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Original article

Empiric Therapy with Low-Dose I-131 in Differentiated Cancer Thyroid: What is the Magic Number?

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Abstract

Low dose radioactive iodine-131 (RAI) has been widely reported in the treatment of patients with differentiated thyroid cancer (DTC) since 1970's. However, the clinical outcomes, dosage of I-131 and criteria for successful ablation are different in various studies. The aim of this study was to assess clinical outcome 18-month after RAI therapy in selected DTC patients and identify factors associated with a good response. In this experimental study, among patients with DTC referred to the Nuclear Medicine Department and had an indication for RAI therapy in the period between December 2008 and January 2011, 108 subjects were selected randomly. The patients were randomly divided into three groups and empiric low dose therapy with 30, 50 or 75 mCi of I-131 was administered. Patients were monitored closely clinically and with serum thyroglobulin assays and I-131 whole-body scans at 6 monthly intervals for 18-month after treatment. Among 105 patients who completed follow-up, 86% were successfully ablated with a single low dose of I-131. There was no statistically significant difference in ablation rates in the subgroups receiving 30.50 or 75 mCi of I-131. Cumulative ablation rate was 99% in patients after the second dose of low dose therapy. If appropriate selection criteria are used in DTC, successful remnant ablation can be achieved with low doses of I-131 in the range of 30-75 mCi. No significant differences were found in results achieved with 30.50 or 75 mCi of I-131. As the majority of the DTC patients fall within the inclusion criteria of this study, they can be treated on an ambulatory basis with associated low cost, convenience, and low whole-body radiation-absorbed dose to the patients.

Keywords: I-131, outcome, radioiodine therapy, remnant ablation, thyroid cancer

Introduction

The current accepted therapy for differentiated thyroid carcinoma (DTC) is total thyroidectomy (TT) or near-total thyroidectomy (NTT) followed by radioiodine (^{131}I) ablation of residual thyroid tissue (remnant ablation). There are several arguments and compelling reasons for remnant ablation in cases of DTC and they have been dealt with in detail elsewhere. Although I-131 has been used for many years to ablate thyroid remnants following thyroid surgery, a single optimal ablation strategy is still not established. Varied reports on the amount of I-131 required to achieve successful ablation, criteria for successful ablation and long-term disease free survival and recurrence rates, show a considerable range.[1,2]

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In this context, multiple studies have established the adequacy of low dose I-131 in successfully ablating remnant thyroid in selected patients with an activity as small as 30-75 mCi.[3-11] The proposed advantages are lower cost, minimizing whole-body radiation exposure and hence lowering the potential risk of leukemogenesis, and the practical advantage of the economy and convenience of outpatient treatment in many countries. Thus, the objective of this study was to find out successful ablation rates in selected DTC patients with small single dose of I-131.

Patients and Methods

Study design

A total of 108 patients with well-DTC were selected to receive 1110-1850 MBq of I-131 for ablation of residual

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functioning thyroid tissue 1.5-month (median) after total or subtotal thyroidectomy in the period between December 2008 and January 2011.

Inclusion criteria

Included in the study were patients having disease confirmed to be limited to the thyroid bed only by clinical, radiological, peroperative, and postsurgical ^{131}I scintigraphic examination and having no evidence of extrathyroid or distant metastases at the time of presentation. The amount of thyroid tissue left behind or completeness of surgery did not affect the dose of I-131 given.

Exclusion criteria

Patients with inadequate surgery, qualitatively defined as significant bilateral thyroid uptake on the first I-131 scan or >5 cm initial tumor size on histology were excluded. Patients with extrathyroid disease in the form of either nodal or distant metastases or with adverse histopathology such as Hurthle cell carcinoma, poorly differentiated carcinoma, insular carcinoma, medullary thyroid carcinoma, and aggressive variant of papillary carcinoma were also excluded. If the first postoperative thyroid scan of patients who had had a TT showed a substantial uptake in the thyroid bed, they were re-classified as having had a subtotal thyroidectomy and excluded from the study.

The median duration of the illness before surgery was 29-month (range, 1-370 months). Mean tumor size was 3.8 ± 1.2 cm. The large tumor size was probably due to late referral to surgery. The initial surgical intervention was not uniform due to different surgical units operating upon them. The surgical procedure followed was NTT/TT in all of the patients. The histopathological diagnosis was established in all patients and classified according to the World Health Organization criteria.[12] A total of 84 patients (80%) had papillary thyroid carcinoma (including follicular variant), and 24 (20%) had follicular thyroid carcinoma.

The interval between surgery and referral to the Department of Nuclear Medicine for remnant ablation ranged from 2 days to 2-month with a median value of 1-month. Postsurgical whole-body scan (WBS) was performed with 0.8-1 mCi of ^{131}I after keeping patients off L-thyroxin for 4-6 week. Preablation serum thyroid-stimulating hormone (TSH) values ranged between 25 and 98 μIU/ml (mean, 54 ± 14) in all patients. Although no special low-iodine diet was prescribed to the patients, they were advised not to take known rich iodine-containing foods and drugs or undergo contrast computed tomography scans. The patients were given oral I-131 as NaI therapeutic capsules with dosages of 30-50 mCi. Informed consent was obtained from all adult patients before administration of ^{131}I. After ^{131}I therapy, WBS (posttherapy scan) was done in all patients to look for any nodal/distant metastases missed on a low dose WBS after 1-week. The patients were then advised to take levothyroxine (2 μg/kg body weight) daily on an empty stomach as suppressive therapy. This was continued until 4-6 weeks before the repeat diagnostic studies 6-month later. The preparation for the 6-month posttherapy evaluation was similar to that for the preablation scan. No recombinant human TSH was used in this study. All patients were prepared by conventional methods with serum TSH >30 μIU/ml. The repeat diagnostic studies consisted of 2-3 mCi ^{131}I WBS and serum thyroglobulin (Tg) assays. The criteria for ablation were as follows: Negative ^{131}I WBS and Tg ≤1 ng/ml. Fulfillment of these two criteria were required to declare successful ablation. If, after the first posttherapeutic evaluation, the patients did not meet the criteria for complete thyroid ablation, then additional ^{131}I treatment (30-50 mCi) was administered. Repeat ^{131}I doses were administered until thyroid ablation was achieved, after which annual check-ups were planned with Tg estimation.

Results

The mean age of the patients was 39 ± 12.7 year with a female to male ratio of 2.6. The mean tumor size was 3.8 ± 1.2 cm. With one dose of ^{131}I, successful remnant ablation was achieved in 90 (86%) of 105 patients with mean Tg being 0.5 ± 0.1 ng/ml. The remaining patients showed partial ablation, objectively assessed by reduction in scan uptake intensity or number of foci and low Tg levels. There was no statistically significant difference in the first-dose outcome (remnant ablation) between patients receiving 30 mCi (44% of patients) or 50 mCi of ^{131}I (32% of patients) or 75 mCi (24% of patients). The remnant ablation rates were almost identical among these patients administered 30-75 mCi of ^{131}I (84%, 92%, and 88% ablation rates, respectively). The results have been summarized in Table 1.

Further evaluations within the groups based on tumor size and other demographical factors did not reveal any statistically significant associations to a successful ablation rate.

Two doses of ^{131}I were administered to 15 patients. The cumulative rate of remnant ablation achieved after the second dose of ^{131}I was 99%. All patients were followed-up for 18-month. So far, no cases of local recurrence or nodal/distant metastasis have been observed in this study cohort. Furthermore, no death has been encountered.

Discussion

There are multiple reports attesting to the efficacy of low-dose (30-75 mCi) ablative therapy for thyroid

Table 1: Demographic, clinical profiles, and treatment outcomes of all patients

Parameters	Total (%)	30 mCi (%)	50 mCi (%)	75 mCi (%)
Age (year)	39±12.7	37.5±11.6	41±13.6	39.9±13.7
Sex (female: male)	2.6:1	2.7:1	2.4:1	3:1
Median duration of illness (months)	18	20	18	16
Tumor size (cm)	3.8±1.2	4.5±1.6	3.6±1.7	5.1±2.1
Surgery NTT	105	46	34	25
Histopathology[a]				
Papillary	84	36	22	18
Follicular	21	10	12	7
Successful ablation (percentage of patients)[a]	90 (86)	39 (84)	31 (92)	22 (88)
Patients requiring second dose	15	7	3	3
Cumulative ablation after second dose (percentage of patients)[a]	104 (99)	45 (97.8)	34 (100)	25 (100)

[a]Number of patients. Age and tumor size are given in terms of mean±SD; duration of illness is given as median. SD: Standard deviation; NTT: Near-total thyroidectomy

remnants since 1970's. One of the first reports of such therapy emphasized its effectiveness relative to a more standard high dose of I-I31.[3]

The initial belief and practice was that a higher amount of ^{131}I should be administered as it is more effective in achieving complete ablation with a single administration. The proponents of this large-activity ^{131}I remnant ablation argue that large administered activity not only ablates remnants, but also ablates possible micrometastatic deposits with the corollary that low-activity is less effective to ablate the micrometastases not visualized in a posttherapy WBS and thereby will lead to a higher recurrence rate and metastases.[10] However, this issue is already addressed by Mazzaferri and Kloos,[11] who found no difference in 30-year recurrence rates (4% and 6%, respectively; $P = 0.1$) between low-activity (29-50 mCi) and high-activity (51-200 mCi) ^{131}I remnant ablation groups.

This study provides additional data on the effectiveness of the 30-50 mCi dose. Our results show that a single 30-50 mCi dose resulted in successful ablation in 86% of patients at 1-year postiodine therapy. A single low dose of I-131 was sufficient in majority of the cases to render the follow-up I-131 scan negative and lower Tg levels considerably. This would not be an unreasonable criterion of successful therapy if the only issue were detection of iodine-retaining malignant thyroid tissue, but it is likely that more complete ablation of nonneoplastic thyroid tissue is necessary to afford its reported advantage in terms of decreased recurrences of thyroid carcinoma and increased patient survival.[11,13-17]

Furthermore, our experience in following patients with minimally positive scans indicates that some may become negative without further I-131 therapy. Nevertheless, since 30 mCi is the largest dose usually approved for outpatients in many countries, it may be reasonable to combine the therapeutic and diagnostic efficacy of 30 mCi doses for ablation of thyroid remnants. The benefits of low dose therapy, in addition to economy and convenience, relate primarily to a reduced total radiation exposure to extrathyroid target organs. Although this reduction pertains mainly to the 86% of patients in whom ablation is achieved with a single 30 mCi dose, repeated low-dose exposures, which allow for tissue repair mechanisms to proceed in the interim, may cause less biologic damage than the same total dose delivered at one time. Therefore, even patients requiring two such doses may benefit. The risk of leukemia and ovarian injury after thyroid ablation doses under 150 mCi is unknown, but is probably very small. Pochin[18] had reported four cases of leukemia in 140 patients who received an average total dose of 735 mCi. Pochin's leukemia cases received 1130-1715 mCi, and other cases gathered from the literature by Brincker *et al*.[19] received 261-1600 mCi. Regarding ovarian injury, Sarkar *et al*.[20] they found no evidence of radiation-induced problems in fertility or in the offspring of 33 young adults treated with 80-691 mCi (average, 196 mCi) and followed for an average of 19 years. Despite the lack of evidence of injury below 150 mCi, it seems prudent to mitigate radiation exposure by using the minimal effective dose to achieve the desired purpose. Reported disadvantages of low-dose therapy are, first, that about half of the patients require more treatment, and thus there are more periods of T3 withdrawal and hypothyroidism, and a longer time to achieve ablation is required. Second, unrecognized metastases may be in adequately irradiated so that the function of the neoplastic cells but not their growth may be reduced. A long-term, prospective randomized controlled study is needed to evaluate the importance of these factors in the efficacy of low-dose ablation therapy. Our results suggest that the use of a single low-dose in the appropriate clinical setting, resulting in successful ablation in a majority of patients, is a reasonable approach to ablation therapy, especially in young subjects with well-DTC. As patients with incomplete initial surgery, poorly differentiated tumors or aggressive histology or with metastatic disease were not included, these results cannot be extrapolated to this population and high-dose ablation therapy may be preferable. Our results also suggest that a minimally positive scan at 6-month after a therapy dose is an indication for further follow-up rather than immediate further treatment.

Conclusion

If appropriate selection criteria are used in DTC, successful remnant ablation can be achieved with low

doses of I-131 in the range of 30-75 mCi. No significant differences were found in results achieved with 30.50 or 75 mCi of I-131. As majority of the patients fall within the inclusion criteria of this study, they can be treated on an ambulatory basis with associated low cost, convenience, and low whole-body radiation-absorbed dose to the patients. The ability to treat with low dose of approximately 30 mCi is of particular significance in India, as the regulatory authorities have kept 30 mCi as the upper limit for outpatient therapy. Thus, deserving patients can be treated without admission and attendant cost even with low dose I-131.

Limitations of the study

Long-term clinical follow-up would be required to assess treatment outcome and recurrence rates.

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