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Survivors of Childhood Malignant Hematopoietic Disorders Treated With Total-Body Irradiation Must Be Checked Periodically for the Appearance of Thyroid Abnormalities

Vivanco M, Dalle JH, Alberti C, Lescoeur B, Yakouben K, Carel JC, Baruchel A, Leger J. 2012. Malignant and benign thyroid nodules after total body irradiation preceding hematopoietic cell transplantation during childhood. Eur J Endocrinol 167:225-233. Epub May 22, 2012.

SUMMARY

Background

Many studies have documented a high frequency of benign or malignant thyroid nodules in children who have undergone irradiation for malignant diseases. Even though there is no unanimity, the prevailing opinion is that these nodules are more frequently malignant than nodules found in control populations. The risk increases with higher doses of irradiation. Additional unfavorable factors are young age at irradiation, the type of cancer treated, the type of chemotherapy, and the resulting immunodeficiency. Conceivably, the individual contribution of each of these factors can be more precisely defined by studying a rather homogeneous group of patients. Thus, the present study is focused on childhood malignant hematopoietic disorders who are receiving total-body irradiation (TBI) in advance of hematopoietic stem-cell transplantation. Even so, there is still some heterogeneity in this group of patients, since TBI can be given as one dose or as fractionated doses over 3 days.

Methods and Results

The retrospective study extended from 1989 to 2009. A total of 76 patients, representing 80% of the survivors, participated. The thyroid observation period varied from 2 to 19 years. The study included patients with major types of leukemia and one lymphoma. Fractionated doses of 1200 Gy were given over 3 days. In 12% of cases, the treatment included cranial irradiation. The criteria for performing thyroid investigations were not specified, and no protocol is provided. The patients were tracked by ultrasound. Nodules of less than 4 mm were considered micronodules. In those larger than 8 mm, fine-needle aspiration biopsy was performed.

During the observation period 21 patients (28%) with one or multiple thyroid nodules were identified. Children receiving TBI earlier in their life were more prone to the development of nodules, although this could be due to their being observed over a longer time span (9.9 years vs. 3.9 years). As illustrated in Figure 1 in the article, the incidence of thyroid nodules increased markedly during the 8 years following TBI, and this increase was mainly due to the appearance of benign nodules. There was no correlation between thyroid nodules and hypothyroidism; 71% of the nodules in the 21 affected patients were benign and 29% were malignant. The malignant nodules were larger than the benign ones, but over time all nodules grew. Therefore, the growth rate was not a reliable criterion for malignancy. Histology consistently revealed papillary cancer or the follicular variant of papillary cancer, and no follicular cancer was reported. Bilateral neck metastasis developed in one child, but no peripheral metastases were found. Treatment with ^{131}I was judged to be necessary in two cases. So far all patients are disease-free.

Conclusions

Short-term and lifelong monitoring, with ultrasound screening for nodules of the thyroid gland, is recommended for survivors who undergo TBI during childhood.

continued on next page

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Vivanco M, et al.

ANALYSIS AND COMMENTARY

Thyroid nodules in healthy children are extremely rare. They tend to appear in adolescents and are a common finding in adults. In patients followed after chemotherapy and/or irradiation for malignancies, benign and malignant thyroid nodules occur more frequently. Here we have the data for young patients who have undergone TBI for malignant hematopoietic disease. Since physical examination alone is unreliable, ultrasound investigation is required. The cumulative incidence of benign or malignant thyroid nodules increased greatly after the first 8 years of observation in this study. The growth rate for both benign and malignant nodules was similar; the doubling time varied between 2 and 8 years. No nodules remained unchanged in size.

This and other studies stress the point that thyroid nodules are much more frequent in patients, particularly children, who have been treated with TBI for a malignant hematopoietic disease. Since all patients received 1200 Gy, nothing can be said concerning the relationship between initial irradiation dose and the later risk of thyroid nodules developing, but it is known from the literature that the incidence of secondary cancers increases with increasing radiation dose. In this series, the occurrence of thyroid nodules over time was very high, reaching 28% at the end of the observation period. Approximately one third of all nodules were papillary thyroid cancers. In this small series the outcome of these cancers was excellent, which is in line with similar reports. There seemed to be a sudden rise in the cumulative incidence of thyroid nodules 8 to 10 years after irradiation. We do not know whether this is due to a more sophisticated ultrasound thyroid investigation, since during the years of observation this method had become a well-established routine.

In practice, it would appear to me that a routine ultrasound examination of patients such as those included in this study should be done every 2 to 3 years. For the moment, we do not know whether there is a reasonable upper time limit to the follow-up time. It is also important to include serum TSH measurement in the follow-up, so as not to miss hypothyroidism; this topic was mentioned only briefly in this article.

— Albert G. Burger, MD