Maximal safe dose of I-131 after failure of standard fixed dose therapy in patients with differentiated thyroid carcinoma

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Abstract

Objective The maximal safe dose (MSD) on the basis of bone marrow irradiation levels allows the delivery of a large amount of I-131 to thyroid cancer tissue. The efficacy of MSD therapy in differentiated metastatic thyroid cancers that persisted after conventional fixed dose therapy is investigated.

Methods Forty-seven differentiated thyroid carcinoma patients with non-responsive residual disease despite repetitive fixed dose I-131 therapy were enrolled in this study. Their postoperative pathologies were 43 papillary carcinomas and 4 follicular carcinomas. The MSD was calculated with the Memorial Sloan-Kettering Cancer Center protocol using serial blood samples. The MSDs were administered at intervals of 6 months. Treatment responses were evaluated using I-131 whole-body scans and serum thyroglobulin measurements.

Results The mean calculated MSD was 12.5 ± 2.1 GBq (339.6 ± 57.5 mCi). Of the 46 patients, 7 (14.9%) showed complete remission, 15 (31.9%) partial remission, 19 (40.4%) stable disease, and 6 (12.8%) disease progression. Of the patients who showed complete or partial remission, 15 (65%) showed response after the first MSD session and 6 (26%) showed response after the second session. Twenty-nine patients (62%) experienced transient cytopenia after therapy, but three did not recover to the baseline level.

Conclusions The maximal safe dose provides an effective means of treatment in patients who failed to respond adequately to conventional fixed dose therapy. I-131 MSD therapy can be considered in patients who fail fixed dose therapy.

Keywords Thyroid carcinoma · I-131 therapy · Maximal safe dose

Introduction

I-131 therapy has been widely used to treat residual disease after thyroid surgery for differentiated thyroid cancer in those patients more than 50 years old, and it is well known that I-131 therapy improves survival and reduces recurrence and death [1, 2].

In general, there are three methods of determining I-131 doses for the treatment of recurrence or metastasis [3]. The most common and simplest method involves the administration of a fixed empirical dose regardless of the tumor lesion percentage I-131 uptake. Doses are usually determined by disease extent. Conventional doses are 3.7–6.5 GBq (100–175 mCi) for cervical lymph node metastasis, and 5.5–7.4 GBq (150–200 mCi) for distant metastasis [4]. The second method involves the use of dosimetry to estimate I-131 tumor uptake, and a dose of
40–50 Gy delivered to a metastatic lesion is likely to be effective. A recent report found that I-124 positron emission tomography (PET) provides quantitative dosimetry of remnant thyroid or metastatic lesions [5]. The third method involves the administration of a maximal safe dose (MSD) that has been calculated to deliver a maximum of 2 Gy (200 rad) to blood [6].

The MSD has a theoretical advantage over fixed dose therapy. The amounts of I-131 delivered to tumors and the radiosensitivities of individual tumors are highly variable and represent a limitation of fixed dose therapy. In practice, more radiation can be equated with a greater likelihood of ablating residual disease and complete remission [7]. The concept of MSD involves the delivery of a maximal I-131 dose to tumor lesions within a safety margin. The method is relatively easy to perform when compared with the quantitative dosimetric method of calculating the I-131 tumor uptake.

Although fixed dose therapy is more widely used in clinics, residual disease after repetitive fixed dose therapy presents an awkward situation in terms of treatment decision making. Moreover, a higher dose within a safety margin is more likely to produce a positive response to radioactive iodine therapy. In this sense, MSD appears to be the more efficient dosimetric method in clinical practice. However, few investigators have reported results of the MSD method [8–10] after it was initially proposed by Benua et al. [6]. In particular, no trial of the MSD method has been conducted in patients with residual thyroid cancer who have failed conventional fixed dose I-131 therapy. Here, the efficacy of MSD in differentiated thyroid cancers which had persisted following fixed dose therapy is investigated.

Patients, materials, and methods

Study population

The inclusion criteria used were: (1) total thyroidectomy followed by fixed dose I-131 therapy for the treatment of residual disease, and (2) no evidence of response to I-131 therapy despite repeated fixed dose therapy (at least two sessions). Patients with negative findings on the initial I-131 posttherapy whole-body scan (WBS) were excluded from the study. Forty-seven patients were enrolled (M : F = 22 : 25). The mean patient age was 48 ± 15 years. Postoperative pathologies consisted of 43 papillary carcinomas, and 4 follicular carcinomas. Stages according to the WHO classification were 6 stage I, 22 stage II, 6 stage III, and 13 stage IV at the time of diagnosis (Table 1). Prior to MSD therapy, all patients provided written informed consent, which mentioned the risks of bone marrow depression, infertility, and the secondary cancer owing to radiation.

Patient preparation

Patients discontinued thyroxine (T4) replacement therapy at least 4 weeks prior to I-131 therapy and were switched to triiodothyronine (T3), which was discontinued 2 weeks prior to I-131 administration. The iodine restriction in diet was initiated 2 weeks prior to I-131 therapy. Serum thyroglobulin levels were measured 1 day prior to radioiodine administration; a serum level of thyroid stimulating hormone of ≥30 IU/ml was considered to be sufficient.

Determination of maximal safe dose

Doses were determined according to the Memorial Sloan-Kettering Cancer Center protocol [6]. In detail, 2 ml blood samples were collected at 2 h, 24 h, 48 h, and 72 h following the oral administration of a 0.2 GBq (5 mCi) tracer dose of I-131. Blood samples and a standard source (10 μCi of I-131) were counted using a gamma counter and decays were corrected to the time of gamma counting. Radioactivities of blood samples were converted to μCi/l by referring to the standard I-131 source. Cumulative radioactivities were calculated for four time periods, i.e., 2–24 h, 24–48 h, 48–72 h, and 72 h to infinity. We assumed that it takes 2 h for orally administered I-131 to be evenly distributed in whole blood. Using λ for biologic clearance from the count at each time, we calculated cumulative radioactivities (μCi/l) for whole time span. We only considered beta radiation; gamma radiation was not considered. Assuming that the average beta energy was 0.2 MeV and that the specific gravity of blood is 1 kg/l, absorptive doses were calculated in Gy, and represent whole-blood absorption dose per unit tracer dose of I-131. By assuming that the absorptive dose to blood should not exceed 2 Gy, MSD was determined. The 80 mCi rule that means accumulated radioactivity in the lung should not exceed 80 mCi (2.16 GBq) at 48 h with lung metastasis was not applied.

Imaging protocol

I-131 WBSs were performed 3–5 days following radioiodine administration using a large field of view gamma camera (ON 410; Ohio Nuclear, Solon, OH, USA) equipped with a high-energy general purpose collimator. A 20% symmetric window was centered at 364 keV. Anterior images of the neck, chest, and abdomen were obtained; 100000 counts were accumulated in each case.