REVIEW ARTICLE
UDC: 616.441-006:615.849.1:57.088

Arch Oncol 2006;14(1-2):45-51.
DOI: 10.2298/AOO0602045M

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

Jasna Mihailović

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*

Department of Nuclear Medicine, Institute of Oncology, Sremska Kamenica, Serbia; Address correspondence to: Dr. Jasna Mihailović, Department of Nuclear Medicine, Institute of Oncology, Institutski put 4, 21204 Sremska Kamenica, Serbia, E-mail: jasnans@eunet.yu; The manuscript was received: 20.01.2006, Provisionally accepted: 24.02.2006, Accepted for publication: 10.04.2006

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 β-emitting radionuclide with a physical half-life of 8.1 days, a principal γ-ray of 364 KeV, and a principal β-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. Radioiodine 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 pT1aN0Mo 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 (8,13).

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 dose to the bone marrow be less than 2 Gy. Dosimetry is indicated in patients who have to be treated with large amounts of radioactive iodine to determine how much ^{131}I can be safely administered. Retention of ^{131}I in the body at 48 hours should be less than 4.44 GBq or 2.96 GBq if diffuse lung metastases are present, to reduce toxicity (15,16). Meier et al. recommend activity of ^{131}I to be in the range of 5.55 GBq to 7.4 GBq for treatment of presumed thyroid cancer in the neck or mediastinal lymph nodes, and activity of more than 7.4 GBq for treatment of distant metastases (14).

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 triiodotyrosin (T3) and 4 to 6 weeks for thyroxin (T4) prior to treatment, to allow endogenous thyrostimulating hormone (TSH) to increase to supernormal levels, at least 30 mU/L (13,14). Recently, recombinant human TSH (rhTSH) 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 (8,13).

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).

Sialoadenitis 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 (8,13). 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 ^{131}I therapy. It is usually followed by transient anemia (36% pts), leucopenia (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 ^{131}I 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 ^{131}I and discharging of patients treated with ^{131}I therapy vary from jurisdiction to jurisdiction. ^{131}I 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 ^{131}I 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).

META^{131}IODOBENZYLGUANIDINE THERAPY (^{131}I-MIBG) OF ADRENAL NEOPLASMS

Metaiodobenzylguanidine (MIBG) labeled with ^{131}I and ^{123}I has been used as an effective radionuclide to image sympatomedulla 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 ^{131}I and ^{123}I 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 ^{131}I- and ^{123}I-MIBG for neuroblastoma are 92% and 99% respectively (19).

Other neuroendocrine tumors of the amine precursor (medullary thyroid carcinoma, carcinoid 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, ^{111}In-DTPA (diethylenetriamine penta acetic acid)-octreotide can also be performed to image the 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 vanillynmandelic acid (VMA) and homovanillic acid (HVA), elevated catecholamine and catecholamine metabolite excretion in the urine, positive ^{123}I or ^{131}I-MIBG scan (10), and ultrasound, CT, MRI finding (20).

Shapiro studied ^{131}I-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).

Hoefnagel et al. suggested that ^{131}I-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 ^{131}I-MIBG as a therapeutic agent with some success. Indications for ^{131}I-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 ^{131}I-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 pheohromocytoma underwent ^{131}I-MIBG therapy twice, in 1998 and 1999. This patient recovered after the treatment and is still alive.

HEPATOCELLULAR CANCER (HCC) THERAPY WITH ^{131}I-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 (cyproceratone 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 HCC. Lipiodol can be used to deliver any lipid-soluble substance, such as the chemotherapeutic agents: cisplatin and epirubicin, into HCC cells. For radionuclide therapy the iodine in lipiodol is replaced with ^{131}I (33).

The first clinical applications of ^{131}I-lipiodol was in Japan in 1984 (34), followed by in France, England, Korea and Germany (35-37). Its first application in Serbia and Montenegro was made in Department of Nuclear Medicine in Institute of Oncology in Sremska Kamenica, in 1998. It was used in a patient with a primary liver carcinoma using a recommended therapeutic dose of 2.22 Gbq; 4 months later, the treatment was repeated with a dose of 1.11 GBq (38).

Patients with small HCC are the most common referral for this kind of therapy. Rarely, this therapeutic option could be performed in holangiocellular carcinoma and intrahepatic metastases (28).

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 ^{99m}Tc-macroaggregated albumin and then infuse 2.22 GBq of ^{131}I-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 ^{131}I) is 96 ± 49 Gy. Other parts of the body absorb much less radiation, which is for nontumoral 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 hepatic lab 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 ^{131}I-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, ^{131}I-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 ^{131}I-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 RADIOIODINE

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 ^{131}I have been studied most widely. Radiolabeled antibody has a relatively high specific activity (up to 800 MBq of ^{131}I 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

marrow) (41).

Radioimmunotherapy using radiolabeled antiboides directed against specific surface antigens 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 different 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 lymphoma still have a poor prognosis (42).

First promising results in patients with refractory and relapsed B-NHL using a murine ^{131}I-labeled 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 ^{131}I-labeled 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 cytotoxicity, complement-dependent cell lysis and cytokine release (47). Behr et al. first used ^{131}I-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 ^{131}I-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 clinical problems. They concluded that radioimmunotherapy is safe and well tolerated with no acute adverse effects (42).

Myelosupression is the dose limiting toxicity and may be particularly problematic in patients heavily pretreated with chemotherapy. Therefore, Boucek and Turner evaluated how to minimize toxicity and improve treatment efficacy. They suggested reliably whole body dosimetry method to be valid and clinically applicable for safe and effective ^{131}I-anti-CD20 rituximab 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 ^{131}I tositumomab (Bexxar) radioimmunoconjugate therapy for indolent and transformed B-NHL. At the present 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 therapy 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 chemotherapy. 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 tositumomab (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 clinical trials are necessary to provide assurance of safety for iodine-131 tositumomab administration (51).

Recently, radioimmunotherapy have started to perform in prostate carcinoma. Prostate specific membrane antigen (PSMA), expressed by virtually all prostate cancers is an ideal target 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 ^{131}I-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 controls. Radioimmunotherapy seems to be promising for treating the patients with prostate cancer (53).

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

RIT as a treatment of medullary thyroid carcinoma (MTC) is at relatively early stage of development. The results of clinical studies show the efficacy of this treatment in controlling of slowly progressive metastatic MTC, even using nonmyeloblastive doses. In contrast, myeloablative doses are necessary to achieve major responses in patients with aggressive disease. 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 ^{131}I-ChL6 radioimmunotherapy in metastatic breast cancer (55).

There were clinical trials in patients with colorectal cancer and small volume metastases using ^{131}I-labeled humanized anti-CEA antibody hMN-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 malignant brain tumors (glioblastoma multiforme, anaplastic astrocytoma and anaplastic oligonendroglioma). ^{131}I-labeled anti-tenascin murine 81C6 monoclonal antibody (mAb) was injected directly into surgically created resection cavities and was followed by conventional external-beam radiotherapy and chemotherapy. Results of the study showed that RIT increased the median survival of patients with glioblastoma multiforme (57).

CONCLUSION

Today, ^{131}I therapy is the most effective therapy in the treatment of differentiated thyroid carcinomas (up to 95%). ^{131}I labeled compounds are less successful in patients with hepatocellular 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 therapeutic option is radioimmunotherapy. The specificity and low toxicity of monoclonal anti-

bodies make them attractive and desirable for the therapy of cancer. Monoclonal antibodies radiolabeled with radioiodine 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

This article has been presented in part as an invited lecture entitled: "Current concepts in systemic radioiodine therapy in endocrinology and oncology: indications, methods and follow up" at the International Siberian Conference: Modern Imaging in Clinics, 2000, June 29- - July 02, Tomsk, Russia.

REFERENCES

1. Goldsmith SJ. Thyroid carcinoma. In: Khalikhali I, Maublant JC, Goldsmith SJ, editors. Nuclear oncology: Diagnosis & Therapy. Philadelphia: Lippincott Williams & Wilkins; 2001. p.197-219.
2. Schlumberger MJ. Papillary and follicular thyroid cancer. N Engl J Med 1998;338:297-306.
3. Rosen IB. Partial Thyroidectomy. In: Clark OH, Noguchi S, editors. Thyroid cancer: Diagnosis and treatment. St. Louis, Missouri: Quality Medical Publishing, Inc.; 2000. p. 241-55.
4. Wartofsky L, Sheraman SI, Gopal J, Schlumberger M, Hay ID. Therapeutic controversy. The use of radioactive iodine in patients with papillary and follicular thyroid cancer. J Clin Endocrinol Metab 1998;83:4197-203.
5. Beierwaltes WH, Rabbani R, Dmuchowski C, Lloyd RV, Eyre P, Mallete S. An analysis of Ablation of thyroid remnants with I-131 in 511 patients from 1947-1984: Experience at University of Michigan. J Nucl Med 1984;25:1287-93.
6. Dietlin M, Moka D, Schicha H. Radioiodine therapy for thyroid cancer. In: Biersack H-J, Grunwald F, editors. Thyroid cancer. Second edition. Berlin Heidelberg: Springer-Verlag; 2005. p. 95-126.
7. Schlumberger M, Pacini F. Thyroid tumors. 2nd ed. Paris: Edition Nucleon; 2003.
8. Dietlein M, Moka D, Schicha H. Radioiodine therapy for thyroid cancer. In: Biersack H-J, Grunwald F, editors. Thyroid cancer. Berlin Heidelberg: Springer-Verlag; 2001. p. 93-120.
9. Cady B. Predictors of thyroid tumor aggressiveness. In Clark O, Duh Q, editors. Textbook of Endocrine Surgery. Philadelphia: WB Saunders; 1997. p. 197-204.
10. Jameson JL, Wetman AP. Disorders of the thyroid gland. In: Braunwald E, Fauci AS, Kasper DL, Hauser DL, Longo DL, Jameson JL, editors. Harrison's Principles of Internal Medicine (monograph on CD-Rom). 15th ed. New York: Mc Graw-Hill; 2001.
11. Mazzaferri EL, Kloos RT. Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86:1447-63.
12. Taylor T, Specker B, Robbins J, Sperling M, Ho M, Ain K, et al. Outcome after treatment of high-risk papillary and non Hurthle-cell follicular thyroid carcinoma. Ann Intern Med 1998;129:622-7.
13. Cavalieri R. Nuclear medicine. In: Clark OH, Noguchi S, editors. Thyroid cancer: Diagnosis and treatment. St. Louis, Missouri: Quality Medical Publishing, Inc; 2000. p.161-93.
14. Meier DA, Brill DR, Becker DV, Clarke SEM, Silberstein EB, Royal HD, et al. Procedure guideline for therapy of thyroid disease with ^{131}Iodine. J Nucl Med 2002;43(6):856-61.
15. Benua RS, Civale NR, Sonenberg M, Rawson RW. The relation of radiation dosimetry to results and complications in the treatment of metastatic thyroid cancer. Am J Roentgenol 1962;87:171-82.
16. Leeper RD. The effect of ^{131}I therapy on survival of patients with metastatic papillary and follicular thyroid cancer. J Clin Endocrinol Metab 1973;36:1143-52.
17. Mazzaferri EL. Radioiodine and other treatments and outcomes. In: Braverman LE, Utiger RD, editors. The thyroid. Philadelphia: Lippincott-Raven; 1996. p. 922-45.
18. Gross MD, Shapiro B. Adrenal scintigraphy. In: Khalikhali I, Maublant JC, Goldsmith SJ, editors. Nuclear oncology: Diagnosis & Therapy. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 461-74.
19. Stefanović Lj, Gudurić B, Šljapić N, Babić J, Miljković Lj, Malešević M, et al. Protocols of diagnostics, treatment and control of malignant thyroid tumors at the Institute of oncology in Sremska Kamenica. Onkološki arhiv 1994;2(2):101-7 (Serb).
20. Kushner BH. Neuroblastoma: A disease requiring a multitude of imaging studies. J Nuc Med 2004;45:1172-87.
21. Shapiro B, Fig LM, Gross MD, Shulkin BL, Sisson JC. Radionuclides in the diagnosis and treatment of malignant tumors.1. Neuroendocrine tumors. In: Atkolun C, Tauxe WN, editors. Nuclear oncology. New York: Springer-Verlag; 1999. p. 1-31.
22. Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei HY. Somatostatin receptor scintigraphy with [^{111}In-DTPA-D-Phel]- and [^{123}I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nuc Med 1993;20:716-31.
23. Shapiro. B. Summary, conclusions and future directions of (^{131}I) mataiodobenzylguanidine therapy in the treatment of neural crest tumors. J Nucl Biol Med 1991;35(4):357-63.
24. Hoefnagel CA, Voute PA, De Kraker J, Valdes Olmos RA. (^{131}I) metaiodobenzylguanidine therapy after conventional therapy for neuroblastoma. J Nucl Biol Med 1991;35(4):202-6.
25. Harbert JC. Nuclear medicine therapy. New York: Thieme Medical Publishers, Inc; 1987. p. 99-108.
26. Mihailović J, Malešević M, Stefanović Lj, Odavić M. ^{131}-J-MIBG for the treatment of Neuroblastoma - A Case Report (Serb). Med Pregl 1992;45:24-6.
27. Malešević M, Selir Z, Srbovan D, Popović V, Janković R, Grossman A, et al. Treatment of malignant paraganglioma in Zuckerkandl's region with 131-I-MIBG. Arch Oncol 1999;7(4):177-9.
28. Hardy MC, Bresard-Leroy M, Billy N. LIPIOCIS™ - a new approach of hepatocellular carcinoma treatment. CIS Bio International 1995.
29. Livraghi T, Bolondi L, Lazzaroni S, Morabito A, Rapaccini GL. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. Cancer 1992;9:25-92.
30. Honda N, Guo Q, Uchida H, Ohishi H, Hiasa J. Percutaneous hot saline injection therapy for hepatic tumors: an alternative to percutaneous ethanol injection therapy. Radiology 1994;90:53-7.
31. Kasugai H, Kojima J, Tatsuta M, Okuda S, Sasaki Y, Imaoka S, et al. Treatment of hepatocellular carcinoma by transcatheter arterial embolisation combined with intraarterial infusion of a mixture of cisplatin and ethiodized oil. Gastroenterology 1989;97:965-71.
32. Chatal J-F, Hoefnagel CA. Nuclear medicine: radionuclide therapy. Lancet 1999;354:931-5.
33. Buscombe JR. Hepatic artery infusion. Part A: Targeted therapy. In: Khalikhali I, Maublant JC, Goldsmith SJ, editors. Nuclear oncology: Diagnosis & Therapy. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 397-8.
34. Kobayashi H, Nakaio M, Shimabukuro K, Shirono K, Sakata H, Dyama T, et al. Possibility of radiotherapy of hepatic cancer by transcatether arterial embolisation with radioactive Lipiodol. Nippon Igaka Hoshasen Gakkai Zasshi 1984;44:96-8.
35. Raoul JL, Bourguet P, Bretagne JF, Duvauferrier R, Coornaert S, Darnault P, et al. Hepatic artery injection of I-131-Lipiodol. Part I. Radiology 1998;168:541-5.
36. Bretagne JF, Raoul JL, Bourguet P, Duvauferrier R, Deugnier Y, Faroux R, et al. Hepatic artery injection of I-131-Lipiodol- Part II. Radiology 1998;168:547-50.
37. Risse JH, Grunwald F, Kersjes W, Palmedo H, Biersack HJ. 2 years experience with the intraarterial I-131-Lipiodol therapy in hepatocellular cancer in Germany. Abstracts of 24th International Symposium, Badgastein, Austria. Eur J Nucl Med 2000;27(1):S85.
38. Stefanović Lj, Nikolić V, Obradović M, Selir Z, Mihoci Z, Mihailović J, et al. 131-I-Lipiodol in Treatment of Liver Carcinoma - Methodology and Case Report (Serb). Med Pregl 2000;54:387-90.
39. Lau WY, Leung TW, Ho SK, Chan M, Machin D, Lau J, et al. Adjuvant intra-arterial iodine-131 Lipiodol for respectable hepatocellular carcinoma. Lancet 1999;353:797-801.
40. Divgi CR. Radiolabeled monoclonal antibodies - Part B: Therapy. In: Khalikhali I, Maublant JC, Goldsmith SJ, editors. Nuclear oncology: Diagnosis & Therapy. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 93-101.
41. Kaminski MS, Zasadny KR, Francis IR, Milik AW, Ross CW, Moon SD, et al. Radioimmunotherapy of B-cell lymphoma with (^{131}I)anti-B1 (anti-CD20) antibody. N Engl J Med 1993;329:459-65.
42. Bienert M, Reisinger I, Srock S, Humplik BI, Reim C, Kroessin T, et al. Radioimmunotherapy using I-rituximab in patients with advanced stage B-cell non-Hodgkin's lymphoma: initial experience. Eur J Nuc Med 2005;32(10):1225-33.

43. Press OW, Eary JF, Badger CC, Martin PJ, Appelbaum FR, Levy R, et al. Treatment of refractory non-Hodgkin's lymphoma with radiolabeled MB-1 (anti-CD37) antibody. J Clin Oncol 1989;7:1027-38.

44. Kaminski MS, Fig LM, Zasadny KR, Koral KF, DelRosario RB, Francis IR, et al. Imaging, dopsimetry, and radioimmunotherapy with iodine 131-labeled anti-CD37 antibody in B-cell lymphoma. J Clin Oncol 1992;10:1696-711.

45. Press OW, Eary JF, Appelbaum FR, Martin PJ, Badger CC, Nelp WB, et al. Radiolabeled-antibody therapy of B-cell lymphoma with autologous bone marrow support. N Engl J Med 1993;329:1219-24.

46. Hennesy BT, Hanrahan EO, Daly PA. Non-Hodgkin lymphoma: an update. Lancet Oncol 2004;5:341-53.

47. Scott SD. Rituximab: a new therapeutic monoclonal antibody for non-Hodgkin's lymphoma. Cancer Pract 1998;6:195-7.

48. Behr TM, Wormann B, Gramatzki M, Riggert J, Gratz S, Behe M, et al. Low-versus high-dose radioimmunotherapy with humanized anti-CD22 or chimeric anti-CD20 antibodies in a broad spectrum of B-cell associated malignancies. Clin Cancer Res 1999;5:3304s-14s.

49. Boucek JA, Turner JH. Validation of prospective whole-body bone marrow dosimetry by SPECT/CT multimodality imaging in ^{131}I-anti-CD20 rituximab radioimmunotherapy of non-Hodgkin's lymphoma. Eur J Nucl Med 2005;32(4):458-69.

50. Wahl RL. Monoclonal antibody therapy. Section N. Hodgkin's disease and Non-Hodgkin's lymphoma. In: Khalikhali I, Maublant JC, Goldsmith SJ, editors. Nuclear oncology: Diagnosis & Therapy. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 493-508.

51. Friedberg JW, Fisher RI. Iodine-131 tositumomab (Bexxar): radioimmunoconjugated therapy for indolent and transformed B-call non-Hodgkin's lymphoma. Expert Rev Anticancer Ther 2004;4(1):18-26.

52. Vallabhajosula S, Smith-Jones PM, Navarro V, Goldsmith SJ, Bander NH. Radioimmunotherapy of prostate cancer in human xenografts using monoclonal antibodies specific to prostate specific membrane antigen (PSMA): studies in nude mice. Prostate 2004;58(2):145-55.

53. Goldsmith SJ, Bander NH. Monoclonal antibody therapy. In: Khalikhali I, Maublant JC, Goldsmith SJ, editors. Nuclear oncology: Diagnosis & Therapy. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 433-9.

54. Juweid ME, Goldenberg DM. Medullary cancer of the thyroid: radiolabeled antibody therapy. In: Khalikhali I, Maublant JC, Goldsmith SJ, editors. Nuclear oncology: Diagnosis & Therapy. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 245-50.

55. DeNardo SJ, Cagnoni PJ, Wong JYC, Richman C. Radionuclide therapy. In: Khalikhali I, Maublant JC, Goldsmith SJ, editors. Nuclear oncology: Diagnosis & Therapy. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 331-42.

56. Goldenberg DM. Radiolabeled antibody detection and therapy. In: Khalikhali I, Maublant JC, Goldsmith SJ, editors. Nuclear oncology: Diagnosis & Therapy. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 361-72.

57. Akabani G, Reardon DA, Coleman RE, Wong TZ, Metzler SD, Bowsher JE, et al. Dosimetry and radiographic analysis of ^{131}I-labeled anti-tenascin 81C6 murine monoclonal antibody in newly diagnosed patients with malignant gliomas: a phase II study. J Nucl Med 2005;46(6):1042-51.