Role of radionuclide in therapy : A review

Ali MM

Introduction
Thyroid disorders are the second most common endocrine problem in Bangladesh. Thyroid disorders may occur in form of abnormality in size, shape, histological structures and function of the gland.

The relative frequency of thyroid disorders may vary in different countries of the world and also in the different regions of the same country, as well as in different socioeconomic status. Cancer is the disease of this century. Proper management is a great challenge for today's medical science. Along with other modalities of treatment nuclear medicine play a great role in the management of cancer.

Nuclear medicine therapy uses unsealed radioactive sources for the selective therapy of radiation to tumours or target organs. For benign disorders such as thyrotoxicosis and arthritis radionuclide therapy provides an alternative to surgery or medical treatments. In cancer treatment, it often combines the advantages of target selectivity with that of being systemic, as with chemotherapy and it may be used as a part of a therapeutic strategy with curative intent or for disease control and palliation.

The basis of successful radionuclide therapy is sufficient uptake & prolongs retension of the radio pharmaceutical in the target tissues. This can be assessed with a tracer study before administering a therapeutic dose. The mechanism of action of radionuclide therapy, with its low irradiation dose rate, is poorly understood. Radiation is delivered selectively by the appropriate radio pharmaceutical, taking advantage of short range, B particles (in the order of millimeters) or ultra short - path- length & particles or auger electron emitting radio nuclides\(^1\). Calculation of the dose delivered to a target remains a challenge mainly because the distribution of the radio pharmaceutical in the target is non-uniform\(^2\). Nuclear medicine therapy is often confined to centers which have a nuclear medicine department equipped and licensed for radionuclide therapy, where patients receiving high doges of radioactivity can be temporarily isolated, in compliance with national legislation\(^3\). Furthermore, there are significant variations in the availability of such facilities between countries.

Discussion
Benign disease
One of the oldest and still most widely used applications of radionuclide therapy is radio iodine for thyrotoxicosis, both the diffuse (Graves) and nodular (Plummer's) forms, which dose not respond to medical treatment. The efficacy of iodine -131 therapy in thyrotoxicosis is beyond dispute and long-term follow-up studies in the USA and the UK have confirmed the safety of this treatment. The reported incidence of induction of hypothyroidism ranges from 7% to 25% in the first year, depending on the dose. The intra-articular administration of radiolabelled colloids (so-called radiosynoviorthesis or radiation synovectomy), is effective in more than 60% of patients with rheumatoid arthritis and other arthritic diseases. The choice of radioisotope, dose and injected volume is determined by the size of the joint; the range of the Beta-particle spectrum is matched to the thickness of the synovium. Yttrium-90\(^{90}\text{Y}\) citrate or silicate is generally used for big joints such as the knee, with rhenium-186 colloid for the shoulder, elbow, hip and ankle and erbium-
169 citrate for small joints in the hands and feet.

Nuclear medicine therapy, advantage and limitation

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity (Radiation dose limited to the target organs.)</td>
<td>Isolation of the patient</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Storage of radioactive waste</td>
</tr>
<tr>
<td>Low toxicity</td>
<td>Availability (Radio- pharmaceuticals/ isolation bed)</td>
</tr>
<tr>
<td>Systemic or loco regional application</td>
<td>High cost of some newer form of therapy</td>
</tr>
<tr>
<td>Excellent palliation</td>
<td>Multidisciplinary approach required</td>
</tr>
<tr>
<td>Limited long term consequence</td>
<td>Need form dosimetry calculation</td>
</tr>
<tr>
<td>Multiple treatment possible</td>
<td>Mechanism is poorly understood</td>
</tr>
</tbody>
</table>

Thyroid carcinoma

For nearly 50 years $^{131}$I has been an integral part of the treatment of differentiated (papillary and follicular) thyroid carcinoma. In most cases, after total or near-total thyroidectomy, an ablative dose of 1.85-3.7 GBq (50-100 mCi) is administered as a liquid or capsule to clear the neck of any remaining (normal) thyroid tissue and to permit the detection and treatment of metastases, which would otherwise not sufficiently take up $^{131}$I in competition with the thyroid remnant. Survival rates for surgery followed by $^{131}$I ablation are better than those for surgery alone. If metastatic or, during follow-up, recurrent disease is detected, therapeutic doses up to 7.4 GBq (200 mCi) $^{131}$I may be administered. In a series of 394 patients with lung and bone metastases from thyroid carcinoma complete remission was attained in 46%. Long-term follow-up confirms the efficacy of $^{131}$I therapy; patients with $^{131}$I avid metastases have significantly better 5 and 10 years survival rates than patients whose metastases do not take up $^{131}$I and cannot be treated this way. The clinical experience that $^{131}$I is curative in patients with pulmonary metastases illustrates the scope for other forms of radionuclide treatment in solid tumours, such as minimal residual disease.

Myeloproliferative diseases

Radioactive phosphorus, as $^{32}$P orthophosphate has been used since 1936 for the treatment of myeloproliferative disorders such as polycythaemia vera and essential thrombocythaemia. Acting by incorporation of radiophosphorus into the DNA of rapidly proliferating cells, $^{32}$P therapy may induce objective remission and prolonged survival. Comparative studies in polycythaemia vera demonstrated that $^{32}$P is associated with fewer thromboembolic complications than repeated phlebotomy but is associated with higher rates of leukaemia, as is chemotherapy for this disease.

$^{131}$I-m-iodobenzylguanidine(MIBG) therapy

Active uptake via the cell membrane and neurosecretory storage granules in the cytoplasm are responsible for the specific retention of $^{131}$I-MIBG in tumours derived from the neural crest (in non-adrenergic tissues uptake is via passive diffusion only), resulting in high tumour/non tumour ratios. More than 90% of phaeochromocytomas and neuroblastomas, around 35% of medullary thyroid carcinomas and 70% of carcinoids concentrate MIBG. $^{131}$I-MIBG therapy for malignant phaeochromocytoma aims at objective tumour regression or tumour control with reduction of the tumours metabolic function and palliation of symptoms, sweats and bone pain. Pooled results in 117 patients showed an overall objective response rate of 56% and subjective improvement and decrease of blood pressure were achieved in more than 60% of patients. Also in malignant (secreting or non secreting) paraganglioma, reports describe objective partial remission, pain relief and improved quality of life.

Since 1984 therapeutic doses of $^{131}$I-MIBG have been given to children with metastatic or recurrent neuroblastoma not responding to conventional treatment. In 1991 pooled results from the major centers for 273 neuroblastoma patients indicated an objective response rate of 35%. Both the $^{131}$I-MIBG therapy and the accompanying isolation are generally well tolerated by children.
children and toxicity is limited to hematological side-effects. For patients with recurrent and progressive disease after conventional treatment 131I-MIBG is probably the best palliative treatment because the invasiveness and toxicity of this therapy compare favorably with those of chemotherapy and external beam radiotherapy. Attempts to combine 131I-MIBG with high-dose chemotherapy, with or without total body irradiation, followed by autologous bone-marrow rescue have met with severe toxicity. In patients with recurrent stage IV neuroblastoma 131I-MIBG is now used in combination with hyperbaric oxygen to try to improve survival. More recently, 131I-MIBG therapy has been inserted early in the treatment protocol, instead of preoperative combination chemotherapy, in children presenting with advanced and/or inoperable neuroblastoma. The objective is to reduce the tumour volume, permitting adequate surgical resection and avoiding toxicity and the induction of early drug resistance. Chemotherapy is reserved for minimal residual disease postoperatively. With this approach 70% of the patients had complete or $>95\%$ resection of the primary tumour or did not require surgery at all and toxicity was less than that of 131I-MIBG after conventional therapy.

Cumulative results of 131I-MIBG therapy of medullary thyroid carcinoma and carcinoid tumours indicate a lower objective response rate but useful palliative effects in more than 50% of the patients. In carcinoid tumours not qualifying for 131I-MIBG therapy because of insufficient tumour uptake, palliation with high dose of unlabelled MIBG has also been successful.

### Current therapeutic indication

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>131I as iodine</td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Radiosynoviorthesis</td>
<td>Arthritic disease</td>
</tr>
<tr>
<td>131I as iodide</td>
<td>Differentiated thyroid carcinoma</td>
</tr>
<tr>
<td>89Sr, 186Re</td>
<td>Painful skeletal metastasis (Ca prostate/breast)</td>
</tr>
</tbody>
</table>

**Palliative therapy of painful skeletal metastasis**

Although radioactive strontium had been used to treat skeletal metastases since 1937, the 1980s saw a revival of this form of therapy as new bone-seeking radio pharmaceuticals became available.

Beside medical treatments for painful bone metastases, external beam radiotherapy - either as a local dose to a single or few painful sites or as a dose up to 8 Gy as half body irradiation in more widely disseminated disease - has been used with success. Upto 80% of the patients respond. However, this approach is very toxic. Systematic treatment with bone-seeking radio-pharmaceuticals is less invasive better tolerated and just as effective because the radiation dose is limited to the metastases and normal tissues are spared. Initial clinical studies of radioactive strontium (89Sr) chloride in patients with metastatic prostatic cancer demonstrated a palliative response rate of 75%, 25% of patients being able to stop taking analgesics. Double-blind studies comparing 89Sr and multicoated controlled studies have shown that 89Sr is as effective as radiotherapy and that the onset of pain at new sites may be delayed by it.

The most frequently used agents for bone palliation today are, besides 89Sr, rhenium-186, etidronate and samarium-153 ethylenediaminetetramethylene phosphonate. 89Sr is a pure Beta-emitter with a long half-life (50.5 days); the other two are Beta/Gamma emitters with half-lives of only 3.8 and 1.95 days, respectively, offering the added advantage of imaging. In most
countries these treatments can be given on an outpatient or daycare basis.

**Locoregional applications of radionuclide therapy**

Inoperable tumours which are localized or confined to an organ may be targeted more directly via the arterial route, exploiting the fact that most tumours have a greater arterial blood supply than surrounding normal tissue does. Example are $^{131}$I-iodized oil and $^{90}$Y glassmicrospheres, which linger or are trapped in the tumours arterioles and capillaries in hepatocellular and capillaries in hepatocellular carcinoma and liver metastases. Therapeutic doses of $^{131}$I-iodized oil resulted in partial remission in more than 50% of patients with hepatocellular carcinoma; in patients with portal-vein thrombosis, a contraindication for chemoembolisation, survival after $^{131}$I-iodized oil was better than that in a control group treated by medical support only.\(^{12}\)

Mesothelioma and malignant pleural effusions may be treated by intrapleural administration of radioactive colloid. Similary radionuclide therapy by intrapericardial, intraperitoneal and intrathecal administration for malignant effusions has been reported, as well as intracystic installation of radiopharmaceuticals into cystic glioma and craniopharyngioma aiming at suppressing the reaccumulation of fluid. Inoperable pancreatic, liver and brain tumours may be approached by direct, intratumoral administration of $^{32}$P-colloid or $^{131}$I-labelled monoclonal antibodies.

**New developments**

**Short term**
- Radioimmunotherapy for non-Hodgkin's lymphoma.
- Radiolabelled peptides for neuroendocrine tumour.
- New radio nuclides (Beta emitters, Y-90, Re-186 & 188, Copper-67).

**Long-term**
- Radioimmunotherapy for residual disease of solid tumours.
- Radioimmunotherapy for non-Hodgkin's lymphoma.
- Radiolabelled peptides for neuroendocrine tumour.
- New radio nuclides (Alpha emitters, astanine-211, Bismuth-213).

Potential new applications in oncology reflects advances in antibody engineering, the identification of tumour antigen targets and the synthesis of regulatory peptide analogues and bifunctional chelating agents for stable and efficient complexing of beta radio nuclides more suitable than $^{131}$I and eventually of alpha emitter.

**Radioimmunotherapy**

Monoclonal antibodies labeled with radio nuclides (mainly $^{131}$I) were directed against various antigens associated with specific tumour type. Non-Hodgkin lymphomas are a privileged clinical target for radioimmunotherapy, as they express well-characterized differentiation antigens and are highly radiosensitive. Anti-CD20 antibodies, which have been evaluated most often for this indication produce a specific cytotoxic action which was not been completely elucidated\(^{13}\). Radioimmunotherapy of solid tumours has been less encouraging with objective response rates of less than 2%\(^{14}\). This disappointing results are attribute to the large size and relative radioresistance of the tumours and to inadequate tumour to normal tissue uptake ratios. Moreover pretargeting techniques significantly increase tumour to normal tissue ratios and prolong the residence time in tumours, thereby enhancing tumour uptake without augmenting toxicity to normal tissue\(^{14}\).

**New radio-nuclides**

Most radionuclide therapy in clinical practice today is with $^{131}$I. Its physical half life is 8 days and two third of its energy is emitted as gamma rays, which do not contribute significantly to therapeutic efficacy. The gamma rays are active in non-specific irradiation of both the patients bone marrow and medical environment of the patient, requiring isolation of patients in shielded rooms for several days. Only one third of the energy is emitted as Beta rays, contributing
directly to the therapeutic effect and 95% of this energy is deposited within 1 mm of the emission source.

Radionuclides with more favorably radio physical characteristics are undergoing evaluation. The pure beta emitter Y90 is more energetic and thus more penetrating, than $^{131}$I, $^{186}$Re, $^{188}$Re and $^{57}$Cu are also promising beta emitters. Alpha radio nuclides such as astatine-211 and bismuth-213 are available for radioimmunotherapy. They are much more cytotoxic than beta emitter but because of their radio physical characteristics, can only be used for microscopic targets (Hematological malignancies readily accessible to injected radioimmunoconjugates). A first phase I clinical study in nine patients with relapsed acute myelogenous leukaemia who were injected with a humanized anti-CD33 antibody (HuMI95) labeled with bismuth-213, showed no extramedullary toxicity and transient reductions in leukaemia cells in peripheral blood and leukaemic blast cells in the bone-marrows.

Conclusion
Thyroid disorders are global health problems with an endemic prevalence in Bangladesh. The relative frequency of thyroid disorders varies in different countries of the world and also in the different regions of the same country as well as in different socioeconomic status. The most popular treatment is radioactive iodine. When thyroid disease is diagnosed early, treatment can control the disorder even before the onset of symptoms. Thyroid diseases are life-long conditions. With careful management, people with thyroid disease can live healthy, normal lives.

References
Review Article