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^{90}Y and Skin Cancer Therapy: A Mini Review

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Abstract
Radiation therapy is a valuable option for treatment of skin cancer. In order to deliver the radiation dose to the superficial skin tumor, an X-ray source, electron beam radiation therapy or a radioisotope is applied. The effectiveness of these procedures is well established in the literature. Findings of some recent studies have indicated that beta particles can be of particular interest in suppressing skin tumor growth. Beta emitting radioisotopes are favorable because of the short penetration depth of their emitted particles. Beta radiation can induce significant damage in superficial skin tumor, and at the same time, result in enhanced protection of the underlying healthy tissues. Skin cancer is the most common malignancy in humans. Therapeutic modalities for skin cancer are local destruction, radiotherapy and surgery. External radiation therapy leads to good results, however, generally5-6 wk of treatment is needed to deliver optimal radiation dose to tumors. 90Y, a beta emitting radionuclide, was immobilized in a bandage patch for possible application for the therapy of superficial maladies such as tumours and skin cancers. The aim was to prepare a radiation source that could deliver uniform dose within a short duration and avoid the inconveniences faced with the gamma sources used in teletherapy and brachytherapy. plays an important role in the treatment of malignant tumors in nuclear medicine.
Keywords: *90Y skin patch, Tumour therapy, Skin tumours*

Introduction

Skin cancer is a serious concern among the fair-skinned population, a majority of which are basal cell carcinomas. More than 95% of basal cell carcinomas, the most common form of skin cancer, occur in patients more than 40 years of age [1]. Skin cancer is not a single tumor with a single cause, but rather three predominant tumors such as basal cell carcinoma, squamous cell carcinoma, and cutaneous melanoma. Both basal cell carcinoma and squamous cell carcinoma are grouped as nonmelanoma skin cancer (NMSC), arising from epidermal basal unit cells and epidermal squamous cells, respectively. Cutaneous melanoma is a potentially lethal cancer that most commonly develops from epidermal melanocytes as a new mole or a preexisting mole that changes [2]-[4]. As the incidence of nonmelanoma skin cancer (NMSC) increases, so does the number of modalities used to treat this condition. Surgery is the most frequent approach used to treat NMSC, and clinicians usually perform Mohs micrographic surgery, conventional excision,

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electrodesiccation and curettage or cryosurgery. The 'gold standard' for treatment continues to be Mohs micrographic surgery, but owing to the time and expense involved with this procedure, it is indicated only in patients with aggressive tumors or those where disfigurement or functional impairment is a risk[5]-[6]. Although radiation therapy is effective, its use is limited because of the side effects induced; radiation therapy can be used in certain patients who are not surgical candidates. Newer noninvasive options for NMSC include topical chemotherapeutics, biological-immune-response modifiers, retinoids, and photodynamic therapy, which can be used particularly in patients with superficial tumors. Treatments should be tailored to tumor type, location, size, and histological pattern, and although surgical methods remain the most frequently used, newer noninvasive treatments can be used in select tumors and may reduce morbidity. Each therapeutic modality has its own advantages and disadvantages. Although surgery is usually preferred, recurrence rates are high and it is not always possible to be practiced [7],[8]. Radiotherapy using external beam therapy is often used for treatment owing to the advantage of treating a visible tumor. However, external radiotherapy has certain disadvantages, such as the necessity for expensive radiation therapy units and the adverse effects of penetration into underlying bone and soft tissues. To overcome some of the disadvantages of external beam radiotherapy such as high cost of therapeutic units, radiation protection of patients and paramedical staff, etc., mould brachytherapy using high-energy β^- emitters has been explored as an alternative treatment modality for achieving adequate dose delivery to the affected area without causing undesired radiation exposure or injury to the neighboring normal tissues. Compared with external radiotherapy, radionuclide therapy is simpler, less traumatic, and less expensive [9]-[11]. As the limitation of the use of radiation therapy is that some damage to healthy tissue is inevitable while administering the radiation dose, the use of a source that can impart a uniform dose to the tumor with minimum dose to normal tissue is highly desirable. The advantages of such radiation sources in overcoming the limitations of radiation therapy while using its beneficial effects can be achieved through the combination of a source of high-energy b-radiation with a custom-made dispositive for its application. In addition, the manufacturing process has to be simple and inexpensive. The preparation and the therapeutic effects of such mold brachytherapy sources incorporating 166Ho, 188Re, 90Y, and 32P have been recently reported by different groups [12]–[18]. The potential therapeutic benefits of beta particles have encouraged the use of beta emitting isotopes for radiation therapy of skin tumors as well. Beta radiation, due to its short range, penetrates a few millimeters in the tissue resulting in severe damage to the superficial target structure with minimum side effects to the healthy tissue nearby. Because of the superficiality of the skin tumors, beta radiation would be an interesting option in the management of the skin cancer. For example, ^{32}P patches have been used, and a study confirmed complete tumor regression in an animal model of skin cancer in a 40 Gy single-dose scheme [19]. In other similar studies, skin patches coated with beta emitter radioisotope 166Ho were successfully applied to treat Bowen's disease where radioactive patches were put on the surface of skin cancer for time periods of 30 to 60 min to deliver a radiation dose of 35 Gy [20]. Similarly, radioactive patches coated with ^{90}Y have been prepared and tested to control superficial tumors in mice. Radioactive patches of up to 100 MBq radioactivity used in that study showed to be a promissory effective treatment for fibrosarcoma [21]. The first radionuclide patch for treating skin cancer was produced by bombarding a 165Ho-incorporated patch in a nuclear reactor by Korean scientists.2 Extending this theme, preparation of skin patches

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incorporating β- emitting isotopes such as 90Y and 188Re for treatment of superficial tumors have been reported by the present study group and other research groups [22]-[24]. The availability of radionuclides, their physical characteristics, and their logistic advantages are of importance when considering the possibility of a treatment employing them. The limitation of using the aforementioned radionuclides is their limited availability and short half-lives, which are not long enough for wide deployment [25]-[27]. 90Y has emerged as an important radionuclide for such therapy owing to its physicochemical properties and commercial availability on demand. It is a pure β- emitter with a maximum β- energy of ~2.28MeV and the advantage of adequately convenient half-life of 64.1 h suitable for wide use, and hence, it is a better choice for use in the proposed application. In recent years, specially designed patches containing 90Y have been developed for contact brachytherapy of skin lesions[28],[29].

90Sr/90Y generators

Yttrium-90 is a therapeutic radioisotope of enormous interest, and several established radiopharmaceuticals with this isotope are currently in use. Radionuclide therapy using radiopharmaceuticals has been in existence for over 60 years and offers substantial benefits to cancer patients, in particular, patients suffering from thyroid cancer. Numerous clinical trials for treating other types of cancer using therapeutic radiopharmaceuticals are in progress, and their success will increase the demand for therapeutic radionuclides in the coming years. Those radioisotopes having short physical half-lives ranging from a few hours to a few days are useful for radionuclide therapy. The use of short lived radioisotopes for radionuclide therapy involves important challenges including the transport of the radionuclides and the need for frequent shipments[30],[31]. Radionuclide generators represent an efficient means for making short lived therapeutic radionuclides more widely available throughout the world. To meet the requirements for sustained growth and future expansion of the application of therapeutic radiopharmaceuticals in nuclear medicine, particularly in oncology, it is important to develop and maintain a constant and reliable supply of therapeutic radionuclides of the required quality in the desired quantities[32]. The IAEA has several activities to support programmes that foster the enhanced availability of therapeutic radionuclides and radiopharmaceuticals in Member States[31]. One such activity was the coordinated research project (CRP) on the development of generator technologies for therapeutic radionuclides, which ran from 2004 to 2007, in which participants from 13 countries worked to develop generator technologies for the preparation of 90Y and 188Re usable for radionuclide therapy[33]. development of 90Sr/90Y and 188W/188Re generators, studies on post-elution concentration of 188Re, the use of higher capacity adsorbents based on zirconium and titanium composites, and analytical techniques developed for the quality control of generator produced radionuclides. Radionuclide therapy using unsealed radioactive sources requires the reliable, cost effective availability of a variety of therapeutic radioisotopes[34]. Therapeutic applications include the treatment of cancer, bone pain (palliation) and rheumatoid arthritis; bone marrow ablation; and inhibition of coronary restenosis. Radioisotopes of current interest for these applications include 131I, 177Lu, 153Sm, 186Re, 166Ho, 188Re and 90Y[35]-[38]. Targeted therapy of cancer using radiopharmaceuticals generally requires the availability of high specific activity radioisotopes. Radioisotopes having short physical half-lives ranging from a few hours to a few days are useful for radionuclide therapy. A major advantage of generator produced

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radionuclides is that they have very high specific activity and can be used for the preparation of radiopharmaceuticals that target low density sites[39]. A major advantage of generator produced radionuclides is that they have very high specific activity and can be used for the preparation of radiopharmaceuticals that target low density sites. Radionuclide generators are also a cost effective way to ensure a continuous and reliable supply of short lived radioisotopes. The CRP on the development of generator technologies for therapeutic radionuclides organized by the IAEA focused on optimizing 90Sr/90Y and 188W/188Re generators that provide carrier free 90Y and 188Re therapeutic radioisotopes, respectively[40],[41][33],[34]. Yttrium-90 is a therapeutic radioisotope of enormous interest, and several established radiopharmaceuticals with this isotope are currently in use. Yttrium 90 (T1/2: 64.1 h; Ebmax: 2.28 MeV) is a pure b– particle emitter that can be prepared by the irradiation of 89Y in a nuclear reactor or by the decay of 90Sr[42]. Yttrium-90 produced from a reactor is of very low specific activity owing to the small neutron capture cross-section (0.001 b) of 89Y. As yttrium is mononuclidic, there is no need for enriched isotopes for irradiation. The radionuclidic purity of this directly (n,g) activated product is generally very high. However, depending on the epithermal flux in the reactor, detectable levels of 89Sr could be present owing to the (n,p) reaction. Because 89Sr is a pure beta emitter, its presence may not be detected by the conventional methods of estimation of radionuclidic purity using gamma ray spectrometry. There is unlimited potential availability of 90Y, since it exists in a secular radioactive equilibrium with 90Sr (T1/2: 28.8 a)[43],[34].

Discussion

Radionuclide therapy is a unique cancer treatment modality, which is alternative for or adjuvant to external radiation and chemotherapy. Recently, expanding availability of suitable radiopharmaceuticals in oncology and endocrinology enable the use of radionuclide therapy. In nuclear oncology, specific tumor-seeking radiopharmaceuticals are being used since they can deliver radiation doses selectively into the target tissues[42]. Superficial skin cancers can be successfully treated using mould brachytherapy sources containing high-energy b– emitters such as 90Y, 188Re, 166Ho and 32P. In conventional radiation therapy, the dose to nontarget organs is a matter of utmost concern, whereas in the use of such sources the nontarget organs are subjected to practically zero dose[44],[45],[30]. Mould brachytherapy using β- emitting radionuclide incorporated patches has been reported as one of the promising alternative therapeutic modalities for topical treatment of skin cancer in areas that are difficult to excise, especially on the face, including eyelids, nose, and lips. This modality received wide attention and appears to be poised for rapid growth. This mode of treatment has numerous advantages as it does not need expensive therapeutic units unlike external beam radiotherapy, and the procedure is simple for preparation as well as application and is noninvasive[34]. Radionuclide therapy using beta-emitters such as 89Sr and 32P, and gamma-emitters such as 106Ru, 125I and 60Co have been used in the past for topical applications in the treatment of ophthalmologic diseases[46]. Improving on this mode of treatment, radioactive beta-emitting paper skin patches were reported in the recent past for the treatment of skin tumours. The radioisotopes used in this mode of treatment were high-energy beta-emitters such as 166Ho and 188Re[9],[11]. The technique used for the preparation of 166Ho patch involved the irradiation of 165Ho incorporated film in a nuclear reactor to get the 166Ho patch. The disadvantage with such a method is the possible instability of the 166Ho-containing film.

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Depending on the constitution of the films, the patches on irradiation might contain undesirable radionuclide 166Ho emits b2-radiation (0.7MeV) with a half-life of 26.7 h, which is short for supply from a centralized radiopharmaceutical laboratory and access availability is dependent on the reactor's operation performance[16]. Hence, it is worth exploring the use of generatorproduced radionuclides with high-energy b2-radiation like 90Y (half-life~64 h) and 188Re (17 h) for such applications. 188Re is commercially available from convenient 188W-188Re generator system[47]. The use of a 90Y skin patch for the effective treatment and regression of superficial fibrosarcoma tumours has been reported [15]. The potential benefits of using 90Y incorporated skin patches for the treatment of skin tumours are as follows: It has aconvenient half-life (64.1 h), for prepare skin patches at a centralized radiopharmaceutical laboratory and for supply to different destinations without much depletion in the radioactivity[48]. whereas this is practically impossible with radionuclides such as 166Ho has a short half-life (26.9 h) which may be a disadvantage for its easy supply. Even though 188Re has favourable characteristics for such applications, its production requires the availability of a high flux nuclear reactor[15]. 166Ho and 188Re incorporated into skin patches have already been reported for treatment of skin tumours [16,24]. The technique used for the preparation of the 166Ho patch involves irradiation of 165Ho incorporated film in a reactor to obtain a 166Ho patch. The disadvantage with such a method is the possible radiation instability of the 166Ho incorporated film and the presence of other undesirable radionuclides[13,14,16,24]. 90Y is an attractive isotope for such treatments. 90Y emits high energy b- radiation (Emax = 2.28 MeV) with maximum tissue range of 11 mm (average tissue range = 3 mm) which is very favourable for such applications. The absence of gamma radiation avoids radiation dose to the physician and the patient, unlike in the case of 166Ho and 188Re. The easy availability of 90Y from a 90Sr-90Y generator, coupled with its convenient half-life (64.1 h), enables its supply from a centralized radiopharmacy[21].

Conclusion

In radiotherapy of skin cancers, the main target is treating skin cancer, but it can also be extended to other applications. In this way, the radioactive patch is of significant important to treat the skin cancers so that the desired amount of cell-killing radiation dose [37] can be applied. ^{90}Y also can be a source for treatment of skin cancers and superficial tumors. In view of ease of preparation and feasibility of making custom-shaped sources, further investigations on ^{90}Y sources may open new windows for skin cancer treatment.

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