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Nuclear Medicine Therapy: Current Status and Future Prospects

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ABSTRACT

Radioisotope therapy began in 1942 with the use of ^{131}I for Graves disease and ^{32}P for poiycythemia vera. Local therapy with radioisotopes includes radiocolloids for malignant pleural and peritoneal effusions, intra-articular radiocolloids for chronic synovitis, intraarterial radioactive microspheres for liver metastases, and intralymphatic administration for malignancies of the lymphatic system.

The most widely practised use of radioisotopes for therapy is for the management of hyperthyroidism by ^{131}I. Each school has developed its own treatment schedule for controlling the disease without producing too unacceptable an incidence of late hypothyroidism. ^{131}I is also being used effectively for thyroid cancer, particularly at the Radiation Medicine Centre, BARC.

There is hope that a new generation 'of radiolabelled compounds is round the comer for therapy. As in the case of radiopharmaceuticals for diagnosis, the shift has been from simple inorganic compounds to tailored organic ones. Radiolabelled monoclonal antibodies aimed against specific tumour antigens have already shown great promise. Another area of interest is the use of minute lipid spheroids (vesicles) enclosing the radioactive drug which can be targeted to the tumour.

1. INTRODUCTION

After nearly five decades, nuclear medicine has come full circle. To begin with, it was a combination of diagnostic techniques and therapeutic applications with radioiodine and radiophosphorous continuing as mainstays for many a year till imaging applications for short-lived, generator-produced radionuclides turned it into essentially a diagnostic speciality. During the last ten years or so steady progress in the therapeutic

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applications of radiopharmaceuticals other than the conventionally used ^{131}I, ^{32}P, ^{198}Au has again brought the therapeutic aspects of nuclear medicine into focus. Just as diagnostic nuclear medicine has moved from inorganic to organic radiopharmaceuticals, more and more radiolabelled organic compounds are finding therapeutic applications.

Radioisotopes were probably first employed for systemic therapy by Stevens, et *al* in 1926 for treating malignant lymphomas with radium chloride (the treatment was soon abandoned)'. Regular use of radioisotopes for therapy, however, began in 1942 with the introduction of radioiodine for treatment of Graves disease by Hertz and Roberts[2] and the use of ^{131}I and ^{32}P by Hamilton and Lawrence[3]. Even after fifty years, radioiodine in the management of hyperthyroidism and differentiated thyroid cancer, and ^{32}P for treating polycythemia vera still remain the most acceptable methods of treatment. There have been, of course, a host of other radionuclides and radioactive drugs used for treating a number of diverse benign and malignant diseases with varying degrees of success. This article reviews some of the more important therapeutic applications which have stood the test of time and to make an attempt at identifying some emerging areas of clinical significance.

2. APPLICATION OF RADIOPHARMACEUTICALS

Radiopharmaceuticals for therapy can either be for local use or can be administered internally.

2.1 Local Applications

2.1.1 Intracavitary Therapy

The most frequently performed therapeutic procedures in this category are the use of radiocolloids for intrapleural and intraperitoneal instillation in patients with malignant pleural effusion and ascites. ^{198}Au, ^{32}P and ^{90}Y colloids are commonly employed purely as a palliative measure in patients with disseminated malignancy presenting with serosal effusion. Colloidal therapy in malignant pericardial effusion often produces very dramatic results. Administration of radioactive colloids in patients with stage I ovarian carcinoma immediately after surgery has been reported to have immensely improved 5-year survival (94 per cent) as compared to those who had undergone surgery (22 per cent)[4].

2.1.2 Intra-Articular Therapy

Radiocolloids of ^{198}Au, ^{32}P, ^{90}Y, ^{169}Er, ^{186}Re have been used for intra-articular therapy for chronic synovitis. Synovectomy is not always successful and recurrence rates are high due to regeneration of synovium. Moreover stiffness and limitation of movement of the joints are also encountered after surgery. Intra-articular use of chemotherapeutic drugs is less invasive but not as efficacious. Best results (54 per cent excellent and 39 per cent good) are obtained in patients with stage I synovitis which drops to 40 per cent excellent and 14 per cent good response in patients with stage III of the disease'.

2.1.3 Intra-Arterial and Intralymphatic Therapy

Liver metastasis from primary colon and rectal cancers has been treated by intra-arterial administration of either ^{90}Y microspheres alone or ^{90}Y microspheres in conjunction with 5-fluorouracil (5FU) with some degree of success[6].

To begin with, ^{131}I-ethiodol and later ^{32}P-ethiodol have been used through the intralymphatic route for treating patients with malignant lymphoma, lymphosarcoma and Hodgkins' disease. Although intra-arterial and intralymphatic therapy is practised in a very limited number of institutes, they have reported encouraging results.

2.2 Internally Administered Isotopes for Therapy

During the forties and fifties, radioiodine (^{131}I) was the most useful and utilised radionuclide both for diagnostic studies and therapy. These. were also the days when a spate of reactor-produced radioisotopes became available and hopes were running high that a radioactive compound capable of selectively localising in a tumour was just round the corner. Inspite of years of sustained effort and evaluation of a host of compounds ranging from Astaline[7] (^{211}At) to Tritium[8], there was no significant addition to the time tested and very useful ^{131}I, ^{32}P and radiocolloids/microspheres of ^{32}P, ^{198}Au and ^{90}Y till a few promising radiolabelled organic compounds suitable for therapy were reported in literature and monoclonal antibodies against tumours were raised and subsequently radiolabelled.

2.2.1 Treatment of Hyperthyroidism with Radioiodine

Nuclear medicine came into being as an established clinical discipline with the use of radioiodine for the treatment of hyperthyroidism in 1942 which still remains the treatment of choice. Dr. Henry Wagner during the course of a panel discussion stated : 'Most valuable use of radioactive iodine is in the treatment of hyperthyroidism. Perhaps 98 per cent of the value of radioisotope therapy has been derived from therapeutic use in hyperthyroidism (not in cancer of the thyroid)'[9]. Dworkin estimated that more than 250,000 hyperthyroid patients had been treated in various parts of the World till 197010. During the last 20 years this number must have atleast doubled. Doubts about the increased incidence of thyroid carcinoma were laid to rest by Dobyns et al. in their report[11] on the cooperative thyrotoxicosis therapy follow-up study initiated in 1961 in which 26 centres carefully followed up 36,000 patients of which 22,000 patients were treated with radioiodine and around 14,000 treated with surgery and antithyroid drugs. Incidence of thyroid carcinoma in radioiodine-treated hyperthyroid group was the lowest (0.1 per cent). In comparison, the incidence of thyroid carcinoma was 0.5 per cent in patients who had undergone surgery and 0.3 per cent of those treated with antithyroid drugs had carcinoma[11]. Safa et al. reported that the reproductive history and progeny amongst the 242 children and adolescents treated with radioiodine for hyperthyroidism was no different from those of the general population, thereby removing another doubt about the genetic hazards associated with radioiodine therapy for hyperthyroidism[12]. The biggest stigma against radioiodine treatment for hyperthyroidism, however, is the rising incidence of late onset hypothyroidism following radioiodine therapy with an annual increment rate of 2-3

per cent with no evidence of plateauing upto atleast 15 years[13]. While early hypothyroidism seen within one year is dose dependent and percentage of patients becoming hypothyroid could be reduced by giving smaller radioiodine doses, late onset hypothyroidism is independent of the dose given. Early and late onset hypothyroidism is also encountered after surgery and also increases at about the same rate[14]. Antithyroid drug treatment also has disadvantages like prolonged treatment upto one to two years under medical supervision and high recurrence rate.

Since the onset of hypothyroidism is insidious and may occur after many years of surgery or radioiodine treatment, the diagnosis may be difficult particularly after ^{131}I therapy as it leaves no scars like after thyroidectomy. Even if it is detected, it entails life long therapy with thyroxine which in poor developing countries is an economic burden and results in poor patient compliance. In spite of all these drawbacks, radioiodine therapy for hyperthyroidism still remains the most acceptable and economical method.

While making a decision regarding the dose of radioiodine to be used for an individual patient, it should be borne in mind that no therapeutic dose, however small, is completely devoid of the risk of causing hypothyroidism. Irrespective of whether it is a single dose or a multidose regime, probability of inducing hypothyroidism in a fraction of patients is always there. Every therapist, therefore, has to make a basic decision as to whether a low dose regime or multiple small dose regime resulting in a larger number of patients needing -retreatment and a larger period for patients to become euthyroid is acceptable, or employment of a larger radioiodine dose associated with a higher incidence of hypothyroidism. At one extreme are those who employ larger doses of radioiodine in the range of 30 to 40 mCi with the aim of making all patients hypothyroid and then putting them on thyroxine for life, avoiding the bother of long term follow-up and uncertainty of hypothyroidism creeping up insidiously during the following years. On the other extreme the unreasonable desire of avoiding occurrence of hypothyroidism has led others to give very small doses of radioiodine (1 mCi or less) repeated at intervals till the patient becomes euthyroid. It cannot be emphatically said that any particular dose regime is superior to the other or that careful dosimetry yields better results than empirical estimation of radioiodine therapy dose. It is nevertheless clear that some strategy of radioiodine treatment, no matter what its premise, should be adopted and consistently applied. Without such a policy the physician can be easily swayed by his most recent experience and other irrelevant factors. Moreover, assessment of results in retrospect is easier and meaningful.

Brigadier Mazumdar was one of the pioneers in the field with vast experience in the management of thyroid diseases. His deep concern for his patients is reflected in radioiodine therapy strategy adopted by him for treating hyperthyroidism. It was not acceptable to him that even a single patient becomes hypothyroid after radioiodine therapy. He therefore advocated multiple small dose radioiodine doses which necessitated frequent follow-up examinations and supportive therapy with antithyroid drugs and beta blockers to keep symptoms under control. Dr. H. Atkins during a discussion of presentations held at a symposium in 1977 also advocated low dose ^{131}I therapy because he felt that many years may elapse before patient becomes hypothyroid

and continued hyperthyroidism with low doses of ^{131}I can be handled with Propanolol and antithyroid drugs[15].

Radiation Medicine Centre (RMC) of Bhabha Atomic Research Centre (BARC) has been following a single dose therapy regime since 1963. Radioiodine dose is calculated individually and is based on estimation of thyroid weight predicted from rectilinear scan, thyroid uptake and biological half-life, and is designed to deliver about 7,000 rads. With this regime 69 per cent patients became euthyroid while 15.4 per cent patients were persistently toxic and needed another dose. Incidence of early hypothyroidism was 5.8 per cent upto 1 year, which rose to 12.2 per cent at 5 years, 14.7 per cent at 10 years and 15.4 per cent at 12 years [16]. It can be unequivocally stated that radioiodine treatment for hyperthyroidism is effective, inexpensive, convenient for both patients and physicians, and is the treatment of choice for most patients of hyperthyroidism (exceptions being pregnancy, lactating mothers, large nodular goitres and probably children).

2.2.2 *Radioiodine Therapy of Thyroid Cancer*

It has long been known that certain differentiated carcinomas of the thyroid and their metastases retain the capability of picking up iodine and synthesising it into iodoproteins and even some thyroxine. Radioiodine therapy for treating adenocarcinoma of the thyroid has, thus, been successfully employed since the early forties. Inspite of long use, its scope and limitations are not widely realised. One of the reasons for failing to get a proper perspective, and the reason why radioiodine is used too little or too late, is due to the infrequency of thyroid cancer. Not more than 5-7 patients of thyroid cancer are seen in a large general hospital in a year. Since administration of radioiodine involves specialised procedures and use of nuclear medical instrumentation like rectilinear scanner, wholebody profile scanner, gamma camera, etc., even these patients have to be referred to centres where facilities are available to treat patients with high doses of radioiodine. In our country there are only three or four centres which are treating thyroid cancer patients with radioiodine on a regular basis.

About 30 per cent of patients with a differentiated carcinoma of thyroid exhibit radioiodine uptake in the tumour/metastasis even in the presence of competing normal thyroid tissue. After thyroid ablation either with surgery (near total thyroidectomy, identifying and saving the parathyroids and recurrent laryngeal nerves) or radioiodine, the probability of radioiodine uptake by metastases from differentiated thyroid carcinoma can be boosted to more than 66 per cent contrary to the generally held belief, radioiodine concentration in metastases from papillary carcinoma of thyroid is also seen fairly frequently, and was found to be 54.3 per cent by us[17].

A large dose ^{131}I scan with 2-3 mCi is performed six weeks after surgery. During this period thyroid hormones and iodine containing medications are withheld. Studies also include whole body profile scan for locating radioiodine concentrating metastases and serum thyroglobulin estimations.

If scan study shows appreciable amount of residual thyroid tissue with radioiodine uptake of more than 2 per cent, then ^{131}I ablation dose is given which ranges between

30-250 mCi depending on the amount of tissue (larger the amount and higher the uptake, smaller is the dose).

For ablating ^{131}I concentrating lymph node, lung or bone metastasis, radioiodine therapy is given with the dose varying between 150 and 250 mCi. Special care has to be taken when treating lung metastases and complications of pulmonary fibrosis and its sequelae have to be borne in mind. Bone marrow suppression has to be avoided when treating patients with extensive bone metastasis.

To date more than 1600 patients of differentiated thyroid cancer have been treated with radioiodine at RMC. Survival data on patients treated between 1963 and 19% was published in 1985. Survival rates at 15 years in patients treated with surgery followed by radioiodine therapy and thyroxine hormone supplement with papillary, follicular and mixed papillary follicular carcinomas with and without regional lymph node metastasis were identical and ranged between 90 and 100 per cent. All patients with lung metastases from papillary and mixed papillary follicular carcinoma of thyroid were alive at 10 years. 92 per cent patients of follicular carcinoma with lung metastases were alive at 10 years which dropped to 67 per cent at 15 years. Survival rates in patients of follicular carcinoma with bone metastasis at 5, 10 and 11 years were 94, 75 and 50 per cent respectively while survival of patients with mixed papillary follicular carcinoma at 8 years was 75 per cent. There were 7 patients with extensive metastases at multiple sites involving more than one system. Three of these patients lived for 3 years".

It can thus be concluded that near total thyroidectomy in patients with a differentiated thyroid carcinoma followed by radioiodine therapy and thyroxine hormone supplement yields the best results. There may be some doubts about giving radioiodine to patients who do not initially have metastases (ablation of normal tissue) but there is no doubt that patients with ^{131}I concentrating metastases benefit greatly from radioiodine treatment.

2.3 Radioactive Phosphorous Therapy

2.3.1 ^{32}P for the Treatment of Polycythemia Vera and Leukaemia

incidence of polycythemia is estimated to be about S/million/year amongst Europeans. It has been reported to be the highest amongst the Jews and the lowest in Africans. In India also primary polycythemia incidence is very low. Lawrence employed ^{32}P in the form of sodium orthophosphate for treatment of leukaemia in 1936 and for polycythemia vera in 1939. With the availability of a' number of effective chemotherapeutic agents and success of multiple drug treatment for leukaemia, ^{32}P is not commonly employed for treatment of chronic leukaemia.

The usefulness of ^{32}P for treating polycythemia was also doubtful primarily because of the doubts about its leukomegenic effects. There have been proponents of keeping polycythemia under control with phlebotomy alone but it has been found adequate in controlling polycythemia only in a few patients, while a majority of patients need additional myelosuppressive therapy. Due to small number of polycythemia vera patients attending individual centres, a multicentre Polycythemia Vera Study Group

(PVSG) was set up in USA in 1967 for conducting controlled studies to determine if phlebotomy alone was enough and for comparing ^{32}P treatment combined with phlebotomy and chemotherapy supplemented with phlebotomy. The study covered 420 patients and was spread over 10 years. It has been shown that ^{32}P with phlebotomy prolongs survival (average survival 16 years) as compared to phlebotomy alone (average survival 8 years). Patients treated with chemotherapy and phlebotomy also developed terminal acute leukaemia[18].

2.3.2 ^{32}P for Treatment of Intractable Bone Pain from Bone Metastases

A number of ^{32}P-labelled radiopharmaceuticals' like ^{32}P-diphosphonate, ^{32}P-ethylenehydroxy diphosphonate (EHDP), ^{32}P-polymetaphosphate, ^{32}P-pyro and orthophosphates have been used either alone or in conjunction with testesterone and parathormone. Relief from pain ranging between 3 to 6 months has been reported. Metastases from carcinoma of the prostate and breast respond best to the treatment[19]. $^{89}SrCl$ has also been employed for therapy of bone lesions.

3. FUTURE PROSPECTS,

During the last 48 years, a host of radionuclides and radioactive drugs have been tried and suggested as potent therapeutic: tools but only radioiodine (^{131}I), radioactive phosphorous (^{32}P) and radiocolloids and microspheres of ^{32}P, ^{198}Au and ^{90}Y have stood the test of time and are being used in clinical practice. However, during the last few years there have been a few promising developments and there is hope that a new generation of radiolabelled compounds of clinical usefulness will be available to the therapists. As in radiopharmaceuticals used for radionuclide imaging, there has also been a shift from relying on simple inorganic chemicals like $Na\,^{131}I$ and $Na_2H\,^{32}PO_4$ to the development of labelled organic compounds for radionuclide therapy. Examples are : attempts to use ^{131}I-19-iodocholestrol, ^{131}I-metaiodobenzylguanidine (MIBG), and synthesis of ^{32}P-labelled organic phosphate compounds for treatment of bone lesions. More such function-related radiopharmaceuticals will become available for therapy. Another area in which beginnings have already been made and much more will be done in the future is radiolabelled monoclonal antibodies raised against specific tumour antigens. ^{131}I-labelled monoclonal antibodies have already been used in patients with melanoma, lymphoma and thyroid cancer.

Another area which has excited the biochemists, biophysicists and the physicians alike is the use of minute lipid spheroids (vesicles) using phospholipids like lecithin. The drug or the radioactive drug can be enclosed inside the vesicle, which can then be targeted to the organ or tumour.

In conclusion it can be stated that though therapeutic appliaations of radioisotopes are limited, yet in these limited areas they have proved to be very useful to the clinicians. There is ample scope for expanding their applications through development of function-related radiopharmaceuticals and use of radiolabelled monoclonal antibodies for therapy.

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