Review article
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An overview of *Regional training course on therapeutic nuclear medicine*

Milena RAJIĆ

DEPARTMENT OF NUCLEAR MEDICINE, CLINICAL CENTER OF NIŠ, SERBIA AND MONTENEGRO

Regional training course on therapeutic nuclear medicine was held in Romania in 2002, in the organization of International Atomic Energy Agency. The program covered several topics from oncology, with great attention paid to the treatment of differentiated thyroid cancer, lymphoma, inoperable hepatocellular carcinoma, neuroendocrine tumors and bone pain caused by metastases. Usage of new radionuclides was also promoted with the aim to improve therapy with open sources of radioactivity. Particular attention was paid to the outcome of high and small dose of radioactive iodine (^{131}I) for remnant ablation, to the use of recombinant human TSH in postoperative follow-up, and to radionuclide therapy for non-iodine concentrating thyroid cancers. A new radiopharmaceutical, ^{188}Re (^{188}rhenium)-lipiodol, already used to treat 30 patients, was promoted and pointed to developing of other radioagents for the cure of inoperable hepatocellular carcinoma. Because the treatment of lymphoma with radiolabeled antibodies was proved as successful, it was noted that approach could become an important part of therapeutic nuclear medicine over the next couple of years. Targeting therapy for bone pain palliation was shown as relatively cheap and successful, but future possibilities should integrate the use of bone-seeking radiopharmaceuticals at an earlier stage in patients at high risk for developing metastases to avoid their occurrence. This training course pointed out some new radiopharmaceuticals and radionuclides, which predict a further rapid development of therapeutic nuclear medicine and its deeper integration in protocols for the treatment of patients with malignant diseases.

KEY WORDS: *Nuclear Medicine; Radioimmunotherapy; Radioisotopes; Thyroid Neoplasms; Liver Neoplasms*

Regional training course on therapeutic nuclear medicine was held in Romania in 2002, in the organization of International Atomic Energy Agency, Department of Technical Cooperation, and covered these main topics from oncology:

1. Radionuclide treatment of thyroid and liver cancer
2. Radioimmunotherapy
3. Peptide therapy
4. Radionuclide treatment of metastatic bone pain and
5. Radionuclide treatment of polycythemia rubra vera and essential thrombocythemia

Apart from radionuclide therapy in oncology, the new accomplishments in endocrinology, rheumatology and cardiology were also discussed, such as radionuclide treatment of hyperthyroidism, radiosynovectomy and prevention of restenosis after percutaneous transluminal coronary angioplasty.

Operative treatment, role of radioactive iodine (^{131}I) for thyroid remnant ablation and treatment of metastases after thyroidectomy, thyroid hormone therapy, external-beam radiotherapy, and chemotherapy were discussed in patients with differentiated thyroid cancer (DTC). Particular attention was paid to the effect of high and small dose for remnant ablation, use of recombinant human TSH (rh TSH) in postoperative follow-up, advantages of diagnostic whole body scan (WBS) with ^{123}I over ^{131}I, and radionuclide therapy of non-iodine concentrating thyroid cancers. The dose of 1850 MBq of ^{131}I was suggested as optimal for remnant ablation following thyroidectomy in patients with differentiated thyroid carcinoma. It represents an effective compromise between a high dose with higher radiation exposure and repeated hypothyroidism caused by multiple small doses. This was documented by the results of Bal et al. (1), who showed successful ablation in 77.8% of patients that received 1872 MBq, and no further increment in the overall success rate of remnant ablation with

Address correspondence to:

Doc. Dr. Milena Rajić, Department of Nuclear Medicine, Clinical Center of Niš, Braće Taskovića 48, 18000 Niš, Serbia and Montenegro, E - mail: mrajic@EUnet.yu

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the increment of the dose (in 76.7% of patients that received 5735 MBq).

In postablation follow-up, the values of both WBS with ^{131}I and thyroglobulin (Tg) level after rh TSH (Thyrogen) application and thyroxin withdrawal were compared. Thyrogen is used to induce a rise in TSH without the need to stop thyroxin therapy and, therefore help to improve accumulation of diagnostic and therapeutic dose of radioiodine in the cells of thyroid origin and, also stimulates releasing of Tg from these cells. In the study of Haugen et al. (2), 229 patients with DTC were underwent rh TSH application and thyroxin withdrawal followed by WBS and Tg assay.

Whole body scans were concordant in 89% patients using both strategies, in 4% superior, but in 7% inferior following rh TSH. Based on high Tg (>2 ng/ml), thyroid tissue or cancer was detected in 52% after rh TSH and in 56% patients after thyroxin withdrawal in thyroid bed and in 100% patients using both strategies in metastatic disease. So, it was concluded that Thyrogen produces comparable diagnostic information as hypothyroid state, and is very helpful for patients who become unwell when thyroxin is stopped. Thyrogen is applied intramuscularly in two consecutive days in the dose of 0.9 mg. On the third day TSH has to be assayed, and if it is above 30 mU/l radioiodine is applied. Whole body imaging is done and Tg is measured on the day 5 or 6.

Radioactive ^{123}I enables visualization of metastases even in the presence of thyroid remnant (3), and does not cause "stunning" effect because of its low burden. The latter may optimize the success of subsequent ^{131}I therapy and therapeutic dose of ^{131}I may be given after 24 h. Because of these properties, ^{123}I is considered as superior over ^{131}I for imaging of patients with DTC.

A great clinical problem is how to treat the patients with DTC who have negative WBS with radioiodine but elevated Tg level. In those patients metastases can be detected by ultrasound, computerized tomography (in chest and abdomen), magnetic resonance (in brain), bone scintigraphy, as well as by alternative non-iodine imaging. Alternative radioagents, such as $^{201}TlCl_2$ (^{201}thallium-chloride), ^{99m}Tc (^{99m}technetium)- sestamibi/tetrofosmin, ^{18}F-FDG (^{18}fluorine-fluorodeoxyglucose), and ^{111}In (^{111}indium)-octreotide/lanreotide enable visualization of the lesions that do not concentrate radioiodine with sufficient sensitivity and specificity. If WBS is positive with these agents, in some institutions, therapeutic dose of ^{131}I is applied because post-therapeutic scans may show accumulation of radioiodine in regional and distant metastases (4). Patients with positive diagnostic scan with ^{111}In-octreotide can be treated with ^{111}In- octreotide or ^{90}Y (^{90}yttrium)-octreotide (3330 to 7400 MBq separated by 4-6 weeks), and patients with positive scan with ^{111}In-lanreotide may be treated with ^{90}Y-lanreotide.

Radionuclide therapy of medullary thyroid carcinoma is reserved for disseminated tumors.

Metaiodobenzylguanadine (MIBG) labeled with ^{131}I is used in patients where MIBG uptake is present. Symptomatic response rather than objective remission is recorded in 50% of treated patients with response time up to 18 months. Therapy with ^{111}In - octreotide is performed in tumors that express somatostatin receptors. Therapy with ^{90}Y-DOTA octreotide is in experimental phase. Therapy with dimercaptossucinic acid labeled with ^{188}Re or ^{186}Re is in progress.

Inoperable hepatocellular carcinoma has been treated with ^{131}I-lipiodol since the 80s, and up to now over 500 patients in France, 300 patients in United Kingdom and 100 patients in Hong Kong were treated. Dr. Buscombe reported experience with radiolipiodol in Royal Free Hospital (London), where 240 patients were treated in the past 13 years (400 treatments). Average post-therapy survival was 18 months, 50 patients are still alive, some of them over 5 years. Deaths were mainly caused by coexistent liver diseases, and only five persons, all with Okuda 2 stage, died due to treatment-induced acute radiation hepatitis. Radiopharmaceutical of choice could be ^{188}Re-lipiodol, which was used to treat 30 patients in Singapore, Vietnam, Columbia, and Mongolia. Results of the first phase of the prospective study of transarterial use of 188Re-lipiodol in the treatment of inoperable hepatocellular carcinoma showed that 13 of 16 patients are alive six months following therapy (5). Partial response was noted in one, progression in two, and a stable disease in 13 patients. Tumor reduction was registered in four and adverse effects in twenty patients (nausea, vomiting, fewer, discomfort in right hypochondrium).

There is a need for standardization of the labeling procedure and establishment of efficacy of ^{188}Re-lipiodol, as well as for developing of the other radioagents, such as ^{188}Re-microspheres, ^{166}Ho (^{166}holmium)-microspheres and ^{166}Ho-cithosan.

Radioimmunotherapy is limited, especially for solid tumors, because of heterogenic intratumoural distribution of radiopharmaceutical, low target to non-target ratio, dilution factor and production of human antimouse antibodies. Infusion of "cold" antibodies one week before infusion of labeled antibodies is recommended to block circulating stem cells with the same antigen which lead to better targeting effect on tumor. Steroid cover may need to be given if there is an antibody reaction. Radioimmunotherapy is successful for treatment of radiosensitive tumors such as lymphomas and melanomas. Refractory B-cell non-Hodgkin's lymphoma, which is CD20 positive, is treated with ^{131}I/^{90}Y-anti CD20 antibodies, and response to therapy is registered in 60%-80% patients (6-8). B-cells lymphoma, which is CD22 positive, could be treated with ^{131}I-anti CD22 antibodies. Response to therapy in T-cell lymphoma is lower (in 30%-40% patients), if CD25 positive lymphoma is treated with 131I-anti CD25 antibodies. Apart from ^{131}I and 90Y, antibodies could be labeled with ^{67}Cu (^{67}copper),

for which is thought to have higher retention in tumor. Treatment of lymphoma will become an important part of therapeutic nuclear medicine over the next couple of years.

Neuroendocrine tumors that possess somatostatin receptors may be treated with radiolabeled somatostatin analogues. Because of their nephrotoxicity it is necessary to protect kidneys with simultaneous infusion of amino acids. The greatest experience in therapy of these tumors with ^{111}In-octreotide has in Rotterdam (9). Disease progression was registered in 17, good response to therapy in five, and partial response in 18 of 40 patients. All ^{90}Y products (octreotide, lanreotide and octreotate) use DOTA to link ^{90}Y onto peptide chain. The greatest experience in usage of ^{90}Y-octreotide has been achieved in Switzerland, where up to now 300 patients have been treated with a response to therapy in 60% of patients. After 3 cycles of 27 MBq of ^{90}Y-lanreotide (154 patients in multi-center trial) above one half of patients have sustained response and 14% have tumors shrinking (10). In Royal Free Hospital in London ^{90}Y-lanreotide was infused in hepatic or carotid internal artery in 13 patients with liver and brain metastases. Disease regression was noted in 61% patients during 6 months. Perspectives of peptide therapy are to find more peptides and better isotopes, e.g., gastrin-based peptides, antivascular endothelial growth factor, and metalloproteinase inhibitor, as well as ^{177}Lu (^{177}lutenium).

Bone pain palliation requires a multidisciplinary approach.

Indication for targeting therapy using bone-seeking radiopharmaceuticals is refractory bone pain due to multi-site metastases that are visualized as "hot" spots on skeletal scintigraphy in patients who do not respond on analgesics or anticancer therapy. This treatment is relatively inexpensive and successful due to acting systemically allows multiple sites to be treated simultaneously with relative sparing of healthy surrounding tissues. Hopeful results have been obtained combining radionuclide with chemotherapy that led to prolonged life of patients with prostate carcinoma, suggesting a tumorocidal effect (11). Future possibilities included the use of bone-seeking radiopharmaceuticals at an earlier phase in patients at high risk for developing metastases to prevent their occurrence. Most commonly used radiopharmaceuticals are ^{89}Sr (^{89}strontium)-chloride, ^{32}P (^{32}phosphorus)-phosphate, ^{153}Sm-EDTMP (^{153}samarium-ethylene diamine tetramethylene phosphonate), ^{186}Re-HEDP (hydroxyethylidine diphosphonate), and ^{117}Sn-DTPA (^{117}tin-diethylenetriaminepentaacetic acid) (12). Palliative effect is similar for all of them and occurs in 60% to 80% patients. The higher doses emitted by short-living radionuclides (^{153}Sm and ^{186}Re) lead to earlier pain relief, so they are recommended to be applied in patients who require faster pain relief. However, the lower doses of long-living isotopes (^{89}Sr and ^{32}P) resulting in longer effect are given to patients with expected longer survival.

Radioactive ^{32}P did not lose its significance for treating polycythaemia rubra vera (PRV) and essential trombocythaemia (ET) in patients who do not tolerate repeated phlebotomy and are older than 60 years for PRV and 50 years for ET. It is applied as fixed dose (111 MBq/m^2), and repeated dose may be administered every three months until an adequate response is obtained.

To take steps to improve radionuclide therapy are also usage of "new" radioisotopes. Usage of ^{188}W (^{188}tungsten)/^{188}Re and ^{225}Ac (^{225}actinium)/^{223}Bi (^{223}bismuth) generators are promoted. Physical half-life of ^{188}W is 69 days and duration of the generator is 4-6 months (elution in 24 h intervals). Eluted ^{188}Re has half-life of 16.9 h, beta particles has energy of 2.12 MeV and gamma rays of 155 KeV that enables posttherapy imaging. Radionuclide ^{223}Bi is alpha emitter. A long half-life of ^{225}Ac (10 days) enables long usage of this very expensive device. Four elutions are possible during 9 hours.

Regional training course on therapeutic nuclear medicine pointed out new radiopharmaceuticals and radionuclides, which indicate a further fast development of therapeutic nuclear medicine and its better incorporation in protocols for treatment of patients with malignant diseases. On the other hand, a great experience and good results in the treatment with some wide used agents gave insight in their suitability in management of cancer patients.

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