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# Pharmacological interventions in radioiodine-negative thyroid carcinoma

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Patients with well differentiated thyroid cancer are at lifelong risk of recurrence and 20 % of these patients develop local or distant metastases. These recurrences can be managed successfully with surgery and/or radioiodine treatment for this reason early diagnosis of recurrence is critical. Follow-up methods include diagnostic WBS and measurement of serum Tg. Serum Tg is the most sensitive test and it should not be detectable in totally ablated patients and if it is detected it signifies recurrent disease in the absence of Tg antibodies. However, during the follow-up it is not uncommon to have patients without any evidence of radioiodine accumulation in the presence of elevated serum Tg and these patients are considered as a clinical dilemma. Blind use of high dose radioiodine may have a beneficial therapeutic effect in these patients especially in those patients with micrometastases.

Most centers prescribe a low iodine diet to increase the radioiodine accumulation. A strict diet of 2 weeks before radioiodine treatment makes the patient iodine deficient and can double the radiation dose given to the cancer tissue. More complex approaches such as diuretics can be used to increase iodine uptake. Use of hydroclchlorothiazide has been shown to be effective for increasing uptake and augmenting I-131 dose of thyroid remnant. The efficacy of radioiodine treatment depends not only on the amount of I-131 accumulation but also the length of time it remains within the tumor. I-131 dose not retain in malignant tumors as long as it retains in normal thyroid. It has been found that lithium inhibited the release of I-131 from the thyroid without any change in iodine uptake. It has been shown that lithium diminishes the release of I-131 from well differentiated thyroid cancer and increases the absorbed radiation dose to the tumor. Lithium is most effective in lesions with poor I-131 retention that are most likely to fail therapy.

Retinoids include all natural and synthetic derivatives of vitamin A, retinol. Retinoids exert their cellular effects by binding to receptors of the steroid/thyroid hormone receptor family. Retinoic acid receptors and thyroid hormone receptor genes are closely related. Retinoids have been shown to affect cell-cycle progression and apoptosis in a variety of cell lines. In addition to growth inhibition redifferentiating effects of retinoids are well established. Retinoids redifferentiate follicular carcinoma cell lines and increase cellular I-131 uptake by a mechanism of up-regulating sodium iodide symporter molecule. In clinical studies there are reports that retinoids may produce a clinical response by redifferentiating thyroid cancer and increasing radioiodine uptake in radioiodine resistant disease. Recently a large multicenter sudy have suggested that iodine uptake and shrinkage occur in a significant number of patients pretreated with retinoic acid. The sodium-iodide symporter is responsible for iodine uptake into thyroid cells. When thyroid cells dedifferentiated into cancer cells they decrease their ability for iodine uptake by the suppression or mutation of NIS gene. Some studies on the enhancing the expression of NIS gene by using a group of chemicals like histone deacetylating inhibitors have been carried out. In thyroid cancer cell lines trichostatin A, a histone deacetylase inhibitor has been shown to increase NIS gene expression which may make radioiodine therapy more effective in tumors with no or low radioiodine uptake.

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