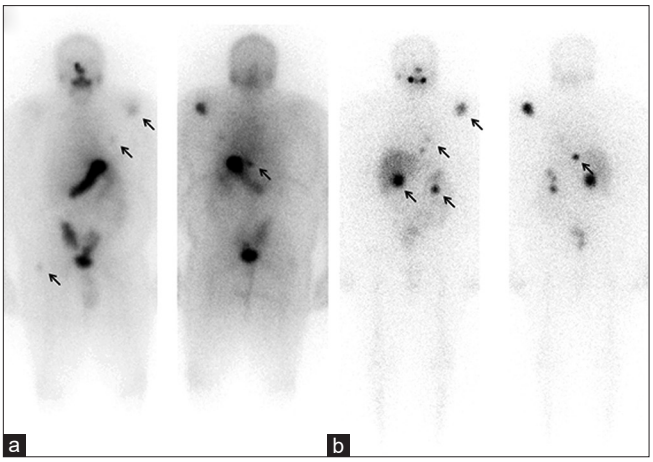

Figure 2: Positive 30 mCi exploratory scan and positive postdosimetrically guided prescribed activity scan. (a) A positive "30 mCi exploratory scan" performed at ~22 h after administration of 28.6 mCi of ^{131}I demonstrated abnormal ^{131}I uptake in the lung, bone, and muscle. The patient was administered the remainder of the planned dosimetrically guided prescribed activity. (b) It was performed 6 days (138.5 h) after the administration of the dosimetrically guided prescribed activity and demonstrated the previous uptake and new uptake in the left kidney. Additional single-photon emission computed tomography/computed tomography (nondiagnostic computed tomography scan for anatomic localization only) showed discrete abnormal focal uptake at T10-T11 vertebrae, discrete abnormal focal uptake co-registered to the right kidney, and smaller but discrete focal uptake co-registered to the left kidney, which was a left renal cyst

In anticipation of a "blind" ^{131}I treatment, the medical team and the patient opted for a 30 mCi exploratory scan. A whole-body dosimetry was performed, and the calculated MTA was 27.2 GBq (735 mCi), of which the medical team agreed on a total DGPA of 12.2 GBq (330 mCi). After the intramuscular injection of 0.9 mg of rhTSH on 2 consecutive days, the patient was given 28.6 mCi of ^{131}I on the next day. Approximately 22 h later, the exploratory scan was performed and demonstrated ^{131}I uptake in the left lung, left humeral head, T10, and right proximal thigh muscle [Figure 2a]. The remainder of the DGPA (i.e., 11.0 GBq [298 mCi]) of ^{131}I was administered within several hours after the scan. On the post-DGPA TxScan and SPECT/CT performed at 6 days (138.5 h), the lesions seen on the ~22 h exploratory scan were confirmed, and an additional lesion was observed in the left kidney [Figure 2b]. These images suggested the potential for a response in the radioiodine-avid lesions; however, no long-term follow-up data are presently available.

DISCUSSION

This report presents a novel approach – "the 30 mCi ^{131}I exploratory scan" – that offers an option to potentially "un-blind" the treating physician and help better determine which patients may benefit from ^{131}I treatment, while helping to avoid ^{131}I treatment and its potential side effects in patients who may have little or no benefit. Management is often problematic for DTC patients who have significantly elevated or rising serum Tg and negative DxScans. Several studies have shown that depending on the patient cohort and the imaging technique, as many as 13%–64% of patients with negative DxScans have uptake in at least some of the metastatic lesions on an ^{131}I TxScan.[5,8,9] Even in patients with negative ^{124}I pretherapy PET/CT, Khorjekar *et al.*,[10] Lammers *et al.*,[11] and Kist *et al.*[12] have observed that 83% (10/12), 83% (5/6), and 33% (4/12) of patients will have a positive ^{131}I TxScan, respectively.

Although patients with a negative 30 mCi exploratory scan may have a positive exploratory scan if higher ^{131}I activities are administered for imaging, we do not recommend this. We submit that even if a metastasis was positive on an exploratory scan performed with a higher ^{131}I activity, it may have a lower likelihood of achieving a meaningful therapeutic effect.

However, the 30 mCi exploratory scan has multiple limitations. First, ^{131}I uptake seen on the 30 mCi exploratory scan may be indicative of radioiodine-avid metastases, but it does not necessarily indicate that a significant therapeutic effect will result from the ^{131}I treatment. Chao systematically reviewed 17 studies with a total of 337 Tg+/DxScan- patients who received an empiric "blind" ^{131}I therapy of 2.8–11.1 GBq (75–300 mCi) and found that 62% had a positive TxScan and 20% (66/337) did not have significant decrease in Tg levels.[13] Structural response was not evaluated in their review. Nevertheless, as patients with a significantly elevated or rapidly rising Tg typically have significant progressive disease with a poor prognosis and few remaining treatment

options, it may be premature to dismiss ^{131}I as a treatment option based on a negative low activity (e.g., 37–185 MBq [1–5 mCi]) DxScan. Although the likelihood of a good response to ^{131}I treatment is lower in these patients, the possibility exists that ^{131}I treatment may be beneficial, at least for some lesions, and this option should be explored prior to considering targeted systemic therapy or immunotherapy. The 30 mCi exploratory scan offers that possibility. A second limitation of a 30 mCi exploratory scan is the possibility of stunning or partial treatment. McDougall has suggested that stunning most likely occurs several days (i.e., ~48–72 h) after ^{131}I administration.[14,15] In our patient, the remainder of the DGPA was given ~24 h after administering 30 mCi, which we believe decreases the likelihood of stunning. In addition, the 5–7 day TxScan demonstrated uptake in those lesions that were visualized at ~24 h, which also argues against stunning, but it does not exclude the possibility of some stunning. Similarly, even if the lesions were not visualized on a TxScan, that does not necessarily indicate stunning; it may depend on other factors such as relative rates of uptake and clearance of the tumor and/or background. Salvatori *et al*.[16] evaluated TxScans and showed that scans performed at 3 days after ^{131}I treatment missed 12% (16/134) of all lesions seen on either the 3-day or the 7-day scan, and scans performed at 7 days after ^{131}I treatment missed 7.5% (10/134) of all lesions. A third limitation is that the remainder of the DGPA was given ~48 h after the second injection of rhTSH; this could potentially reduce the uptake of the ^{131}I activity as the TSH levels are rapidly declining. In addition, the pharmacokinetics of thyrotropin alfa were studied in 16 DTC patients to show that TSH level reached a mean peak of 116 ± 38 mIU/L at 3–24 h and the mean half-life was 25 ± 10 h after a single intramuscular dose of 0.9 mg.[17] Duntas *et al*. performed serial TSH measurements in seven DTC patients and showed that the TSH level at 48 h after the second thyrotropin alfa injection was above 25–30 mIU/L, which has been proposed as sufficient for ^{131}I treatment.[18]

CONCLUSION

We report on the 30 mCi exploratory scan as a novel method to facilitate the decision whether or not to administer ^{131}I treatment to a patient who has a significantly elevated or rapidly rising Tg and a negative DxScan. Although this novel approach will not be infallible in predicting which patients will or will not benefit from an ^{131}I treatment, it provides an option for potentially safer and better management of these patients.

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Consent for publication

Consent to publish the case was obtained from the individual in this case report.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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