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Treatment Related Hypothyroidism, a Viewpoint from Cancer Therapy and Hematopoietic Stem Cell Transplantation

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1. Introduction

Hypothyroidism is the most common disorder of thyroid dysfunction. Sometimes, it can be caused by a variety of medical treatments that leads to a decrease in thyroidal production and secretion of thyroxine and triiodothyronine. Radiation treatment, either radioactive iodine treatment of hyperthyroidism or external radiation treatment for cancer therapy is a major cause of treatment related hypothyroidism. Others include various drugs associated with thyroid suppression, include lithium, iodine, iodine-containing drugs, radiographic contrast agents and cytotoxic chemotherapy. Thyroid dysfunction is one of the most common complications in endocrine system after hematological stem cell transplantation. This chapter will discuss certain type of primary hypothyroidism, including those encountered commonly in clinical practice, such as radioactive iodine therapy, tyrosine kinase inhibitor, hematological stem cell transplantation or other entities.

2. Causes of treatment related hypothyroidism

<i>Thyroid ablation</i>	Surgery Radioactive iodine External radiotherapy
<i>Pharmacological agent</i>	Lithium Interferon-alpha Interleukin-2 Amiodarone Tyrosine kinase inhibitor Cytotoxic chemotherapy Aminoglutethimide Ethionamide Sulfonamides
<i>Hematological stem cell transplantation</i>	Autologous stem cell transplantation Allogeneic stem cell transplantation

Fig. 1. Causes of treatment-related hypothyroidism

2.1 Hypothyroidism due to thyroid ablation

Radioactive iodine therapy

Thyroid ablation using radioactive iodine for thyroid cancer is one of the most common causes of nonspontaneous hypothyroidism since the treatment modality is an important step in adjuvant or palliative setting of thyroid cancer. Radioactive iodine is an effective agent for delivering high radiation doses to the thyroid tissue with low spillover to other portions of the body. The radiation dose to the thyroid tissue is related to the tissue concentration, the ratio between the total tissue uptake and the volume of functional tissue, and the effective half-life of radioactive iodine in the tissue. Radioactive iodine therapy generally results in hypothyroidism, necessitating levothyroxine treatment. In thyroid cancer, total ablation of thyroid function can be achieved after administration of either 100 mCi or 30 mCi in more than 80% of patients who had at least a near-total thyroidectomy. After less extensive surgery, ablation can be achieved in only two thirds of patients with 30 mCi.

External radiotherapy

Radiotherapy is a frequently applied treatment in patients with head and neck cancer, and sometimes in patients with inoperative thyroid cancer as well as lymphoma. Despite its beneficial effects on locoregional tumor control, radiation may also cause a variety of acute or late side effects, which may be progressive and hamper health-related quality of life (Langendijk et al. 2008). Hypothyroidism may develop within the first year after radiotherapy, especially in patients under 20 years of age. After external radiotherapy, hypothyroidism develops at a median interval of 1.4-1.8 (range 0.3-7.2) years, but may continue to develop many years following therapy (Mercado et al. 2001; Tell et al. 2004). Approximately 30% of patients with solid tumors of the head and neck cancer treated with external radiotherapy develop hypothyroidism (Tami et al. 1992). In stem cell transplantation, hypothyroidism occurs in approximately 9% to 16% of adults who undergo total body irradiation (Al-Fiar et al. 1997). From a 30 years' experience at the Fred Hutchinson Cancer Research Center in treating children with stem cell transplantation, hypothyroidism is the most common type of thyroid dysfunction as 30% developed hypothyroidism at various times after stem cell transplantation. The incidence of hypothyroidism increased with total body irradiation and the use of busulfan-based regimen (Sanders et al. 2009).

2.2 Hypothyroidism due to therapeutic pharmacological agents

Several drugs can cause hypothyroidism by interfering with thyroid hormone production or provoking thyroid autoimmunity. Pharmacological iodine, such as those to which patients treated with amiodarone or other iodine-containing compounds are exposed, can inhibit thyroid hormone production, especially when combined with underlying autoimmune thyroiditis, and cause hypothyroidism.

Amiodarone

Amiodarone is a commonly prescribed anti-arrhythmic drug because of its ability to treat various types of cardiac arrhythmia including ventricular arrhythmia, paroxysmal

supraventricular tachycardia, atrial fibrillation and flutter with minimal negative inotropic and proarrhythmic effects. It is benzofuran derivative containing 37.5% iodine by weight. Daily maintenance dosages of 100 to 600 mg result in a 35 to 140 fold excess in recommended daily iodine intake of 100 to 150 μg . Such a high iodine content and inherent effects of amiodarone and its active metabolite desethylamiodarone are postulated to result in thyroid dysfunction in 14 to 18 % subjects after 2 to 3 years of treatment (Martino et al. 2001). Amiodarone induced hypothyroidism is due to the inhibition of iodine oxidation because of excess intrathyroidal iodine, which is known as the Wolff-Chaikoff effect (Eng et al. 1999). In addition to iodine related effects, amiodarone can alter the activity of deiodinase enzymes. The inhibition of iodothyronine deiodinase activity in peripheral tissues results in decreased triiodothyronine concentration, increased total thyrosine concentration and increased reverse triiodothyronine concentration in serum (Martino et al. 2001). Whether to discontinue amiodarone is still controversial. Withdrawal of the drug may precipitate dysrhythmia, especially as most other alternative anti-arrhythmics are seldom as effective. The treatment of choice for amiodarone induced hypothyroidism is levothyroxine. Amiodarone can be continued at discretion of the cardiologist, keeping in mind that spontaneous remission of hypothyroidism may occur. If amiodarone treatment is discontinued, the decision to initiate thyroid hormone replacement can be delayed (Cohen-Lehman et al. 2010).

Lithium

One in 200 people receives lithium for treatment of bipolar disorder. Lithium has many actions on thyroid physiology. The most important clinical relevant action is the inhibition of thyroid hormone release. The effect of lithium on inhibition of cyclic AMP-mediated cellular events and its inhibitory effect on the phosphoinositol pathway help to explain the intracellular disturbances, but the full mechanism is still not clear. The immunological influence of lithium on thyroid antibody concentrations leads to a more rapid onset of thyroid autoimmunity characterized usually by goiter and hypothyroidism. The clinical side effects of the drug are goiter in up to 40% and hypothyroidism in about 20% (Lazarus 2009). Treatment of lithium-induced hypothyroidism with levothyroxine is no different from treatment of primary hypothyroidism. In these cases there is often a concern that even mild hypothyroidism may contribute to depressive symptoms and that increased thyroid stimulating hormone levels may favor further growth of goiter. The presence of thyroid abnormalities alone is almost never a reason for lithium discontinuation, as this medication is often crucial in maintaining these patients free of the most severe manifestations of their psychiatric illness (Barbesino 2010).

Interferon alpha

Interferon alpha is used for the treatment of hepatitis B and C, as well as various neoplasms, including malignant carcinoid, Kaposi's sarcoma and hairy cell leukemia. Dose-limited side effects of interferon alpha are common, most frequently malaise, depression and hematological side effects. Thyroid dysfunction during interferon alpha is also quite common. Hypothyroidism was initially described as a side effect of interferon alpha therapy in patients receiving long-term interferon alpha treatment for breast cancer (Fentiman et al. 1985). Thyroid effects of interferon alpha have been classified as

autoimmune and nonautoimmune, mostly based on the presence or absence of markers of thyroid autoimmunity such as serum thyroid peroxidase and / or thyroglobulin antibodies (Mandac et al. 2006). The observed incidence of interferon alpha associated hypothyroidism in patients with hepatitis C has been reported from approximately 6% to 10% (Deutsch et al. 1997; Koh, Greenspan, and Yeo 1997). Transient hypothyroidism occurs more commonly with interferon alpha therapy than does persistent hypothyroidism, although pooled data from several series indicates that 30% to 44% of patients who develop hypothyroidism during interferon alpha treatment develop persistent thyroid failure (Preziati et al. 1995).

Interleukin-2

Interleukin-2 is used in the treatment of melanoma and renal cell carcinoma. In one series, 32% of 111 patients with cancer developed hypothyroidism during interleukin-2 treatment, and 14% had hypothyroidism postimmunotherapy, persisting from 44 to greater than 149 days (Schwartzentruber et al. 1991). Earlier studies showed a higher incidence of hypothyroidism up to 21% after treatment of interleukin-2 in combination with lymphokine-activated killer cells (Atkins et al. 1988). Most patients who developed hypothyroidism had positive thyroglobulin or thyroid peroxidase antibodies, suggesting autoimmune thyroiditis. Similarly to interferon alpha-induced thyroid disorders, hypothyroid patients are easily treated with thyroid hormone, while destructive thyrotoxicosis only requires symptom control with beta-blockers.

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors have recently emerged as promising chemotherapeutic agents in several types of malignant neoplasms, including thyroid cancer. Several tyrosine kinase inhibitors exert distinctive effects on thyroid function. Tyrosine kinase inhibitors affect thyroid function through two major mechanisms: by increasing thyroid hormone requirements in patients on thyroid hormone replacement and by causing primary hypothyroidism in patients with previously normal thyroid function. In a small clinical report, imatinib caused a fourfold increase in thyroid stimulating hormone level in all eight patients taking levothyroxine after total thyroidectomy for medullary thyroid cancer. The effect was reversible after discontinuation of treatment and it could be corrected by a doubling in the daily levothyroxine dosage in some patients. There was no change in total thyroxine to suggest increased serum protein binding of thyroid hormone as a possible explanation. Hence, these effects of imatinib are most likely related to increase liver metabolism of thyroid hormone (Barbesino 2010; de Groot et al. 2005). Sunitinib is an oral, multitargeted tyrosine kinase inhibitor of vascular growth receptors, stem cell factor receptor and platelet-derived growth factor receptors. It has been approved for the treatment of gastrointestinal stromal tumor and metastatic renal cell carcinoma. Hypothyroidism has been observed as an adverse event and a clinically relevant toxicity of sunitinib. In one study, 36% of patients with gastrointestinal stromal tumor treated with sunitinib, developed primary hypothyroidism (Desai et al. 2006). Rini et al reported that hypothyroidism occurred in 56 (85%) of 66 patients with metastatic renal cell carcinoma (Rini et al. 2007). Although the mechanism behind this complication remains unclear, it is considered that treatment with levothyroxine can control subclinical and overt

hypothyroidism. There have been cases of thyroid atrophy following sunitinib treatment, suggesting a direct effect of sunitinib that leads to degeneration of thyroid follicular cells (Shinohara et al. 2011).

Cytotoxic chemotherapy

Cytotoxic chemotherapy can alter thyroid function in a small proportion of patients. An increased incidence of primary hypothyroidism has been documented in patients treated with multiple drug regimens (Yeung et al. 1998). There is some evidence that L-asparaginase can cause pituitary hypothyroidism, which is resulted from reducing the thyroid stimulating hormone response to thyroid releasing hormone (Heidemann, Stubbe, and Beck 1981). In patients with testicular cancer who received combinations of cisplatin, bleomycin, vinblastine, etoposide, and dactinomycin, 4 of 27 individuals (15%) developed hypothyroidism. In particular, the cumulative doses of cisplatin and vincristine seem to exacerbate these symptoms (Stuart et al. 1990). Forty-four percent of patients who received six cycles of MOPP regimen (mechlorethamine, vinblastine, procarbazine, and prednisolone) for Hodgkin's disease developed an elevated serum thyroid stimulating hormone concentration (Sutcliffe, Chapman, and Wrigley 1981).

2.3 Hypothyroidism after hematopoietic stem cell transplantation

Thyroid dysfunction is an important problem in patents receiving hematopoietic stem cell transplantation and several forms of thyroid disorders have been reported including hypothyroidism, euthyroid sick syndrome, transfer of autoimmune thyroiditis, graft-versus-host disease, and secondary thyroid tumors (Kami et al. 2001). Hypothyroidism is one of the common forms of thyroid disorder after hematopoietic stem cell transplantation. Its frequency was found to be as high as 40% (Borgstrom, and Bolme 1994; Sklar, Kim, and Ramsay 1982) and it appeared to increase with the duration of post-transplant follow-up. In less common instance, patients appeared to have hyperthyroidism after stem cell transplantation, even six months later from clinical reports (Feng et al. 2008). Development of hypothyroidism has been attributed largely to exposure to radiation (Sanders 1990), but it also does occur after chemotherapy-based preparative regimens.

Mechanism of thyroid dysfunction after hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation is a potentially curative procedure for a variety of malignant and non-malignant conditions. When developed initially, hematopoietic stem cell transplantation was considered an approach to rescue patients from toxic side effects of supralethal doses of radiation and chemotherapy used to treat various underlying diseases by transplanting hematopoietic stem cells, which had the ability to reconstitute hematopoiesis. In allogeneic hematopoietic stem cell transplantation, healthy hematopoietic stem cells are harvested from a separate, related or unrelated, ideally human leukocyte antigen-matched donor, and used to replace the patient's own abnormal hematopoietic stem cells. Conditioning regimen for allogeneic hematopoietic stem cell transplantation often combine total body irradiation and high-dose chemotherapy to eradicate the patient's malignant cell population at the cost of partial or complete bone marrow ablation. Autologous hematopoietic stem cell transplantation requires the extraction of hematopoietic stem cells from the patient. The harvested hematopoietic stem cells return to the patient's

body to resume normal blood cell production after conditioning treatment. Individuals successfully treated with hematopoietic stem cell transplantation are at risk of developing post-transplant complications as a result of drug and radiation toxicity, as are those treated with allogeneic hematopoietic stem cell transplantation as a consequence of graft versus host disease. Endocrine complications are among the most prevalent late effects observed in hematopoietic stem cell transplantation recipients (Chemaitilly, and Sklar 2007; Hows et al. 2006). Several thyroid abnormalities have been described following hematopoietic stem cell transplantation. These include therapy-induced primary hypothyroidism, autoimmune thyroid disease, and thyroid neoplasms.

Autologous hematopoietic stem cell transplantation

Autologous hematopoietic stem cell transplantation is performed more frequently than any allogeneic type of organ transplantation worldwide. The endocrine system is one of the most common targets of post-transplant complications. The relative risk of developing endocrine disorders was found to be related to underlying diseases, previous treatments, use of radiation therapies and type of irradiation schedule, post-transplant treatment and age (Brennan, and Shalet 2002; Shalet et al. 1995). Carlson et al. described hypothyroidism developed in 20 of 111 (18%) individuals after autologous stem cell transplantation and the incidence of hypothyroidism was more frequent in patients treated with total body irradiation (Carlson et al. 1992). There were some reports on development of hypothyroidism after non-total body irradiation preparative regimens (Michel et al. 1997; Toubert et al. 1997). Considering the wide differences in the total doses of radiation applied, during treatment of Hodgkin's disease versus preparative conditioning for hematopoietic stem cell transplantation, the incidence of hypothyroidism after hematopoietic stem cell transplantation remains striking. These findings suggest that irradiation of the thyroid gland may not be the sole cause of hypothyroidism after hematopoietic stem cell transplantation. Early effect of thyroid dysfunction was reported by Tauchmanova in patients first year after autologous hematopoietic stem cell transplantation. Subclinical hypothyroidism was diagnosed in 10% of patients and worsened progressively in all but one patient (Tauchmanova et al. 2005).

Allogeneic hematopoietic stem cell transplantation

Hypothyroidism have been reported to be as high as 52% of patients with allogeneic hematopoietic stem cell transplantation (Al-Hazzouri et al. 2009; Bailey et al. 2008; Berger et al. 2005; Sanders et al. 2009). The time course of developing hypothyroidism after hematopoietic stem cell transplantation varied based on the conditioning regimen. In one study, patients who received single fraction total body irradiation developed compensated hypothyroidism at a mean of 3.2 (range 1-8.2) years after hematopoietic stem cell transplantation and progressed to overt hypothyroidism about 1-2 years later (Thomas et al. 1993). Hypothyroidism was recognized between 0.9 and 7.3 (median 4.1) years after hyperfractionated radiation and at a median of 4.2 years in patients conditioned with busulfan and cyclophosphamide (Boulad et al. 1995). In a 30 year-surveillance of post-transplant, 30% of children developed hypothyroidism at various times after hematopoietic stem cell transplantation and among these 20% were treated with thyroid hormone. Thyroid dysfunction continues to occur as long as 28 years after hematopoietic stem cell

transplantation conditioning with total body irradiation and as long as 10 years after busulfan-cyclophosphamide preparative regimen (Sanders et al. 2009).

The mechanism for hypothyroidism after transplant is unknown. Donor antibody transfers, immune-mediated injury, conditioning treatment effects, post-transplant medications and patient susceptibility may play a role in post-hematopoietic stem cell transplantation hypothyroidism. Case studies have shown that a donor with autoimmune thyroid disorder may transfer cell capable of injuring the recipient's thyroid gland after hematopoietic stem cell transplantation (Lee et al. 2001; Marazuela, and Steegman 2000). Immune-mediated thyroid injury arising in the host has been suggested in other studies and may be a form of graft-versus-host-disease (Kami et al. 2001; Katsanis et al. 1990; Somali et al. 2005). Patients receiving single-agent graft-versus-host-disease prophylaxis were found to have a 9.5 times greater risk of developing hypothyroidism than patients with multi-agent prophylaxis (Katsanis et al. 1990). From an immunological standpoint, stem cells from matched sibling donors are thought to be less immunologically reactive than those from unrelated donors. Patients who received stem cells from an unrelated donor had over an eightfold increased risk of hypothyroidism compared to those who received matched sibling stem cells (Bailey et al. 2008). Total body irradiation is a well established risk factor for hypothyroidism after hematopoietic stem cell transplantation and used of fractionated instead of single-dose total body irradiation decreases its risk (Boulad et al. 1995). Other risk factor for developing hypothyroidism after hematopoietic stem cell transplantation includes young age at transplantation and stem cell transplantation during second complete remission (Berger et al. 2005; Ishiguro et al. 2004). A study focused on reduced-intensity conditioning regimen in hematopoietic stem cell transplantation disclosed that the incidence of post-transplant hypothyroidism was similar in myeloablative or reduced-intensity conditioning regimen (Al-Hazzouri et al. 2009).

3. Conclusions

The endocrine system is one of the most common targets of post-treatment complications in cancer survivors. The relative risk of developing endocrine disorders was found to be related to underlying diseases, previous treatments, use of radiation therapies, and post-transplant treatments. Thyroid dysfunction has been frequently reported after hematopoietic cell transplantation. Radiation has been considered the main cause for this and for thyroid malignancies, but in the context of hematopoietic cell transplantation, total body irradiation has been considered to be the major cause. The incidence of post-transplant thyroid disorder ranging from 0% to 57% was reported previously. Sick euthyroid syndrome was more frequently observed. Most patients developed a mild compensated primary hypothyroidism that may be transient and can be resolved spontaneously. Hypothyroidism can be an early complication but is usually considered as a late complication identified several years after hematopoietic cell transplantation. Approximately 15 % of patients develop overt primary hypothyroidism and 30% have compensated hypothyroidism. The incidence is lower in patients treated with autologous hematopoietic cell transplantation or conditioned with chemotherapy alone.

With the cumulative experiences in hematopoietic cell transplantation and advances in supportive care, the number of long-term survivors has increased. Knowledge about

increased risk for long term complications due to cancer therapy and pre-hematopoietic cell transplantation preparative regimen should encourage each physician to improve their quality of care.

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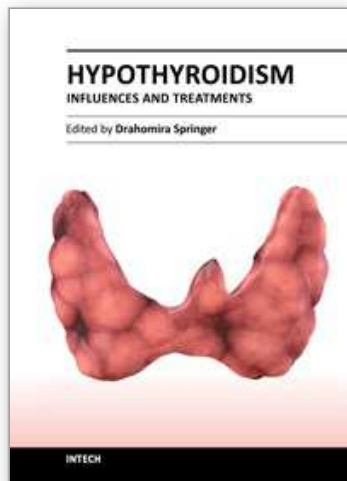
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Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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