Clinical experience of treating Graves’ hyperthyroidism complicated with malignancy—The possible role of potassium iodide for avoiding the risk of thionamide-associated neutropenia

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Abstract. The treatment of Graves’ hyperthyroidism (GD) complicated with malignancy is challenging, as anti-thyroid thionamide drugs (ATDs) and anti-cancer chemotherapy are both associated with a risk of neutropenia. Treatment with conventional ATDs, radioactive iodine (RAI) or potassium iodide (KI) was attempted in 8 patients with malignancy (34–80 years of age; 2 males and 6 females) in whom GD had been fortuitously diagnosed during a detailed systematic examination. Three patients requiring surgery were initially treated conventionally with methylmercaptoimidazole (MMI), MMI and KI or RAI (group A; one patient each). The patients became euthyroid on days 17–31 and underwent surgery on days 25–47. RAI therapy was administered to one patient after surgery. The patients were then treated with KI during chemotherapy. Five other patients who did not require surgery were initially treated with 100 mg KI monotherapy (group B). The serum free T4 level declined immediately in all of these patients, and they became euthyroid on days 7–18, remaining almost entirely euthyroid for more than 120 days. Anti-cancer chemotherapy was successfully completed for three of the patients while taking KI, despite the patients experiencing repeated episodes of anti-cancer chemotherapy-induced neutropenia. Our present findings suggest that, in patients with GD and malignancy, MMI + KI or RAI may be required if immediate surgery is scheduled, but KI monotherapy may be worth trying, if anti-cancer chemotherapy is scheduled, thus avoiding the possibility of thionamide-induced neutropenia.

Key words: Hyperthyroidism, Antithyroid drug, Agranulocytosis, Malignancy, Potassium iodide

THYROID DISEASE and cancer diagnoses are common conditions that are likely to coexist [1]. Recent progress in diagnostic imaging methods has fortuitously revealed many patients with mild or sometimes asymptomatic Graves’ hyperthyroidism (GD) without severe complications such as arrhythmia, heart failure, severe eye changes or mental manifestations during pretreatment examination for malignancy. A careful physical examination or the swelling of the thyroid gland on ultrasonography, computer tomography or magnetic resonance imaging may reveal unrecognized GD during a complete check of the body. These patients may require immediate surgery and/or chemotherapy for malignancy. Even during treatment, thyroid dysfunction is frequently observed during revolutionary cancer therapy with immune checkpoint inhibitors (ICIs) [2]. Although the thyrotoxicosis observed during ICI treatment is mainly of the destructive type, some patients with GD or exophthalmos have been reported during melanoma treatment [3, 4].

Regarding the use of antithyroid drugs (ATDs) to treat GD, the American Thyroid Association Guideline strongly recommends, as follows: “Methylmercaptoimidazole (MMI) should be used in virtually every patient who chooses ATD therapy for GD, except during the first trimester of pregnancy when propylthiouracil (PTU) is preferred, in the treatment of thyroid storm, and in patients with minor reactions to MMI who refuse radioactive iodine (RAI) therapy or surgery [5].” However, MMI induces neutropenia or hematopoietic damage as a side effect [6-9].

The concomitant treatment of cancer and GD is a challenging problem, for which there are currently no specific guidelines [10]. The important points are 1) to make the patient euthyroid as soon as possible if surgery is
required, and 2) to avoid the drugs that may damage bone marrow if cancer-chemotherapy is scheduled. Watanabe et al. reported that the incidence of ATD-induced hematopoietic damage among 50,385 patients with GD was 0.3%. The median interval between the initiation of ATD therapy and the onset of agranulocytosis and pancytopenia were 69 days (range, 11–233 days) and 41 days (range, 32–97 days), respectively [7]. Although the incidence is low, it may be difficult to differentiate chemotherapy-induced neutropenia from thionamide-induced side effects at the early stage of treatment. Thus, when treating patients for whom chemotherapy-induced neutropenia was a concern, we attempted 1) conventional MMI and/or RAI therapy before surgery, and 2) potassium iodide (KI) monotherapy to reduce the risk of ATD-associated neutropenia. Although iodide or iodine-containing drug is not usually recommended as an ATD [5], iodide in higher doses is an established and time-honoured treatment of hyperthyroidism [11-13], especially for preoperative preparation and in thyrotoxic crisis. Following the development of modern assays for serum thyroid hormone levels, a study reported a decrease in serum thyroid hormone levels after 4 to 11 days of iodide therapy in GD [14]. However, escape was observed in two-thirds of the patients. This high incidence of escape might encourage switching GD therapy from iodide to thionamide, which has a more potent antithyroid effect despite its many serious side effects. However, the number of patients in that study was very small [14] and the clinical significance of the escape phenomenon remains unclear. Later studies suggested the usefulness of KI or iodine-containing drug such as ipodate [15-20] when other conventional ATD were unsuccessful or contraindicated [19, 20]. Recently, KI has been shown to be effective in patients suffering from side effects to thionamide [20]. Escape was observed in less than one third of the patients in that study. In Japan, the habitual ingestion of large amounts of seaweed might ameliorate GD, while iodide restriction might exacerbate it in elderly patients [21], suggesting iodine-sensitivity in elderly patients with GD and the clinical significance of the autoregulatory mechanisms of iodide handling in the hyperthyroid gland [22].

Patients and Methods

Between 2004 and 2011, eight patients visited our hospital for the treatment of GD that had been fortuitously found during a medical check-up before or during the treatment of malignancy (Tables 1 and 2). Three patients requiring immediate surgery and then chemotherapy (group A) were treated conventionally by 1) MMI (patient 1), 2) MMI and KI (patient 2), or 3) RAI and KI (patient 3), in order to make the patients euthyroid as soon as possible before surgery. RAI was performed after surgery and before chemotherapy in patient 2. The other five patients who did not require surgery (group B) were treated with KI monotherapy rather than thionamide, due to the possibility that they might require anti-cancer chemotherapy during the clinical course.

GD was diagnosed in patients with an elevated serum free T4 (fT4) level and a suppressed serum TSH level, when a thyroidal radioactive iodine (123I) uptake test (RAIU) was high or the patient was positive for either TSH-binding inhibitor immunoglobulin (TBI) or thyroid-stimulating antibodies (TSAbs). None of the patients showed serious complications, such as arrhythmia, heart failure or severe eye changes. The pulse rate at the diagnosis of GD was 90.3 ± 16.7 (mean ± standard deviation), and only 2 patients showed tachycardia (>100/min).

The serum free triiodothyronine (fT3), fT4, and TSH levels were measured by electrochemiluminescence immunoassays (Roche Diagnostics GmbH, Mannheim, Germany). TBII was determined using a second-generation TBII assay with the human recombinant TSH receptor (DYNOtest TRAB human kit, Yamasa Corporation, Chiba, Japan). Thyroid-stimulating antibodies were detected using cultured porcine thyroid cells (Yamasa Corporation). Anti-thyroglobulin or anti-thyroid peroxidase antibodies (A-Tgs or A-TPOs) were measured by an RIA (radioimmunoassay) (Cosmic Co., Tokyo, Japan) [23]. The estimated thyroid volume was calculated using ultrasonography with the following formula: 0.7 × the maximum width (cm) × the maximum thickness (cm) × the maximum length (cm) for each lobe [24]. The RAIU was performed as previously reported [25].

Results

Patients requiring immediate surgery (group A)

As shown in Table 1, three patients required immediate surgery for cancer of the uterus, lung and duodenum (one each). As shown in Table 2, GD was diagnosed before surgery. Patient 1 was treated with MMI (15 mg) as usual [26, 27] and became euthyroid on day 31. Patient 2 was treated with MMI (15 mg) and KI (100 mg) and became euthyroid on day 17 (Fig. 1A). Patient 3 opted for RAI and was treated with 13.5 mCi 131I. KI (200 mg) treatment was started on day 8 and the patient became euthyroid on day 21 (Fig. 1B). These three patients were successfully treated by surgery on days 47, 25 and 29 (Table 1). After surgery, MMI was changed to KI (100 mg) in Patient 1. Patient 2 underwent RAI therapy (12.0 mCi) on day 53. The RAIU values 7 days after
withdrawal of MMI (15 mg) and KI (100 mg) were 49.0% after 5 h and 71.0% after 24 h. The patient was then treated with KI (100 mg) monotherapy on day 60 (Fig. 1A). In these three cases, anti-cancer chemotherapy was successfully performed with KI treatment, despite slight neutropenia (Table 1).

**Patients treated by KI monotherapy (Group B)**

Five other patients with malignancy were treated with KI monotherapy (group B) (Tables 1 and 2) because they did not require surgery but were predicted to potentially require anti-cancer chemotherapy. Chemotherapy was scheduled for the post-surgical exacerbation of cancer of the uterus with lung metastasis and for stomach cancer with peritoneal dissemination for patient 4 (Fig. 2) and 5, respectively. Patient 6 had lung cancer that was inoperable due to bone metastasis and chemotherapy was scheduled. Mild GD was found in two other patients during follow-up period after successful surgery and chemotherapy for ovarian (patient 7) or prostate cancer (patient 8).

With regard to the thyroid function in Group B (Table 2), the elevation of the serum fT4 level was mild with suppressed serum TSH levels, and TBII and TSAb were detected. The RAIU results were extremely high, and either A-Tg or A-TPO was positive in four patients who underwent measurement. The estimated thyroid volume was slightly enlarged in three patients but normal in two.

As shown in Fig. 3, an increase in the serum fT4 level was observed during iodide restriction for seven days before the RAIU test (performed in 4 cases), from 3.7 ± 2.2 ng/dL to 4.9 ± 2.1 ng/dL (n = 4, an average increase of approximately 32%). In contrast, after the initiation of KI treatment, the serum fT4 level decreased dramatically from 4.7 ± 1.9 ng/dL to 1.1 ± 0.2 ng/dL (n = 5, an average decrease of approximately 75%) and normalized after 7–18 days.

During KI treatment, scheduled anti-cancer chemotherapy was successfully completed by three patients (Table 1). Patient 4, experienced 5 repeated episodes of severe neutropenia (<500/μL) during chemotherapy (Fig. 2). KI treatment was continued and neutropenia was successfully treated by granulocyte-colony stimulating factor (G-CSF). Although the serum fT4 level was slightly elevated after four months (Fig. 2), she completed the scheduled chemotherapy. Patients 5 and 6 also completed 12 and 4 courses of chemotherapy, respectively, despite slight neutropenia (Table 1). Fortunately, cancer recurrence was not observed in patients 7 or 8, and chemotherapy was not performed during GD treatment.

**The long-term prognosis of the thyroid function (Table 2)**

In group A, patient 1 became hypothyroid on day 486 (fT4 0.4 ng/dL, TSH 40.5 μU/mL) and was treated with a combination of KI 100 mg and synthesized l-thyroxine (L-T4 25 μg). TBII became negative on day 6,167 and she entered remission thereafter. Patients 2 and 3 became hypothyroid on days 763 and 189 after RAIU.

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**Table 1 Patients with Graves’ hyperthyroidism complicated with malignancy**

| Case | SEX | AGE | Malignancy | Surgery | Operation (days)b | Chemotherapy (days)b | Chemotherapy
d | Neutrophil before/μL | Neutrophil minimum/μL |
|------|-----|-----|------------|---------|------------------|---------------------|------------------|---------------------|---------------------|
| A: Conventionally treated before surgery followed by potassium iodide (KI) therapy during chemotherapy | | | | | | | | | |
| 1 | F | 40 | Uterus | Hysterectomy | 47 | na | PTX, CBDCA | na | na |
| 2 | F | 66 | Lung | Pulmonary lobectomy | 25 | 73 | CBDCA, PEM | 2,960 | 1,586 |
| 3 | F | 52 | Duodenum | Pancreatoduodenectomy | 29 | 42 | GEM, CDDP, TS-1 | 5,371 | 1,270 |

B: Initially treated by potassium iodide (KI) monotherapy

| Case | SEX | AGE | Malignancy | Surgery | Operation (days)b | Chemotherapy (days)b | Chemotherapy
d | Neutrophil before/μL | Neutrophil minimum/μL |
|------|-----|-----|------------|---------|------------------|---------------------|------------------|---------------------|---------------------|
| 4 | F | 48 | Uterus | Postope (Hysterectomy) | –22 | PTX, IFM, CBDCA | 2,642 | 300 |
| 5 | F | 67 | Stomach | Postope (Gastrectomy) | –6 | CDDP, TS-1 | 2,788 | 2,169 |
| 6 | M | 34 | Lung | Inoperable | 0 | CDDP, CPT-11 | 6,453 | 3,398 |
| 7 | F | 64 | Ovary | Postope (Oophorectomy) | | | | |
| 8 | M | 80 | Prostate | Postope (TUR-BT)b | | | | |

### Table Notes

a) PTX, Paclitaxel; CBDCA, carboplatin; PEM, pemetrexed sodium hydrate; GEM, gemcitabine; CDDP, cisplatin, potassium; TS-1, tegafur gimeracil oteracil; IFM, ifosfamide; CPT-11, irinotecan hydrochloride hydrate

b) The days after the initiation of treatment

c) TUR-BT, Transurethral resection of the bladder tumor

d) Data not available
significant morbidity and mortality. The risk of FN overtly hypothyroid during KI monotherapy (TSH 73.6–3.81) was 4.2–3.8 μU/mL, respectively) and were treated with the combination of KI and L-T₄. Patient 7 went into remission after six years of treatment with KI and L-T₄, when she became negative for TBII.

Patients 3, 4, 5 and 6 were transferred to a palliative care hospital after chemotherapy with KI and/or L-T₄, necessitating thionamide treatment, even during chemotherapy. If patients are prepared to undergo radiation exposure, RAI may help protect against thionamide-induced agranulocytosis. However, the combined effects of antineoplastic drugs and RAI are unclear, which is a matter of concern [10, 30].

The present study was approved by the Ethics Committee of Kyushu University.

## Discussion

Chemotherapy-induced neutropenia or febrile neutropenia (FN), defined as an absolute neutrophil count of <0.5 × 10⁹/L with a fever or clinical signs of sepsis, is a serious adverse effect of chemotherapy and can result in significant morbidity and mortality. The risk of FN varies (0%–64%), depending on both patient-specific factors (e.g. cancer type and stage, co-morbidities, and age) and the myelotoxicity of the chemotherapy regimen received [28]. In patients with GD complicated with malignancy requiring chemotherapy, the well-reported side effects of sudden-onset granulocytopenia or neutropenia during thionamide treatment may result in dose reduction and/or delays in chemotherapy, although their frequency is quite low (0.1%–1.75%) [6-9].

Thionamide drugs have been mainly used for the treatment of malignancy-associated GD. Remission of GD after chemotherapy was observed in a fortuitous case in which MMI was discontinued before adjuvant chemotherapy [10]. However, thyrotoxic crisis induced by cytotoxic chemotherapy has also been reported [29], necessitating thionamide treatment, even during chemotherapy. If patients are prepared to undergo radiation exposure, RAI may help protect against thionamide-induced agranulocytosis. However, the combined effects of antineoplastic drugs and RAI are unclear, which is a matter of concern [10, 30].

Three patients in Group A who required immediate surgery were conventionally treated by 1) MMI, 2) MMI and KI, and 3) RAI followed by KI, respectively, because it was important for the patients to become euthyroid as soon as possible before surgery. Patient 2 was treated by RAI after surgery and before chemotherapy. Even if hyperthyroidism persists after RAI, KI therapy may be effective [31]. During chemotherapy, patients were treated with KI monotherapy in order to reduce the risk of neutropenia, which may be induced by

### Table 2

The thyroid function of patients with Graves’ hyperthyroidism complicated with malignancy

| Case | Thyroid Volumea) (mL) | RAIf) (5%5 hr) | TSH (μU/mL) | FT₄ (ng/dL) | FT₃ (pg/mL) | TBIIg) | TSH-binding inhibitor Ig Activity d) | TSAbh) | ATIg) (U/mL) | ATPo) (U/mL) | Treatmenti) | Time required for normalization of FT₄ (days) |
|------|----------------------|---------------|-------------|-------------|-------------|--------|-------------------------------|--------|------------|------------|-------------|-----------------------------------------------|
| A: | | | | | | | | | | | | | |
| 1 | 38.6 | 45.0 | <0.01 | 3.6 | 12.5 | 5.4 | 339 | 78.4 | 43.3 | MMI→KI+LT₄→Remission | 31 |
| 2 | 27.7 | 15.6 | <0.01 | 2.8 | 10.0 | 24.4 | 782 | <0.3 | <0.3 | MMI+KI→RAI→KI→LT₄ | 17 |
| 3 | 62.4 | 79.0 | <0.01 | 4.9 | 16.3 | 20.1 | 183 | 20.9 | 24.0 | RAI→KI→LT₄ | 21 |
| B: | | | | | | | | | | | | |
| 4 | 31.4 | 69.1 | <0.01 | 6.7 | 19.9 | 137.6 | 464 | 41.0 | 102.5 | KI→KI+LT₄ | 10 |
| 5 | 39.1 | 54.2 | <0.01 | 2.0 | 6.9 | 8.2 | 953 | 117.0 | 1,160.0 | KI→KI+LT₄→Remission | 12 |
| 6 | 29.2 | 67.8 | <0.01 | 3.9 | 6.7 | 4.2 | 207 | 0.3 | 53.0 | KI | 11 |
| 7 | 12.8 | 59.9 | <0.01 | 2.2 | 17.2 | 62.3 | 439 | 0.8 | <0.3 | KI→KI+LT₄→Remission | 18 |
| 8 | 10.0 | na | <0.01 | 4.1 | na | 8.5 | 300 | na | na | KI | 7 |

a) Thyroid volume estimated by ultrasonography  
b) Thyroidal radioactive iodine (¹³¹I) uptake test  
c) TSH Binding Inhibitor Immunoglobulin Activity  
d) Thyroid-stimulating antibody  
e) Anti-thyroglobulin or anti-thyroid peroxidase antibody  
f) MMI, methylmercaptoimidazole (15mg); KI, Potassium Iodide (100-200mg); RAI, radioactive iodine; LT₄, synthesized L-thyroxine  
g) Data not available
Since KI has shown efficacy in patients suffering from adverse effects of thionamide [20], KI was administered outright in five patients with GD fortuitously identified during the systemic evaluation of malignancy in Group B. As shown in Table 2 and Fig. 3, the serum fT₄ level became normal within 7–18 days in all of the patients in this study. The average time required to achieve a euthyroid status was 1.7 ± 0.6 weeks, which was much faster than the times of 5.3 ± 3.6 weeks or 6.7 ± 4.6 weeks in studies of patients with MMI-treated GD [26, 27]. Therefore, KI was considered to be effective for the initial treatment of untreated mild GD complicated with malignancy, carrying no risk of neutropenia which might occur following treatment with thionamide. Anti-cancer chemotherapy was started immediately or even before GD treatment. The characteristic repeated episodes of chemotherapy-induced severe neutropenia were observed in patient 4 (Fig. 2). If we had treated the patient with MMI, then we might hesitate to continue MMI in the

**Fig. 1**  (A) The clinical course of patient 2 (group A) with Graves' hyperthyroidism and lung cancer. After 17 days, she became euthyroid with methylmercaptoimidazole (MMI; 15 mg) and potassium iodide (KI; 100 mg), and surgery was performed. After surgery, she was treated with 12.0 mCi ¹³¹I on day 53. The RAIU values 7 days after withdrawal of MMI and KI were 49.0% (5 h) and 71.0% (24 h). She was then treated with 100 mg KI and became euthyroid again. Chemotherapy with carboplatin (CBDCA) and pemetrexed sodium hydrate (PEM), and radiotherapy (60 Gy) were completed despite slight neutropenia. 

(B) The clinical course of patient 3 (group A) with Graves' hyperthyroidism and duodenal cancer. She was treated with 13.4 mCi ¹³¹I followed by KI (200 mg). She became euthyroid after 21 days. Endoscopic retrograde cholangiopancreatography (ERCP) and surgery were performed, followed by chemotherapy with gemcitabine (GEM), cisplatin (CDDP) and tegafur gimeracil otaraclid potassium (TS-1). Repeated neutropenia was observed during chemotherapy. KI (50 mg) was administered when the patient was thyrotoxic. She became hypothyroid on day 189 and was treated with L-thyroxine (L-T₄).

MMI (Fig. 1A and 1B).
presence of severe neutropenia even if it was induced by anti-cancer chemotherapy. Since the patient achieved a euthyroid status with KI (100 mg) monotherapy, which was continued during chemotherapy with G-CSF treatment, we could therefore concentrate on the treatment of uterus cancer.

In patient 4, a slightly elevated serum fT4 level was observed after four months on KI when chemotherapy was almost completed (Fig. 2). Further studies were not performed; however, increasing the dose of KI or combination therapy with KI and low-dose thionamide (e.g. MMI [5 mg]) might be useful when KI has an insufficient effect [20]. The risk of neutropenia in patients treated with low-dose thionamides may be low [32].

An interesting finding was the elevated serum fT4 level during iodide restriction for the RAIU test noted in four patients (Fig. 3), suggesting the susceptibility of the hyperthyroid gland to changes in the daily iodide intake [21] and the possible effectiveness of KI treatment.

Our preliminary data obtained from treating 504 untreated GD patients with KI suggested that approximately one-third of GD patients were sensitive to KI and showed a good prognosis without thionamide treatment [33]. Escape was suggested only in about one-third of patients. Interestingly, escape was suggested only in 20% of patients when the serum fT4 level was <5 ng/dL and only in 10% of patients >65 years of age [33], probably due to the decreased handling of iodide excretion in the aging kidney [34]. The serum fT4 level was lower than 5 ng/dL in 7 of the 8 patients in this study, and patients with malignancy are usually elderly. These might be the reasons for failure to detect any apparent escape in the present study. It was then suggested that the incidence of escape phenomenon might be less than that reported in the literature [14], especially in cases of fortuitously found mild GD in elderly patients.
Even when escape occurred, the patients were effectively treated with the combination of KI and low-dose MMI or RAI [20, 33]. The main concern with KI as initial therapy may be the elimination of RAI as a viable therapeutic option. However, excess iodide can be excreted into urine. An RAIU test administered 5–7 days after the withdrawal of KI showed values as high as 60%/5 h [33], and the patients were successfully treated with RAI if necessary, as shown in patient 2 (Fig. 1A) in this study.

In conclusion, our study suggested that patients with malignancy in whom GD was fortuitously diagnosed during a detailed systematic examination might require MMI + KI with or without RAI if immediate surgery is scheduled, and KI monotherapy may be effective if anticancer chemotherapy is scheduled. It is recommended that a large amount of KI (more than 100 mg) be administered, as GD patients exhibit various degrees of sensitivity to KI, and because there are few side effects other than hypothyroidism [20, 33]. If the decrease in the serum fT4 level is not obvious, low-dose MMI may be added [20, 33] or RAI followed by KI therapy may be recommended in order to reduce the risk of thionamide-associated neutropenia during chemotherapy.

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Author Disclosure Statement

None of the authors have any potential conflicts of interest associated with this research.

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