DOSIMETRIC CALCULATION OF $^{131}$I DOSES MAY BE MORE EFFECTIVE THAN EMPIRIC DOSES FOR PATIENTS WITH LOCALLY ADVANCED DIFFERENTIATED THYROID CANCER


SUMMARY

BACKGROUND
Radioiodine-131 (RAI) has been used for over 50 years for the treatment of metastatic or persistent differentiated thyroid cancer (DTC). It is usually administered in arbitrary or empiric doses that are based on the extent of the metastases or residual disease. Some institutions use a method called "dosimetry," which involves measurements of blood activity after a small test dose, such as 1 or 2 mCi of $^{131}$I, as well as measurements in the lesions at various time intervals. The purpose of the dosimetry is to achieve a balance between the maximum dose that can be given without depressing the bone marrow or causing radiation pneumonitis and restrictive lung disease and yet getting an effective dose into the lesions. The use of dosimetry often shows that much larger $^{131}$I doses can be given than doses based on the empiric method; for example, in the empiric method, doses of 200 mCi are often given for metastatic disease, but this dose is seldom exceeded, whereas dosimetry may show that it is safe to give a larger dose; or conversely, the 200-mCi dose may produce serious side effects and dosimetry would have indicated that a lower dosage was more appropriate or safe. In theory, dosimetry is more scientific, but it has not become the standard of care because it is very time-consuming and the results to date had not shown that dosimetry was clearly better than using empiric doses of $^{131}$I. The current study is a comparison of the results of dosimetric RAI dosage practiced at one institution and empiric dosage given at another institution in the Washington, DC, area in groups of matched patients.

METHODS
This was a retrospective study of patients with DTC monitored at two Washington area hospitals between 2006 and 2009. The inclusion criteria included evidence of distant metastases (DM) or locoregionally advanced disease based on pathological data, imaging studies, and documented RAI-avid disease, and at least one complete follow-up examination. One hospital used dosimetry (D-Rx) to determine RAI doses and the other used empiric doses (E-Rx). The dosimetric method is based on calculation of the maximum tolerated activity of $^{131}$I that would deliver a radiation dose to the blood (as a surrogate for the bone marrow) of 200 rad (2 Gy) or less in order to decrease the likelihood of an adverse bone marrow effect and to ensure that whole-body retention at 48 hours does not exceed 120 mCi (4.44 GBq) with iodine-avid distant nonpulmonary disease or 80 mCi (2.96 GBq) with iodine-avid pulmonary disease.

Patients received 1 to 3 mCi $^{131}$I as a tracer and blood samples were obtained at 2, 24, 48, 72, 96, and 144 hours to assess blood radiation doses; whole-body scans were performed at approximately the same time points to estimate the tumor radiation. The response to therapy was based on the Response Evaluation Criteria in Solid Tumors (RECIST) and secondarily on thyroglobulin measurements. Side effects monitored included leukopenia, thrombocytopenia, chronic dry mouth, and pulmonary fibrosis.

RESULTS
The 87 patients studied included 48 women and 39 men. There were 29 patients with DM in the D-Rx group and 14 in the E-Rx group. For those with DM, the first dose of RAI was significantly higher for the D-Rx group than for the E-Rx group (mean, 251 vs. 164 mCi; P<.05). The total cumulative prescribed activity received by these patients during the follow-up period was not significantly higher in the D-Rx group (mean, 393 mCi vs. 348 mCi). The responses by the RECIST criteria were not significantly different between the two dosage regimens; the 5-year survival was about 60% in each group.

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There were 14 patients with locally advanced disease in the D-Rx group and 30 in the E-Rx group. For those with locally advanced disease, the first treatment was significantly higher for the D-Rx group as compared with the E-Rx group (303.5 mCi vs. 148.9 mCi; \(P<0.05\)); the total cumulative prescribed activity was also significantly higher in the D-Rx group (362.9 mCi vs. 226.8 mCi; \(P<0.05\)). There was a significantly higher rate of complete remission in D-Rx group as compared with the E-Rx group (5 of 14 [35.7\%] vs. 1 of 30 [3.3\%]). There was a trend favoring progression-free survival in the D-Rx group.

The frequency of side effects did not differ between patients treated with D-Rx as compared with those treated with E-Rx.

**CONCLUSIONS**

The higher efficacy of dosimetric RAI therapy with a similar safety profile as compared with empiric RAI doses supports the rationale for using individually prescribed activity in high-risk patients with locally advanced DTC.

**COMMENTARY**

The few thyroid cancer specialists who use dosimetry to determine optimal RAI doses for advanced DTC have been outspoken advocates of this approach, but there has not been a previous comparison of the two dosage methods during a similar time period. The investigators are to be commended for performing this study, but for several reasons it must be considered a pilot study. The number of patients in each group was small, and the groups were not balanced with regard to the number of subjects with metastatic disease or locally advanced disease for each dosage regimen. Perhaps there was a referral bias by sending patients with metastatic disease to the institution that used the dosimetric approach. Not surprisingly, the doses calculated using the dosimetric approach were larger than those using the empiric method. The most impressive result is that a larger number of patients with locally advanced disease had complete remission, with the larger doses calculated by the dosimetric method being safe and effective. For those of us who are “stuck” with the empiric approach, perhaps we should use larger doses in patients with advanced local disease, such as 200 mCi rather than 100 or 150 mCi. However, earlier studies from this group as well as the Sloan-Kettering group indicated that such large empiric doses may constitute excessive radiation doses above 2 Gy, especially in the elderly and those with pulmonary metastases (1, 2). Surprisingly only about 10\% of patients in each group had chronic dry mouth due to salivary-gland damage.

The current study indicates that a large randomized, multinstitutional controlled study of these two methods is needed, preferably with randomization in the same institutions. This is needed because we are seeing many more patients with thyroid cancer. It is more likely that such a study will be done in Europe or Asia than in the United States because medical investigators in these areas seem to be able to plan and initiate these studies more easily than those of us in the United States, perhaps because they have more centralization of referral centers than we have here.

— Jerome M. Hershman, MD

**REFERENCES**

1. Kulkarni K, Van Nostrand D, Atkins F, Aiken M, Burman K, Wartofsky L. The relative frequency in which empiric dosages of radioactive iodine would potentially overtreat or undertreat patients who have metastatic well-differentiated thyroid cancer. Thyroid 2006;16:1019-23.