Editorial

Pediatric Differentiated Thyroid Cancer: Can the Prescribed Activity of I-131 Be Increased?

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The two primary methods for selecting the prescribed activity of I-131 for the therapy of locoregional and/or metastatic differentiated thyroid carcinoma are empiric and dosimetry. Empiric is defined by *Webster's New World Dictionary* as ". . . relying on or based on practical experience without reference to scientific principles." Dosimetry is based on the calculation of the radiation absorbed dose to the tumor to maximize the likelihood of control of that tumor (1, 2) and/or the calculation of the maximum prescribed activity that can be administered to limit damage of normal tissue to acceptable levels (3–5). Because these calculations are based on one or both of the fundamental principles of radiation therapy planning, multiple authors believe that dosimetrically determined prescribed activity is superior to empirically determined prescribed activity for I-131 therapy (1–5). Nevertheless, most facilities still use empiric methods of selecting the prescribed activity of I-131 because these methods are easier than dosimetric methods. To offer simplified alternatives to rigorous dosimetry as a replacement for the empiric methods (6–9) or to identify factors that might help the physician modify his/her empiric prescribed activity in selected patients to minimize undesirable side effects, multiple reports have been published (10–13). To date, the dosimetric studies have predominantly involved adults; however, in this issue of the *JCEM*, Verburg *et al.* (14) reported an evaluation of the maximum prescribed activities of I-131, which may allow those physicians using an empiric method to alter their prescribed activity of I-131 for pediatric and adolescent patients for initial treatment (remnant ablation) or additional treatments for advanced differentiated thyroid cancer.

Verburg *et al.* (14) concluded that ". . . it is possible to administer at least 100 MBq (2.7 mCi) of I-131 per kg body weight for initial I-131 treatment and 200 MBq (5.4 mCi) of I-131 per kg body weight for further I-131 therapy for children with advanced differentiated thyroid carcinoma." This is a very important study, not only to call our attention to the difficulty in selecting a prescribed activity of I-131 in children, but also to report a provocative observation that in the case of children it might be possible to administer a higher empiric prescribed activity than that determined by other methods (15, 16).

However, the treating physician who is selecting the prescribed activity of I-131 for children must be very careful in simply selecting at least 100 MBq (2.7 mCi) of I-131 per kg body weight for initial treatment or 200 MBq (5.4 mCi) of I-131 per kg body weight for children with advanced differentiated thyroid carcinoma for several reasons. These include several issues involving the underlying assumptions, methodology, clinical responses, and assessment of functioning tumor burden. An important assumption that is fundamental to most approaches to determine the prescribed activity for children—and this includes the study of Verburg *et al.*—is that the sensitivity of the bone marrow to radiation is the same in a pediatric patient as it is in an adult. To our knowledge, this assumption has not been validated. A further assumption is that the risk for developing secondary primary malignancies is the same in children as adults. Whether due to increased sensitivity of the bone marrow to radiation or the longer potential period of time to develop a secondary primary malignancy in children, this may not be the case (17). In regard to the methodology, the approach of Verburg *et al.* (14) is based on work originally published by Thomas *et al.* (6) and expanded by Hänscheid *et al.* (9), both of which have substantive simplifications of the original Benua *et al.*

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Abbreviations: ANC, Absolute neutrophil count; WBC, blood cell count.

methodology (4). Although we support methods to simplify the more rigorous dosimetric methods, we agree with Verburg *et al.* (14) that their methodology needs further validation. For example, in Refs. 8 and 9, the blood time-activity was inferred from the whole body clearance and in some cases was based on a single time point such as the percentage of whole body retention at 48 h after dosing. Similarly, Verburg *et al.* (14) also assumed that the blood activity can be estimated using 14% of the whole body measurement, a value determined from an adult population. Furthermore, this represents an average value for which Thomas *et al.* (6) reported the range to be 3–25%, and Hänscheid *et al.* (9) reported a mean of 13% with a range of 7–21%. Because the activity in the blood compartment accounts for the major component (*e.g.* as high as 60–90%) of the radiation dose to the blood, which is the surrogate for the bone marrow, this range is not insignificant. Based on the data of Hänscheid *et al.* (9) and Van Nostrand *et al.* (8) and to ensure that it is unlikely that any patient would exceed the maximum prescribed activity calculated from more rigorous dosimetric methods, one should not administer a prescribed activity of I-131 that exceeds 65 and 70% of the maximum prescribed activity calculated using a simplified model based on the percentage 48-h whole body retention, respectively. Accordingly, we believe that with the potential for serious untoward events as a result of possibly overtreating a pediatric patient further clarification and validation of the methodology are warranted. Obtaining clinical responses is also important. The study of Verburg *et al.* (14) calculates a prescribed activity not exceeding 200 cGy (rad) to the blood (*e.g.* bone marrow), and based on these calculations, the authors state that they ". . . can safely administer 200 MBq (5.4 mCi) of I-131 per kg without risking bone marrow toxicity after L4 withdrawal." We believe caution is in order. There are no supporting clinical data such as response of white blood cell counts (WBC), absolute neutrophil counts (ANC), and/or platelet counts after administering these levels of prescribed activities that would deliver by calculation 200 cGy (rad) to the blood in children or adolescents to confirm that there is no bone marrow toxicity. Understandably these data could not be obtained because none of the patients of Verburg *et al.* (14) actually received prescribed activities of 200 MBq (5.4 mCi) of I-131 per kg; however, this does not negate the importance of confirmatory clinical responses of administering 200 MBq (5.4 mCi) of I-131 per kg. Also Verburg *et al.* (14) have only focused on bone marrow toxicity. They did not evaluate the side effects of any other organs such as the salivary glands (*e.g.* sialoadenitis and xerostomia) or secondary primary malignancies, both of which are equally important as bone marrow toxicity. The amount of functioning tumor burden in each child may also be an issue. As noted within this study and in the presence of significant functioning tumor burden such as diffuse pulmonary metastases, the child would have exceeded 200 cGy (rad) to the blood (a surrogate for the bone marrow) had the prescribed activities of 200 MBq (5.4 mCi) of I-131 per kg been administered. This is most likely the result of significant functioning tumor burden with resultant delayed clearance. However, other than the three patients with diffuse pulmonary metastases, no information of the functioning tumor burden (*e.g.* the location, number of sites, presence or absence of function metastases on pretherapy scan or only posttherapy scan, percentage uptake, and/or volume on ultrasound or other imaging studies) was reported in the 34 patients who had distant metastases. Again, we believe one must be cautious in extrapolating a prescribed activity of 200 MBq (5.4 mCi) per kg of I-131 to children who might have larger functioning tumor burdens than what was present in the 34 patients studied. As a result of assumptions and the lack of validation of methodology, documentation of clinical responses, and assessment of functioning tumor burden, we agree with the authors' comment that "their findings are not to be equated with an advice to generally use such increased fixed activity in therapy of young thyroid cancer patients," and we agree with the authors' additional comment that they ". . . recommend . . . performing a pretherapeutic dosimetry as an alternative to the traditional dosing based on body weight . . . ."

In summary, we believe that this is an important publication that raises attention to the difficult problem in the selection of prescribed activities of I-131 for the treatment of differentiated thyroid cancer in children. In addition, this paper reports a provocative observation regarding the potential of administering higher prescribed activities of I-131 in children. However, at this time we do not recommend that either the formula of 100 MBq per kg for initial treatment or 200 MBq per kg for subsequent treatment become a method to determine the empiric prescribed activity of I-131 for pediatric patients with or without advanced metastatic differentiated thyroid cancer. Until further data are available, we recommend continuing with empiric approaches such as modifications based on Reynolds' method using weight or body surface area (15), other approaches reviewed by Dinauer *et al.* (18) or preferably more rigorous dosimetry [*e.g.* ≥5-d measurements, daily blood counts, anterior-posterior geometric mean whole body counting, *etc.* (3–5, 19)] with consideration of reduction of the calculated prescribed activity. This reduction may be based on factors such as objectives of the I-131 therapy (*e.g.* remnant ablation, adjuvant treatment, palliation, or cure), uptake of radioiodine, laboratory tests (*e.g.*

WBC, ANC, and platelet count), risk, tolerance, and plans for aggressiveness treatment of side effects (*e.g.* nausea, vomiting, sialoadenitis, xerostomia, and neutropenia), and the desires of the patient as well as the guardian's opinion, to name a few.

Although prospective studies with 100 MBq (2.7 mCi) of I-131 per kg and 200 MBq (5.4 mCi) of I-131 per kg would be ideal, there are ethical issues for such studies in children, who otherwise have an overall excellent prognosis based on current methods. However, retrospective studies—despite being less than ideal—may be of value. These studies may obtain additional information regarding either empiric or dosimetric methods that are already being performed in various facilities. This additional information may help characterize the relationship of the actual administered prescribed activity with factors such as response of WBC, ANC, and platelet counts, frequency and severity of nausea and vomiting despite aggressive prophylactic treatment, and frequency and severity of sialoadenitis despite aggressive prophylactic use of sialagogues. With this information, we may determine that we are already at the maximum prescribed activity of I-131 or that, as suggested by Verburg *et al.* (14), there may be the potential to safely increase the prescribed activity of I-131 over that presently used in pediatric patients with advanced differentiated thyroid cancer.

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