I-124 pre-therapy dosimetry for the treatment of differentiated thyroid cancer: A single center experience

Original Article

Said Mohamad Aminudin, Lee Boon Nang, Ali Norsalita

Nuclear Medicine Department, Institut Kanser Negara, Putrajaya, Malaysia

(Received 13 December 2016, Revised 7 February 2017, Accepted 16 February 2017)

ABSTRACT

Introduction: The maximum tolerable activity (MTA) of I-131 in radioiodine therapy is an established surrogate quantity to ensure that the therapeutic activity does not produce severe damages to the bone marrow and lung. The aim of this study was to estimate the MTAs for high-risk patients using I-124 pre-therapy dosimetry and to compare the results with published literature.

Methods: A total of 15 thyroid cancer patients, who received I-124 pre-therapy dosimetry procedure, had underwent serial blood sampling and whole-body external measurements at approximately 1–2, 4, 24, 48, and 96 h or longer after I-124 administration. The blood sampling and whole-body external measurements were used to calculate the MTA for each individual using published dosimetry procedures.

Results: The estimated MTAs ranged from 14 to 34 GBq. The range of blood residence and whole-body residence times were 2.6 h and 22.4 h, respectively; the 48-h whole-body retention value ranged from 2% - 14%. An overall good MTA agreement can be found between our centre and the results of the well-established centre (Essen, Germany) that included 108 patients.

Conclusion: I-124 pre-therapy dosimetry provides toxicity levels similar to published values. Further prospective studies are warranted to assess the benefits of I-124 pre-therapy dosimetry for the individual patient and, in particular, the patient outcome.

Key words: I-124; I-131; Dosimetry; Thyroid cancer

Iran J Nucl Med 2017;25(2):105-109

Published: July, 2017

http://irjnm.tums.ac.ir

Corresponding author: Said Mohamad Aminudin, Nuclear Medicine Department, Institut Kanser Negara, No 4, Jalan P7, Presint 7, 62250 Putrajaya, Malaysia. E-mail: aminhpj@gmail.com

INTRODUCTION

Radioiodine therapy is widely established to treat differentiated thyroid cancer (DTC) disease. In current clinical practice, the amount of I-131 activity administered to the patients is often limited to 7.4 GBq (200 mCi). However, therapy activities more than 7.4 GBq (200 mCi) may be applied with proper safety procedures using pre-therapy dosimetry assessment to ensure that the patient-specific toxicity level is not exceeded. Recently, the application of positron-emitting I-124 in radioiodine therapy planning was proven to project the maximum tolerable I-131 activity (MTA) [1-3]. The unique property of I-124 provides an excellent target for PET thyroid cancer imaging for pre-therapy dosimetry described in multiple publications [1-7]. The role of pre-therapy dosimetry is to estimate the optimum therapy activity that is, providing an acceptable absorbed dose to the tumour while maintaining below the toxicity level of the organs at risk. The organs at risk for radioiodine therapy are the bone marrow and lung [8, 9]. In order to avoid possible toxicity effects, the amount of absorbed radiation dose given to these dose-limiting organs has to be estimated. There are limited data regarding the accurate radiation absorbed dose given to the organs at risk, and therefore, empirical surrogate quantities were introduced to predict possible toxicities [8, 9].

A pilot study was conducted to estimate the bone-marrow and lung toxicity levels using surrogates. Of note, tumour dose estimates using PET imaging were not included in the pilot study that can be derived as well [4, 6, 7]. The standard operational procedure for pre-therapy dosimetry involves a series of both blood sampling and external whole-body counting over a period of 4 d or longer [3, 10]. The data are used to calculate the MTA that would deliver 2 Gy to blood (surrogate for bone marrow toxicity) or would result in a whole-body retention activity of 3.0 or 4.4 GBq after 48 h (surrogates for lung toxicity) in the presence or absence of diffuse pulmonary metastases, respectively [3,10].

Thus, the aim of this study was to estimate the MTAs for selected high-risk patients using I-124 pre-therapy dosimetry and to compare the results with published literature.

METHODS

A total of 15 thyroidectomised patients before their first radioiodine therapy were included. All patients signed a written informed consent. Patients were selected by Nuclear Medicine Physicians to undergo the I-124 pre-therapy dosimetry procedure. The following patient's data were extracted: age, gender, weight, height, tumour histology, and stage of disease. Patient preparation was performed after either a thyroid hormone withdrawal or administration of recombinant human thyroid-stimulating hormone (TSH) to obtain sufficient TSH levels (≥25 mIU/L). The patients were orally administered 37-50 MBq of I-124. I-124 was supplied from VU University Medical Center in Amsterdam (The Netherlands). The I-124 was placed onto a sugar cube and placed inside a copper container in order to absorbed low level x-ray energy before measured inside the dose calibrator for accurate activity measurement [11].

In estimating the MTA, serial blood sampling (approximately 1.5 ml) and whole-body external measurements at approximately 1–2, 4, 24, 48, 96 h were conducted after I-124 administration. A probe was positioned 2 meter from the patient for an anterior and a posterior whole body counting measurement. The geometric mean of the whole body counting measurements was calculated for each time point. The blood samples were measured in a well-counter. After projecting the I-124 measurements to the (therapeutic) I-131, the blood absorbed dose per unit administered therapeutic activity (BDpA) was calculated as follows [3]:

$$\mathrm{BDpA}\left(\frac{\mathrm{Gy}}{\mathrm{GBq}}\right) = 108 \times \frac{\tau_{\mathrm{blood}/\mathrm{h}}}{V_{\mathrm{BS}/\mathrm{ml}}} + 0.0188 \times \frac{\tau_{\mathrm{wc}/\mathrm{h}}}{m_{\mathrm{p}/\mathrm{kg}}^{2/3}},$$

where τ_{Blood} (in h) is the blood residence time, V_{BS} (in ml) is the patient's blood volume [12], τ_{WC} (hr) is the whole body residence time, and m_p (in kg) is patient's weight.

To avoid ambiguity and maintain consistency, no curve-fitting was applied. The blood and whole-body residence times were determined by separating the blood and whole-body uptake curves into 3 phases, that is, an early, a mid, and a late phase [3]. In particular, an instant uptake was assumed, that is, the uptake at the zero time point equalled the uptake value of the early time point (early phase). The mid phase, the region between the early and the last uptake point (96 h), was parameterized using multiple single mono-exponential functions. In the late phase, the uptake decreased exponentially either with an I-131 half-life, which equalled the effective I-131 half-life of the last exponential function of the mid phase.

The MTA was calculated on the basis of a blood dose threshold of 2 Gy and an activity threshold of 3.0 or 4.4 GBq retained in the whole-body at 48 h in the presence or absence of diffuse pulmonary uptake, respectively. The blood dose per administered activity and the 48-h whole-body retention (R_{48}) were used to determine the MTA. More precisely, 2 Gy divided by BDpA yielded the critical activity for possible bone marrow toxicity and 3.0 or 4.4 GBq divided by R_{48} yielded the critical activities for possible lung toxicities. The lowest critical therapy activity was taken as the MTA.

Table 1: Summary of important dosimetry quantities in estimating the MTA for each patient.

Patient ID	τ_{blood}	τ_{WC}	Blood dose per administration (Gy/GBq)	R_{48} (%)	Critical activity for bone marrow (GBq)	Critical activity with diffuse lung mets. (GBq)	Critical activity without diffuse lung mets. (GBq)	MTA (GBq)
1	2.04	40.6	0.11	8	18	37	56	18
2	3.08	34.5	0.11	8	18	36	54	18
3	3.38	25.7	0.14	14	14	22	32	14
4	2.03	19.1	0.11	4	18	82	123	18
5	2.78	18.6	0.11	4	18	80	119	18
6	2.22	18.2	0.06	6	33	49	74	33
7	2.73	14.2	0.08	4	25	78	116	25
8	2.25	24.4	0.12	9	17	33	49	17
9	3.50	21.1	0.13	14	15	21	31	15
10	2.52	35.1	0.11	7	18	45	68	18
11	2.35	19.8	0.07	5	29	59	88	29
12	1.88	14.2	0.11	2	18	157	236	18
13	2.27	15.8	0.10	3	20	85	128	20
14	2.75	18.3	0.07	7	29	42	64	29
15	2.45	16.6	0.10	7	20	42	63	20

RESULTS

Table 1 lists a summary of important dosimetry quantities and the MTA for each patient. There was a large variation for the MTAs, ranging from 14 to 33 GBq. It can be derived that, in all patients, the dose-limiting organ is the bone marrow. Blood residence time ranged from 1.88–3.50 h, whole body residence time from 14.2–40.6 h, 48-h retention values from 2–14 %, and BDpA value from 0.06–0.14 Gy/GBq. Examples for a whole-body retention curve and blood uptake curve are shown in Figures 1 and 2, respectively.

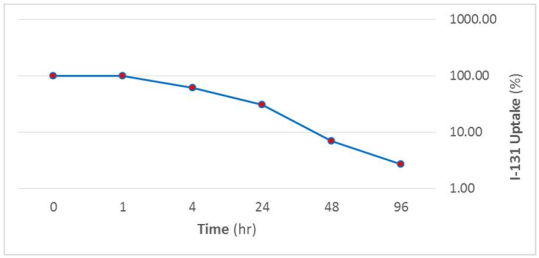

Fig 1. Example for a whole body uptake I-131 retention curve, the predicted percentage activity retained in the patient's body (half logarithmic plot). Solid circles represent the measurements and the solid lines between the points are the mono-exponential functions.

For comparison purposes, Table 2 list important values from our center and the center of the Nuclear Medicine Department at University of Essen (Germany). Statistically, our result in Table 2 demonstrated similar finding with patients prior to their first radioiodine therapy [3].

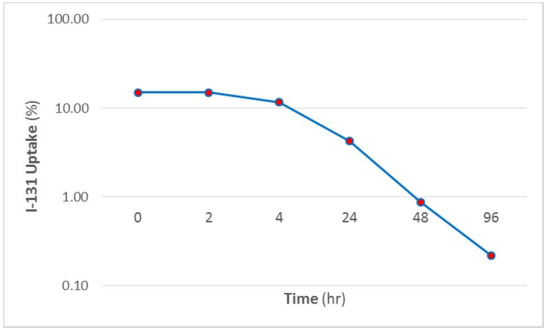

Fig 2. Example for a blood I-131 uptake curve, the predicted percentage of activity in the entire blood (half logarithmic plot). Solid circles represent the measurements and the solid lines between the points are the mono-exponential functions

DISCUSSION

Our present pilot study focused on the estimation of the MTA for patients undergoing their first radioiodine therapy. The MTA was determined by using serial blood sample and also serial patient's whole body counting measurements [3]. Statistically, our result in Table 1 demonstrated similar finding with another centre [3]. In current study, the whole body exposure measurement was done by using calibrated well counter with two meter distance from patients and the different technique with other researchers [13], they performed whole body measurement with gamma camera in conjugate view (anterior and posterior) counts as suggested by previous study [10,14]. According to the [5], whole body measurement with

gamma camera is not suitable with I-124 due to it's physical property. The well counter technique is a simple procedure and need less than five minutes to finish each measurement. Generally, both measurement techniques was acceptable and depending with the type of radionuclide property.

Another study [15] conducted I-131 pre-therapy I-131 dosimetry with 47 patients. They found MTAs of 12.5 ± 2.1 GBq which, on average, was approximately by factor of two lower than our result (12.5 GBq vs. 21 GBq). However, Lee et al. [15] used a different methodology to estimate the MTA, using only serial blood sampling from 2 to 72 h after 200 MBq of I-131, that is, gamma radiation was not considered. Consequently, the notable MTA difference probably resulted in a different approach in estimating the absorbed dose to blood [8]. Another Italian group from Bologna [16], who performed pre-therapy I-124 dosimetry with 30 patients, demonstrated that the mean±standard deviation absorbed dose to the blood per unit administered activity based the standard operation procedure [10] was 0.07±0.02 Gy/GBq and the calculated respective mean±standard deviation MTA (for bone-marrow toxicity only) was 33±10 GBq. The time activity curves were fitted using monoexponential or bi-exponential functions and integrated to infinity to obtain the respective residence times (blood and whole body compartment). The notable mean MTA difference between our and the published study [16] is probably associated in the heterogeneous patient cohorts. The authors suggest a mixture of patients, who underwent their first and more radioiodine treatments.

Thus, the variations of the MTAs between the different studies may be related with (a) the different methodologies used such as frequency of blood and whole-body measurements, basic formula, and method of analysis and (b) heterogeneous patient cohort. We suggested that more study shall be conducted in order to standardize the methodology in estimating the MTA.

CONCLUSION

The MTAs derived in this study are comparable with other recently published results. The technique and protocol as well as the patient cohort influence the MTA result. Further prospective studies are warranted to assess the benefits of I-124 pre-therapy dosimetry for the individual patient and, in particular, the patient outcome.

REFERENCES

1. Freudenberg LS, Jentzen W, Görges R, Petrich T, Marlowe RJ, Knust J, Bockisch A. 124I-PET dosimetry in advanced differentiated thyroid cancer: therapeutic impact. Nuklearmedizin. 2007;46(4):121-8.
2. Schwartz J, Humm JL, Divgi CR, Larson SM, O'Donoghue JA. Bone marrow dosimetry using 124I-PET. J Nucl Med. 2012 Apr;53(4):615-21.
3. Jentzen W, Bockisch A, Ruhlmann M. Assessment of simplified blood dose protocols for the estimation of the maximum tolerable activity in thyroid cancer patients undergoing radioiodine therapy using 124I. J Nucl Med. 2015 Jun;56(6):832-8.
4. Jentzen W, Hoppenbrouwers J, van Leeuwen P, van der Velden D, van de Kolk R, Poeppel TD, Nagarajah J, Brandau W, Bockisch A, Rosenbaum-Krumme S. Assessment of lesion response in the initial radioiodine treatment of differentiated thyroid cancer using 124I PET imaging. J Nucl Med. 2014 Nov;55(11):1759-65.
5. Cascini GL, Niccoli Asabella A, Notaristefano A, Restuccia A, Ferrari C, Rubini D, Altini C, Rubini G. 124 Iodine: a longer-life positron emitter isotope-new opportunities in molecular imaging. Biomed Res Int. 2014;2014:672094.
6. Wierts R, Brans B, Havekes B, Kemerink GJ, Halders SG, Schaper NN, Backes WH, Mottaghy FM, Jentzen W. Dose-Response Relationship in Differentiated Thyroid Cancer Patients Undergoing Radioiodine Treatment Assessed by Means of 124I PET/CT. J Nucl Med. 2016 Jul;57(7):1027-32.
7. Jentzen W, Verschure F, van Zon A, van de Kolk R, Wierts R, Schmitz J, Bockisch A, Binse I. Response assessment of bone metastases from differentiated thyroid cancer patients in the initial radioiodine treatment using iodine-124 PET imaging. J Nucl Med. May 19, 2016.
8. Benua RS, Cicale NR, Sonenberg M, Rawson RW. The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. Am J Roentgenol Radium Ther Nucl Med. 1962 Jan;87:171-82.
9. Benua RS, Leeper RD. A method and rationale for treating metastatic thyroid carcinoma with the largest safe dose of I-131. In: Medeiros-Neto G, Gaitan E. Frontiers in Thyroidology. New York, NY: Plenum Medical Book Co; 1986. p. 1317–21.
10. Lassmann M, Hänscheid H, Chiesa C, Hindorf C, Flux G, Luster M; EANM Dosimetry Committee. EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy. Eur J Nucl Med Mol Imaging. 2008 Jul;35(7):1405-12.
11. Beattie BJ, Pentlow KS, O'Donoghue J, Humm JL. Humm. A recommendation for revised dose calibrator measurement procedures for 89Zr and 124I. PLoS One. 2014 Sep 9;9(9):e106868.
12. Pearson TC, Guthrie DL, Simpson J, Chinn S, Barosi G, Ferrant A, Lewis SM, Najean Y. Interpretation of measured red cell mass and plasma volume in adults: Expert Panel on Radionuclides of the International Council for Standardization in Haematology. Br J Haematol. 1995 Apr;89(4):748-56.
13. Piruzan E, Haghighatafshar M, Faghihi R, Entezarmahdi SM. Calculation of Blood Dose in Patients Treated With 131I Using MIRD, Imaging, and Blood Sampling Methods. Medicine (Baltimore). 2016 Mar;95(11):e3154.
14. Siegel JA, Thomas SR, Stubbs JB, Stabin MG, Hays MT, Koral KF, Robertson JS, Howell RW, Wessels BW, Fisher DR, Weber DA, Brill AB. MIRD pamphlet no. 16: Techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in

human radiation dose estimates. J Nucl Med. 1999 Feb;40(2):37S-61S.

15. Lee JJ, Chung JK, Kim SE, Kang WJ, Park DJ, Lee DS, Cho BY, Lee MC. Maximal safe dose of I-131 after failure of standard fixed dose therapy in patients with differentiated thyroid carcinoma. Ann Nucl Med. 2008 Nov;22(9):727-34.

16. Pettinato C, Spezi E, Nanni C, Grassetto G, Monari F, Allegri V, Civollani S, Cima S, Zagni P, Mazzarotto R, Colletti PM, Rubello D, Fanti S. Pretherapeutic dosimetry in patients affected by metastatic thyroid cancer using 124I PET/CT sequential scans for 131I treatment planning. Clin Nucl Med. 2014 Aug;39(8):e367-74.