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Radionuclide therapy in the treatment of thyroid malignancy

KEYWORDS: Thyroid Neoplasms; Radiotherapy; Carcinoma, Papillary, Follicular; Carcinoma, Medullary; Radioimmunotherapy; Iodine Radioisotopes; Survival Rate

ABSTRACT

In this paper we presented the principles of performance of radionuclide therapy, its adverse effect, together with mentioned complications, obligation to use it only according to directions and the success of the therapy, which is seen through the length of a patient's survival rate. All types of thyroid malignancies are primarily cured surgically, by the total or near-total thyroidectomy, together with lymph node dissection of the neck and with a long-term suppressive-therapy or only substitutive L-thyroxin therapy. Radionuclide therapy is used only for the types of thyroid malignancies where a radionuclide was detected, beta emitter which is distinguished by its selective entering into the primary tumor and metastatic tissue. This therapy is used for patients with differentiated papillary and follicular thyroid carcinoma (DTC) and patients with medullary thyroid carcinoma (MTC). By the means of ¹³¹I we additionally cure patients with DTC, by MIBG-¹³¹I we treat patients with MTC, but we also try to cure this malignancy by the specific monoclonal antibodies, marked by ¹³¹I or ⁹⁰Y, which is still a part of clinical trial studies. It is very likely that the radioimmune therapy will be the means of cure for malignant thyroid lymphoma (MLT), since this therapy is successful in healing the lymphomas in other locations.

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INTRODUCTION

Radionuclide therapy is based on the performance that beta and alpha particles have in a malign tumor cell and its metastases. For this therapy in hierology so far, only beta emitters are used. The principle how such a therapy works is as follows: 1. They enter the metabolic course of both malign and healthy cells; 2. They enter a malign cell through a damaged cell membrane; 3. They bind to the surface of a malign cell; 4. They form a bond with specific monoclonal antibodies or specific receptors. In such a form, radionuclides most safely enter the malign cell and by their beta particles dissolve the malign cell (1,2). This therapy has undesired effects, which are exerted as: 1. Early complications: local swelling, painfulness, gastrointestinal, hematological, pulmonary, renal toxicity, and cardiovascular problems; 2. Late complications: decreased organ function, genetic abnormalities (changes in karyotype), cancerogenesis (secondary malignancy), and 3. Late general complications (lung fibrosis) (1). Therefore, this therapy should be used according to directions, which are suggested by the protocol (3). Radionuclide therapy is used in thyroid oncology in treatment of highly differentiated papillary and follicular carcinoma (DTC), medullary carcinoma (MTC) and most certainly this therapy can treat a malign lymphoma of thyroid (MLT). A primary treatment of this malignancy is a surgical one, and only afterwards, according to a diagnostic scintigram and pTNM, together with precisely issued directions by the protocol, we can conduct an additional treatment by the means of this therapy. The aim of the paper is to give a review of DTC and MTC with a special emphasis on the additional radionuclide treatment of thyroid malignancy, the follow-up and the survival of patients, according to our and literature data.

RADIOINUCLIDE TYPES

Radionuclide types which are used in the treatment of thyroid malignancy are: ¹³¹I (T_{1/2}= 8.1 days, beta and gamma emitter, beta energy 610 Kev and a reach of 2.0mm); ⁹⁰Y (T_{1/2}=64 days, beta emitter, energy 2280 Kev and a reach of 12.0mm). Radioactive ¹³¹I is used in the form of a solution or in capsules as an additional form of DTC treatment. Meta-iodobenzylguanidine, marked by ¹³¹I (MIBG - ¹³¹I) is used as an additional way of MTC treatment, as well as antibodies to CEA, (hMN-14), which are marked as ¹³¹I or ⁹⁰Y-90. Therapy for such a treatment of MTC is highly specific, and requires quite an engagement of the educative team, because of the possible post therapeutic complications, of which the most difficult is a catecholamine crisis. This therapy is always given in the form of infusion (4, 5).

¹³¹I therapy in DTC is undertaken after the total or near total thyroidectomy together with dissection of lymph nodes of the neck; after the diagnostic whole body scintigram by ¹³¹I, in a dose of 185 MBq and estimation of 24 hours radioiodine fixation (r. f.) (r.f. must be >0.5% at the moment of taking of Dg scintigram and TSH should have the value (30 lu/l) (6). Therapy of ¹³¹I in DTC must be undertaken according to the directions by the protocol (3). For patients with papillary carcinoma (PAP), indications for this therapy are as follows: pathological Dg. scintigram together with the estimated pathological tumor size (pT>1 cm). For follicular carcinoma (FOL) it is enough that Dg. scintigram is a pathological one, no matter what size is pT. The criteria for the therapy of this carcinoma are stricter, because FOL is spread hematogenously, so metastases emerge faster (3). ¹³¹I therapy dose can be ablative and tumorous. The ablative therapy is administered in order to destroy the postoperative thyroid remnants, and it is given in a dose of 3.7 GBq (6) or 1.1 GBq (7). Tumor dose is given in order to destroy the thyroid remnants and the possible metastases: locoregional, in the lungs and bones. A dose of 5.55 GBq is for elimination of locoregional spread of DTC and its metastases in lungs. A dose of 7.4 GBq is administered to destroy bone metastases (6). Additional therapies of ¹³¹I are given in 12 months, exceptionally in 6 months (6). A sum dose of ¹³¹I, which a patient receives in more partial doses, is 29.6 GBq or 800 mCi (8). The patient stays in the therapeutic department until the activity falls to 0.40 GBq or 10.8mCi (8). Post-therapeutic



check-ups are at 1.5; 3; 6 and 12 months after which we perform Dg. whole body scintigram. Check-ups are with hematogram finding (until normalized), TSH and Tg (3,6). Pregnancy is not allowed for 3 to 5 years after the last ¹³¹I therapy, with an approval of a geneticist (9). Patients with DTC have to be under a permanent, suppressive-substitutive L-thyroxin therapy and therefore TSH therapy is necessary.

THErapy OF MEDULLAR CARCINOMA (MTC) BY THE MEANS OF RADIONUCLIDES

This therapy is still not used enough and it is partly in a phase of a clinical trial, especially the part which is related to radioimmune therapy where antibodies to target tumor antigen are marked by ¹³¹I or ⁹⁰-Y (2). Medullar carcinoma MTC is surgically treated in the first place, by the means of a total thyroidectomy with an extremely good dissection of lymph nodes of a neck and upper mediastinum. Afterwards, a Dg. scintigram is made by ^{99m}Tc-DMS(V), or better by MBIG-¹³¹I; if there is a pathological finding, the treatment by MBIG ¹³¹-I is undertaken. This therapy is highly complex, because we have to take care of a very difficult complication: a catecholamine crisis (10). Patients are followed-up each 1.5; 3; 6 and 12 months by checking the findings of hematogram, TSH, TCT and CEA. A patient has to be under a satisfying substitution of L-thyroxin (3).

SURVIVAL OF PATIENTS

The first results of the survival of patients with DTC additionally treated by ¹³¹-I were presented by the author of this therapy Beierwaltes in 1982. He showed that in course of 20 years, 103 patients with DTC who underwent a total thyroidectomy and ¹³¹-I treatment together with a good L-thyroxin hormone therapy had 3 times better survival rate than the ones who were only operated and had a hormone treatment (6). Similar results were shown by Mazzaferri in 1981, on more patients (576), but only for PAP, followed for 10 years (11). We conducted a 20 year follow-up of 239 patients (1978-1998) and showed that the survival rate (SR) for all patients was 0.91; SR=0.93 for PAP; SR=0.83 for FOL; SR=0.99 for I stage; 0.91 for II Stage; 0.93 for III stage and 0.33 for IV stage (12). We estimated the survival rate for patients with DTC for pT3 for the period of 25 years, and it was SR = 0.73 for all the patients while it was SR = 0.94 for patients with PAP and 0.25 for patients with FOL carcinoma. If we consider the stages of disease for pT3, the data are as follows: SR=0.83 for I stage, patients with II stage were all alive; SR=0.75 for III stage and 0.45 for IV stage (13). The survival rate for patients with DTC pT4 was estimated. We estimated that SR=0.90 in 5 years, SR=0.84 in 10 years and 0.76 in 15 years (14). For patients with DTC with distant metastases (M1): SR=0.63 in 5 years, SR=0.49 in 15 years and SR=0.33 in 20 years (12,15). We also estimated the survival rate for the patients with DTC who had a spread into a lymph nodes of a neck (N1 a/b). We obtained the following results: SR=0.87 in 5 years, SR=0.71 in 10 years and SR=0.56 in 20 years of follow-up (16).

At the Institute of oncology in Sremska Kamenica we determined 25 year survival rate for patients with MTC generally, as well as according to the stages of disease (17). We could not determine the survival rate of MTC patients who were additionally treated by radionuclides, because we did not use such a therapy because of economic reasons. In literature we have not found any larger series of patients with MTC, who were treated by MIBG ¹³¹-I and whose survival rate was followed. On the other hand, treatments with radioimmune therapy, where the specific monoclonal antibodies to CEA are marked with ¹³¹-I or ⁹⁰-Y are still in a phase of a clinical trial. It is expected that the survival of patients with MTC who will be additionally treated by radioactive beta and maybe alpha emitters, is to be much better than present results. We are to expect a better survival rate of patients treated by radioimmune therapy with ⁹⁰-Y because it has a high energy and a good reach of beta particles (2). In our material, the survival of patients with MTC, treated by total

thyroidectomy with LGN dissection, radiotherapy and chemotherapy SR=0.61 for 25 years (17), and according to literature data SR=0.80 for 5 years (18).

CONCLUSION

Radionuclide therapy should be used according to directions prescribed by the protocol (3). Survival rate of patients who are additionally treated by the radionuclide therapy is significantly better in comparison to those patients who are treated by hormone therapy or surgically. The early diagnosis of thyroid malignancy certainly contributes to such a high survival rate.

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