Current concepts of $^{131}$I therapy in oncology: Indications, methods and follow up

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ABSTRACT

Radioiodine in various forms (as sodium iodide and as the iodinated compounds MIBG, LIPIODOL, et al.) has been used as a therapeutic agent in oncology. Differentiated thyroid carcinoma (DTC) has been successfully treated by $^{131}$I therapy. Neuroendocrine tumors can be treated by palliative therapy, including Meta $^{131}$Iodobenzylguanidine therapy ($^{131}$I-MIBG). Diagnostic $^{131}$I or $^{123}$I-MIBG scintigraphy is usually performed to image neuroblastoma and malignant pheochromocytoma. Following the establishment of the diagnosis, $^{131}$I-MIBG may be applied as a therapeutic agent but with limited success. Hepatocellular carcinoma (HCC) is treated by surgery only in 10% of patients. In others, palliative therapy should be administered. Radionuclide therapy for this disease is a therapeutic option with a major advantage compared to systemic chemotherapy, estrogen and progesterone therapy, and immunotherapy. $^{131}$I-lipiodol can be used to treat HCC without side effects. Compared to untreated patients, those who received $^{131}$I-lipiodol, showed significantly better survival and a decreased recurrence rate. The modern aspect of the neoplasm treatment involves radioimmunotherapy with radioiodine and some other radionuclides. Monoclonal antibody therapy with radioiodine has been extensively succeeded in the therapy of B-cell non-Hodgkin’s lymphoma, prostate cancer. Radioimmunotherapy is also efficiently performed in some other malignancies such as: medullary thyroid carcinoma, breast cancer, colorectal cancer and malignant brain tumors. Radioimmunotherapy will play a key role in the treatment of malignant diseases, especially hematopoietic neoplasms during this millennium.

KEY WORDS: Oncology, Medical; Thyroid Neoplasms; Adrenal Gland Neoplasms; Carcinoma, Hepatocellular; Iodine Radioisotopes; Radioimmunotherapy

INTRODUCTION

Radioiodine therapy has been established as a therapeutic option with significant role in treating several endocrinologic and oncologic diseases. Oral administration of radioactive iodine ($^{131}$I) in the form of sodium iodide has been performed for over 40 years as a successful treatment of differentiated thyroid carcinoma, after partial or total thyroidectomy. $^{131}$I is a $\beta$-emitting radionuclide with a physical half-life of 8.1 days, a principal $\gamma$-ray of 364 KeV, and a principal $\beta$-particle with a maximum energy of 0.61 MeV, an average energy of 0.192 MeV, and a range in tissue of 0.8 mm. Radioiodine, as a label for different radiopharmaceuticals, has been used also as a powerful agent in nuclear oncology. Initially, radioiodine therapy was widely used for treatment of thyroid carcinomas. Patients with differentiated thyroid carcinoma, treated with surgery and radioiodine, have a survival rate that exceeds the rate of most other neoplasms. Radioiodine therapy with $^{131}$I labeled to other molecules has also been used as a palliative therapy of other cancers, such as hepatocellular carcinoma and neuroendocrine tumors (neuroblastoma and malignant pheochromocytoma).

$^{131}$I THERAPY OF DIFFERENTIATED THYROID CARCINOMA

Thyroid carcinoma is the most common malignant tumor of the endocrine glands. Ninety percent of malignant thyroid nodes are well-differentiated thyroid carcinomas (DTC), including papillary and follicular carcinomas (1). The first step in treating DTC is surgery. The thyroid glands and affected neck lymph nodes should be removed. Today, despite existing controversy about the extent of thyroid surgery, there are strong arguments supporting total or near-total thyroidectomy (leaving no more than 2 to 3 g of thyroid tissue) in all patients and modified radical neck dissection if necessary (2,3). Total or near-total thyroidectomy improves ability of $^{131}$I to ablate the remaining gland and to concentrate in regional and distant metastases.

Radioiodine therapy still remains an area of controversy in thyroid cancer management (4). It has frequently been divided into radioiodine ablation and radioiodine therapy. $^{131}$I ablation is necessary to eliminate remaining normal thyroid tissue and destroy occult microscopic carcinoma. Two important conditions should exist in order to perform $^{131}$I therapy: thyroid remnants must be seen on whole body scan (WBS), and the 24-hours radioiodine uptake must be >0.5% (“significant uptake” – Beierwaltes, 1984) (5).

DTC patients treated by surgery alone have a high recurrence rates. In contrast, patients treated with surgery and $^{131}$I have a survival rate that exceeds the rate for most other malig-
nancies (6). Regarding beneficial effects of $^{131}$I therapy in terms of recurrence and mortality rates, many physicians advocate that $^{131}$I ablation should be administered selectively. Radioidine therapy has no benefits in "low risk" patients (intra-thyroid tumors $<$1-1.5 cm) and no impact on recurrence rates in patients with lymph node-positive papillary thyroid microcarcinoma (7). Therefore, most papillary thyroid carcinoma patients (PTC) in the pHNOMO stage (primary tumors $<$1 cm) can usually be managed postoperatively with thyroxin suppression, without $^{131}$I ablation, as the risk of recurrence and mortality are very low (8). High-risk patients for recurrent disease should be treated with $^{131}$I therapy, since this treatment decreases both recurrence and death rates (2,9). Therefore, in patients with larger papillary carcinoma spread to the adjacent lymph nodes, follicular thyroid carcinoma (FTC), and in those with evidence of distant metastases, thyroid ablation and radioiodine treatment are generally indicated (10). The recommendation for this kind of treatment protocol is supported by several clinical studies. Mazzaferri followed big series of patients with a primary tumor $<$1.5 cm in diameter and detected lower 30-year recurrence rates in a group of patients treated with $^{131}$I (16% compared with 38%) and cancer-related deaths (3% compared with 8%) than those not treated with $^{131}$I (11). Similar results have been confirmed in a prospective multicentric study studied on 385 "high-risk" patients: reduction of cancer-specific mortality and recurrence rates have been detected in patients who were treated with radioiodine ablation (12).

Many institutions give a standard amount of $^{131}$I for ablation of 1.1 GBq, which is the largest quantity that can be administered to outpatients in most countries. Other centers give an arbitrary amount of 3.7 GBq which currently requires that the patient is hospitalized for 1 to 3 days to avoid excessive radiation exposure to family and the public (13). According to the procedure guideline written by Meier and al. postoperative ablation of thyroid bed remnants should be done by administering of 2.75 to 5.55 GBq $^{131}$I, depending on the radioiodine uptake and amount of residual functioning tissue present (14).

The term $^{131}$I therapy is usually used to indicate the treatment of residual or recurrent thyroid cancer at the thyroid bed or of metastatic lesions elsewhere, whether or not remnant thyroid tissue is present (6,13).

There are a variety of approaches to select the amount of administered activity. The most widely used method is to administer a fixed dose, regardless of the radioiodine uptake in the remnants or metastatic lesions. Modification of dose based on factors, such as tissue mass and tracer uptake, and patient-specific dosimetry, are also available for radioiodine therapy (1).

An alternative approach to $^{131}$I therapy of metastatic DTC is the one originally employed by Benua et al. and Leeper. The major complications to be avoided are bone marrow suppression and pulmonary fibrosis. Most experts recommend that the estimated radiation quantity that can be administered to outpatients in most countries. Other centers give an arbitrary amount of 3.7 GBq which currently requires that the patient is hospitalized for 1 to 3 days to avoid excessive radiation exposure to family and the public (13). According to the procedure guideline written by Meier and al. postoperative ablation of thyroid bed remnants should be done by administering of 2.75 to 5.55 GBq $^{131}$I, depending on the radioiodine uptake and amount of residual functioning tissue present (14).

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Patient preparation

All patients must discontinue use of iodide-containing preparations, iodine supplements, thyroid hormones, and other medications that could potentially affect the ability of thyroid tissue to accumulate iodide for a sufficient time before $^{131}$I therapy. The standard approach to evaluating DTC patients with WBS involves withdrawing thyroid hormone replacement, 2 weeks for triiodothyronin (T3) and 4 to 6 weeks for thyroxin (T4) prior to treatment, to allow endogenous thyrostimulating hormone (TSH) to increase to supornormal levels, at least 30 mU/L (13,14). Recently, recombinant human TSH (rTSH) has been developed and used in many clinical trials. It stimulates thyroid tissue without requiring the discontinuation of thyroid hormone therapy. Human rTSH is not approved for use in patient preparation for $^{131}$I therapy, but it can be used in patients with functioning metastases that preclude elevation of serum TSH following thyroid hormone withdrawal (1,13).

Many experts recommend a low iodine diet for 7 to 10 days before administration of therapy to improve iodine uptake. A patient should avoid iodized salt, milk and diary products, eggs, seafood, seaweed and kelp products, commercial bread made with iodide conditioners, chocolate, iodide-containing multivitamins and red dye which is found in many processed red-or pink-colored foods, and medications (13,14).

Method

The treating physician must explain the procedure, treatment, complications, clinical side effects, therapeutic alternatives, and expected outcome to the patient. The patient’s identity must be confirmed by ID and written patient’s agreement to the $^{131}$I therapy must be obtained before administration of $^{131}$I.

The treating physician must review the operative and histology reports, complete blood count, chest X ray, recent measurements of TSH, and baseline TG level in the hypothyroid state (13,14). Seventy-two hours after the radioiodine therapy, WBS is performed in order to detect tumor or metastatic tissue, which was not seen on diagnostic WBS. Repeated scanning and therapy are required at 6 to 12 months intervals until the tumor no longer concentrates $^{131}$I, large doses are reached or adverse effects appear. The total cumulative dose of $^{131}$I given to one patient with serious distant metastases during his life is 37 GBq (17). Pregnancy should not be allowed before one year after the last performed therapy (14).

Follow-up

Life-long Levothyroxin therapy follows $^{131}$I therapy. After the radioiodine therapy DTC patients should be followed for the rest of their lives (13). Long term follow-up should include periodically physical examination, chest X-ray and measurements of thyroid hormone and TG and WBS. Successful radioiodine ablation results in the absence of radioiodine uptake at the WBS and a normal TG level. Whole body scan is usually recommended one year after the treatment in patients with low risk. In patients with higher risk WBS may be performed as early as 4 to 6 months after the radioiodine therapy. After the first negative WBS, any further follow-up scanning intervals are controversial. It has been suggested to perform WBS annually for 2 years. On the contrary a conservative approach represents repeated scanning and TG levels at 4 and 5 years and then at 5-years interval (8).

Complications of radioiodine therapy

Short and long term complications may follow radioiodine therapy.

Short-term complications: Radiation thyroiditis following radioiodine ablative therapy may occur in 20% of patients who have large thyroid remnants. The symptoms usually appear 2 to 4 days after $^{131}$I administration with diffuse neck and ear pain, painful swallowing, and tenderness and swelling in the region of the thyroid. These symptoms are transient and usually respond to anti-inflammatory drugs and analgesics. Occasionally corticosteroids are necessary. The radiation-induced thyroiditis may cause transient hyperthyroidism, which can be ameliorated with beta-adrenergic blocking drugs (6,13).

Thyroid storm rarely occurs in patients who have hyperthyroidism secondary to large masses of functioning metastases, due to the radiation-induced release of thyroid hormone
from the metastases. In such patients, pretreatment with antithyroid drugs prior to radioiodine therapy may minimize or prevent this complication. The use of beta-adrenergic blocking medication is helpful (13).

Sialadenitis may occur in 12% of treated patients. It usually begins on the second day after treatment and resolves after 3 days. Symptoms are manifested by swelling and tenderness in the salivary glands, dry mouth and metallic taste for several weeks. Symptoms are transient and can be minimized or prevented altogether by increasing salivary flow by having the patient suck on hard sour candy or lemon drops and encouraging fluid intake beginning on the day of therapy (8,13).

Gastrointestinal symptoms are reported in 67% of patients. Nausea is the most common gastrointestinal symptom and is thought to be caused by radioiodine uptake in the stomach wall. A mild nausea without vomiting begins 2 hours after therapy and lasts for several days after the radioiodine therapy. The patients are told not to eat solid food from midnight on the day prior to therapy until 2 hours after the therapy to speed absorption of the radioiodine and minimize retention in the stomach. It is important to prevent vomiting of the radioiodine, by antiemetics given intramuscularly or rectal, at the first sign of nausea (6,13). Taste dysfunction is reported with an incidence of 48% and is characterized by loss of taste, with or without taste distortion (phantom, metallic or chemical taste). It usually occurs after 24-168 hours (8). Bone marrow depression is transitory and occurs within the first month after 131I therapy. It is usually followed by transient anemia (36% pts), leukopenia (10% pts), and thrombocytopenia (3% pts). It resolves spontaneously (8,13).

Local effects induced by radiation include inflammation, manifested by pain, hemorrhage and edema, at the site of metastases. They should be treated by analgesics. When cerebral metastases are known or suspected, pretreatment with large doses of corticosteroids is advised to prevent the acute swelling that often follows radioiodine therapy (13).

**Long-term complications:** Gonad function may be depressed by radioiodine therapy rarely. A dose dependent decline in sperm count and reduction in sperm motility has been described. This effect of radioiodine is reversible in most of the cases. Long-term storage of semen is recommended to the patients who have to be treated with a high-dose cumulative therapy. There are no reported data of influence of radioiodine to infertility, miscarriages, and premature births, congenital abnormalities in women previously treated with radioiodine (8,13).

Leukemia has been reported very sporadically. According to some studies, diagnostic and therapeutic doses of radioiodine do not result in an increase of leukemia. Nevertheless, this complication is of concern when the cumulative doses of radioiodine exceed 37 GBq (8). Solid tumors appear with low incidence and the relationship to treatment is unclear in treated patients. To reduce bladder exposure, the patient should be adequate hydrated during the first 24 hours after the 131I therapy (8).

Pulmonary fibrosis must be considered if large amounts of radioiodine are used to treat patients with diffuse or widespread multiple pulmonary metastases. It is recommended to limit the lung uptake to 3 GBq retained at 24 hours (8,13).

**Radiation safety**

Licensure to possess 131I and discharging of patients treated with 131I therapy vary from jurisdiction to jurisdiction. 131I therapy requires hospitalization of patients in a private room with a shower and toilet to avoid radiation exposure to other patients, hospital personnel and the public (13,14).

Nursing staff is instructed to limit close contact with the patients, to perform only essential nursing functions including daily dosimetry, and to avoid contamination by saliva and excreta. Dosimetry is performed daily following 131I therapy to determine when the patient may be discharged from the hospital. On the day of discharge, a patient must be given written instructions to safeguard the family, particularly young children and pregnant women from the external exposure (13).

In Serbia and Montenegro radioiodine therapy of DTC was performed the first time in 1958 at the Institute of Oncology and Radiology in Belgrade and this institution continued to perform radioiodine treatment until 1990. After that time, and today, this therapy is still performing at the Institute of Oncology in Sremska Kamenica only (this hospital started to perform radioiodine therapy in 1977). In Institute of Oncology in Sremska Kamenica there are protocols for treating DTC patients, including therapy by radioiodine, which have been published in 1994 (18).

**META131IODOBENZYLGUANIDINE THERAPY (131I-MIBG) OF ADRENAL NEOPLASMS**

Metaiodobenzylguanidine (MIBG) labeled with 131I and 123I has been used as an effective radionuclide to image sympathomedulla neoplasms, such as neuroblastoma and pheochromocytoma. Excellent uptake and rapid clearance of MIBG has been used as the basis for radionuclide therapy of such tumors with larger doses (19).

Neuroblastoma is the most common extra cranial solid tumor of childhood and the most common neoplasm in the first year of life. It arises from the sympathetic nervous system primary sites in adrenal glands and in paraspinal locations from neck to pelvis. There are high urinary levels of catecholamine in more than 90% of cases. The most common primary site of this tumor is the retroperitoneum (adrenal gland more often than paraspinal ganglia). Less common primary site of origin are the posterior mediastinum and neck; rarely, no primary site is identified. This embryonic neoplasm often invades vascular structures and usually presents with metastatic disease (bone, bone marrow, lymph nodes, liver, and rarely in lungs) (20). MIBG labeled with 131I and 123I can be used to localize malignant pheochromocytoma at remote sites (skull and femur) and of intra-adrenal recurrences. The sensitivity and specificity of MIBG for pheochromocytoma has been reported as 87% and 99% respectively. Radiolabeled MIBG has also been used in the identification, staging and assessment of the therapeutic response in patients with neuroblastoma. Diffuse uptake in primary tumor and also in metastases like liver, bone, or lymph nodes can be detected with MIBG. The sensitivity and specificity for 123I- and 131I-MIBG for neuroblastoma are 92% and 99% respectively (19).

Other neuroendocrine tumors of the amine precursor (medullary thyroid carcinoma, carci-
noid tumors, parangangliomas) have been imaged with variable success. They share the same mechanisms of presynaptic uptake into sympatomedulla tissues with deposition into neurosecretory granules. Their sensitivity and specificity for radioiodinated MIBG is much less than in neuroblastoma and pheochromocytoma (19). According to the literature, 111In-DTPA (diethylenetriamine penta acetic acid)-octreotide can also be performed to image neuroendocrine tumors, paragangliomas) have been imaged with variable success. They share the same mechanisms of presynaptic uptake into sympatomedulla tissues with deposition into neurosecretory granules. Their sensitivity and specificity for radioiodinated MIBG is much less than in neuroblastoma and pheochromocytoma (19). According to the literature, 111In-DTPA (diethylenetriamine penta acetic acid)-octreotide can also be performed to image neuroendocrine tumors, specifically neuroblastoma and pheochromocytoma with approximately the same sensitivity as MIBG (21,22).

Diagnosis of adrenal neoplasms is based on: elevated and/or insuppressible concentrations of plasma catecholamines, such as vanillylmandelic acid (VMA) and homovanillic acid (HVA), elevated catecholamine and catecholamine metabolite excretion in the urine, positive 123I- or 131I-MIBG scan (10), and ultrasound, CT, MRI finding (20).

Shapiro studied 131I-MIBG therapy in the treatment of neural crest tumors and reported a significant fraction of patients entered partial remission but complete remission was rare and relapses frequent. He concluded that treatment of patients should be at earlier tumor stages combined with other therapy modalities such as granulocyte-stimulating factor and marrow transplantation (23).

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Hoefnagel et al. suggested that 131I-MIBG therapy has a definitive place in the treatment of neuroblastoma after conventional treatment has failed. He reported that this therapy is the best palliative treatment for patients with advanced recurrent neuroblastoma. He obtained the best results in patients with voluminous soft tissue disease. The invasiveness and toxicity of this therapy was comparable with that of chemotherapy, immunotherapy and external beam radiotherapy and was well tolerated by children (24).

Avid uptake of radiolabeled MIBG in pheochromocytoma and neuroblastoma permits the use of 131I-MIBG as a therapeutic agent with some success. Indications for 131I-MIBG therapy are: if no other treatment is possible (surgery, chemotherapy, external beam radiotherapy), when at least 1 year survival is expected, all or most identifiable lesions should accumulate tracer on the MIBG scan, and a radiation dose of 0.5 cGy/MBq can be delivered to the tumor. Heart rate, blood pressure and electrocardiographic pattern should be continuously monitored to avoid catecholamine crisis. No serious side effects were reported except for nausea and vomiting which may occur during the first three days after the therapy (25).

In the Institute of Oncology in Sremska Kamenica 131I-MIBG therapy was performed in 2 patients and results were published (26,27). First patient with neuroblastoma received therapy in 1990, but due to the terminal stage of the disease, died soon after the therapy. The second patient with metastatic malignant pheochromocytoma underwent 131I-MIBG therapy twice, in 1998 and 1999. This patient recovered after the treatment and is still alive.

**HEPATOCELLULAR CANCER (HCC) TREATMENT WITH 131I-LIPIODOL**

Primary hepatocellular carcinoma (HCC) is successfully treated by surgery only in 10% of patients (28). Percutaneous ethanol injection treatment and percutaneous hot saline injection therapy for hepatocellular carcinoma ending with tumor necrosis are effective only in solitary tumors, but they are not an alternative to surgical treatment (29,30).

Palliative therapy including systemic chemotherapy, clinical trials with progesterone (cyproterone acetate), antiandrogenic therapy, and immunotherapy (with specific antibodies) is ineffective (28). A treatment of hepatocellular carcinoma by transcatheter arterial embolization combined with intra-arterial infusion of a mixture of cisplatin and ethiodized oil has been carried out in Japan in 1989 (31).

The good tolerance of radionuclide therapy is a major advantage compared with chemotherapy. In general, radionuclide therapy permits specific targeting, thereby limiting detrimental effects on normal organ systems (32).

Lipiodol (iodized lipid obtained from poppy seed oil) is selectively taken up and retained by hepatocellular carcinoma, the nuclear medicine specialist should check the line placement for radioiodine therapy such as pregnancy and lactation (28). Antibodies labeled with 131I have been studied most widely. Radiolabeled antibody has a relatively high specific activity (up to 800 MBq of 131I per milligram) and has been shown to be stable for a long period of time (40). If we neglect radioiodine cytotoxic beta minus emission, its high-energy gamma radiation permit dosimetric measurements. Based on the quantification of radioactivity in the body and in serum, some trials are able to be done (studies are based on the radiation absorbed dose to critical normal organs such as a bone

Contraindications for lipiodol therapy are: extrahepatic metastases, severe pulmonary and kidney dysfunction, allergic reactions to iodine, contraindications for hepatic angiography, and leukopenia <1.5x10^9/L or thrombocytopenia <50x10^9/L, and general contraindications for radioiodine therapy such as pregnancy and lactation (28). This methodology is very complex and demands multidisciplinary experts. The nursing and medical staff receives significant radiation doses. The thyroid gland should be blocked with Lugol’s solution. After a catheter is placed into a hepatic artery branch that supplies the hepatocellular carcinoma, the nuclear medicine specialist should check the line placement with 99mTc-macroaggregated albumin and then infuse 2.22 GBq of 131I-Lipiodol during 10 minutes. Lipiodol is very viscous, and once injected, it cannot be removed. In case the catheter is misplaced into the gastroduodenal artery, lipiodol perfuses the stomach and causes severe radiation necrosis of the gastric mucosa (28). In order to avoid this complication, catheter placement was performed in our hospital in cooperation by invasive cardiologists.

There are different opinions about isolation period for patient. According to the literature, the patient should be isolated for 7 days. According to the measurements of effective half-life of radioiodine, that we performed, and published data, 30% to 50% of radioactivity is excreted in the urine over 7 days (28). According to our radiation safety law, 14 to 20 days are necessary for patient hospitalization (17).

**Dosimetry**

According to the literature, the absorbed radiation dose to tumor (if treated with 2.22 GBq 131I) is 96±49 Gy. Other parts of the body absorb much less radiation, which is for non-tumoral liver tissue about 11±9 Gy, for lungs 7±2 Gy, and for gonads and whole body about 1 Gy (28).

Relatively common transient clinical side effects are: nausea, vomiting, and general weakness. Transient fever appears in 29 patients, moderate and temporary dysfunction of hepatobiliary tests in 20% patients, and abdominal pain during the application of lipiodol in 12.5% patients. Moderate and reversible leukopenia appears in 7% and respiratory symptoms in 3% patients. Severe respiratory failure appears very rarely, in 0.5% patients only (28).

Based on the experience with 131I-lipiodol therapy, which was performed in our hospital, tumor growth was arrested but general symptoms worsened. Life duration was significantly prolonged (compared to the expected life duration), but without improvement in the quality of life (38).

In a randomized controlled trial over a period of 1 to 5 years, 131I-lipiodol was administered as a neoadjuvant treatment in patients with small HCCs after surgery. Patients were randomized into two groups: first group of 21 HCCs treated with 1.85 GBq of 131I-lipiodol within 6 weeks of surgery, and a second group of 22 HCCs with no postoperative treatment. Lau et al. reported a 3-year survival of 86.4% in the treated group and 46.3% in the untreated group. In the treated group, the recurrence rate was 29%, compared to 59% in the untreated group. The median disease-free survival in the treated group was 57.2 months, versus 13.6 months in the untreated group (39).

**RADIOIMMUNOTHERAPY WITH RADIODINE**

Today the modern trends in the treatment of malignant disease include the use of radionuclide-conjugated antibodies. This kind of therapy, known as radioimmunotherapy (RIT), is based on radionuclide-conjugated antibody accumulation in tumor which will permit selective delivery of cytotoxic radioactivity and thus tumor regression (40).

Antibodies labeled with 131I have been studied most widely. Radiolabeled antibody has a relatively high specific activity (up to 800 MBq of 131I per milligram) and has been shown to be stable for a long period of time (40). If we neglect radioiodine cytotoxic beta minus emission, its high-energy gamma radiation permit dosimetric measurements. Based on the quantification of radioactivity in the body and in serum, some trials are able to be done (studies are based on the radiation absorbed dose to critical normal organs such as a bone.
Radioimmunotherapy using radiolabeled antibodies directed against specific surface anti-
gens is a new treatment option and provided a new hope for many patients with B-cell Non-
Hodgkin lymphomas (B-NHL) (42). B-NHL lymphomas are a heterogeneous group of lymphoproliferative malignancies with dif-
f erent biological behavior and response to therapy. Most patients respond well to standard 
chemotherapy treatment (cyclophosphamide, doxorubicin, vincristine and prednisone-
CHOP). Patients with low-grade lymphoma may have long courses of disease and may 
require follow-up or moderate treatment only, whereas with a large tumor burden and high 
proliferative activity usually have aggressive course of disease. In these patients, relapses 
occur very frequently after chemotherapy with shorter response duration. Despite modern 
therapeutic options, patients with relapsed, progressive or transformed low-grade lym-
phoma still have a poor prognosis (42).

First promising results in patients with refractory and relapsed B-NHL using a murine 131I-
labelled anti-CD37 antibody have been published by Press et al (43) and Kaminski et al. 
(44). Kaminski et al. found a response of 2-6 months in 6 of 11 pts, whereas Press et al. 
found complete response in all 4 treated pts with high-dose radioimmunotherapy. Few 
years later, Press et al. published results with a 131I-labelled murine anti-CD20 antibody 
and found 16 of 19 treated patients with a complete response (45).

Most B-NHL expresses the CD20 antigen, a lineage-restricted differentiation antigen located 
on the cell surface. Rituximab is a chimeric monoclonal antibody (IgG1 type) that binds to 
the CD20 antigen, but is not internalized (46). It induces apoptosis, cell-mediated cyto-
toxicity, complement-dependent cell lysis and cytokine release (47). Behr et al. first used 
131I-rituximab for treatment of B-NHL. Radiolabeled rituximab has a longer effective half-life 
and is less immunogenic compared with its murine counterparts, which can induce human 
anti-murine antibodies (HAMA) (48).

Authors from Germany evaluated the safety, toxicity and therapeutic response of 131I-anti-
rituximab radioimmunotherapy in nine patients with relapsed, refractory or transformed B-NHL 
(previously treated with chemotherapy and radiotherapy). They found responses in four out 
of ten therapies and severe hematological toxicity in seven patients, with no significant clini-
cal problems. They concluded that radioimmunotherapy is safe and well tolerated with no 
acute adverse effects (42).

Myelosuppression is the dose limiting toxicity and may be particularly problematic in patients 
heavily pretreated with chemotherapy. Therefore, Boucek and Turner evaluated how to min-
imize toxicity and improve treatment efficacy. They suggested reliably whole body dosime-
try method to be valid and clinically applicable for safe and effective 131I-anti-CD20 ritux-
imab radioimmunotherapy of NHL (49).

Radioimmunotherapy of NHL can be marrow-ablative or not. In marrow-ablative treatment, 
where patients undergo very high doses of radioactivity, the lethally damaged marrow must 
be reconstituted after RIT is done with stored marrow or stem cells. In this aggressive form 
of therapy, the maximum possible radiation dose is delivered to the tumor, with increased 
toxicity and possible complications. Today, there is a more often used treatment, in which 
lower doses of radioactivity are performed, so that the marrow may be reversibly damaged 
but not destroyed. This treatment is safer, but possibly less effective, than myeloablative 
treatment (50).

In 2004 Friedberg and Fisher have reviewed several clinical trials using 131I tositumomab (Bexxar) radioimmunoconjugate therapy for indolent and transformed B-NHL. At the pres-
ent time the use of radioimmunoconjugate therapy is largely limited to patients with disease 
refractory to rituximab therapy and transformed disease not amenable to high-dose thera-
py and autologous stem cell support. The iodine-131 tositumomab regimen was approved 
by the US Food and Drug Administration in June 2003 for the treatment of patients with 
CD20-positive, follicular non-Hodgkin’s lymphoma, both with and without transformation, 
whose disease is refractory to rituximab (Rituxan) and has relapsed following chemothera-
py. Tositumomab is an immunoglobulin G murine monoclonal antibody that binds to the 
CD20 antigen on the surface of normal and malignant human B-cells. Tositumomab is 
linked covalently with iodine-131 to produce the radioimmunoconjugate iodine-131 tositu-
monab (Bexxar). The dose-limiting toxicity of this therapy is bone marrow suppression and 
resulting cytopenias. In contrast to chemotherapy, the majority of nonhematologic adverse 
effects associated with radioimmunoconjugate therapy are mild to moderate in nature and 
usually self-limited. Friedberg and Fisher concluded that longer follow-up of ongoing clini-
cal trials are necessary to provide assurance of safety for iodine-131 tositumomab admin-
istration (51).

Recently, radioimmunotherapy have started to perform in prostate carcinoma. Prostate spe-
cific membrane antigen (PSMA), expressed by virtually all prostate cancers is an ideal tar-
get for targeted therapy of prostate cancer. Radiolabeled J591 monoclonal antibody (mAb) 
binds with high affinity to an extracellular epitope of PSMA and localizes specifically in 
PSMA positive prostate cancers in vivo. Pre-clinical radioimmunotherapy studies using 131I-
huJ591 were studied in nude mice by authors from New York (52). They reported of increased median survival time 2 to 3 times in treated group in contrast to untreated con-
trols. Radioimmunotherapy seems to be promising for treating the patients with prostate 
cancer (53).

Radioimmunotherapy is also efficiently performing in other malignant tumors, such as: 
medul lary thyroid carcinoma, breast carcinoma, glioblastoma (54-57).

RIT as a treatment of medullary thyroid carcinoma (MTC) is at relatively early stage of de vel-
opment. The results of clinical studies show the efficacy of this treatment in controlling of 
slowly progressive metastatic MTC, even using nonmyeloablative doses. In contrast, mye-
loablative doses are necessary to achieve major responses in patients with aggressive dis-
ease. First experiences indicate that myeloablative RIT combined with chemotherapy may 
be beneficial for the treatment of metastatic MTC (54).

RIT may be also efficiently performed in patients with breast cancer. There are publications 
of using 131I-ChL6 radioimmunotherapy in metastatic breast cancer (55).

There were clinical trials in patients with colorectal cancer and small volume metastases 
using 131I-labeled humanized anti-CEA antibody hM-14 radioimmunotherapy. In these 
patients, an overall 60% response rate was achieved, including an 18% objective tumor 
response rate, with very minor adverse effects and no anti-human antibody (HAMA) 
responses (56).

Recently in the field of radioimmunotherapy, there was a clinical trial in patients with malign-
ant brain tumors (glioblastoma multiforme, anaplastic astrocytoma and anaplastic oligo-
endroglioma). 131I-labeled anti-tenascin murine 81C6 monoclonal antibody (mAb) was 
injected directly into surgically created resection cavities and was followed by convention-
al external-beam radiotherapy and chemotherapy. Results of the study showed that RIT 
increased the median survival of patients with glioblastoma multiforme (57).

CONCLUSION

Today, 131I therapy is the most effective therapy in the treatment of differentiated thyroid 
carcinomas (up to 95%). 131I labeled compounds are less successful in patients with hepa-
tocellular carcinoma and neuroendocrine tumors because these patients are usually treated 
in the final stage of disease and the therapy only has a palliative effect. Most promising ther-
apeutic option is radioimmunotherapy. The specificity and low toxicity of monoclonal anti-
bodies make them attractive and desirable for the therapy of cancer. Monoclonal antibdies radolabeled with radioidine have been successfully used in the treatment of some hematopoietic neoplasms (B-cell non-Hodgkin lymphoma, T-cell lymphoma and leukemias) and prostate cancer.

Note
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REFERENCES


