I-131 Activities as High as Safely Administrable (AHASA) for the Treatment of Children and Adolescents with Advanced Differentiated Thyroid Cancer

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Aim: Differentiated thyroid carcinoma (DTC) in children and young adults is rare, can be aggressive, and often presents at advanced stages. In a population of young Belarusian patients with advanced DTC after the nuclear reactor accident at Chernobyl, we determined the activities that are as high as safely administrable (AHASA).

Patients and Methods: In 180 children and adolescents, we studied 133 courses of I-131 thyroid remnant ablation (median age at ablation, 14.3 yr) and 250 courses of I-131 therapy (median age at therapy, 15.7 yr). Remnant ablation was performed with weight-adapted I-131 activities of a median of 51.8 MBq/kg (range, 23.9–73.8 MBq/kg); and residual disease therapy was performed with a median activity of 98.0 MBq/kg (range, 56.7–164.7 MBq/kg). The radiation absorbed dose to the blood (BD) per unit of activity administered for each treatment was deduced from whole-body retention data measured twice daily using ceiling probes. The AHASA activity was calculated assuming an upper limit of 2 Gy BD.

Results: For I-131 ablation, the median weight-adjusted AHASA activity leading to a BD of 2 Gy was 407 MBq/kg (range, 137–661 MBq/kg). In three patients with extensive diffuse pulmonary metastases, the AHASA was lower than 200 MBq/kg. For patients receiving additional I-131 treatments after ablation, a median body weight-adapted AHASA activity of 406 MBq/kg (range, 210–775 MBq/kg) was calculated.

Conclusion: Children and adolescents with advanced DTC can be treated with I-131 activities of at least 200 MBq/kg. For children with extensive pulmonary metastases, pretherapeutic dosimetry is needed to determine the AHASA. (J Clin Endocrinol Metab 96: E1268–E1271, 2011)

It is agreed that adults with differentiated thyroid carcinoma (DTC) can be treated with I-131 without significant hematological toxicity if the maximum radiation absorbed dose to the blood (BD) does not exceed 2 Gy per treatment course (1–3). Nearly all patients with DTC treated with I-131 will require more than 7 GBq to reach this limit (3). At present, studies of I-131 activities used for therapy of advanced DTC that can safely be administered to children are lacking. Our experience in treating advanced DTC using high activities of I-131 (3), which in-

Abbreviations: AHASA, As high as safely administrable; BD, absorbed dose to the blood; DTC, differentiated thyroid carcinoma; LT4, levothyroxine; rhTSH, recombinant human TSH.
cluded pediatric patients, suggests that the safe BD limit in children and adolescents will be 2 Gy or higher.

After the Chernobyl nuclear reactor explosion, a large number of children from Belarus who developed DTC were regularly treated and had follow-up at our center. To determine the activity that is as high as safely administrable (AHASA) in children and adolescents, we examined I-131 whole-body retention data gathered during the treatment of these patients to assess the activities that can be administered without expectant toxicity.

**Patients and Methods**

**Patients**

We reviewed data from 383 courses of I-131 treatment in 180 Belarusian children and adolescents less than 20 yr of age at the time of treatment who were treated for advanced DTC in our department between January 1995 and December 2007. The clinical characteristics of these patients are presented in Table 1.

All patients were initially treated with total thyroidectomy, with or without central compartment lymph node dissection performed at the Thyroid Cancer Centre in Minsk, Belarus. I-131 dosaging was weight adjusted: 50 MBq/kg was used for initial I-131 remnant ablation therapy if no distant metastases were known; 100 MBq/kg was used for subsequent treatment courses in patients with incomplete remnant ablation or residual disease.

Levothyroxine (LT4) therapy was stopped for 4 wk before I-131 therapy to achieve sufficient TSH (>30 μU/ml) stimulation before each course of I-131.

**Tumor staging**

The histological and TNM (tumor, lymph node, metastases) classification given in the original pathology report (fifth edition of the TNM system until 2002, sixth edition from 2003 onward) was used.

**Estimation of the BD**

All I-131 treatments were performed while patients were hospitalized. Patients stayed between 2 and 7 d in our dedicated radionuclide therapy ward until radiation levels fell below the German legal limits for discharge (exposure rate of 3.5 μSv/h in 2-m distance). Patient radiation levels were monitored using a dose rate meter that was located 2 m above each patient’s bed. The first measurement was obtained about 2 h after administration of the I-131; thereafter measurements were performed every morning and evening at 0800 and 2000 h.

The 48-h whole-body I-131 retention was determined for each patient from a biexponential decay curve based on the measurements. This retention value was used to calculate the BD using the method recently introduced by Hänscheid et al. (4). Briefly, a mathematical relationship between radioiodine retention in the whole body and the BD was calculated. Calculations were based on the assumptions that the whole-body activity decays exponentially and 14% of the whole-body residence time can be attributed to the blood. The mean of the absolute deviations between BD estimates obtained with the assumption and actual BD was found to be 11% under study conditions when the whole-body retention was measured 2 d after radioiodine administration.

For the calculation of blood volumes necessary to determine BD values, we used the method described by Hänscheid et al. (4) for individuals with at least 40-kg body mass. For children weighing less than 40 kg, we used sex- and weight-specific formulas of Linderkamp et al. (5) to calculate blood volumes. Using the BD estimated in this manner, the AHASA activity was determined based on a threshold of 2 Gy BD (2).

**Results**

The median administered I-131 activity was 51.8 MBq/kg (range, 23.9–73.8 MBq/kg) for 133 patients receiving their initial I-131 treatment. Ninety-nine children without distant metastases received 52.5 MBq/kg (median); 34 children in whom therapy revealed distant metastases received 50.1 MBq/kg. This treatment resulted in an estimated median BD of 232 mGy (range, 162–733 mGy). In absolute terms, I-131 AHASA activities associated with a BD level of 2 Gy were between 6.6 and 39.0 GBq (median, 20.7 GBq). From these data, an AHASA activity of median 407 MBq/kg (range, 137–661 MBq/kg) was derived, with

**TABLE 1.** Patient characteristics of the young Belarusians included in the study

<table>
<thead>
<tr>
<th>Characteristics of the study population</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of treatment (yr)</td>
<td></td>
</tr>
<tr>
<td>Ablation, no. of courses</td>
<td>133 (64.9)</td>
</tr>
<tr>
<td>Median age</td>
<td>14.3</td>
</tr>
<tr>
<td>Range</td>
<td>9.4–19.7</td>
</tr>
<tr>
<td>Therapy, no. of courses</td>
<td>250 (100)</td>
</tr>
<tr>
<td>Median age</td>
<td>15.2</td>
</tr>
<tr>
<td>Range</td>
<td>8.9–19.9</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>104 (47.4)</td>
</tr>
<tr>
<td>Male</td>
<td>76 (32.7)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>170 (74.4)</td>
</tr>
<tr>
<td>Follicular variant of papillary carcinoma</td>
<td>9 (4.0)</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>T stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>T2</td>
<td>75 (31.7)</td>
</tr>
<tr>
<td>T4</td>
<td>100 (42.6)</td>
</tr>
<tr>
<td>Tx</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>N stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>N1</td>
<td>174 (73.0)</td>
</tr>
<tr>
<td>Nx</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>M stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>105 (41.7)</td>
</tr>
<tr>
<td>M1</td>
<td>75 (30.3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>Remnant ablation</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>51</td>
</tr>
<tr>
<td>Range</td>
<td>27–103</td>
</tr>
<tr>
<td>&lt;40 kg, n (%)</td>
<td>20 (15.0)</td>
</tr>
<tr>
<td>Residual disease therapy</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>56</td>
</tr>
<tr>
<td>Range</td>
<td>30–105</td>
</tr>
<tr>
<td>&lt;40 kg, n (%)</td>
<td>22 (18.1)</td>
</tr>
</tbody>
</table>

M0, No distant metastases; M1, distant metastases present.
values lower than 200 MBq/kg seen in three patients with extensive diffuse pulmonary metastases. A median activity of 98.0 MBq/kg (range, 56.7–164.7 MBq/kg) was administered in the 250 additional I-131 therapy courses, resulting in BD estimates of median 466 mGy (range, 246-1016 mGy). From these data, a median AHASA activity of 23.1 GBq (range, 8.3–47.2 GBq) or 406 MBq/kg (range, 210–775 MBq/kg) was calculated. The distribution of the AHASA activities is illustrated in Fig. 1A. The AHASA activity is similar for initial I-131 ablation and for further I-131 therapy. Figure 1B shows the (non) dependence of the AHASA activity on the age at the time of therapy.

**Discussion**

The present study provides new insights into I-131 treatment of children with DTC. At present, data are not available to determine an AHASA I-131 activity that will avoid significant bone marrow toxicity in children. Our findings define the AHASA for a pediatric population.

I-131 therapy is important in the treatment of pediatric DTC because it results in cure and reduces the risk of recurrence (6, 7). Supporting this notion, Handkiewicz-Junak et al. (7) found that not administering I-131 to children with DTC was the second strongest predictor of recurrence after the presence of distant metastases.

In adults, several studies have defined the maximum activities for I-131 treatment of advanced disease. Tuttle et al. (8) found that in 8% of all adult DTC patients and in up to 38% of individuals over 70 yr of age, the AHASA activity leading to a blood dose of 2 Gy would be less than 7400 MBq I-131. This corresponds to an administered activity of about 100 MBq/kg of I-131. Similarly, Verburg et al. (3) found a maximal tolerated activity of 7 GBq in one of 10 patients treated with high activities of I-131 after pretherapeutic dosimetry. In contrast, in less than 1% of all courses of ablative and subsequent I-131 treatment studied in this report, the tolerable activity was below 200 MBq/kg (equivalent to 14 GBq in a 70-kg adult). We can only speculate about the cause of this considerable difference with adults. It is conceivable, for example, that the kidney function in children is retained much better in hypothyroidism than in (especially elderly) adults; however, we do not have adequate data to make this comparison.

The patients with high BD estimates had high I-131 uptake in diffuse pulmonary metastases. Thus, in these patients it is important to ascertain that 24-h I-131 uptake in the lungs does not exceed safety limits (3 GBq for adults; for children thus far no separate studies have taken place) to prevent pulmonary fibrosis (1). Because the methodology described in the present study does not specifically analyze the pulmonary uptake, a complete dosimetry including lung dose estimate remains the only method to assess safe I-131 activities in patients with such extensive pulmonary metastases.

A source of uncertainty in this study is the method of BD calculation used. Hänscheid et al. (4) demonstrated excellent correlation between the BD and BD estimates from a single whole-body retention measurement in patients aged 14 yr or more. One third of the patients in our investigation were younger, with five children being less than 10 yr of age at the time of therapy. We did not observe age-related differences of AHASA in our population.

A weakness of the present study is the lack of experimental data on the upper safe limit for the blood radiation absorbed dose. The upper limit of 2 Gy first reported by Benua et al. (1) was deduced after measuring different blood radiation absorbed doses and then comparing these with the subsequent drop in blood count values. For children and adolescents, who are generally thought to be
more susceptible to the harmful effects of radiation, solid
data are still missing. Although our experiences in treating
a small number of children and adolescents with high ac-
tivities of I-131 after extensive pretherapeutic dosimetry
suggest that no serious drops in blood count values are to
be expected when the radiation BD does not exceed 2 Gy
(3); this remains to be validated in a larger prospective
study.

A similar distribution of the AHASA activities between
initial I-131 ablation and further therapy courses was ob-
served as well. This observation indicates that the presence
of thyroid remnant tissue is no major influence on the
whole-body retention and thus the blood I-131 kinetics.

It is important to note that our findings are based on
data obtained after LT4 withdrawal. It is likely that
AHASA activities will be even higher under recombinant
human TSH (rhTSH) stimulation because the blood dose
per MBq after rhTSH administration is lower than after
LT4 withdrawal (9). rhTSH, however, is not approved for
use in children.

Collectively, our data show that the AHASA activity in
children is at least twice that of previous estimates. Our
data suggest that we can safely administer 200 MBq I-131
per kg without risking bone marrow toxicity after LT4
withdrawal. For initial ablation, even if pulmonary me-
tastases may be present, our data show that at least 100
MBq I-131 per kg can be administered safely.

Because 200 MBq/kg of I-131 represents the lower limit
of AHASA activities, it is possible to treat patients with
significantly (2- to 3-fold) higher activities than are con-
tventionally applied. Our findings are not to be equated
with advice to generally use such increased fixed activities
in the therapy of young thyroid cancer patients. We thus
recommend a risk-adapted treatment ideally after per-
forming a pretherapeutic dosimetry as an alternative to the
traditional dosing based on body weight, especially in pa-
tients without extensive pulmonary metastases. In chil-

Conclusion

It is possible to administer at least 100 MBq I-131 per
kg body weight for initial I-131 treatment and 200 MBq
I-131 per kg body weight for further I-131 therapy of
children with advanced DTC.

Acknowledgments

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