Alternative Medical Treatment for Radioiodine-Refractory Thyroid Cancers

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Abstract Thyroid cancer is one of the most rapidly increasing cancers in many countries. Although most thyroid cancers are differentiated cancers and easily treated with radioiodine (RI), a portion of differentiated and undifferentiated cancers is refractory not only to RI therapy, but also to radiotherapy and chemotherapy. Thus, various alternative therapies have been tested in RI-refractory thyroid cancers. These alternative therapies include two major categories: redifferentiation therapy and recent molecular target therapy. Several clinical trials have investigated these therapies. They demonstrated potential effects of the therapies, although the results have been somewhat limited so far. Thus, the future strategy for undifferentiated thyroid cancers will involve individualized, lesion-specific, and combined therapy. In this review, the basic mechanism of each redifferentiation and molecular target therapy is discussed, and results of recent clinical trials using these therapeutic agents are summarized.

Keywords Radioiodine-refractory · Redifferentiation · Tyrosine kinase inhibitor · Thyroid cancer

Introduction

Thyroid cancer is one of the most rapidly increasing cancers in many countries. In Korea, the total incidence of thyroid cancer was 26,923 in 2008 and 21,178 in 2007 [1, 2]. In the US, the incidence was estimated as approximately 48,000 in 2011, but as 37,200 in 2009 [3, 4]. However, the number of deaths from thyroid cancer was only 347 in Korea in 2008, and was estimated to be 1,730 in the US in 2011. This low death rate in contrast with high incidence is chiefly due to three factors: (1) the indolent nature of thyroid cancer itself, (2) high efficacy of radioiodine (RI) therapy, and (3) early detection of cancers with screening programs.

RI therapy is the most effective treatment for advanced differentiated thyroid cancers (DTC) after thyroidectomy. As about 85–95% of thyroid cancers are DTCs, most thyroid cancers are an appropriate indication for RI therapy. However, a portion of DTC is refractory to RI therapy. About 5% of thyroid cancers are poorly differentiated or anaplastic cancers that are refractory to RI therapy. Additionally, some DTCs are converted to dedifferentiated cancers with disease progression, losing expression of the sodium-iodide symporter (NIS) [5]. For these undifferentiated thyroid cancers no effective treatment currently exists except complete surgical resection, although it is not always available. In case local treatment is available, recent methods of radiofrequency ablation and laser ablation could be alternative methods to conventional surgery. Usually undifferentiated thyroid cancers are also refractory to external radiotherapy or chemotherapy. Thus, several alternative medical treatments have been investigated in recent years.

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Alternative treatments include two major categories: redifferentiation therapy and molecular target therapy. Redifferentiation means reinduction of NIS expression and RI uptake. Several drugs that affect the epigenetic process of a cell have been investigated for redifferentiation therapy. These drugs are expected to induce reversion of cancer cells to RI-avid DTC cells. Molecular target therapy is a more recent strategy. As several gene mutations have been revealed in thyroid cancers, specific therapeutic agents targeting these mutations could be effective therapies.

In this review, the basic mechanism of each redifferentiation and molecular target therapy is discussed, and results of recent clinical trials using the therapeutic agents are summarized.

Redifferentiation Therapy

Retinoic Acids

Retinoic acid (RA) is a biologically active metabolite of vitamin A. RA binds to nuclear receptors designated as RA receptors (RAR) or retinoid X receptors (RXR), and these bound complexes induce expression of specific retinoid-target genes by functioning on the RA-responsive element (RARE) that is located in the promoter sites. RA affects

cellular differentiation, proliferation, and apoptosis. In thyroid cancers, RA induces redifferentiation of cancer cells and expression of NIS gene [6, 7]. As a result, RI uptake of tumors and the serum thyroglobulin (Tg) level are expected to increase with RA treatment (Fig. 1). Additionally, some oncogenic processes such as angiogenesis are inhibited by RA [8], and RA seems to directly inhibit tumor proliferation to some degree.

In dedifferentiated thyroid cancers that show no RI uptake, RA has been used as an alternative treatment for the last 15 years. In the first clinical trial for RA, Simon et al. described an increase in RI uptake of thyroid cancer cells in 40% (4/10) of patients [9]. Likewise, other initial clinical trials also reported that about 40–50% of RI-refractory patients showed an increase in RI uptake [10–12]. However, the following clinical trials reported much lower rates of RI uptake increase. Gruning et al. tested RA treatment in 25 patients, and only 5 (20%) of them showed some degree of increased RI uptake. Similar disappointing results were described later by Short et al., Courbon et al., Handkiewicz et al., and Kim et al., who reported increased RI uptake in only 1/16 (6%), 2/11 (18%), 9/53 (17%), and 2/11 (18%) patients, respectively [13–16]. Additionally, although increased RI uptake is an easily assessable biomarker, the more critical question regarding RA treat-

Fig. 1 Enhanced radioiodine uptake induced by retinoic acid. This 72-year-old female patient showed increased radioiodine uptake at the mediastinal lesions after 6-week therapy with 13-*cis*-retinoic acid (1.5 mg/kg/day). **(a)** Basal I-131 scan (7.4 GBq), **(b)** post-retinoic acid scan (7.4 GBq)

ment is its therapeutic efficacy. For this point, controversial evidence exists. In an early trial, 19/50 (38%) patients were reported to show response, 10 with partial remission (PR) and 9 with stable disease (SD) [12]. Zhang et al. also reported 5 PR and 2 SD cases in 11 patients who underwent RA-pretreated RI therapy [17]. However, several other studies reported no definite therapeutic effect. When patients were assessed with regard to tumor size, no tumor regression was observed in spite of increased RI uptake [15, 18]. Also, when Tg was used as a biomarker, no response was observed [16]. Therefore, more studies are required to understand the real effect of and specific indications for RA-pretreated RI therapy. In this regard, a recent study analyzed predicting factors for response to RA-pretreated RI therapy, in which patient age (less than 45 years) was the most significant predicting factor [19]. Likewise, specific selection of therapy indications may enhance the therapeutic efficacy in the near future.

So far, most RA used in studies has been 13-*cis*-RA (isotretinoin) or all-*trans*-RA (tretinoin). Bexarotene, another drug that directly agonizes RXR, was also tested in thyroid cancer patients, but resulted in no significant therapeutic effectiveness in spite of a mild increase in RI uptake [20] (Table 1).

HDAC Inhibitor

Histone deacetylase (HDAC) induces tight binding between the histone and DNA, as deacetylated histone has high affinity to DNA. Histone-bound DNA is silenced, and thus,

HDAC decreases gene expression. On the contrary, HDAC inhibitors induce gene expression at the epigenetic level. This function of HDAC inhibitors is expected to induce redifferentiation of thyroid cancer cells by increasing expression of thyroid-specific genes.

The potential of HDAC inhibitors in RI-refractory thyroid cancers has been investigated since a decade ago. In many in vitro studies, HDAC inhibitors demonstrated enhanced expression of thyroid-specific genes such as NIS and thyroid peroxidase. Consistent results were observed with various HDAC inhibitors, including depsipeptide [21, 22], trichostatin A [23], valproic acid (VPA) [24], and suberoylanilide hydroxamic acid (SAHA) [25]. Moreover, HDAC inhibitors were reported to directly affect proliferation and apoptosis of thyroid cancer cells. Catalano et al. reported that VPA induced apoptosis and cell cycle arrest in poorly differentiated thyroid cancer cells [26], and Shen et al. also reported similar growth inhibition and apoptosis induction with VPA [27]. Direct inhibition of cell growth or induction of apoptosis was also observed with other HDAC inhibitors such as SAHA [28] and MS-275 [29]. However, clinical trials of an HDAC inhibitor in RI-refractory thyroid cancers were not satisfactory. At present, SAHA is the only drug that has been used in clinical trials of thyroid cancers. Kelly et al. used SAHA in various solid and hematologic malignancies, including six thyroid cancer cases, as a phase 1 trial [30]. In the trial, one patient showed PR, and others showed prolonged SD. Among three patients for whom an RI scan was performed after SAHA treatment, one showed increased RI uptake and the potential of

Table 1 Clinical trials of redifferentiation therapies for thyroid cancers

Agent	Reference	No. of patients	RAI uptake increase*	Response rate
13- <i>Cis</i> -RA	[9]	10	4 (40%)	N/A
13- <i>Cis</i> -RA	[10]	12	5 (32%)	N/A
13- <i>Cis</i> -RA	[11]	20	10 (50%)	N/A
13- <i>Cis</i> -RA	[12]	50	21 (42%)	19by image, Tg
13- <i>Cis</i> -RA	[13]	16	1 (6%)	N/A
13- <i>Cis</i> -RA	[14]	11	2 (18%)	No CR or PR
13- <i>Cis</i> -RA	[15]	53	9 (17%)	N/A
13- <i>Cis</i> -RA	[16]	11	2 (18%)	N/A
All- <i>trans</i> -RA	[17]	11	4 (36%)	5 PR, 2 SD
13- <i>Cis</i> -RA	[18]	27	19 (70%)	7 PR
13- <i>Cis</i> -RA	[19]	47	N/A	1 CR 9 PR, 9 SD
Bexarotene	[20]	11	8 (73%)	N/A
SAHA	[30]	6	1/3 (33%)	1 PR
Vorinostat	[31]	19	N/A	No CR or PR
Rosiglitazone	[44]	5	1 (20%)	N/A
Rosiglitazone	[45]	10	4 (40%)	N/A
Rosiglitazone	[46]	20	5 (25%)	5 PR, 3 SD
Rosiglitazone	[47]	23	6 (26%)	N/A

*Including all definite and faint increases

N/A, not assessed; Tg, thyroglobulin; CR, complete remission; PR, partial remission; SD, stable disease

Table 2 Clinical trials of tyrosine kinase inhibitors for thyroid cancers

Agent	Reference	No. of patients	PR	SD	PFS
Sorafenib	[51]	30	7 (23%)	16 (53%)	79 weeks
Sorafenib	[52]	41	6 (15%)	23 (56%)	15 months
Sorafenib	[53]	34	5 (15%)	25 (74%)	>19 months
Sorafenib	[54]	9	3 (33%)	4 (44%)	42 weeks
Sorafenib	[55]	31	8 (25%)	11 (34%)	58 weeks
Sorafenib/sunitinib	[56]	15	3 (20%)	9 (60%)	19 months
Axitinib	[57]	45 DTC	14 (31%)	19 (42%)	18 months
Motesanib	[58]	93	13 (14%)	62 (67%)	40 weeks
Pazopanib	[59]	37	18 (49%)	N/A	12 months
Gefitinib	[60]	25	0	24% at 6 months	3.7 months

PR, partial remission; SD, stable disease; DTC, differentiated thyroid cancer; N/A, not assessed

SAHA as a new therapeutic agent. However, a more recent study that enrolled 19 thyroid cancer patients reported no cases of remission [31]. Although the real effectiveness of HDAC inhibitors is still a question, combination therapy with HDAC inhibitors and other agents may be an answer. In several in vitro studies, an enhanced effect was observed with combination therapy, such as depsipeptide combined with p53 gene therapy [32], doxorubicin combined with VPA [33], and HDAC inhibitors combined with proteasome inhibitor [34]. Particularly SAHA showed a synergistic effect with all of the target therapy agents in a cell study [35]. Also, a case was reported in which VPA, chemotherapy, radiotherapy, and surgery were combined [36].

PPAR γ Agonists

Peroxisome proliferator-activated receptor γ (PPAR γ) is a nuclear receptor that activates transcription of various genes, particularly related with adipogenesis, inflammation, cell cycle control, and apoptosis. Thiazolinediones (glitazones), an agonistic ligand group for PPAR γ , were originally therapeutic drugs for diabetes. They were reported to affect the growth and proliferation of thyroid cancer cells about a decade ago. In an initial study, Karger et al. reported that mRNA for PPAR γ is downregulated in papillary thyroid cancer cells [37], and Chung et al. reported that troglitazone inhibits growth of anaplastic thyroid cancer cells [38]. Similar results have been consistently observed in other anaplastic or dedifferentiated thyroid cancer cells, that is, various thiazolinediones induce cell growth inhibition, cell cycle arrest, and apoptosis [39–41]. This activity is explicitly correlated with PPAR γ activation because PPAR γ -lacking thyroid cancer cells did not demonstrate such effects, and restoration of PPAR γ resulted in restoration of response to thiazolinediones [39, 42]. Interestingly, activation of

apoptosis by thiazolinediones was not related to p53, but to p21 or p27 [38, 39, 41].

Besides growth inhibition and apoptosis activation, PPAR γ agonists induce differentiation of thyroid cancer cells. Frohlich et al. observed that thiazolinediones enhance expression of NIS and Tg in porcine thyrocytes and follicular cancer cells [43]. This effect resulted in increased uptake of ^{125}I in cell uptake assays. Park et al. also reported upregulation of mRNA for NIS after treatment with troglitazone in various cancer cells, including papillary, follicular, and anaplastic thyroid cancer cells [40].

Based on these in vitro studies, several clinical trials were performed for PPAR γ agonists in dedifferentiated thyroid cancers. In an initial pilot study, Philips et al. tried rosiglitazone in five patients who showed negative iodine whole body scans with high serum Tg, and only one of them showed a faint increase in iodine uptake [44]. On the contrary, Kebebew et al. reported a more positive result: 4/10 patients showed a significant increase in iodine uptake after rosiglitazone treatment [45]. However, the same group reported somewhat disappointing results several years later. Although rosiglitazone induced an increase in iodine uptake or decrease in serum Tg to some degree in 5/20 patients, a clinically significant response such as CR (complete response) or PR was not observed [46]. Thus, the clinical trials so far have not demonstrated very satisfactory results, but selection of more specific indications may be an answer. Tepmongkol et al. tried rosiglitazone in 23 Tg-negative and iodine scan-positive patients with regard to histopathological PPAR γ expression in cancer cells. They observed positive scan conversion in 7/9 patients with strong PPAR γ expression, whereas none of the 7 patients with no PPAR γ expression showed scan conversion [47].

So far, rosiglitazone is the only drug that has been tried in thyroid cancer patients [45–49]. However, as troglitazone was reported to be more effective than any other thiazolinedione in a cell study [43], appropriate drug selection will be an issue. A

new PPAR γ agonist has been tested in combination with paclitaxel chemotherapy and showed a synergistic effect. [50].

Molecular Target Therapy

Tyrosine Kinase Inhibitors: Sorafenib

Tyrosine kinase inhibitors (TKI) block intracellular binding of ATP or substrates to receptor tyrosine kinases, such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), hepatocyte growth factor receptor, and RET receptors. As oncogenic kinase activity plays important roles in tumor growth, TKIs have been examined as molecular target-therapy agents in various tumors. Also in thyroid cancers, TKIs have been examined as a new therapy in recent years (Table 2).

Among various TKIs, sorafenib is the most widely tested agent at present. In an initial clinical trial, Gupta-Abramson et al. tested sorafenib for 16 weeks in 30 metastatic RI-refractory thyroid cancer patients and reported promising results. In the trial, 7 patients (23%) had PR and 16 (53%) had SD; this was described as an overall clinical benefit. Median progression-free survival (PFS) was 79 weeks [51]. In a following study, Kloos et al. tried sorafenib in PTC and other types of thyroid cancers, and reported similar results [52]. In 41 PTC patients, 6 (15%) showed PR and 23 (56%) showed SD; thus, the overall clinical benefit was 71%. Median PFS was 15 months, which was similar to previous studies. Interestingly, they observed PR only in PTC and not in other subtypes.

Sorafenib was recently tested in country- and race-based studies. In a UK-based population, Ahmed et al. assessed radiological response to sorafenib in 34 thyroid cancer patients, including 19 DTCs and 15 MTCs [53]. After 6 months, radiological response was observed in 5 (15%) patients, and 25 (74%) showed SD. The effectiveness of sorafenib was also reported in a Chinese population. Chen et al. tried sorafenib in nine Chinese patients with progressive RI-refractory PTC and pulmonary metastasis [54]. They reported three (33%) PRs and four (44%) SDs after 13-week treatment. The mean PFS was 42 weeks.

Although overall the response rate is considerably high, response to sorafenib seems to be affected by lesion site. Hoftijzer et al. tried sorafenib in 31 DTC patients and observed overall PR in 8 (25%) and SD in 11 (34%), with a mean PFS of 58 weeks [55]. However, the effect was significantly low in bone metastatic lesions. They also assessed reinduction of RI uptake by sorafenib, but observed no change. A consistent result was reported by Cabanilas et al., who tested sorafenib and sunitinib in 13 and 2 DTC patients, respectively [56]. In their study, overall PR and SD were observed in three (20%) and nine (60%) patients, with great effect in lung metastatic lesions.

However, progressive disease was observed in pleura and bone metastatic lesions.

So far, most of the previous studies reported that sorafenib induced PR in 15–30% and overall response (including PR and SD) in 60–80%, with a median PFS of 1–1.5 years. The most common adverse effect is skin problems, such as skin reactions on the hands and feet. However, it seems to have a different effect according to lesion location and certain pathological subtypes. Thus, greater effectiveness is expected with more sophisticated selection of indications. Sorafenib was also tested by several investigators in patients with medullary thyroid cancer; these studies were not reviewed here.

Tyrosine Kinase Inhibitors: Others

Various TKIs other than sorafenib have also been tested in RI-refractory thyroid cancers. Although only a few clinical trial results exist, some TKIs showed better results than sorafenib. Cohen et al. tested axitinib in 60 thyroid cancers that were RI-refractory (45 DTCs and 15 other cancers) [57]. In 45 DTCs, PR was achieved in 14 (31%) and SD was observed in 19 (42%). With inclusion of all histological types, PR and SD were 30% and 38%, respectively, and the median PFS was 18.1 month. This response rate and PFS are nearly the highest performance that has been achieved by sorafenib. Motesanib was tested by Sherman et al. in 93 advanced progressive DTC patients [58]. PR and SD were observed in 13 (14%) and 62 (67%) patients, respectively. Additionally, among 75 patients in whom serum Tg was assessed, 61 (81%) had decreased Tg levels during treatment. Estimated median PFS was 40 weeks. More recently, pazopanib was tested in 37 DTC patients, of whom 18 (49%) had PR [59]. This PR rate is the highest reported in TKI clinical trials, although the median PFS was only 11.7 months and the diseases ultimately progressed.

However, some TKIs did not show satisfactory results. Gefitinib was tested in 25 RI-refractory, locally advanced, or metastatic thyroid cancers. There were no objective responses, although SD was observed in 48%, 24%, and 12% after 3, 6, 12 months of treatment, respectively. Median PFS was 3.7 months [60].

Conclusion

Advanced undifferentiated thyroid cancers are a great challenge in cancer treatment as they are refractory to conventional therapeutic modalities, including radiotherapy, chemotherapy, and RI therapy. For these RI-refractory thyroid cancers, redifferentiation therapy and molecular target therapy are potential alternatives, as was reviewed above. So far, however, the effects of these therapies have been limited in

various clinical trials. Redifferentiation therapy did not prove to have a survival gain in spite of partial reversion of RI uptake ability. TKIs have demonstrated effectiveness in many phase II clinical trials, with response rates (PR and SD) of about 70–80% and PFSs of about 1–1.5 years. Phase III clinical trials are now in progress.

The future strategy for undifferentiated thyroid cancers will be individualized, lesion-specific, and combined therapy. Previous clinical trials have already demonstrated that the drug effect varies according to patient characteristics, lesion location, histology, and other biomarkers of cancers. It is crucial to specify the most appropriate indications for optimization of therapy. Additionally, optimal combinations of effective therapies will result in the best therapeutic effects. This will be a realization of the concept of ‘personalized and tailored therapy.’

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