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Therapeutics in Nuclear Medicine

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From the Desk of Director Research

Therapeutic nuclear medicine is rapidly developing as an additional treatment modality. Oncology applications of nuclear medicine have entered into a new era as a result of greater understanding of the biological characteristics of tumors. In recent years, there has been greater emphasis on "targeted therapies", designed to affect only the cancerous cells. There are currently hundreds of new pathway-targeted anticancer agents undergoing phase II and phase III clinical trials. Targeted radionuclide therapy is just one among the category of "targeted therapies." At present, effective targeted radiopharmaceutical therapeutics have been developed and validated for a few tumor types, such as malignant lymphoma; and many other tumor types. The older nonspecific types of cancer treatments are still the dominant form of therapy.

Radionuclide therapy is changing dynamically. Monoclonal antibody therapies for non-Hodgkins lymphoma using I-131; or imaging with Indium-111, followed by yttrium-90, are the next wave of a new generation of therapies. The basis of radionuclide therapy is simply the placement of the radionuclide in intimate contact with the target tissue. Particularly if short-range particle emitters are used, the absorbed dose to the target is very high as compared to non-target tissues. The route of administration may also pose different radiation safety issues. Oral or intravenous administration of radionuclides is very common, but other methods of administration also exist, such as insertion directly into a body cavity.

Radionuclides are also gaining increasing importance by providing palliative and curative treatment in an increasing number of malignant diseases. Majority of radionuclides used in radionuclide therapy emit beta particles which have a low range of tissue penetration. A few emit auger electrons and alpha particles, and several others emit gamma rays and X-rays during their decay. The most successful radionuclide for thyroid therapy uses Iodine-131 as the nuclide for the treatment of benign hyperthyroid conditions, thyroid carcinoma, and peptidoreceptor radionuclide therapy (PRRT) for Neuroendocrine tumors. Both of which are successfully practiced.

The present issue of Cancer News"Nuclear Medicine: Beyond Diagnostic" highlights the newer advances in the field of Radionuclide Therapy in cancer and features the regular articles, such as Special Feature, Guest Article, Perspective, In Focus, Research and Development, New Technologies, Globe Scan, In Focus and Clinical Trial.

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Suggestions/ comments from the readers are welcome.

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SPECIAL FEATURE

OVERVIEW OF PET/CT IN RADIOTHERAPY PLANNING

Introduction

Positron Emission Tomography (PET) is the use of radiopharmaceuticals labelled with positron emitters (radiation) to study physiologic processes in the body. This is opposed to CT which provides three-dimensional anatomical detail. The combination of PET and CT in an integrated scanner since the 1990's has allowed the fusion of physiological and anatomical information on the disease to be viewed in one image, and can, therefore, be used in radiotherapy planning. The most useful utility of PET has been improved staging, restaging and therapeutic monitoring of the disease. PET imaging with various radiotracers takes advantage of the phenotypic changes that occur in cancer cells to identify protein/ receptor expression and metabolic changes that are specific for tumors or are overexpressed compared to normal tissue.

Since the 1920s, cancer cells have been shown to demonstrate an increased rate of glycolysis, requiring more glucose. Fluoro-2-deoxyglucose is molecularly similar to glucose which is transported into cells via GLUT1 receptors, where it is phosphorylated by hexokinase but remains trapped within the cells as fluoroglucose-6-phosphate which cannot enter the glycolytic pathway. When labeled with ^{18}F, the molecule is able to be detected by PET scanner which is increased in tumor cells due to increased GLUT1 receptors in tumour cells. ^{18}F-FDG PET has been shown to be the most accurate non-invasive method to detect and stage many types of cancers. This has resulted in the improvement of patient management, avoiding unnecessary treatments and associated morbidity and costs.

Radiotherapy is the use of ionizing radiation to treat cancer by targeting cancer cells in a particular radiation field. Although this inevitably includes normal cells surrounding the cancer cells, the normal cells can recover from the radiation, but not the cancer cells. Radiotherapy is usually given with curative or palliative intent, and the dose given does depend on tumor type and the surrounding tissues/organs. The advancement of technology to incorporate both structural imaging with

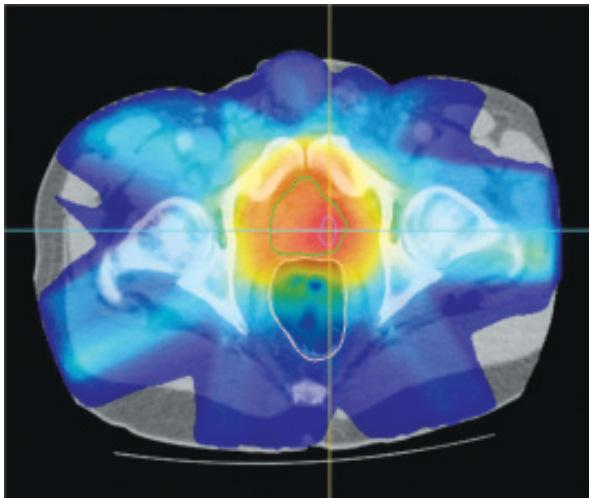

Fig 1: Example of 3D conformal radiotherapy. Higher doses provided to the tumor (orange) than surrounding tissues in the treatment field

CT or MRI, either in the same scanner system or with software registration, has allowed the integration of functional imaging obtained on PET with structural imaging provided by CT or MRI, to enable image-guided radiotherapy (IGRT).

Radiotherapy planning has evolved over time, initially with the use of conventional x-ray which mimics optical and alignment properties of a linear accelerator, with contours done along the central axis of the beam and digitized into the treatment planning computer. This includes standard external beam radiotherapy, conformal 3D-radiotherapy and intensity modulated radiotherapy (Fig 1). In conformal 3D-radiotherapy, there is no variation in intensity across each beam. More recently, there has been an explosion in the use of "Intensity Modulated Radiotherapy" (IMRT), in which advanced 3D high precision radiotherapy is provided using computer controlled linear accelerators to deliver precise doses to specific areas within a tumor. The dose conforms more precisely to a 3D shape of the tumor by controlling the intensity of the radiation mean in multiple small volumes, and allows the concentration of certain doses within certain areas of the tumor, whilst minimising the dose to the surrounding normal tissue. The ratio of normal to tumor tissue dose is reduced, resulting in a higher and more effective radiation dose to tumor, with fewer side effects. IMRT is most extensively used to treat prostate, head & neck and CNS malignancies, with increasing use in other solid tumors.

PET in Radiotherapy Planning

The use of FDG PET imaging has had a significant impact on approximately 30-50% of disease

Table 1: Non-FDG PET Radiopharmaceuticals Used in Oncology

Radiopharmaceutical	Tumour Biology	Clinical Applications
^{18}F-FDG	Glucose Metabolism	All tumours
^{11}C-methionine ^{11}C-choline ^{18}F-DOPA ^{18}F-methyltyrosine (MET)	Proteins/amino acids	Brain tumour Prostate cancer Carcinoid tumour Musculoskeletal tumour
^{18}F-thymidine (FLT)	DNA Proliferation	Treatment response (all)
^{18}F-annexin V	Apoptosis	Treatment response (all)
^{18}F-misonidazole (FMISO)	Hypoxia	Radiation planning (all)
^{18}F-estradiol	Receptor binding	Breast cancer
^{18}F-acetate	Membrane/lipid synthesis	Hepatocellular carcinoma

management[1], particularly in the appropriateness and type of surgery, chemotherapy or radiotherapy in patients. PET/CT has been the modality with the most significant effect on radiotherapy planning recently, with an estimated 55-60% of patients who have functional imaging, have potential changes in the target volumes and/or dose distribution parameters. Whilst this most commonly refers to FDG, other radiopharmaceuticals are also used to assess underlying tumor biology (Table 1), which is beyond the scope of this article. PET/CT has been shown to improve disease diagnosis and staging, assist in tumor volume delineation, define tumor phenotype or biological tumor volumes, to assess treatment response and in-beam monitoring of radiation dosimetry (Table 2).

The use of 3D conformal radiotherapy has resulted in a need to identify the optimal viable regions for boosting radiation dose. PET has emerged as one of the most accurate methods to identify viable tumor in masses seen on CT/MRI, and the incorporation of PET data into treatment planning has been shown to improve the accuracy of dose delivery and outcomes in treated patients. ^{18}F-FDG PET has been shown to improve target volume, and assist in avoidance of relapse due to undiagnosed nodal or distant metastases, in a range of tumours including lung cancer and head and neck cancer (Fig 2) [2-4].

In addition, the incorporation of PET/CT data directly into radiation treatment planning systems has been demonstrated to markedly improve the accuracy of radiation delivery to tumour. This is an area of continued development and it is likely that PET/CT will have an increasingly important role in radiotherapy of malignancy in the future.

PET-based tumor volumes are strongly affected by the choice of threshold and result in significant changes in target radiation dose [5]. Various methods, including an automated contouring function based on progressively greater threshold levels to the co-registered PET/CT images of eight head and neck cancer patients and to a

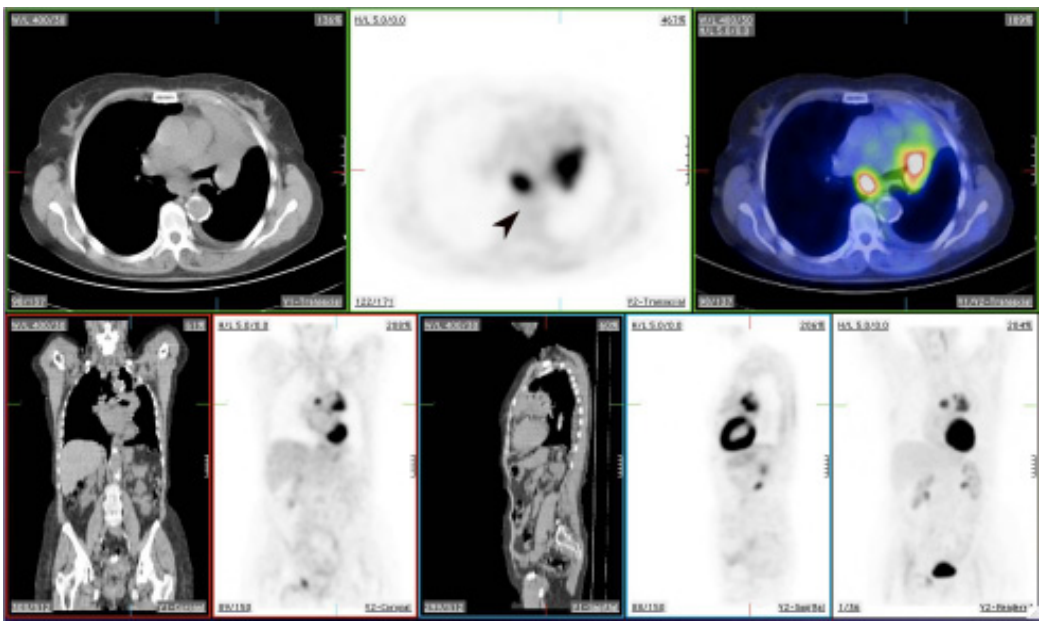

Fig 2: PET/CT for staging in a patient with non-small cell lung carcinoma, where a subcarinal node (arrow) was identified on PET/CT.

phantom containing 6 FDG-filled spheres, and intensity-modulated radiation therapy and boost plans were developed for all Gross Tumour Volumes (GTV). There is a significant effect on GTV as a result of choice of threshold level which translated into significant dose variations. However, routine therapy plans include a margin around the GTV to allow for microscopic extent of disease (Clinical Tumour Volume – CTV), followed by a further margin around that to include day-to-day variations in setup, known as Planning Tumour Volume (PTV) which is the prescribed dose [6].

In head and neck carcinoma, IMRT is shown to be most promising, enabling the delivery of complex dose distributions, at multiple dose of and at different risk regions, whilst sparing critical structures nearby (eg. carotid artery). It has been shown to be excellent for locoregional control and for identifying or excluding nodal metastasis [7].

In non-small cell lung carcinoma, a dose of >70Gy with conventional fractionation is required for local control, with the dose limiting organs being the normal lung and spinal cord. However, with IMRT, doses of 10-20 Gy to the normal lung are possible, resulting in no significant lung toxicity. Several physics and dosimetry studies have compared 3-D CRT and IMRT treatment plans for the treatment of locally advanced lung cancer, with the resulting dose distributions and dose volume histograms showing better sparing of normal tissues with IMRT, thereby enabling to deliver lower doses to the healthy lung, oesophagus, heart, and spinal cord [8-10]. In addition, higher doses of radiotherapy delivered to the cancer, result in improved local cancer control [11,12]. Newer techniques such as stereotactic body radiotherapy, use extreme hypofractionation schedules and strict target margins (to ~0.5cm) with good results.

The most significant issue concerning providing radiotherapy to the lung is that respiratory motion and general setup error results in a significantly larger PTV, as the PTV margin must be drawn to encompass the entire range of motion. More recently, methods to reduce the effect of respiratory motion have been developed including breath hold during treatment, "gating" in which the beam is turned on or off in synch with the respiratory cycle [13], and "tracking" in which the beam follows the tumor based on imaging technology [14,15]. Planning is performed using a 4D CT, ie, a CT that takes multiple volumetric images and sorts them according to the breathing cycle to produce a 3D movie loop, and the 4th dimension refers to time [16]. Similar technology is currently being applied to PET/CT systems [17,18]. Internal target volumes generated from 4D-PET MIP better match than CT-MIP compared to ungated PET images, based on the metrics of volumetric overlap and relative volumes and visual interpretation [19]. Respiratory gated-PET/CT in lung cancer can affect the volume and shape of PTV, as demonstrated by the assessment of gated PTVs outside standard PTV. Therefore the use of a gating technique is thus crucial for better delineating PTV by tailoring the target volume to the lesion motion in lung cancer patients [20].

In the gastrointestinal system, FDG PET has been most commonly used to stage and monitor the treatment of oesophageal carcinoma and rectal carcinoma. In oesophageal carcinoma, the addition of FDG PET has resulted in a change of tumor volume in 57% patients, which could have potentially resulted in underdosing and ineffective treatment [21]. In rectal carcinoma, not only has the inclusion of FDG PET resulted in the change in staging and tumor delineation, when the PTVs were compared to MRI-generated PTVs, the PET-generated PTVs also had a better correlation with complete pathological response on subsequent resection [22]. Increasing use of IMRT in the treatment of rectal carcinoma has seen the prescription of focal dose escalation to FDG-avid regions while providing normal tissue protection in patients with postoperative local recurrent rectal cancer [23].

In gynaecological cancers, the primary use of FDG PET has been in treatment planning of cervical and endometrial carcinomas, particularly by detecting positive pelvic and para-aortic nodes [24-26]. IMRT planning using FDG PET can also affect the definition of primary tumour in cervical carcinoma [27,28], whilst FDG PET has also been used to assist in target definition for brachytherapy [29].

Accurate and early assessment of response to therapy is crucial in the current practice of oncology, which is principally being performed with ^{18}F-FDG. Accurate evaluation of response to both chemotherapy and radiotherapy, which often occurs prior to anatomical changes on CT scans, have been reported in many tumor types, including glioma, colorectal, non-small cell lung carcinoma, lymphoma, head and neck tumors, and soft tissue sarcomas [30-36]. PET can provide information on response to therapy earlier than most conventional imaging

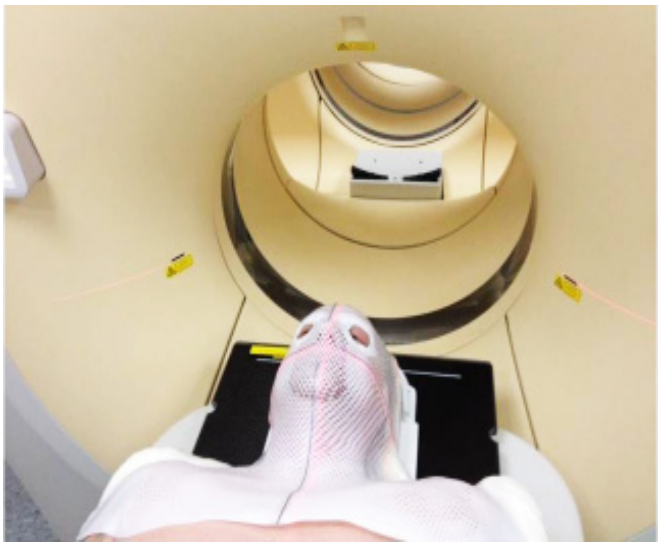

Figure 3: Patient for head & neck radiotherapy in planning mask, on flat bed and laser positioning in place

techniques, therefore providing earlier confirmation of the efficacy of the chosen treatment, or alternatively allowing an early change to alternate treatments that may have better efficacy and survival. The timing and reliability of ^{18}F-FDG PET studies in predicting tumour response is the subject of numerous prospective studies. The implications of this approach are significant in terms of optimizing treatments, minimizing unnecessary morbidity and reducing costs.

Practicalities of PET/CT in Radiotherapy Planning

In order to maximize the use of PET in radiotherapy planning and treatment, there needs to be a close collaboration between the PET and radiotherapy departments, with jointly developed imaging protocols incorporating the optimal requirements of a PET scan for these purposes. For starters, physical co-location is critical to allow for exchange of knowledge between personnel, use of ancillary equipment and common imaging protocols and easier data transfers. This will not only improve patient experience, but improve geometric accuracy with potentially higher cure rates and ultimate cost savings.

The invention of hybrid PET/CT scanners is ideal for image guided radiotherapy planning. It allows 'perfect' image co-registration, which is reproducible with lasers, placement of fiducial markers and temporary/permanent tattooing as appropriate. There needs to be regular and close interaction between the department personnel to develop imaging protocols, co-registration of images, accurate determination of tumor volumes, tumor staging, and overall management decisions within the context of a multidisciplinary environment is also imperative of optimal patient treatment and management.

Table 2: Role of PET/CT imaging in Radiotherapy Planning

Tumour staging (up or down) - change in treatment intent
Treatment field modifications - inclusion of locoregional nodal disease
Localised symptom control
Sites or residual or metastatic disease
Therapy response evaluation

There are aspects of using hybrid PET/CT scans for radiotherapy planning which need to be considered, the most important being contouring, which requires detailed protocol consistent co-registration with suitable windowing of the images in consultation with a nuclear medicine physician in order to recognise various processes which may lead to FDG uptake (such as infection, inflammation, physiologic brown fat activity, movement artifacts, etc). The ability to recognise local treatment failure is also extremely important. Consideration must also be given to the use of contrast (IV or oral) for radiotherapy planning of several tumour sites which improves the accuracy of PET/CT in specific scenarios. In particular, diagnostic quality, multiphase CT imaging acquisition may need to be considered, with low density oral contrast agents to be used to aid in the evaluation of gastrointestinal FDG uptake.

Logistically, patients with specific probability of requiring definite radiotherapy are booked for PET/CT scan on the same day as a radiotherapy appointment. The preparation for the PET/CT is the same as for a routine PET/CT. The patient is positioned in the radiotherapy treatment position on the flat top radiotherapy planning table, with localization lasers and immobilization aids integrated into the scanner (Figure 3). Other aids such as skin marks (tattoos), internal contrast, temporary skin fiducials or positioning aids, can also be utilized. Acquisition protocols are optimised to allow accurate PET/CT fusion and dataset transfer to the radiotherapy planning workstation, for the radiotherapy team to use for planning. New generation hybrid PET/CT scanners can allow for lower doses of FDG and low dose CT scans to be used more regularly for treatment planning.

Conclusion

PET/CT scans have a crucial role in radiotherapy planning, with the ability to improve staging, improve target delineation, and reduce the dose to surrounding normal tissue. Logistics and close collaboration between the PET department and radiotherapy departments are crucial to an effective setup. Whilst non-FDG radiotracers

have not been elaborated in this article, novel radiotracers improve the understanding of underlying tumor biology which allows specific targeting of target tumors, potentially leading to better patient outcomes.

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GUEST ARTICLE

TARGETED METABOLIC THERAPY OF NEUROENDOCRINE TUMORS BY I-131 MIBG

Historical Perspective

The development of radionuclide therapy for neuroendocrine tumors by metabolic tumor targeting with radioiodinated meta-iodobenzylguanidine (MIBG) dates back to the 1960's, when Prof William Beierwaltes and colleagues at the University of Michigan worked on the development of tracers for the adrenal cortex and medulla and the heart. Using ^{14}C-epinephrine for neuroblastoma (1967) and ^{14}C-dopamine for pheochromocytoma (1973) initially, they switched to radioiodinated bretylium analogs and quaternary ammonium derivatives for the purpose of imaging. In 1980, the imaging of the dog's adrenal medulla by ^{131}I-para-iodobenzylguanidine was described and in 1981, Sisson et al reported the scintigraphic diagnosis of pheochromocytoma in man by ^{131}I-meta-iodobenzylguanidine (MIBG).

Subsequently, ^{131}I-MIBG with low and high specific activity (for imaging and therapy, respectively) became commercially available in Europe and since 1984 on, several groups have reported its successful use for scintigraphy and therapy of pheochromocytoma, paraganglioma, neuroblastoma, carcinoid tumors and medullary thyroid carcinoma. In 1987, ^{123}I-labeled MIBG became available, which had better imaging properties allowing SPECT. This proved to be a good cardiac agent too, as a specific tracer for sympathetic innervation of the myocardium. By 1999, combined therapeutic results in 534 patients demonstrated objective response rates of around 50% in malignant pheochromocytoma, paraganglioma, as well as in children with neuroblastoma, refractory to other forms of treatment. In contrast, in carcinoid tumors and medullary thyroid carcinoma, objective reponses were far fewer or even absent, although stabilization of disease, metabolic effects and palliation were observed in about 60% of the patients as also associated with significantly prolonged survival.

Targeting Mechanisms

Neuroendocrine tumors, like pheochromocytoma, neuroblastoma, carcinoid, paraganglioma, chemodectoma, medullary thyroid carcinoma, islet cell tumors, gastrinoma, small cell lung cancer, melanoma and Merkel cell tumor, vary considerably in their clinical presentation, location and histology, but do have in common their origin in the same embryonic tissue, i.e. the neural crest. Therefore, they express several unique characteristics, which may be utilized to target radiopharmaceuticals, both for diagnosis and therapy of these tumors [1]. Specific targeting of neuroendocrine tumors may be achieved via the metabolic route (MIBG), receptor binding (peptides) or the immunological route (antibodies).

Both ^{123}I- or ^{131}I-MIBG and ^{111}In-pentetreotide, being sensitive and highly specific tracers, are the most widely used. Comparative studies demonstrate the complementary role of these procedures [1].

An active uptake 1 mechanism at the cell membrane and neurosecretory storage granules in the cytoplasm of neural crest tumors are responsible for the uptake and retention of ^{123}I- or ^{131}I MIBG, respectively. Although the radiopharmaceutical may be released from the granules, reuptake through this specific mechanism maintains prolonged intracellular concentration, in contrast to nonadrenergic tissues which rely on passive diffusion only; this results in high tumor/non-tumor ratio's. A number of drugs may in-ter-fere with the uptake and/or the retention of MIBG.

Adrenergic Radiopharmaceuticals for Imaging and Therapy

For conventional scintigraphy of the whole body, either ^{123}I-MIBG (α-emitter, $T_{1/2fys}$=13h, photonenergy 159 Kev) or ^{131}I-MIBG (β/γ-emitter, $T_{1/2fys}$=8d, photonenergy 364 KeV) may be used. ^{123}I-MIBG scintigrams have better quality and results are more readily available, whereas ^{131}I-MIBG enables delayed imaging over several days; SPECT/CT using ^{123}I-MIBG enables improved detection, as well as accurate localization of neuroendocrine tumor sites by hybrid imaging.

PET/CT and/or PET/MR using novel, specific PET tracers, e.g. ^{124}I-MIBG, ^{11}C-hydroxyephedrin, 6-^{18}F-dihydroxy-phenyl-alanine (DOPA), ^{11}C-5-hydroxy-tryptophan (HTP), are currently the most accurate diagnostic modalities for neuroendocrine tumors, linking great sensitivity and specificity with high quality hybrid imaging. ^{18}F-fluorodeoxyglucose (FDG) though does not have high degree of specificity, but can be used to detect dedifferentiating, rapidly growing tumors.

For therapy of neuroendocrine tumors, high doses of ^{131}I-MIBG may be applied when tumors have a high concentration and prolonged retention of this radiopharmaceutical.

Diagnostic Scintigraphy

The cumulative sensitivity of ^{123}I- or ^{131}I-MIBG scintigraphy in patients with pheochromocytoma is 88% [1]. Although CT and MR imaging of adrenal masses provide better anatomical detail to the surgeon, a positive MIBG scan is a highly specific finding. The scintigraphic technique is superior for localizing extra adrenal, recurrent, multifocal and malignant disease [2].

As 92% of neuroblastomas concentrate MIBG, ^{123}I/^{131}I-MIBG scintigraphy allows the detection of primary tumors, residual or recurrent disease and metastases, regardless their localization, in a single procedure. Together with the urinalysis for catecholamine metabolites, MIBG imaging is the most sensitive and highly specific indicator of neuroblastoma [3]. The uptake of MIBG is so tissue specific, that in a child presenting with a tumor of unknown origin ^{123}I/^{131}I MIBG scintigraphy can noninvasively establish the diagnosis neuroblastoma, and rule out differential diagnoses, e.g. WILMS' tumor, EWING sarcoma, rhabdomyosarcoma, osteosarcoma and malignant lymphoma [4]. ^{123}I/^{131}I MIBG scintigraphy has an established role in the staging of disease and as a parameter in the criteria of response.

In patients with carcinoid tumors, the cumulative sensitivity of ^{111}In-octreotide scintigraphy is higher than that of ^{131}I-MIBG scintigraphy (86% and 70%, respectively) [1] and is, therefore preferred for initial diagnosis. Combined use of both techniques may serve as a key to therapy.

^{123}I/^{131}I-MIBG scintigraphy may also be used for medullary thyroid carcinoma (although the cumulative sensitivity is only 35%) and is useful for the detection of ganglioneuroma, paraganglioma and chemodectoma; it is of limited or no use in other neuroendocrine tumors [1].

As a highly specific procedure for neural crest tumors, ^{131}I-MIBG scintigraphy is virtually always negative in non-neural crest tumors, unlike scintigraphy with radiolabeled peptides [1,4].

For many indications, PET/CT using ^{18}F-DOPA and ^{11}C-HTP [5] is taking over the diagnostic role, with high sensitivity and specificity and great anatomical detail.

Indications/Contraindications for ^{131}I-MIBG Therapy

Any malignant neural crest tumor, showing sufficient uptake and prolonged retention of ^{131}I-MIBG on a diagnostic tracer study (ideally >1% of the administered dose, depending on tumor volume), is a candidate for radionuclide therapy. Apart from tracer concentration, the availability and feasibility of other treatment modalities, as well as the patient's condition determine the indication.

The principal indications for ^{131}I-MIBG therapy are malignant pheochromocytoma and paraganglioma, neuroblastoma stage III and IV, medullary thyroid carcinoma and symptomatic, metastatic carcinoid tumors. Contraindications for radionuclide therapy in general are: pregnancy, continued breast feeding, myelosuppression and renal failure. In addition, an unstable condition of the patient, not allowing isolation, as well as lack of understanding or cooperation with respect to the radiation protection guidelines are relative contraindications.

Malignant Pheochromocytoma and Paraganglioma

The aim of ^{131}I-MIBG therapy may be objective tumor volume reduction (complete or partial response), tumor arrest (stabilization of previously progressive disease), reducing the tumor's metabolic function (as the prognosis in pheochromocytoma may depend on long term consequences of catecholamine hypersecretion, which may actually prolong survival), and palliation of symptoms (e.g. hypertension, bone pain, sweats or constipation) [6].

In 1999, the EANM Radionuclide Therapy Committee gathered results of ^{131}I-MIBG treatment in 534 patients with neural crest tumors, among whom 77 with malignant pheochromocytoma and 34 with paraganglioma (Table 1). The cumulative objective response rates with respect to tumor volume were 51% and 48% respectively, more than 50% decrease in catecholamine excretion was observed in 68% and 51%, while symptomatic palliation occurred in 68% of the patients. These results compare favorably with the best reported results of combination chemotherapy and were attained with a single agent treatment, which is non-invasive and associated with minimal side effects.

Also in malignant paraganglioma long lasting objective responses have been reported, both in secreting and non-secreting types.

Table 1. Pooled results of ^{131}I-MIBG therapy (EANM Radionuclide Therapy Committee, 1999)

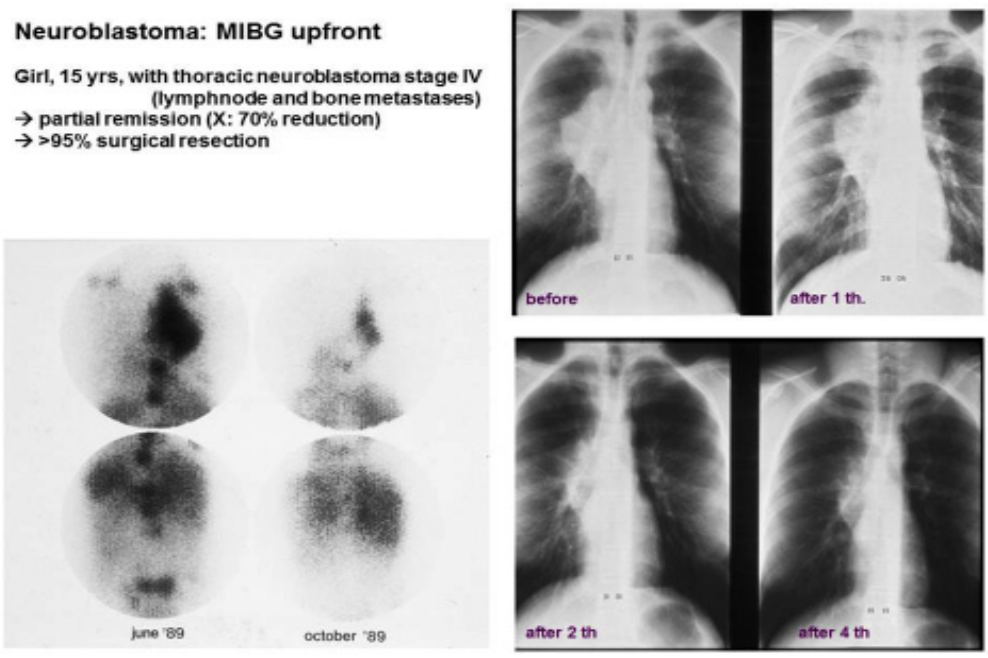
Disease	Patients	Objective response: tumor volume	Objective response: biochemical	Subjective response: palliation
Phechromocytoma	77	51%	68%	68%
Paraganglioma	34	48%	51%	70%
Neuroblastoma	229	51%	n.a.	most patients
Medullary thyroid ca.	29	23%	60%	60%
Carcinoid	159	8%	24%	60%
Other	6	2/6	n.a.	n.a.
TOTAL	534			

Recently published results in 20 patients with malignant pheochromocytoma or paraganglioma treated with moderate administered doses (7.4 GBq) at the Netherlands Cancer Institute (objective response 47%, metabolic response 67% and subjective response 89%) [7] compare well with those reported by the group at Duke University, Durham, who treated 18 patients with moderate doses (7.4 GBq) and 15 with high doses (18.5 GBq) (objective response 38%, metabolic response 60%, subjective response 86%) [8]. Moreover, it was demonstrated that both a metabolic response and a subjective response may have an important influence on survival and quality of life, even in the absence of objective volume response.

Neuroblastoma

Since 1984, therapeutic doses of ^{131}I-MIBG have been administered to children with metastatic or recurrent neuroblastoma failing conventional treatment. In 1999 pooled results of the major centres (229 patients) indicated an objective response rate of 51% (Table 1). Most of these patients had stage IV, progressive and intensely pretreated disease, and were only treated with ^{131}I-MIBG after other treatment modalities had failed. Both the ^{131}I-MIBG therapy and the isolation are generally well tolerated by children; hematological side effects may occur. Apart from objective response, the palliative effect was often impressive. For patients with recurrent and progressive disease after conventional treatment, ^{131}I MIBG therapy is probably the best palliative treatment as the invasiveness and toxicity of this therapy compare favorably with that of chemotherapy and external beam radiotherapy [14].

More recently, ^{131}I MIBG therapy has been integrated in the treatment protocol as the initial therapy instead of preoperative combination chemotherapy in children presenting with advanced disease/inoperable neuroblastoma. The objective is to reduce the tumor volume, enable adequate surgical resection and to avoid



toxicity and the induction of multiple drug resistance. Chemotherapy is reserved to treat minimal residual disease postoperatively. Initial results demonstrated the feasibility and effectiveness of this approach: a higher objective response rate (>70%) and considerably less toxicity compared to ^{131}I-MIBG therapy after conventional treatment [10]. By 2001, results in 56 patients showed that ^{131}I-MIBG is equally effective as chemotherapy in attaining operability of neuroblastoma: 43 of 56 evaluable patients (77%) had complete or >95% resection of the primary tumor or did not require surgery at all. At follow-up (ranging 13-144 months), the 5-year survival rate is 37%. Based upon these results, upfront ^{131}I-MIBG therapy was integrated in the treatment of neuroblastoma in two ways: patients with favorable parameters receive a less aggressive therapy, consisting of 2 cycles of ^{131}I-MIBG followed by surgery, whereas in patients with unfavorable parameters (high risk group) the ^{131}I-MIBG therapy is intensified and combined with the topoisomerase I inhibitor Topotecan to enhance the radiation induced cytotoxicity.

Compared to ^{131}I-MIBG therapy after chemotherapy, upfront ^{131}I-MIBG therapy has significantly less toxicity, the most frequent side effect now being nausea/vomiting (21%) and grade IV hematological toxicity in less than 5% of patients. [11].

Carcinoid Tumors and Medullary Thyroid Carcinoma

Palliative treatments for metastatic carcinoid tumors include long-acting somatostatin analogs (Sandostatin), alpha-interferon, hepatic artery embolisation, ^{131}I-labeled and unlabeled MIBG, and ^{90}Y- or ^{177}Lu-labeled octreotide therapy.

Cumulative results of ^{131}I-MIBG therapy in 159 patients with symptomatic, metastatic disease show an objective response rate of only 8% and >50% decrease in 5-HIAA excretion in 24% (Table 1). Despite the absence of objective response, palliation occurs in 60% of patients without significant side effects. In view of the often indolent character of this disease, the value of a prolonged symptomatic response should not be underestimated: in a study at Duke University Medical Center, involving 98 patients with metastatic carcinoid treated with ^{131}I-MIBG, subjective response was found to be correlated with prolonged survival.

In carcinoid tumors, not qualifying for ^{131}I-MIBG therapy because of no or insufficient tumor uptake, palliative treatment with high doses of unlabeled MIBG also proved beneficial in 60% of the cases, be it with a shorter mean duration [13]. Improved biochemical and palliative effects of ^{131}I-MIBG treatment due to enhanced tumor/non-tumor ratio by predosing with non-labeled MIBG have also been reported [14]. Combination of higher doses of ^{131}I-MIBG and unlabeled MIBG is used for therapy, whenever comparative scintigraphy demonstrates a >20% increase of the T/NT-ratio by adding unlabeled MIBG.

Pooled results in 29 patients with medullary thyroid carcinoma treated with ^{131}I-MIBG (Table 1) show an objective response rate of only 23% and tumormarker response in 60%; nevertheless palliative effects, which may be quite meaningful, occurred in 60% of the patients. However, only a minority of patients demonstrate sufficient uptake of ^{131}I-MIBG.

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PERSPECTIVE

SYSTEMIC RADIONUCLIDE THERAPY FOR BONE PAIN PALLIATION IN CANCER PATIENTS

Painful bone metastasis is a common clinical problem faced by every oncologist. Analgesic, bisphosphonates, radiotherapy, chemotherapy and hormonal therapies are the most preferred methods. Systemic radionuclide therapy for bone pain palliation is commonly underutilized due to unavailability and short of experience. Misconception of toxicity is another factor of less referral for these bone seeking radiopharmaceuticals. Often patients are referred for radionuclide bone pain palliation therapy after consuming maximum analgesics and have progressed on other treatments. Multiple painful bony metastasis not responding to mild to moderated degree of combined analgesics ought to be treated with systemic radionuclide therapy. Integration of systemic radionuclide therapy in the early course of disease results in better and sustained outcome.

Over 80% of bone metastasis cases belong to prostate & breast cancer and mostly osteoblastic and mixed type respectively. Generally pure lytic lesions have dismal response to radionuclide therapy as compared to osteoblastic and mixed type. A good concentration on a recent (less than 8 days) 99mTc-MDP bone scan corresponding to painful sites is a prerequisite. Sclerotic lesions on x-ray are not adequate for planning of radionuclide therapy. Treating asymptomatic osteoblastic metastasis in view of delaying clinical outcome is not recommended currently. Bone metastasis with spinal cord compression or impending fracture must be treated in conjunction with local modalities. Neurogenic and muscular pain must be excluded.

Choice of radionuclide depends upon bone marrow reserve, availability and extent of involvement. Commonly used radionuclides with their physical properties are given in Table 1.

Patients with progressive disease with pain warranting quick relief are best treated with short lived radionuclides (^{153}Sm or ^{186}Re). Patients with early phase of disease with good marrow reserve can be treated with $^{89}SrCl_2$ for long duration of effect. ^{32}P- Sodium Phosphate is rarely used worldwide due to considerable toxicity. ^{153}Sm-ethylene diamine tetraethylene phosphonate (EDTMP), also known as lexidronam is most commonly used bone seeking radiopharmaceutical for bone pain palliation now. Its bone localization is by chemi-absorption of the tetraphosphonate and by formation of samarium oxide on hydroxyapatite molecule. 50% of injected activity binds to the bone and rest gets rapidly excreted in urine essentially within 6 hours. 5:1 is relative ratio of uptake for tumor to normal bone.

Clear understanding of purpose of treatment is essential. Patients should be informed that this therapy would not cure the cancer even thought it might kill some cancer cells. The whole idea is to control pain and improve quality of life. In 10-15% of cases, there may be increase in pain (flare phenomena) within 72hrs of injection. This has been postulated with local inflammation due to radiation and relates with good response. Generally, flare is mild and selflimting within a week. Analgesics should be continued after the therapy because it takes 2-4 weeks for response to develop. With time as response develops, analgesics can be reduced both in terms of dose and frequency. An analgesics drug chart should be maintained to assess the degree of response. 83% response rate has been reported with 153Sm-lexidronam. Pain relief is generally reported within 2 weeks and lasts a duration of 4-40 weeks. Repeat therapy is generally

Table 1: Most Commonly Used Bone Seeking Radiopharmaceuticals and their Comparison

Radiopharmaceutical	Dose	Half life (days)	Beta energy max (MeV)	Gamma Energy KeV (%)	Maximum tissue penetration	Remarks
P-32	5-10 mCi	14.3	1.71	None	8 mm	FDA approved but rarely used now
Sr-89 chloride	4 mCi	50.5	1.46	910 (0.01%)	6 mm	FDA approved
Sm-153 EDTMP (Lexidronam)	1 mCi/Kg	1.9	0.81	103 (28%)	2.5 mm	Most commonly used in USA
Re-186 HEDP	35 mCi	3.8	1.07	137 (9%)	4.5 mm	Approved in Europe

given after 3-6 months if pain persists and hematological and biochemical requirements are fulfilled.

Chemosensitization is a well known method of improving radiotherapy. Some research papers are claiming better response of combining chemotherapy and bone seeking radionuclides. However in current clinical practice, combin treatment options has not been recommended. Nevertheless, withholding of chemotherapy 6 weeks prior to systemic radionuclide therapy is recommended.

Pregnancy is an absolute contraindication while breast feeding should be permanently stopped before radionuclide therapy. Life expectancy of less than 4 weeks forbids radionuclide therapy as well. Patients should not receive myelosuppressive chemotherapy 6-8 weeks before and 12 weeks after radionuclide therapy due to combine toxicity. External hemibody radiation also should have been stopped 2-3 months before radionuclide therapy due to combine myelosuppressive effect, however regional radiotherapy could be continued simultaneously. Hormone therapy should also be continued along with radionuclide therapy with no effect of toxicity reported. Using bisphosphonates along with bone pain palliation agents were thought to be doing competitive inhibition but so far, in literature, this hypothesis have n't been proved. So concurrent use of bisphosphonates and bone pain palliation radionuclide can be done; however just before next bisphosphonates injection radionuclide therapy is preferred by most of the experts.

Patients should remain well hydrated before, during and after the procedure. There is no need of fasting before the injection. Radiopharmaceutical should be injected slowly by intravenous catheter to avoid infiltration. In case of extravasation, local heat application will enhance reabsorption to reduced radiation exposure locally. Hospitalization is not required for the therapy per say but patients need to be observed for 4-6 hours in the nuclear medicine department. A whole body scanning should be done after 4 hours/24 hours with ^{153}Sm-lexidronam to confirm adequate uptake of tracer and for dosimetry. Radiation safety precautions should be followed for one week. Patients should maintain rigorous hygiene to avoid contamination. Double toilet flush is recommended after urination. Patients should avoid soiling of underclothing and should wash soiled cloths separately. Incontinent patients should be catheterized for 24 hours for ^{153}Sm-lexidronam therapy. Pregnancy should be avoided for 6 months with ^{153}Sm-lexidronam and 12 months for long lived radionuclides.

Complete blood counts (CBC) should be done within 7 days or preferably on the day of therapy. A good marrow reserve determines patient's tolerability.

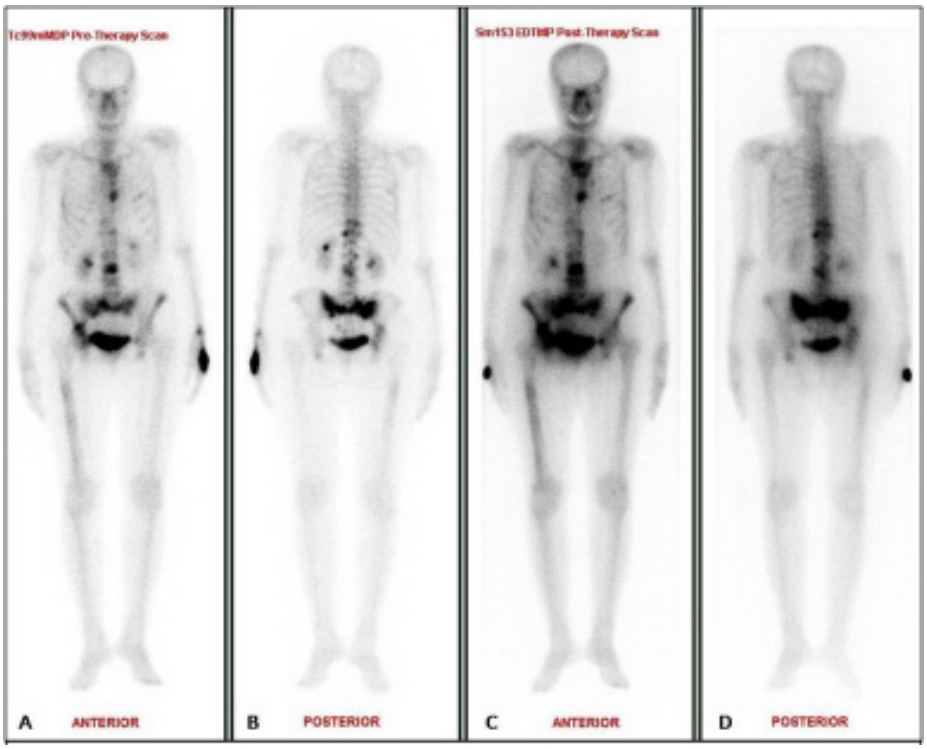

Figure (A&B) showed multiple bony metastasis in pelvis, spine and sternum on MDP bone scan. Figure (C&D) showed good concentration of 153Sm-EDTMP on whole body scan at the known bony metastatic sites

Hemoglobin > 9 gl^{-1}, total leukocytes counts (TLC) > 3.5 X 10^9 l^{-1} and platelets counts > 100 x 10^9 l^{-1} are preferred. Values below these are relative contraindication yet radionuclide therapy can still be continued after ruling out disseminated intravascular coagulation (DIC) and a downward trend. Due to renal excretion of these radiopharmaceuticals, a good kidney function is warranted. GFR > 60 ml/min and serum createnine < 2 mg/dl are preferred. GFR < 30 ml/min is an absolute contraindication; however if GFR is between 30-60 ml/min, a dose reduction is recommended (approx. 50%).

Hematological toxicity is the main side effect. Therefore periodical hematological monitoring should be followed up to 4-6 weeks for ^{153}Sm-lexidronam. Degree of toxicity depends upon bone marrow reserve, extent of disease and physical properties of radionuclide used. Good baseline marrow reserves signify mild myelosuppression which usually is transitory and complete recovery expected in next 3 months.

In conclusion, current available bone seeking systemic radiopharmaceuticals for bone pain palliation are effective. By a simple intravenous injection of radionuclide, generalized bony pain due to metastasis can be controlled for a regional duration. This cost-effective option should be considered in the early phase of disease rather than last resort for better outcome.

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GLOBE SCAN

GMP Grade Rhenium-188-HEDP

Bone-targeting therapeutic radiopharmaceuticals are effective agents for treatment of painful bone metastases. Rhenium-188-HEDP is such a therapeutic radiopharmaceutical and has advantages over commercially available alternatives in terms of efficacy, safety and the ability to be produced on-site. Unlike many other radiopharmaceuticals, there are no standardized preparation methods for Rhenium-188-HEDP. Furthermore, for support of clinical studies with Rhenium-188-HEDP as an investigational medicinal product, preparation of this radiopharmaceutical has to be performed under GMP conditions. Till now no group has reported on the preparation of Rhenium-188-HEDP under GMP conditions or on stock production of sterile non-radioactive starting materials. The author present the production of GMP grade Rhenium-188-HEDP for application of this therapeutic radiopharmaceutical in routine clinical practice and for support of clinical studies. In addition, bio-distribution data of Rhenium-188-HEDP in mice and in patients with bone metastases originating from prostate cancer are presented.

(Netherlands: Inj J Pharma, Apr 25, 2014)

Nuclear Medicine Therapy

For patients who fail to respond to current first-line and second-line treatments for colorectal cancer liver metastases (also known as salvage patients), radioembolization with Y-90 microspheres could extend survival. A structured review was performed by researchers to gather all available evidence on radioembolization for the specific group of patients with colorectal cancer liver metastases. Among the studies, disease control rates (i.e., complete response, partial response and stable disease) ranged from 29-90 percent in the monotherapy studies, which involved 901 patients. In the studies in which Y-90 radioembolization was combined with chemotherapy, involving 472 patients, disease control rates ranged from 59-100 percent. Therefore, in this group of salvage colorectal cancer liver metastases patients who otherwise have no regular treatment options and a life expectancy of less than six months, Y-90 radioembolization seems to be a hopeful treatment option. Finally, this overview of the literature shows which topics have not been the focus of much research and may thus be interesting for further work."

(Netherlands: J Nucl Med, Nov, 2013)

RESEARCH & DEVELOPMENT

Radioiodine Therapy & Circulating Epithelial Cells

A pilot study investigated the changes of circulating epithelial cells in the blood of patients with differentiated thyroid cancer after radioiodine-therapy with I-131. Epithelial cells were assessed before radioiodine-therapy, as well as 2 days, 14 days, and 3 months after therapy. Two patient groups were examined: 1) patients with thyroid cancer receiving a first radioiodine-therapy after thyroidectomy (RIT first, n=13); and (2) patients with thyroid cancer in need of repeated radioiodine-therapy due to local or metastatic recurrences (RIT rep, n=15). Patients with an early decrease of cells after radioiodine-therapy (RIT first 7/13; RIT rep 2/15) showed an increase of serum-thyroglobulin in most of the cases (RIT first 5/7; RIT rep 2/2). In the RIT rep group, a decrease in cell counts 2 days after radioiodine-therapy indicated a clinical response in 90% of the cases. This study indicates that the number of circulating epithelial cells in differentiated thyroid cancer undergoes changes in response to radioiodine-therapy.

(Exp Clin Endocrinol Diabetes, Apr 2014)

(153)Sm-EDTMP & Docetaxel in Prostate Cancer

Researchers in Italy have investigated whether docetaxel administered to metastatic castration-resistant prostate cancer (mCRPC) patients after treatment with samarium-153-labeled ethylene-diamine-tetra-methylene-phosphonic acid (Sm-EDTMP) increased toxicity and/or reduced antitumor efficacy. Thirty mCRPC patients with skeletal metastases received standard therapy with docetaxel (75 mg/m2 intravenously every 21 days for at least six cycles) on average 6 weeks after Sm-EDTMP (37 MBq/kg). Over 80% patients showed favorable biochemical responses. Median time to progression was 9.1 months (mean 9.8, 95% CI 7.8-9.9), and median overall survival was 19.9 months (mean 24.5, 95%CI 16.9-22.8); 5 patients were still alive over 5 years after enrollment. No additional hematological toxicities were observed when docetaxel was administered after Sm-EDTMP other than those expected when administering the agent alone. This work justifies further investigations on the possible synergistic effects of combined strategies with the two agents.

(Nucl Med Commun, Jan 2014)

NEW TECHNOLOGIES

New Diagnostic and Therapeutic Techniques

A new research shows the potential of recently developed radiopharmaceuticals with benzamide for the imaging of metastases and a targeted systemic therapy. The researchers used a theranostic approach where a molecule was first given as a diagnostic isotope (^{123}I-BA52) to identify the patients probability benefiting from therapy and then as a therapeutic pharmaceutical (^{131}I-BA52) for the patients who benefitted. Some of the patients treated with ^{131}I-BA52 were found to have a survival rate of more than 2 years. The researchers believe that the tracer could be useful in setting of a combination therapy in patients with earlier stage metastasized melanoma. In the second study, a specific single photon emission computed tomography (SPECT) radiopharmaceutical; ^{123}I-BZA2 for malignant melanoma was developed. To compare its accuracy in staging and restaging, the imaging of patients with both ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) and ^{123}I-BZA2 SPECT was performed. The sensitivity of ^{18}F-FDG for diagnosis of melanoma metastases was observed to be higher than that of ^{123}I-BZA2 (80% versus 23%); however, the specificity of ^{18}F-FDG was lower than ^{123}I-BZA2 (54% versus 86%). The researchers concluded that ^{123}I-BZA2 could be theoretically used for the diagnosis but not for melanoma staging.

(Science Daily, Jan 7, 2014)

Neuroendocrine Tumor Management

The radiopharmaceutical Gallium-68 (DOTA0-Phel-Tyr3) octreotide (Ga-68 DOTATOC) has been designated as an orphan drug by the US Food and Drug Administration for management of neuroendocrine tumors (NET). A drug is given this designation when it treats a rare disease/condition. For a drug to qualify for orphan designation, the disease/condition must affect fewer than 200,000 people. Ga-68 DOTATOC meets this requirement as the prevalence of NET patients is nearly 110,000 in The United States. Orphan drug status could speed up the regulatory approval by requiring fewer patients per clinical trial and releasing grant funds for its development. Ga-68-labeled NET positron emission tomography (PET) radiopharmaceuticals would reduce the time taken for imaging of a NET patient from 2-3 days to just a few hours. In addition, the exposed dose of radiation is lower than the current standard of care.

(www.snmmi.org, Nov 18, 2013)

IN FOCUS

ALPHA RADIUM (Ra^{223}) THERAPY: OPENING A NEW WAY TO TREAT BONE METASTASIS IN PROSTATE CANCER

Bone metastasis is a result of the natural progression of diseases like Prostate Cancer, Genito-Urinary Malignancies, Lung and Breast Cancers. The presentation of bone metastasis could be silent as in prostate carcinomas or present as focal bone pain which on investigation would reveal expensive bone lesions. Bone pain is the hallmark of bone metastasis with the spectrum ranging from mild pain to severe pain with restriction of movements and poor Karnoffsky's Index. Chemotherapeutic drugs, focal or targeted radiotherapy and radiopharmaceuticals are employed to control pain. Radiation in any form is by and large an efficient way of controlling pain due to bone metastasis. However, when the disease is extensive and has spread all over the body, the conventional approach of a focused radiation or hemi-body radiation is not effective. Radioisotope therapy employs by the virtue of the bio-distribution of radio-pharmaceuticals that are labeled with radioisotopes with physical properties that are conducive with delivering significant amount of radio-activity over time.

Historically, strontium-85 and phosphorus-32 which are bone seekers, were employed for this task. The high beta energy from these while effectively irradiated the lesion, it also damaged the red marrow resulting in significant toxicity. An ideal isotope for therapy is one that emits a convenient beta energy in the intermediate range, has a long half-life, is stable when labeled with bone metastasis seeking pharmaceuticals, and also emits a fraction of its energy as gamma which could be used for imaging with a gamma camera. Strontium-89, Samarium-153 EDTMP and now Lutetium-177 EDTMP are popular radiopharmaceuticals for bone pain palliation. Strontium-89 has a long half-life and shelf life but is expensive as it is cyclotron produced. This is the agent of choice in most developed countries. Samarium-153 EDTMP is the next popular drug of choice which is cheaper as it is reactor-produced but availability and scheduling are an issue in many countries. As a replacement of this, Lutetium-177 EDTMP is being projected as an equally effective alternative but with better availability due to its longer half-life. In a few countries, Rhenium-188, eluted from 188W (Tungsten) Generator, and labeled with HEDP, is indeed a viable alternative of the above mentioned reactor and cyclotron produced radiopharmaceuticals as the presence of the generator in the department provides access to isotope therapy for pain palliation within 24 hours. It is to be seen that all the above-mentioned isotopes are beta-emitters whose beta-energy is used for radiation effects and with the impact of its half-life, the effective dose is delivered to its metastatic sites.

Alpha emitters deposit directly the highest quanta of energy so when such an isotope reaches a bone metastatic site, it delivers a large amount of energy and because of its restricted penetration spares relatively the red marrow which is beneath the site.

Radium Ra-223 Dichloride is a new product which has cleared the mandatory clinical trials and is now approved for regular clinical use.

Stromal targeted therapies in prostate and renal cancers is becoming popular with newer concepts and increasing knowledge. Survival and growth of metastatic cancer cells are promoted by the tumor micro-environment which includes stromal elements, such as extra-cellular matrix, various mesenchymal cells, their soluble products and nutrients carried by vascular endothelial cells. Osteoblasts, osteoclasts and hematopoietic cells are additional cells formed in bone metastasis. There is evidence that cancer cells can induce stromal changes and microenvironment conducive to their own growth. Manipulating a stroma for therapeutic benefits is a relatively recent concept. Radium-223 and Strontium-89 target the inorganic bone matrix. Zoledronic acid which is a biphosphonate, targets bone matrix and osteoclasts. Targeted agents like Sorafenib, Sunitinib, etc., target VGEF receptors. Either independently or in combination, they manipulate the tumor environment.

There are advantages to alpha emitters that are not present with other forms of radiation. The half-life of Ra-223 is 11.4 days which enables a repetition of injection every 4 weeks if necessary. As a consequence of the alpha particle charge and mass, the deposition

of alpha particle energy occurs over a very short path (40-100 microns). Alpha particles have approximately 7300 times the mass of a beta particle. The Radium-223 alpha particle decay chain comprising of 4 alpha particles has an overall energy of approximately 28 MeV – as compared to 0.81 MeV of energy from the beta particles emitted by Sm-153 EDTMP. The alpha particle deposition occurs over a very short distance and results in relatively little damage to non-targeted tissues despite its destructive actions on both the tumor and tumor micro-environment. This feature is demonstrated by the bone stromal effects that can be measured by sharp decreases in the marker levels, such as bone derived Alkaline Phosphatase and Urinary–N-Telopeptide. The direct anti-tumor effects can be measured by serum anti-prostate specific antigen levels which decrease after therapy.

Radium-223 successfully completed phase I trial and data from the randomized phase II trial suggested that Ra-223 may prolong survival in bone metastatic castrate resistant prostate carcinoma (hormone resistant prostate carcinoma). A 900-patient phase III trial that indeed the prolonged the overall survival from 11.2 months in the placebo arm to 14 months in the Ra-223 arm (P=0.002, hazard ratio= 0.699). Besides the survival benefit, it has a favourable toxicity profile.

The alpha emitter showed in its studies mild and reversible bone marrow toxicity in all dose escalations with no evidence of a dose effect. Most adverse effects were gastro-intestinal, including nausea (43%), vomiting (24%), diarrhea (22%), constipation (20%), fatigue (16%), decreased haemoglobin (15%), UTI (15%) and peripheral edema (12%). Minor decrease in platelet counts, white cell counts and neutrophils were observed in those levels from 50-100kBq per kg which peaked in the first 2 weeks of treatment and subsequently returned to baseline. An additional benefit seen with Ra-223 therapy has been a 5.8 month delay in median time to first symptomatic skeletal event-15.6 months vs 9.8 months; HR=0.66. 95%, CI: 0.5-0.83. The recommended dosage of Ra-223 is 50kBq per kilogram body weight. It may be given once every 4 weeks for a total of 6 injections.

Patient Selection

Bone specific radio-isotope therapy preferentially targets newly formed bone at the tumor/bone interface. In prostate cancers, this stromal matrix is also prevalent throughout the central part of the sclerotic metastases. The hydroxyl-apatite of newly formed bone matrix is the target of both BSRs and the biphosphonates. In conventional bone scan, the agent primarily provides pain relief at confirmed osteoblastic metastatic sites that are hot on bone scan. 18F-Sodium Fluoride PET scan, when available, is the preferred option. The sodium fluoride diffuses from the vasculature to bone by chemisorption that occurs at the surface of hydroxyl-apatite in a manner similar to that of bone specific radioisotopes.

Selection over External Beam Radiotherapy includes several considerations, such as patients with multi-focal pain requiring multiple radiation fields, and patients who previously have been treated to maximal normal tissue tolerance with external beam radiation but having persistent or progressive or recurrent symptoms at the treated site. While bone specific radioisotope therapies have been combined with chemotherapy, this approach has not yet been tried with Ra-223. Currently, routinely available radionuclides can only be used for pain palliation in patients with prostate cancer. However alpha radin is also therapeutic in nature and has survival benefits . Due to its dual role a much wide acceptance is expected in today clinical practice. In view of short path length alpha particle the radiation-safety issues are less complicated. However, special emphasis is needed to avoid internal contamination.

Bone metastatic disease is not curable with current technologies and multiple therapy targets are now available. A suitable harmonization among them is necessary. However, the demonstration of this novel alpha emitting agent that it can improve survival has again brought isotope therapy to the forefront.

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RGCON- 2014: HIGHLIGHTS

Rajiv Gandhi Cancer Institute & Research Centre (RGCI & RC) organized its 13th Annual International Conference from 15th- 16th February 2014 at India Habitat Centre, Lodhi Road, New Delhi. The theme of the conference was Lymphoma "Biology to therapy". The conference has brought together eminent pathologists and clinicians from around the world to share their knowledge and the latest information on the scientific progress in lymphoma.

On the first day after the registration, first session was started that was based on the low grade lymphomas, in which talks were delivered on diagnosis and treatment of Follicular lymphoma. A very attractive lecture on evolution, classification of lymphoma was given by Dr Anita Borges, Tata Memorial Hospital, Mumbai. To have a scientific exchange of thoughts, debate had also been included apart from lectures, the topic of the debate was "wait & watch versus Rituximab for advanced Follicular lymphoma". As diffuse large B cell lymphoma (DLBCL) is a fast-growing, aggressive form of NHL and despite the addition of Rituximab in the standard chemotherapy, approximately 40% of the patients could not be cured, therefore the evening session was dedicated for DLBCL. The session comprised of the talks on its morphological diversity, biology and treatment. Most of the lectures were delivered by foreign delegates complemented by an interactive panel discussion. Following this the prestigious Raman Chadha Oration was delivered by Dr Rekha Pai, Scientist, CMC Vellore, she gave a lucid presentation on molecular techniques and interpretations in lymphoma.

The formal inauguration of the conference was held in the evening at 7 pm. RGCON-2014 was inaugurated by Dr T Ramasami, Secretary, Dept of Science & Technology Minister, Government of India. He is recipient of very prestigious awards as Padam Shree and Padam Vibhushan. The "guest of Honour" for this occasion was Dr GK Rath, Chief, Dr B R A Institute-Rotary Cancer Hospital, AIIMS, New Delhi. Other members presented on the dias were Mr. Rakesh Chpora, Chairman, he gave the vision of RGCI & RC followed by addresses by various dignitaries including Mr. DS Negi (CEO), Dr A K Dewan (Medical Director), Dr D C Doval (Chairman organizing committee). On this occasion the RGCON 2014 Souvenir was released by Dr. T Ramasami and awards were presented by Dr. GK Rath. To recognize and promote quality contributions to academic research and writing among doctors and researchers" Dr P S Raman Memorial Award", an annual award, for the best paper published for the year 2013 was presented to Ms. Rupal Sinha, Research Officer for her paper entitled "Kras Gene Mutation and RASSF1A, FHIT and MGMT Gene Promoter Hypermethylation: Indicators of Tumor Staging and Metastasis in Adenocarcinomatous Sporadic Colorectal Cancer in Indian Population" published in journal PLOS ONE. The Raman Chadha oration award

(L to R: Dr A Mehta, Orginizing Secretary; Dr D C Doval, Chairman- Organizing Committee; D S Negi, CEO; Dr G K Rath, AIIMS; Dr T Ramasami, DST; Mr Rakesh Chopra, Chairman; Dr A K Dewan, Medical Director and Dr Vineet Talwar, Organizing Secretary)

(Sh D S Negi, CEO of RGCI&RC, Addressing the Audience)

(Dr Anurag Mehta, Orginizing Secretary, Addressing the Participants)

was given to Dr. Rekha Pai, both the awards were presented by the guest of Honour Dr. GK Rath. This was followed by a cultural programme. Final vote of thanks was given by Dr. Vineet Talwar (organizing Secretary).

The second day of the conference provided a comprehensive update and a multi-disciplinary perspective on Hodgkin Lymphoma, Pediatric lymphomas, Peripheral T cell lymphoma and HIV associated lymphomas. A very impressive and interactive talk on new approaches to treat Hodgkin lymphoma was delivered by Dr. Ranjana Advani, Professor of Oncology, Stanford University, she gave deep insight into the management of lymphoma. Prof. h.c. H.K. Muller, Professor Emeritus University of Wurzburg Wissenchafts Germany, apprised the audience about three newly recognized entities in lymphomas, which could be confused with other lymphomas, so that unnecessary morbidity due to treatment could be avoided.

One of the highlights of RGCON 2014 was the parallel symposium on the 2nd day along with the scientific sessions to deal with cancer survivorship issues. In this session general lecture on dietary and other issues was delivered by Dr. Meenu Walia, Consultant Medical oncology, Dharamshila Hospital. Followed by the talk, directed panel discussion and open discussion was held which allowed substantial sharing of ideas among the participants. Postgraduate trainees, residents, researchers were provided the opportunity to present their research work and to compete for the awards for best poster and oral presentation. Of the total submitted 53 abstracts, 5 were shortlisted for oral presentation. The presenters with best studies in both the categories were honoured with awards by the CEO in the form of cash prize.

(Dr h c Stefano A Pileri, International Speaker, Addressing the Audience)

The conference witnessed a galaxy of senior International speakers, who were stalwarts in the field of lymphoma. In the field of pathology, the main speakers were Professor h. c. H. K. Muller - Hermelink; Professor Dr. Dr. h. c. Stefano A. Pileri; Dr. S. David Hudnall and Professor Bharat N Nathwani and Dr Hermlink. Amongst the clinical side, represented by Dr Wolfgang Hiddemann from Germany and Dr Ranjana H Advani from USA.

Thus, the 2 day event of was closed on 16th February with Valedictory function. Over five hundred delegates attended the conference by truly multidisciplinary teams including pathologist, young researchers, physicians, medical, surgical and radiation oncologists, nuclear medicine physicians and radiologists from different part of the country with huge enthusiasm. This conference was focused on the most topical, interesting or thought-provoking issues in the diagnosis and treatment of lymphoma. All the session were stringently kept on time and were completed as per schedule which was well appreciated by all the delegates and faculty members.

(Dr Anurag Mehta, Director Laboratory Services & Blood Bank, RGCI&RC)

Rajiv Gandhi Cancer Institute and Research Centre

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