UDC 616.441-006.6-08:615.849 **NIGORA RASULOVA^{1,2}, KALEVI KAIREMO**¹

¹Department of Molecular Radiotherapy & Nuclear Medicine, Docrates Cancer Center (Helsinki, Finland) ²Nuclear Medicine Department of Republic Specialized Center of Surgery (Tashkent, Uzbekistan)

RECOMMENDATIONS FOR DIFFERENTIATED THYROID CANCER TREATMENT BY I-131 AND CASE REPORTS

*Authors to whom correspondence should be addressed:

The aim of this paper is to give the protocol of ablation and differentiated thyroid cancer treatment by I-131: indications, contraindications, patient preparation, precautions, information for the patient, I-131 treatment (recommended activities) and follow up. Case report with initial incorrect management of the

thyroid cancer patient and successful treatment of bone metastases by I-131 also presented. Key words: I-131; differentiated thyroid cancer; ablation; radioiodine treatment.



Nigora Rasulova



Kalevi Kairemo

Introduction:

Differentiated thyroid cancer (DTC) includes both papillary and follicular subtypes and accounts for >90% of cases of thyroid cancer (85% and 10-15% accordingly) [1, 2]. Arising from thyroid follicular epithelial cells, DTC is retaining basic biological characteristics of healthy thyroid tissue such as thyroglobulin production (specific protein, predecessor of thyroid hormones) and expression of the sodium iodide symporter (NIS) – the key cellular feature for specific iodine uptake [3].

In Russian:

In English:

niga_r@mail.ru

www.docrates.com

Nigora Rasulova, MD, PhD

Professor Kalevi Kairemo, MD,PhD Kalevi.Kairemo@docrates.com

> Standard treatment of thyroid cancer includes total thyroidectomy, radioactive iodine (RAI) ablation, and levothyroxine replacement (dosed at levels sufficient to suppress thyroid-stimulating hormone [TSH]) [4, 5]. A 10-year survival rate of 92% has been reported in those with metastatic disease who attain a negative whole-body iodine scan after RAI treatment [6].

> Targeting mechanism is shown in figure 1, kindly provided by C.A.Hoefnagel

In contrast, survival in patients with metastatic disease that

does not concentrate iodine remains poor (10-year survival, 10%–18%) [7, 8].

I-131 treatment [9]:

Indications: Treatment of differentiated thyroid cancer with radioiodine should be considered in the postsurgical management of such patients with any of the following conditions: tumor size >1.5 cm; tumor size <1.5 cm if there is unfavorable histology (tall cell, sclerosing or other variants); lymph node metastases; multifocal disease, which could represent intrathyroidal metastases; lymphatic or vascular inva-



Figure 1 – Skull metastasis from follicular thyroid cancer. A- bone scan demonstrates reactive "normal" bone surrounding the metastasis. B- I-131 therapy scan demonstrates incorporation of I-131 into tumor cells. This case provided by C.A.Hoefnagel. National Cancer Institute, Amsterdam

sion; capsular invasion or penetration including peri-thyroidal soft tissue involvement; metastases to lung, bone, liver, etc. Brain sites must be approached with caution as intracerebral bleeding and cerebral edema may occur. In general, the greater the invasive quality of the cancer, the higher the dosage consideration should be.

Contraindications: a) absolute: pregnancy and breastfeeding b) relative: 1. bone marrow depression, if administration of high I-131 activities is intended; 2. pulmonary function restriction, if a significant pulmonary I-131 accumulation is expected in lung metastases; 3. salivary gland function restriction, especially if I-131 accumulation in known lesions is questionable; 4. presence of neurological symptoms or damage when inflammation and local edema caused by the RAIT of the metastases could generate severe compression effects.

Before the treatment, nuclear medicine physician should be provided by full information about history disease: the result of post-surgical histology; pre-surgical ultrasound of the neck and lymph nodes; non-contrast of the chest's CT; calcium level, createnine, ECG, blood samples, thyroglobulin level in hypothyroid condition or after rhTSH stimulation.

Patient preparation: The effectiveness of RAIT depends on the patient's serum TSH level being sufficiently elevated. A TSH level of \geq 30 mU/L is believed to increase NIS expression and thereby to optimize radioiodine uptake [11]. Such TSH elevation can be reached by 1) waiting at least 3 weeks after thyroidectomy or 4-5 weeks after discontinuing treatment with levothyroxine (LT4). However, if large volume of functioning thyroid tissue remains TSH may not rise to this level. 2) Alternatively for attaining TSH elevation is rhTSH administration can be applied with "mini-withdrawal" of thyroid hormone for a short period (e.g. 2 days each) before and after RAIT [10,11]. 3) To avoid competitive handling by NIS of non-radioactive iodine rather than radioiodine, with a resultant diminution in efficacy of RAIT, patients should be advised to avoid iodinecontaining medications, e.g. iodinated contrast agents, antiseptics, eye drops or amiodarone, and iodinecontaining foods, e.g. iodinated multivitamins or mineral supplements or seafood, for 4-6 weeks prior to RAIT. A low-iodine diet, when possible, <50 μ g/day, starting 1–2 weeks prior to radioiodine administration is recommended optionally [12]. 4) Abundant food intake may alter the resorption of orally administered radioiodine. Patients should fast or at a minimum 2 hours prior to and 1 hour after radioiodine administration. 5) Physicians should ensure that national regulations for radioiodine administration, including those regarding radiation protection, are carefully observed. Special care should be exercised to ensure that patients living with young children are properly informed of radiation protection measures.

Precautions: 1) to maximize the therapeutic effect of subsequent I-131 treatments "stunning" should be avoided: Stunning is defined as diminution of RAIT uptake and efficacy due to suboptimal therapeutic effects, biological effects, or both, of prior diagnostic radioiodine administration. In cases where RAIT clearly will be necessary, pre-therapeutic I-131 dxWBS or thyroid bed uptake measurement should be avoided because their results will not modify the indication for RAIT and these procedures may induce stunning. To reduce the possibility of stunning when it is not yet known whether RAIT is indicated, thyroid bed uptake quantification or I-131 dxWBS performed before the potential RAIT should employ low radioiodine activities. Recommended quantities are approximately 185 MBq (5mCi) for WBS. Alternatively, use of 40–200 MBq (5.4 mCi) of I-123 for diagnostic imaging minimises the risk of stunning. 2) Minimisation of physiological radioiodine uptake and retention: In the 24 h following radioiodine administration, liberal oral hydration and use of lemon juice or sour candy or chewing gum increases salivary flow and reduces radiation exposure of the salivary glands. 3) Pregnancy, breastfeeding and conception: Pregnancy must be excluded 72 hours prior to therapy, Patients should be advised to discontinue breastfeeding for 6–8 weeks before radioiodine administration. Conception should be avoided by means of effective contraception for 6 months after RAIT.

Information for the patient:

Patient should be informed that: the main purpose of the treatment is to destroy normal and cancerous thyroid tissue; more than one I-131 treatment may be necessary; it possible that patient may experienced side effects a) early one may include nausea, occasional vomiting, pain and tenderness in the salivary glands, loss of saliva or taste, unusual, often metallic-like alterations in taste, neck pain, decreasing white blood cell count that may result in increased susceptibility for infection, but generally, these side effects are temporary b) late side effects may include temporary infertility, but if dosages progressively exceed 200-300 mCi, damage to the salivary glands, dental caries, reduced taste and dry eyes. However side effects are rarely seen and should not deter a patient from taking 1311 for treatment of thyroid cancer. Patient should receive information about radiation safety rules, and explained that salivary, urine and active sweating will be radioactive, that there are 3 main factors, which can influent on patient's radioactivity: 1) distance - radiation decreases significantly with increasing distance. 2) time: radiation exposure to other people depends on how long they remain near patient. Therefore, avoid prolonged contact with other people. 3) hygiene – good hygiene minimizes the possibilities of direct contamination with radioactive iodine. Because most of the iodine is excreted by the urine, it is very important that patient should wash hands thoroughly after going to the toilet, to prevent of contamination: toilette has to be flash twice after using, Men are advised to urinate sitting down to avoid splashing urine outside the toilet bowl or in its borders. In nearest days after treatment, patient should avoid kissing and sexual intercourse, sleep alone during the first days after the treatment. Females should stop breast-feeding 4-6 weeks before therapy because the iodine is excreted into breast milk. 4-6 months after therapy pregnancy is not recommended, during 2 weeks following after therapy patient should avoid close and prolonged contacts with children less than 5 years old and pregnant women who are more sensitive to radiation than the rest of the population. Patient should be aware about isolation during the treatment, at the time of discharging patient will receive information about radioactivity he/she exposes at 1 meter distance, how long in public transportation safely for other people.

Treatment: 1) For ablation: the "optimal" activity for radioiodine ablation of post-surgical thyroid residues macroscopic disease is generally a single administration of 30-100mCi [13].

In patients with large persistent remnants, re-operation may be an option. 2) For treatment: in late adolescents and adults, inoperable iodine-avid distant metastases are typically treated with multiple administrations, each 100–200 mCi or more, given every 4–8 months during the first 2 years following diagnosis of metastatic disease and at longer intervals thereafter [14]. According to Society of NM guadline: 1. for postoperative ablation of thyroid bed remnants, activity of I-131 in the range of 75–150 mCi is typically administered, depending on the RAIU and amount of residual functioning tissue present. 2.For treatment of presumed thyroid cancer in the neck or mediastinal lymph nodes, activity in the range of 150–200 mCi is typically administered.

3. For treatment of distant metastases, activity of >200 mCi is often given. The radiation dose to the bone marrow is typically the limiting factor. Most experts recommend that the estimated radiation dose to the bone marrow be less than 200 cGy [200 rads]). Detailed dosimetry may be indicated in patients who are treated with large amounts of radioactive iodine to determine how much 1311 can be safely administered. Retention of radioiodine in the body at 48 h should be <2.96 GBq (80 mCi) [15].

Treatment has to be done by qualified personal in isolated shilded room with separated toilet and shower. Radiation level from the 1 meter from patient at the time of discharging should not exceed 15mZv/hour. After this WB scan with following SPECT/CT usually performed. In Finland according to national regulations the toilet draining is directly to the main sewer, however in some countries according to national regulation system of radiation waste disposal separate suige is mandatory.

Follow up: Two to three months after initial treatment, thyroid function tests (FT3, FT4, TSH) should be done to check the adequacy of LT4 suppressive therapy. First year after treatment thyroglobulin and antithyroglobuline level should be monitoring every 3 months, if negative second year – every 6 months and following years every 12 months. If serum thyroglobulin (Tg) is detectable under basal conditions, the chance that the patient has visible disease is very high, and thus imaging techniques US of the neck, chest's CT without contrast, diagnostic scanning with I-123 must be applied. If serum Tg is detectable in the low range after rhTSH stimulation, the probability of serum Tg changing from detectable to undetectable during follow-up is approximately 50% [16].

Case reports and discussion:

Patient 53 years old, was operated in Russia in 2000 due to suspicion on having DTC (hemi thyroidectomy of the left lobe). Histological result was doubtful and patient was sent home. In 2003 due to enlarged lymph nodes of the neck (left lymph nodes) patient was re-operated. Histology results: in half of lymph nodes metastases of papillary carcinoma. In December 2013 patient started to have back pain and went to Israel where on MRI suspicious lesions in lumbar spine and sacrum were found. On FDG-18 PET/CT, PET part was negative, however CT part shows enlarged lymph nodes in a left para-tracheal zone. Biopsy shows 5 lymph nodes in the left (0.5x1.3cm) papillary cancer, solid node in right lobe (0.3x0.5 cm)- papillary cancer. 21.1.14 hemi-thyroidectomy of the right lobe, bilateral resection of para-tracheal lymph nodes. Histology: in right lobe there were 2 lesions and one of 3 lymph nodes - papillary carcinoma, in the left side 5 out of 9 lymph nodes with metastases from papillary carcinoma. Patient was advised to start with 200 mg daily of levothyroxine and receive radioiodine therapy. Radioiodine therapy was done in Docrates Cancer Center (Helsinki, Finland). Treatment: withdrawing levothyroxine 2 days before



7.3.2014 Normal physiologic activity is seen in nasopharynx, salivary glands, stomach, GI tract and urinary bladder. SPECT/CT demonstrates that the thyroid activity (13% of the whole body activity) lies in the right lobe (41% of the thyroid residual activity) and another focus (59%) is seen almost in the midline and on the left (isthmus/ left lobe). SPECT/CT demonstrates two small marginal iodine avid uptakes in the skeleton, one in L2 on the left (7:1; 1 cm) and another in sacrum S2 (22:1; 2 cm), which are not visible on PET imaging.

4.6.2014 Normal physiologic activity is seen in nasopharynx, salivary glands, stomach, Gl tract and urinary bladder. SPECT/CT does not demonstrate any thyroid activity. The skeletal foci seen in the SPECT/CT with therapeutic dose in III/14, both in L2 and in sacrum have totally disappeared

Figure 2 – Successful treatment of bone metastases by I-131

therapy. 3 and 4 march 2014, intra-muscular injection of 0.9 mg rTSH. 5.3.2014 TSH level was 143uU/L, thyroglobulin level 2 ng/ml. 5.3.2014 patient received 150mCi of I-131 in isolated hotel room. 7.3.2014 radiation from the 1 meter distance from the patient was 15mZv/hour and WB and SPECT/CT scan was done: Whole body imaging demonstrates a moderate bilateral thyroid residue. Two small marginal iodine avid uptakes can be seen in the lumbar vertebra and pelvic region in planar imaging. Three months after therapy no pain syndrome, patient went for diagnostic scanning with I-123. Levothyroxine withdrawing 2 days before scanning; 2 and 3.6.2014 intra-muscular injection of 0.9 mg rTSH. 4.6.2014 TSH level was 91.7 uU/L, thyroglobulin level 0.2 ng/ml. 4.6.2014 I-123 was injected intravenously with 5 mCi activity. 5.6.2014 on WB and SPECT/CT demonstrates no thyroid residue. No iodine avid skeletal metastases. No new findings.

This case demonstrates the wrong management of the patient. Firstly in 2000 histology finding were not verified in other laboratory, and after 2 two years neck lymph node metastases were developed. But after second operation with confirmed histology papillary carcinoma's metastases total thyroidectomy and radioiodine therapy were not done that leaded to developing metastases in lumbar spine. As we can see from laboratory tests stimulation by rTSH was enough, the level of TSH was higher 30 uU/L and thyroglobulin level dropped down in 10 times that confirms the efficacy of radioiodine therapy. Patients with negative whole-body iodine scan after RAI treatment has favorable prognosis [6]. Thyroglobulin level more than 2 ng/ ml is a sign of recurrence. In case thyroglobulin level is 2 ng/ml or less, rTSH stimulation is recommended, in case it is increasing it is necessarily to perform the methods of visualization. In case thyroglobulin level is stable, patient has to be on follow up [17, 18].

In case patient has antibody to thyroglobulin, it may influence on serum thyroglobulin level.

From the other hand, the level of antibodies will increase proportionally increasing the level of thyroglobulin and measurements of antibody to thyroglobulin may help in patient's monitoring [19].

Conclusion: in histology verified DTC the main goal of treatment is to remove primary tumor and cervical lymph nodes, after this – radioiodine ablation with following estimation the level of TSH, T3 and T4 for correction the levothyroxine dosage. Monitoring of thyroglobulin and antibody to thyroglobulin levels helps to estimate recurrence and start treatment in time.

REFERENCES

1 Sherman SI. Thyroid carcinoma // Lancet. – 2003. – N.361. P. 501-511

2 Hundahl SA, Fleming ID, Fremgen AM, Menck HR 1998 A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995 // Cancer. – N.83. – P. 2638–2648

3 Hodgson NC, Button J, Solorzano CC. Thyroid cancer: is the incidence still increasing? // Ann Surg Oncol. 2004. – Vol. 11(12). – P. 1093–7

4 Cooper DS, Doherty GM, Haugen BR et al . Management guidelines for patients with thyroid nodules and differentiated thyroid cancer // Thyroid. -2006. - N.16. - P. 109-142

5 Perros P, editor; British Thyroid Association Royal College of Physicians; Report of the Thyroid Cancer Guidelines Update Group. Guidelines for the Management of Thyroid Cancer. Second Edition. London: London Royal College of Physicians; 2007. – P. 1-92

6 Durante C, Haddy N, Baudin E et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: Benefits and limits of radioiodine therapy // J Clin Endocrinol Metab. -2006. - N.91. - P. 2892-2289

7 Schlumberger M, Challeton C, De Vathaire F et al. Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma // J Nucl Med 1996. - N.37. - P. 598-605

8 Haq M, Harmer C. Differentiated thyroid carcinoma with distant metastases at presentation: Prognostic factors and outcome // Clin Endocrinol (Oxf). – 2005. – N.63. – P. 87-93

9 Cooper DS, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer // Thyroid. 2006. – Vol. 16(2). – P. 109–42

10 Luster M. Acta Oncologica Lecture. Present status of the use of recombinant human TSH in thyroid cancer management. // Acta Oncol. 2006. – Vol. 45(8). – P. 1018–30

11 Barbaro D et al. Recombinant human thyroid-stimulating hormone is effective for radioiodine ablation of post-surgical thyroid remnants // Nucl Med Commun. 2006. – Vol. 27(8). – P. 627–32

12 Pluijmen MJ et al. Effects of low-iodide diet on postsurgical radioiodide ablation therapy in patients with differentiated thyroid carcinoma // Clin Endocrinol (Oxf). 2003. – Vol. 58(4). – P. 428–35

13 Hackshaw A et al. 1311 activity for remnant ablation in patients with differentiated thyroid cancer: a systematic review // J Clin Endocrinol Metab. – 2007. – Vol. 92(1). – P. 28–38

14 M. Luster & S. E. Clarke et al. Guidelines for radioiodine therapy of differentiated thyroid cancer // Eur J Nucl Med Mol Imaging. – 2008 Oct. – Vol. 35(10). – P. 1941-59

15 Silberstein EB, Alavi A, Balon HR, Clarke SE. The SNMMI practice guideline for therapy of thyroid disease with 1311 // J Nucl Med. – 2012 Oct. – Vol. 53(10). – P. 1633-51

16 Kloos RT. Thyroid cancer recurrence in patients clinically free of disease with undetectable or very low serum thyroglobulin values/ / J Clin Endocrinol Metab. – 2010. – N95. – P. 5241–5248

17 Pacini F, Schlumberger M, Dralle H et al. European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium // Eur J Endocrinol. -2006. - N.154.- P. 787-803

18 American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Cooper DS, Doherty GM, Haugen BR et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer // Thyroid. – 2009. – N.19. – P. 1167–1214

19 Spencer CA. Clinical review: Clinical utility of thyroglobulin antibody (TgAb) measurements for patients with differentiated thyroid cancers (DTC) // J Clin Endocrinol Metab. – 2011 Dec. – Vol. 96(12). – P. 3615-27

онкология

Т ¥ Ж Ы Р Ы М НИГОРА РАСУЛОВА^{1,2}, КАЛЕВИ КАЙРЕМО¹

¹Дократес онкологиялық орталығының молекулярлы радиотерапия және ядролық медицина бөлімі (Хельсинки, Финляндия)

²Акад. В. Вахидов атындағы Республикалық Мамандандырылған Хирургия Орталығының радиоизотопты диагностикалық лабораториясының бөлімі (Ташкент қ., Өзбекстан)

ДИФФЕРЕНЦИЯЛАНҒАН ҚАЛҚАНША БЕЗІН РАДИОЙОД-ПЕН ЕМДЕУДІҢ ҰСЫНЫСТАРЫ. ТӘЖІРИБЕДЕН АЛЫНҒАН ЖАҒДАЙ

Бұл мақаланың мақсаты дифференцияланған қалқанша безін радиойодпен емдеу мен абляцияның хаттамасын көрсету болып табылады: көрсетілімдері, кері көрсетілімдері, емделушіні дайындау, сақтық шаралары, емделушіге арналған ақпарат, радиойодпен емдеу және радиойодтың ұсынылған белсенділігі, сонымен қатар, кейінгі зерттеу. Тәжірибеден емделушінің бастапқы кезден бастап өзін дөрекі ұстауы туралы және сүйекті метостаздардың сәтті емделуі туралы жағдайлар келтіріліп отыр.

Негізгі сөздер: І-131; дифференцияланған қалқанша безінің ісігі; абляция; радиойодпен емдеу.

РЕЗЮМЕ

НИГОРА РАСУЛОВА^{1,2}, КАЛЕВИ КАЙРЕМО¹ ¹Отделение молекулярной радиотерапии и ядерной медицины онкологического центра Дократес (Хельсинки, Финляндия)

²Отделение радиоизотопной диагностической лаборатории Республиканского Специализированного Центра Хирургии имени акад. В. Вахидова

(г.Ташкент, Узбекистан)

РЕКОМЕНДАЦИИ ПО ЛЕЧЕНИЮ ДИФФЕРЕНЦИРОВАННО-ГО РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ РАДИОЙОДОМ. СЛУЧАЙ ИЗ ПРАКТИКИ

Цель данной статьи предоставить протокол абляции и лечения дифференцированного рака щитовидной железы радиойодом: показания, противопоказания, подготовка пациента, меры предосторожности, информация для пациента, лечение радиойодом и рекомендованные активности радиойода, а также последующее наблюдение. Представлен случай из практики об изначально некорректном ведении пациента и успешном лечении костных метастазов радиойодом.

Ключевые слова: I-131; дифференцированный рак щитовидной железы; абляция; лечение радиойодом.