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Upon completion of this educational activity, participants should be able to:

- identify a patient in whom dosimetric RAI may provide a clinical benefit
- describe the procedures involved in dosimetric RAI
- describe the potential clinical benefit of dosimetric RAI
- perform the medical procedure of dosimetric RAI in cooperation with a medical physicist

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The following JCEM Editors reported no relevant financial relationships: **Paolo Beck-Peccoz, M.D.; David Ehrmann, M.D.; David Handelsman, Ph.D.; Michael Kleerekoper, M.D.; Merrily Poth, M.D.; Constantine Stratakis, M.D.**
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Activity release date: October 2013
Activity expiration date: October 2015

Approach to the Patient: Role of Dosimetric RAI Rx in Children With DTC

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Context: Pediatric differentiated thyroid cancer (DTC) patients frequently present with lymph node and/or distant (lung) metastases. Such patients warrant an aggressive treatment consisting of surgical removal of all surgically accessible local metastases as well as further treatment with one or more courses of radioiodine therapy (RAI). It is still a subject of debate in literature how much I-131 should be administered to pediatric patients. Patients can either be given a fixed (possibly body weight adjusted) activity or a dosimetry based activity, which is often considerably higher.

Objective: Here, we will present a typical case of a pediatric patient who was treated using a dosimetric approach. Then we will discuss the basis of dosimetry and the procedures involved, followed by a discussion of when to use dosimetric RAI as well as the pros and cons of the various approaches in pediatric patients.

Results: In general, two opposite approaches to dosimetry exist: either the activity that is as high as safely administrable (AHASA) is determined based on the radiation exposure to the critical organs at risk (in pediatric patients these are the bone marrow and, in patients with lung metastases, the lungs), or a lesion-based approach in which the activity that is required to deliver a certain radiation dose to the metastatic lesion(s) is determined.

Conclusion: Because the latter approach requires an accurate volumetry of the target lesion(s), which is not possible in children with disseminated pulmonary metastases, which are often not visible with morphologic imaging techniques, we advocate using the AHASA approach in children with extensive metastatic DTC. (*J Clin Endocrinol Metab* 98: 3912–3919, 2013)

A 15-year-old, 152-cm, 46-kg girl from abroad was diagnosed with differentiated thyroid cancer (DTC) at the University Hospital Aachen in September 2007; here she underwent total thyroidectomy with central lymph node dissection. After histological analysis, she was classified as having a unifocal, pT3 pN1a pMx papillary thyroid cancer. The tumor diameter could not be determined reliably due to local tumor invasion. A prophylactic central lymph node dissection was not per-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received May 16, 2013. Accepted July 19, 2013.

Abbreviations: AHASA, as high as safely administrable; ALARA, as low as reasonably achievable; CT, computed tomography; DTC, differentiated thyroid cancer; pedDTC, pediatric DTC; PET, positron emission tomography; rh, recombinant human; RAI, radioiodine therapy; rxWBS, posttherapy whole-body scintigraphy; Tg, thyroglobulin.

formed. The one positive lymph node concerned a micrometastasis in a lymph node in the perithyroidal fat, which was removed with the thyroid. During the 4 weeks between thyroidectomy and ablative radioiodine therapy (RAI), the patient did not receive thyroid hormone therapy.

A pre-RAI uptake measurement using 2.8 MBq (76 μCi) I-131 (legally required in Germany) was performed before RAI; the low activity was chosen to prevent possible stunning. Scintigraphy of the neck revealed a 3.1% uptake in the thyroid remnant.

She then underwent ablative RAI with a standard fixed activity of 3700 MBq (100 mCi) in the Department of Nuclear Medicine of the RWTH University Hospital Aachen in October 2007. Thyroglobulin (Tg) levels at the time of ablation were 22 ng/mL, anti-Tg autoantibodies were negative and TSH levels were greater than 100 mU/L. On posttherapy whole-body scintigraphy (rxWBS), she showed multiple cervical lymph node and pulmonary metastases (see Figure 1). Thereafter she was referred to the Department of Nuclear Medicine of the University Hospital Würzburg for further treatment.

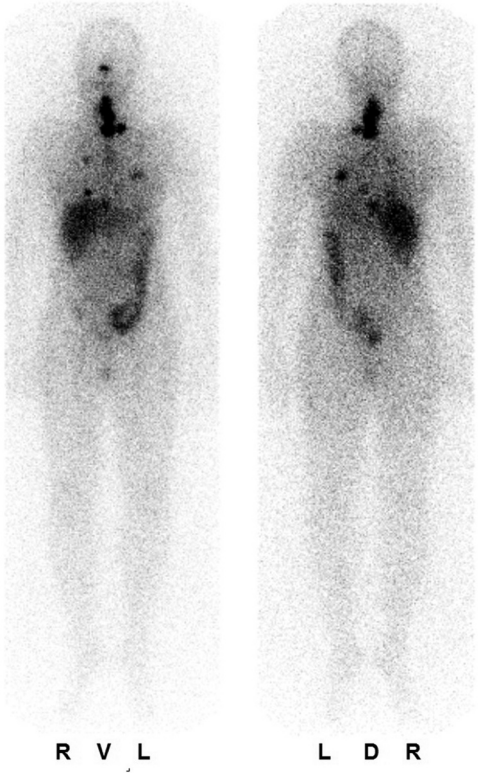

Figure 1. Whole-body scintigraphy of the patient acquired after ablative radioiodine therapy with ventral (left) and dorsal (right) images. Aside from the thyroid remnant, multiple cervical lymph node and pulmonary metastases can be seen. D, dorsal; L, left; R, right; V, ventral.

Case Report

Background

Pediatric DTC (pedDTC)

DTC is a rare disease in children and adolescents with a standardized incidence of 0.54 cases per 100 000 persons (1). Nonetheless, it concerns approximately 1.4% of all pediatric malignancies with rising incidence (2). pedDTC is rare and unrelated to gender in young children. Affected individuals are most often female adolescents (2, 3) with a well-differentiated form of papillary thyroid cancer, which avidly takes up radioactive iodine. As a result, prognosis is excellent when appropriate treatment is administered, even though the patients not infrequently present with lymph node and/or disseminated lung metastases. The latter usually become apparent only after RAI because they are usually not visible when morphological imaging techniques such as x-ray computed tomography (CT) are used.

Initial treatment

Given the comparative lack of therapy optimization studies in pediatric patients, determining what exactly constitutes the appropriate treatment can be challenging. The rarity of pedDTC, the good prognosis, and the ethical concerns of performing medical trials in juvenile patients make prospective studies difficult if not impossible to conduct. It is without question that every pedDTC case warrants total thyroidectomy and, if possible, surgical resection of any involved lymph nodes (1, 4, 5). The indications for RAI are less clear. For those patients without lymph node or distant metastases, the indication for RAI is subject to debate (5) because it is unclear whether RAI will improve survival. In contrast, in patients with lymph node and/or distant metastases, there is clear evidence to show that disease-free survival is improved by RAI (4, 6). Because prospective studies in pedDTC patients focusing on long-term recurrence and survival are unlikely to be completed in the near future, the precise identification of which patients should receive RAI at all will remain a subject of debate and controversy among the physicians involved.

No evidence is available in literature on which I-131 activities are required for successful RAI in pediatric patients. Usually an empiric fixed activity is used, the level of which may be tied to the patients' stage of disease and may/should be adjusted for body weight, at least in preadolescent children. Alternatively, a strategy is used in which the patients' individual iodine biokinetics are determined to calculate the activity to be administered. The latter strategy, also referred to as dosimetry, is often confined to a subgroup of patients with extensive disease.

Hereafter we will discuss dosimetric strategies as well as the clinical considerations for a dosimetric approach.

Dosimetric strategies

In radioiodine therapy of differentiated thyroid carcinoma, several parameters are equally or even more important than the administered activity for the radiation absorbed dose to the target tissue: 1) its iodine avidity, which in turn depends on DTC differentiation and TSH stimulation; 2) the residence time of the radioiodine per volume of blood plasma, which represents the bioavailability of the I-131; 3) the effective I-131 half-life in the target volume; and 4) the mean energy deposited per decay, which is mainly determined by the size and shape of the accumulating mass (7).

The high individual variation of all these parameters (7) fundamentally questions the value and feasibility of the quest for the single best fixed therapeutic activity for all DTC patients. Any study that disregards such parameters is not likely to succeed.

To overcome the uncertainty of individual biokinetics, 2 dosimetry-based approaches have been introduced: 1) Benua and colleagues (8, 9) aimed to determine the activity that is as high as safely administrable (AHASA), thus targeting safety; and 2) Maxon et al (10), targeting efficacy, first determined the activity that is as low as reasonably achievable (ALARA) and also delivering a desired radiation absorbed dose to the tumorous lesions.

In both approaches, dosimetry is performed prior to RAI by measuring the patient's iodine kinetics after administration of a tracer activity. Either I-131 or I-124 can be used for the assessment. I-124 offers the advantage of better imaging with higher sensitivity and spatial resolution through positron emission tomography (PET) and allows a more accurate lesion dosimetry. However, I-131 is usually used because it is ubiquitously available and relatively affordable. In addition to being much more expensive, as far as we know, I-124 PET imaging is not reimbursed by health care insurance companies in the United States or the rest of the world.

The patients' metabolic state (ie, hypo- or euthyroidism) should be identical during dosimetry and therapy. The metabolic state will affect kidney function and thus the I-131 clearance rate. Therefore, in patients who will be treated after levothyroxine withdrawal, dosimetry should be performed after levothyroxine withdrawal as well. Those children who are treated with recombinant human (rh) TSH on a compassionate-use basis should undergo dosimetry in a euthyroid state as well, ie, during levothyroxine therapy.

Blood/bone marrow dosimetry

As early as in 1962, Benua et al (8) reported that administering the AHASA activity and thus the AHASA absorbed dose to tumor tissue was most effective in RAI. The dose-limiting organs are the bone marrow and, for those patients with a heavy burden of disseminated lesions and high iodine uptake, the lungs. The easily measurable absorbed dose to the blood was found to be a good surrogate and conservative estimate for the red marrow absorbed dose. Therefore, Benua et al suggested to limit the absorbed dose to the blood to 2 Gy and the whole body activity in RAI in adults to 80 mCi or 3 GBq I-131 at 48 hours after the administration. This should avoid severe damage to the hematopoietic system as well as pneumonitis or pulmonary fibrosis, respectively.

The blood-absorbed dose per activity administered can be determined with adequate accuracy after oral application of an I-131 activity as low as 10 MBq (0.3 mCi). The activities in samples of whole blood and the total body should be measured over the course of several days until the whole-body activity has decayed to less than approximately 5% of the administered activity. The areas under the time-activity curves (time integrated activity coefficients, also known as residence times) are then determined to calculated the AHASA activity based on the 2-Gy threshold. Figure 2 shows a whole-body scan from the dosimetry procedure performed in the patient described above. The time-activity functions were deduced from the net counts in the total body region of interest and from activities in samples of whole blood over the course of 4 days. A detailed description of the procedure with adaption of the calculations to current Committee on Medical Internal Radiation Dose algorithms can be found in the European Association of Nuclear Medicine standardized operating procedure for I-131 dosimetry (11).

The limit of 2 Gy is, however, based on only a few cases of severe bone marrow suppression in adults (8). A study targeting at 3 Gy red marrow dose (12) and the observation that particularly older patients treated with fixed activities of 7.4 or 11.1 GBq frequently exceed the safety limit reported by Benua without corresponding rates of severe hematotoxic reactions indicate that the limit of 2 Gy might be regarded as conservative (13, 14). Nonetheless, in the absence of rigorous scientific evidence on the safety of higher limits, it appears advisable to currently maintain the threshold of 2 Gy as an upper safety limit.

The second constraint, no more than 80 mCi or 3 GBq I-131 in the whole body on day 2 of RAI, was settled for adults. Therefore, it likely must be adapted for use in children and adolescents to take the lower lung mass into account, which scales to the total body mass in normal nonobese individuals (15, 16). Lung dosimetry is indi-

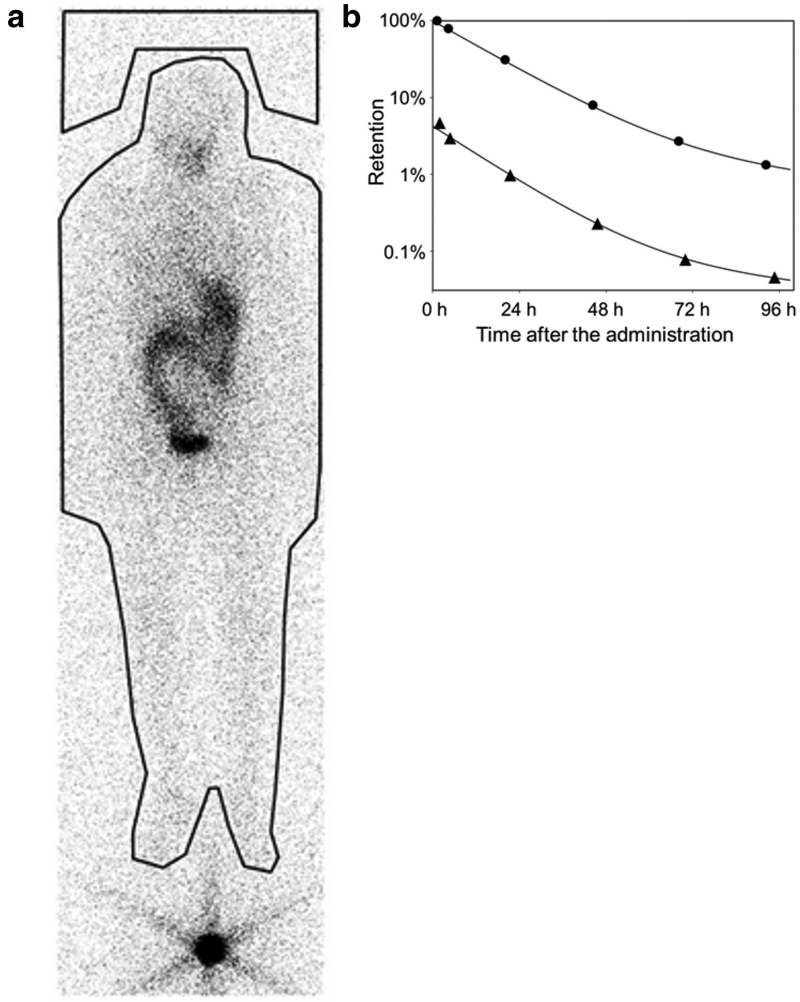

Figure 2. Blood dosimetry performed before the AHASA I-131 therapy in the 16-year-old female patient from the case described here. a, A whole-body scan 20 hours after the administration of 10 MBq (270 μCi) I-131 with a total body region of interest and a region above the head used for background subtraction. The activity standard at the feet represents 10% of the administered activity. b, The measured activities in total body (dots) and per liter of whole blood (triangles) normalized to the administered activity are shown together with biexponential fits of the retention time functions.

cated in children with high I-131 uptake in disseminated lung metastases (17–19). To identify patients at risk of excessive lung doses when the AHASA blood dose is administered, the whole-body scans of the dosimetry study can be used to measure the residence time of the activity in the lungs. It can be shown that 3 GBq I-131 at 48 hours after the administration decaying with an effective half-life of 48 hours or more corresponds to a cumulated activity of at least 350 GBq/h or 5 GBq/h per kilogram of body mass in normal adults. When adapting this for pediatric patients, therefore, the lung might be the dose limiting organ in children for whom 5 times the body mass (in kilograms) divided by the lung residence time (in hours) falls below the activity (in gigabequerels) calculated to induce 2 Gy blood absorbed dose. In such patients, an accurate lung dosimetry, preferably by generating a 3-dimensional dose map of the lung based on I-131 integrated simultaneous single photon emission computed tomography and x-ray computed tomography (SPECT/CT) or I-124 PET/CT images, should be considered. In a hypothetical 40-kg pediatric patient with a measured residence time in the lungs of residence time = 50 hours, such extensive lung dosimetry would be indicated if the AHASA activity for the 2-Gy blood dose exceeds 5·40/50 = 4.0 GBq.

Lesion dosimetry

Maxon et al (10, 20) first aimed at a specified radiation absorbed dose to the target tissue, namely 300 Gy to thyroid remnants and 80 Gy for the treatment of cervical lymph node metastases. More recent studies based on measurements with improved equipment (PET/CT) and more suitable tracers for lesion dosimetry (I-124) support the hypothesis that therapeutic outcome correlates with the absorbed dose administered to the target tissue (12, 21, 22).

The tracer activity must be high enough to enable lesion imaging over several days until the iodine biokinetics of the tumor are ascertained. However, activities exceeding 10–12 MBq are reported to impair the biokinetics in the target tissue (stunning) (23, 24), potentially adversely affecting the success of the subsequent therapy. Assessment of biokinetics is therefore confined to larger lesions. Furthermore, lesion dosimetry suffers from uncertainties in the determination of the target mass and how much of the energy is imparted to surrounding tissue. This matter always poses a challenge, especially for small and irregularly shaped tissues. Disseminated pulmonary metastases as seen in children are sometimes recognizable with state-of-the-art morphological imaging techniques but often also may go unnoticed using conventional morphological imaging. Even when recognizable, the full extent and volume of such lesion is impossible to determine reliably.

The main argument in adult DTC patients against the approach of Maxon et al (10, 20) arises from later findings

that absorbed doses may vary considerably between different lesions within the same patient and that the distribution of the absorbed dose in a tumor can be inhomogeneous (21, 25). This may lead to the undertreatment of lesions not included in the dosimetric evaluation or with supposedly sufficient absorbed dose but inhomogeneous activity distribution.

For further details on dosimetry-based activity selection, we refer to papers by Van Nostrand et al (26) or Lassmann et al (27).

Clinical considerations

Benefit and harm

Strategies using fixed activities in patients with high tumor load rely on the administration of multiple RAI courses to achieve treatment success. However, multiple administrations of lower activities in a fractionated therapy lead to changes in tumor/lesion biokinetics. Samuel et al (28) have shown that the uptake is reduced in subsequent therapies and that the dose to the target tissue per administered amount of activity declines. This suggests that the least radioiodine avid cells are more likely to remain unaffected when a submaximal activity of I-131 is given. This results in a loss of therapeutic efficacy along the sequence of fixed activity administrations and potentially induces the dedifferentiation of the tumor by selective survival of undifferentiated cells. Therefore, the administration of a single, high I-131 activity is likely more effective than the administration of the same activity cumulatively spread over multiple RAI courses. This hypothesis was supported by a recent study by Klubo-Gwiezdzinska et al (29), who showed that adult high-risk patients who received dosimetry-guided RAI had a significantly better progression-free and disease-specific survival.

On the other hand, the extent of harmful effects of high cumulative I-131 activities is still debated. It is well known that such high activities may induce leukemia. This was in fact already described in some of the first DTC patients treated with I-131 (30) and has been reported in multiple subsequent case reports. This included patients treated with low activities or multiple times within a short time frame. Certainly a more frequent radiation exposure or an exposure to higher cumulative doses will lead to a higher risk of such complications, but to what degree and at what point cannot be determined with the evidence presently available in literature. Furthermore, the risk of second primary tumors may be elevated after I-131 therapy (31). Hay et al (5) reported a significant excess mortality due to nonthyroid malignancies in survivors of pedDTC between 30 and 50 years after diagnosis. However, in the latter study, only a minority of patients received I-131 treatment, so the excess mortality may be due to other, likely genetic, causes. Reiners et al (6) treated a large cohort of children and adolescents with high-risk radiation-induced pedDTC after Chernobyl by repeated RAI and did not observe secondary malignancies during a median 11.3-year follow-up after the last RAI.

The risk of malignancy due to RAI in pedDTC patients has not been clarified definitively. Other potential side effects of high-activity RAI like permanent xerostomia can severely impact the quality of life. It is therefore important to select the right treatment for the right patients and use the minimum amount of I-131 necessary to achieve the desired goal. Overtreatment with the risk of causing more harm than good should be avoided according the old medical principle of primum non nocere.

Which patients require dosimetric RAI and which do not?

As described above, dosimetry is a difficult procedure, which is not ubiquitously available because it requires specialized knowledge and experience. Therefore, empiric dosaging by fixed-activity concepts is usually preferred in clinical practice. In patients with uncomplicated cases of DTC in whom the tumor was resected completely and who show only low Tg levels without a clear remaining morphological correlate in ultrasound, CT, or magnetic resonance imaging, it is likely that a normal, fixed-activity RAI will suffice to achieve a disease-free status. Adjustment of the administered activity for body weight should be the minimum individualization in this setting, eg, administration of 50 MBq (1.35 mCi) or 100 MBq (2.7 mCi) I-131 per kilogram of body weight can be adapted from activities of 3.7 GBq (100 mCi) or 7.4 GBq (200 mCi) recommended in adults for remnant ablation or treatment of persistent disease, respectively (6). In contrast to adults (13, 14), the 2-Gy blood dose limit will most likely not be exceeded by this dosage regimen because iodine excretion is typically fast in young individuals (32–34), even when hypothyroid (35). In fact, even when the activities mentioned above are doubled to 100 MBq and 200 MBq I-131 per kilogram of body weight, respectively, the blood dose limit of 2 Gy will not be exceeded in pedDTC patients (35).

Dosimetry is typically reserved to selected patients with extensive cervical lymph node metastases or distant metastases. Lesion dosimetry can be an option when the disease is limited to cervical lymph node metastases in which the masses can be determined accurately with x-ray CT or MRI. Reoperation must be considered as well in these patients. However, it is important to note that relatively high endocrine complication rates, on the order of 6% for high-volume surgeons, are reported in children undergoing primary thyroid surgery (36). Although data on the complication rate of surgery for recurrent pedDTC are

lacking, the complication rate is likely even higher. In contrast to older adult patients (aged ≥45 y), in whom lateral lymph node metastases are associated with a decreased life expectancy (37), RAI is a viable alternative treatment to reoperation in children.

Candidates for an AHASA therapy typically have distant metastases. This group particularly includes patients who have shown little or moderate regression after ablative RAI. Distant metastases in children often present in the form of disseminated, morphologically small lesions of which the volume cannot be determined accurately enough to perform a lesion dosimetry. Nonetheless, pulmonary fibrosis should be prevented by a careful lung dosimetry.

In most patients who will require a dosimetrically determined, high-activity RAI, this will become clear only when extensive remaining cervical lymph node metastases or distant metastases are first identified on rxWBS. If metastases are known before the initial ablative RAI, dosimetric RAI should already be considered in the initial ablative situation. If metastases are discovered on rxWBS, the second RAI should be performed as dosimetric RAI using the AHASA approach. The only (rare) exception to this rule should be made for patients with known distant metastases in whom Tg during TSH suppression becomes undetectable after initial RAI. In these patients the presence or absence of disease should first be ascertained through diagnostic whole body scintigraphy and TSH-stimulated Tg measurement. If no metastases are visible on dxWBS but Tg is still detectable, a standard RAI is sufficient. In patients who show iodine-avid distant metastases on dxWBS, however, we would recommend dosimetric, AHASA-based RAI. Table 1 summarizes which dosaging strategy appears suitable for which pedDTC patient.

Open clinical questions and perspectives

As described above, many aspects of treatment of pedDTC patients are still subject of debate. The matter of whether to use dosimetric RAI will in the end largely be determined by the attending physicians' preferences and experiences as well as the availability of experts in medical physics with knowledge of and experience with dosimetric RAI.

It is always possible to perform dosimetric RAI, even in simple pediatric pedDTC cases to ensure standardized conditions and to maximize the chances of successful ablation. The blood-absorbed dose not only is a surrogate for the dose to the red marrow but also closely reflects the true amount of I-131 available to the target tissue (38). In thyroid-remnant ablation, it seems to correlate better with therapeutic success than the administered activity alone (39, 40). Compared with the AHASA therapy strategy, the aim should be for much lower blood doses. In adults, ablation was significantly more often successful in patients who achieved a blood dose of 350 mGy or more (39). In fact, in a collective of children treated with Chernobyl-related DTC, we were able to show that an increasing blood dose could compensate a higher tumor mass as indicated by the tumor marker Tg (40). These findings suggest a new indication for dosimetric ablative RAI if they can be confirmed by prospective randomized studies.

Certainly the limit of the 2-Gy absorbed dose to the bone marrow has not been rigorously scientifically proven. Little is known about the applicability of this limit for a single RAI to children. In our experience, 2 Gy appears to be a safe limit. Even of more concern are the risks of cumulated doses from several therapies, raising the question of when to stop repeating RAI. Most physicians in the course of their career will encounter one or more pediatric patients who will appear RAI refractory because

Table 1. An Overview of the Different Possible I-131 Dosaging Strategies and Their Application in Various Clinical Constellations in PedDTC

Strategy	Concept	Appropriate Clinical Constellation
Empiric dosaging	Weight-adapted 50–100 MBq/kg	I-131 ablation without known metastases
Empiric dosaging	Weight-adapted 100–200 MBq/kg	I-131 therapy in patients with small/limited metastases (negative Tg during TSH suppression)
Lesion dosimetry	ALARA (can be combined with AHASA for assessment of feasibility)	I-131 therapy in patients with large lymph node or distant metastases measurable on US/CT
Blood/bone marrow dosimetry	AHASA	I-131 therapy in patients with diffuse metastases/metastases not measurable on US/CT

Abbreviation: US, ultrasound.

Tg levels will no longer fall or dxWBS or rxWBS does not improve further after multiple courses of RAI. Although one could consider repeating treatment as long as pathological I-131 uptake is present, there is now a considerable body of evidence in literature to support a restrained approach. Under stringent TSH-suppressive levothyroxine therapy, these patients in multiple studies appear to enjoy a very good long-term prognosis with apparently spontaneous further remission occurring without further RAI (41, 42). Therefore, we would advocate ceasing RAI once Tg levels fail to respond to RAI or no further remission of disease is observed on dxWBS or rxWBS whole-body scintigraphy. Even stopping RAI at an even earlier time point in the course of pedDTC treatment may be justifiable because such patients have thus far fared well under TSH-suppressive therapy alone (41, 42).

Returning to the patient

Considering the distant metastatic spread in the lungs, it was decided to treat the patient with a second RAI with the AHASA I-131 activity aiming at a maximum blood dose of 2 Gy. The Tg level had been reduced by the first RAI by a factor of 6 to 4 ng/mL after levothyroxine withdrawal. The risk of pulmonary fibrosis was considered negligible because metastasis was of a focal rather than a diffuse, disseminated nature, and significant lung uptake could be excluded from the imaging during the dosimetric procedure (Figure 2A). As a rule we repeat RAI 3–4 months after initial RAI in patients with metastasized DTC. Therefore, dosimetry was performed in February 2008 over the course of 4 days until the activities in both total body and blood fell below 1% of the initial values. Subsequently, 4 months after the initial ablative RAI, the patient received a second RAI course of 15.4 GBq (417 mCi), resulting in a blood dose of 1.9 Gy. rxWBS revealed persistence of the previously diagnosed lung metastases. Other than a mild sialadenitis and a transient mild drop in leukocyte count (nadir 3.310^9/L 1 month after RAI), the patient suffered no immediate or late side effects of the dosimetric RAI.

The patient returned to us for follow-up after rhTSH stimulation 4 months later; a dxWBS after the administration of 170 MBq (4.6 mCi) I-131 showed no remaining pathological I-131 uptake. The concurrent stimulated Tg was barely detectable at 0.4 ng/mL. A further course of RAI was therefore not necessary. Further follow-up of this patient has thus far been unremarkable, and at the last follow-up in our institution in June 2011, the rhTSH-stimulated Tg level was at the detection limit of our assay (0.2 ng/mL), whereas neck ultrasound and chest CT were negative.

Conclusions

In pediatric differentiated thyroid carcinoma patients with metastasized disease, RAI therapy should preferably be given using high activities where possible. These activities should be patient tailored by means of dosimetry. Especially in pediatric thyroid cancer patients with disseminated lung metastases, dosimetry is necessary to give the maximum safe amount of I-131 without running the risk of bone marrow depression or pulmonary fibrosis. However, dosimetric RAI can be quite a complex procedure, requiring an intensive collaboration between experts in endocrinology, nuclear medicine, and medical physics.

Acknowledgments

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Disclosure Summary: F.A.V. has received speakers' fees and research support from Genzyme Corp and is a paid member of an advisory board for Roche Healthcare. C.R. has received speakers' fees and research support from Genzyme Corp. H.H. has nothing to disclose.

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