Radioiodine Therapy in Differentiated Thyroid Cancer: The First Targeted Therapy in Oncology

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Iodide uptake across the membranes of thyroid follicular cells and cancer cells occurs through an active transport process mediated by the sodium-iodide symporter (NIS). The rat and human NIS-coding genes were cloned and identified in 1996. Evaluation of NIS gene and protein expression is critical for the management of thyroid cancer, and several approaches to increase NIS levels have been tried. Identification of the NIS gene has provided a means of expanding its role in radionuclide therapy and molecular target-specific theragnosis (therapy and diagnosis using the same molecular target). In this article, we describe the relationship between NIS expression and the thyroid carcinoma treatment using I-131 and alternative therapeutic approaches.

Keywords: Differentiated thyroid cancer; Radioiodine therapy; Sodium-iodide symporter; Target-specific therapy; Theranosis

INTRODUCTION

The incidence of thyroid carcinoma is increasing in many countries, including Korea [1]. Differentiated thyroid carcinoma (DTC) accounts for most thyroid cancers and is characterized by slow growth and a good prognosis. The specific accumulation of iodide in the thyroid gland was first detected in 1915, and radioiodine was first applied in the diagnosis and treatment of thyroid cancer in 1942 [2]. Improvements in diagnosis and treatment using radioiodine have reduced DTC-associated mortality [3].

Iodide uptake across the membranes of thyroid follicular cells and cancer cells occurs through an active sodium-iodide symporter (NIS) [4]. The rat and human NIS-coding genes were cloned and identified in 1996 [5]. Low levels of NIS are present in thyroid carcinoma cells and are responsible for radioiodine uptake in metastatic lesions. However, one-third of all differentiated thyroid cancers and all anaplastic thyroid cancers do not concentrate radioiodine and, accordingly, have a poor prognosis. Thus, evaluation of NIS gene and protein expression is critical in the management of thyroid cancer [2].

RADIOIODINE THERAPY IN DTC

DTC is one of the most curable cancers, with a 10-year survival rate of 80% to 95% [4,6]. Surgical resection followed by radioiodine therapy is considered to be the ideal treatment for high-risk tumors. However, recurrence in the thyroid bed or cervical lymph nodes develops in 5% to 20% of patients with DTC, and some patients develop distant metastatic disease, which decreases the 10-year survival rate of patients by 50% [7,8]. Significant controversy persists regarding which patients will benefit from radioactive iodine treatment and the method of radioiodine application.
Postoperative remnant ablation
Radioiodine ablation of remnant thyroid following thyroidec-
tomy is performed for several theoretical reasons. First, radio-
iodine is used to ablate any residual remnant thyroid tissues
after surgical resection, which increases the sensitivity of sub-
sequent tests based on serum thyroglobulin (Tg) measurement
and radioiodine whole body scanning. Second, it also serves
as an adjuvant treatment of potential residual tumors [4].

Over the past 20 years, 2,036 thyroid carcinoma patients have
been treated at Seoul National University Hospital (SNUH) [4]:
1,873 with papillary thyroid carcinoma (92%) and 163 with fol-
licular carcinoma (8%). Of these 2,036 patients, 468 (22.9%)
had lymph node metastasis and/or distant metastasis according
to I-131 posttherapy whole body scans. Specifically, 313 pa-
tients (15.4%) had regional lymph node metastasis, 83 (4.1%)
mediastinal lymph node metastasis, 109 (5.3%) pulmonary me-
tastasis, and 25 (1.2%) bone metastasis.

Radioiodine therapy for metastatic disease
The most common sites of distant metastases from DTC are
the lungs and bone, followed by the brain, liver, kidneys, and
muscle [8]. Older patients (>45 years old) with distant meta-
static thyroid cancer are classified as having stage IVc disease
according to the American Joint Committee on Cancer (AJCC)
criteria (sixth edition). These patients have a 5-year survival
rate of only ~30% to 40% [8-10]. Aggressive surgery, radioio-
dine therapy, and levothyroxine suppression therapy can im-
prove overall survival and disease-specific survival in this
subgroup of patients. The therapeutic options in patients with
locally advanced or metastatic thyroid cancer with no response
to radioiodine are limited. Unfortunately, many of these pa-
tients ultimately die from advanced disease. Other therapeutic
approaches are needed.

Lungs
At SUNH, patients with pulmonary metastasis underwent sev-
eral courses of I-131 therapy (range, 3.7 to 7.4 GBq) over 40
months (range, 6 to 171) and were treated on average 5.1
times (range, 1 to 14). During follow-up, pulmonary meta-
stasis completely disappeared in 38 of the 109 patients (35%),
and partial remission occurred in 44 (40%) (Table 1). Of the
109 patients, 45 (41%) had a diffuse pattern of I-131 lung up-
take on whole body scans. Combined nodular and diffuse up-
take was observed in 35 patients (32%), and nodular uptake
without diffuse uptake in 29 (27%). The response to and bene-
fit of I-131 treatment in pulmonary metastases is variable and
at least partially dependent on the degree and pattern of radio-
iodine uptake in metastases as determined by radioiodine
whole body scan (Fig. 1). Lesions with diffuse uptake were
found to respond better than those with nodular uptake: of the
45 patients with diffuse lung uptake, 51% achieved complete
remission [4].

Age is an important prognostic factor, and pediatric patients
with radioiodine-avid pulmonary metastases have an excellent
prognosis, even without I-131 treatment [11].

Table 1. Radioiodine Treatment Results for Lung Metastases
in Patients with Differentiated Thyroid Cancer

| Response          | No. of patient (%) |
|-------------------|-------------------|
| Complete remission| 38 (35)           |
| Partial remission | 44 (40)           |
| Stable disease    | 16 (15)           |
| Progressive disease| 11 (10)        |
| Total             | 109 (100)         |

Adapted from Chung et al. Nucl Med Mol Imaging 2010;44:4-14,
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I-131 therapy of patients with negative iodine scans
At present, there is no consensus regarding radioiodine therapy for Tg-positive and radioiodine-negative cancer [13,14]. The preference for empirical I-131 therapy in DTC patients with raised Tg levels and negative scan results is based on reducing the Tg levels and the increased likelihood of positive scan results after a high dose of radioiodine.

The role of fluorine-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET) in patients with DTC, high serum Tg levels, and negative radioiodine scans is still controversial. F-18 FDG uptake by DTC is associated with more aggressive biological behavior of the tumor and a worse prognosis. Moreover, high expression of the glucose transporter type 1 gene supports the use of PET with specific tracers in the clinical management of such cancers, and BRAF-V600E point mutations may lead to less differentiated phenotypes and lower expression of NIS, suggesting a worse prognosis [15]. However, discordant findings between PET and traditional nuclear medicine radioiodine imaging (the “flip/flop phenomenon”: uptake of I-131 with no FDG uptake and vice versa) are observed frequently (Fig. 2) [16]. We suggest that the evaluation of NIS expression will guide I-131 therapy.

NIS expression and its effectiveness for radioiodine therapy
NIS is an intrinsic membrane protein with 13 transmembrane domains and is composed of 643 amino acids. The recent cloning of the NIS gene enabled better understanding of the molecular mechanisms underlying iodide transport and has provided a means of expanding its role in the management of thyroid cancer [5].

The efficacy of I-131 is dependent in part on translocation of NIS protein to the cell membrane. In thyroid cancer, native NIS expression and radioiodide uptake are reduced. Stimulation of NIS expression by increasing serum levels of thyroid stimulating hormone (TSH) is required. Normal thyroid tissue incorporates the trapped iodide into Tg, a process referred to as organification, resulting in longer iodide retention. Iodide in most thyroid cancers is not incorporated efficiently into proteins and hence is more easily discharged from cancer tissues [17]. Greater NIS expression in thyroid cancer is associated with a greater uptake of radioiodide as well as a better prognosis.

Positive immunostaining of human NIS (hNIS) in primary thyroid cancer could predict I-131 accumulation and the effectiveness of I-131 therapy in recurrent lesions (Fig. 3). At SNUH, while one-third of patients with metastasis but without NIS expression on tissue immunostaining responded to radioiodine therapy, 80% of patients with NIS expression responded to the therapy [18].

ALTERNATIVE THERAPEUTIC APPROACHES
NIS expression on thyroid cancer cell membranes depends on
the differentiation status of the cells, and poorly differentiated thyroid cancer cells lose their ability to accumulate radioio-
dine. In such cases, other therapeutic options may be attempt-
ed, such as supportive chemotherapy using tyrosine kinase in-
hibitors [19] or preconditioning using retinoic acid (RA) for re-
differentiation and restoration of NIS expression [20].

Lesion-specific therapy
Several studies have reported alterations in gene expression and phenotypic heterogeneity between metastatic and primary cancer sites [21]. The heterogeneity is primarily caused by dif-
fferences in gene expression at different metastatic sites. The therapeutic effect of β-emitting radionuclides is correlated with tumor size [22].

In patients with multiple metastases, a heterogeneous re-
sponse to I-131 therapy is not so uncommon, and other ther-
apiess should be considered for the lesions that do not respond
to I-131 therapy. In such cases, lesion-specific evaluation is
essential, and F-18 FDG PET can be a useful method to dis-
criminate lesional differences in tumor characteristics.
Enhancement of NIS in thyroid cancer
One of the main methods for increasing NIS levels in tissues is to enhance NIS promoter activity such as redox factor-1 (Ref-1), early growth response 1 (Egr1), paired box-8 (Pax-8), NIS TSH-responsive factor-1 (NTF-1), or thyroid transcription factor-1 (TTF-1) [23]. However, these proteins are still not applicable clinically. The second method involves the use of exogenous agents to enhance the expression of NIS mRNA and protein.

Several medications have been investigated as potential re-differentiation agents [24]. The basic mechanisms involved are unclear but appear to be related to blocked access of tumor cells to free glutamine, isoprenylation of RAS family proteins, RA receptor activation, histone acetylation, peroxisome proliferator-activated receptor-γ activation, and demethylation. Clinical pilot studies have shown that the ability to accumulate iodide may be restored by RA treatment [25]. However, the effectiveness and legitimacy of using RA in clinical practice remain controversial.

We combined RA therapy with radioiodine in 47 patients with radioiodine-refractory DTC. The overall response rate was 21.3% (n=10/47); one patient achieved a complete remission and nine patients showed a partial remission. Interestingly, age was the most important factor determining the response to RA/radioiodine combined therapy: patients less than 45 years of age were found to have more clinical benefit from RA application [26].

Some kinase inhibitors were reported very recently to have the potential to restore NIS expression in radioiodide-refractory thyroid cancer. Approximately 70% of papillary thyroid cancers have mutually exclusive gene mutations encoding the growth factor receptors RET and NTRK1, the three isoforms of RAS (N, H, and K), and BRAF [27]. Constitutive activation of these proteins stimulates mitogen-activated protein kinase (MAPK) signaling, which inhibits the expression of thyroid hormone biosynthesis genes, including NIS and thyroid peroxidase, which facilitate iodine uptake and organification, respectively [28]. Selumetinib, a selective MAPK pathway antagonist, was reported to cause clinically meaningful increases in iodine uptake and retention in a subgroup of patients with radioiodine-refractory thyroid cancer. These results suggest the potential of combined therapy with enhanced radioiodide uptake by small molecule-targeted drugs.

Radionuclide gene therapy using NIS
Cloning and characterization of the NIS gene have paved the way for the development of a novel radionuclide gene therapy, because the targeted expression of functional NIS in cancer cells enables these cells to concentrate iodide from the plasma, thus offering the possibility of radioiodine therapy [4]. This strategy could also be applied to nontumor cancers. The NIS gene can be transfected into a variety of cell types using non-viral or viral vectors, which can increase radioiodine uptake up to several hundred-fold [4]. Combination therapies based on targeting and expression of the NIS gene plus radioiodine treatment could also be used to treat nontumor malignant diseases, such as melanoma and cervical, breast, liver, and colon cancers.

CONCLUSIONS
Radioiodine remains a mainstay of therapy in patients with radioiodine-avid DTC because of the presence of the target molecule NIS. In fact, this is the first and still the most widely used targeted therapy in oncology. NIS expression is quite variable among DTC patients and even among different lesions in the same patient. As a result, there are controversies regarding I-131 therapy. Evaluation of hNIS expression or functional integrity in cancer tissues by immunohistochemical staining would enhance patient management and is recommended. Molecular imaging modalities including radioiodine scanning and F-18 FDG PET should be used for this purpose. Patients with progressive, radioiodine-resistant metastatic disease could be considered for clinical trials evaluating alternative approaches.

CONFLICTS OF INTEREST
No potential conflict of interest relevant to this article was reported.

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