REVIEW ARTICLE

A brief review of targetted radionuclide therapies

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ABSTRACT

Personalized medicine is an emerging medicalfield. Targetted radionuclide therapies forbenign and malignant diseases have been inuse since 1945. Over the last 20 years due toadvancements in the nanotechnology andtargetting cell receptors, radionuclidetherapies have emerged as a subspecialty of nuclear medicine. Through this article we would like to briefly describe the evolution of radionuclide therapies and their different clinical applications as personalized medicine.

Key words: Radionuclide therapy, ^{131}Imetaiodobenylguanidine therapy, CD-20targeted therapies, radioembolization,metastatic bone pain palliation

INTRODUCTION

Radiotherapy techniques have proved important in treating as well as prolonging the patients' lives depending on the type of cancer in question. However, the success of these techniques is limited by their lack of specificity as the anti-cancer agents or cytotoxic technologies do no distinguish between the cancerous regions and the normal tissues [1]. Most of the traditionally used radiotherapy techniques apply a non-discriminatory destruction of the cells exhibiting uncontrolled growth without any degree of selection leading to the destruction of the healthy cells. Unlike external radiotherapy which damages cells' DNA with the aim of killing those with uncontrolled growth, targetted radionuclide therapy offers a systemic treatment by delivering toxic levels of radiolabelled molecules to the target sites for a highly selective destruction of the site [2].Radionuclide therapy acts the same way as chemotherapy by targetting specific cells, but it is more advanced in that radionuclides also kill tumour cells lacking tumour-specific receptors and thus it has ability for direct as well as a bystander effect which ultimately kills the tumour cells. The biological effect of targetted radionuclide therapy results from energy absorption of radiation emitted by the radionuclide. After the first description of radioimmunotherapy by Korngold and Pressman in 1953, numerous radiopharmaceuticals have been developed by advanced techniques in genetic engineering and chelating techniques [3]. Targetted radiotherapy involves the utilization of three particulate particles, which are capable of irradiating tissue volumes with subcellular, cellular and multicellular dimensions. These particles include Auger electrons, alpha particles, and beta particles.

Auger electrons and Auger-electron-emitting radionuclides

Auger electrons are particles released by some elements in a phenomenon referred to as the Auger effect. In this phenomenon, an atom emits an electron after filling an inner-shell vacancy resulting in energy release. Some of the current available or prospective Auger electron emitters include indium-111, iodine-125, iodine-123, and bromine-77. These radionuclides can be used alongside targetting vehicles to localize sub-cellar radiations near the cellular DNA leading to an effective and a specific killing of the tumour cells. Using auger-emitting radionuclide therapeutics, highly tailored targetted radiotherapeutics could be engineered to fit the specific needs of a cancer patient [4].

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Beta particles and beta-emitting radionuclides

Beta particles are fast-moving electrons emitted by the nucleus during radioactive decay. Some of the currently approved betaemitting radionuclides used in radiotherapy include yttrium-90 and iodine-131 (for non-Hodgkin's lymphoma treatment), strontium-89-chloride and samarium-153-EDTMP (for bone metastases). Other potential betaemitting radionuclides include rhodium-105, gold-199, copper-67, rhenium-186, and lutetium-177 amongst others. The major advantage of beta particles is that they have minimal tissue penetration. These particles are emitted at high speed, but they become rapidly attenuated by biological tissues. As a result, when administered as a radiopharmaceutical it does not affect the surrounding tissues as it cannot travel beyond specific range within a biological structure. An additional protection of the un-targetted tissue is also achieved by radioimmuno targetted therapy [4].

Alpha particles and alpha-emitting radionuclides

Alpha particles comprise of two protons as well as two neutrons, and they are identical to helium atom's nucleus. Alpha-emitting radionuclides emit particles of only a few cell diameters in tissue. One of the advantages of alpha particles is that they have a high linear energy transfer that makes them more biologically effective as compared to the conventional radiotherapy techniques. In this vein, fewer alpha particles are capable of killing human cancer cells. Some of the available radionuclides that emit alpha particles include radium-223, astatine-211, and bismuth-2013. Alpha particles are preferred for radiotherapy for their ability to deliver lethal radiation, within a range of 50-90 µm in diameter. This allows the emitter to specifically target cancerous tissue without destroying the adjacent healthy tissues. Alpha particles offer a therapeutic benefit by breaking the DNA double strand and thus breaking the cell cycle. Also, these particles cause chromosomal instability in the nearby cells leading to a bystander effect as observed in radiotherapy [4].

Radionuclides as therapeutics

Radionuclides used in cancer treatment release energy in the form of beta particles, Auger electrons or alpha particles to cause the destruction of cancer cells and result in improvement of the patient's condition. The radionuclides applied for the purposes of treating cancer depend on several factors, including: the nuclear emission properties, mode of radioactive decay, physical half-life, radionuclide production route, pharmacological features of the resultant radio-conjugate, radiation type and its energy, and the stability of the resultant daughter nuclides. Most of the cancer-destroying radionuclides have a physical half-life of between 10 hours to 10 days allowing them to deposit a large radiation dose. They also emit high LET radiation near the target cancer tissue and their daughter nuclides are stable and long-lived to increase the therapeutic effect of the radionuclide [5].

CLINICAL APPLICATIONS

Iodine-131 and thyroid cancer treatment

Iodine-131 is highly radioactive and has a half-life of 8.02 days, and when used in small doses it is used in cancer treatment. When iodine-131 is taken orally, it crosses the gastrointestinal wall, and is concentrated in the thyroid gland where it decays into xenon-131, with the release of gamma radiations and beta particles.

On the global scale, the use of radioactive iodine in differentiated thyroid cancer treatment has been the most common and the oldest targetted radiotherapy. The aim of the use of iodine-131 in differentiated thyroid cancer treatment is to destroy cancer cells in order to ablate the remnant thyroid tissue in order to optimise follow-up and reduce cancer recurrence rate [6]. The significance of radioactive iodine treatment in targetted radiotherapy is derived from the ability of both the follicular and the papillary cancers to express sodium iodide symporter for radioactive iodine uptake by cancer cells. Low doses of radioactive iodine have high levels of efficacies as well as high safety profiles making it the most acceptable thyroid cancer management modality across the world. Furthermore, the disintegration of the respective radionuclides results in additional cytotoxic effects on the target cells [7].

Neuroblastoma/ neuroendocrine tumours and ^{131}I-metaiodobenylguanidine

Since the 1980s, treatment of neuroendocrine tumours have been treated using ^{131}Imetaiodobenylguanidine (^{131}I-MIBG) because of its high efficacy in treating chromaffin cell tumours (paraganglioma, pheochromocytoma,and neuroblastoma).

^{131}I-MIBG uptake happens in a similar version to noradrenaline and increases after catecholamine excretion or adrenergic innervation. Stage III and IV patients with neuroblastoma are difficult to manage via chemotherapy and surgery and most cases resort to the administration of ^{131}I-MIBG to control tumour growth as well as for symptom relief [8]. A management plan for neuroblastoma using ^{131}I-MIBG involves taking the patient through a series of studies including tissue biopsies, MRI/ CT studies, ultrasonography, ^{123}I-MIBG scintigraphy and FDG-PET/CT before the commencement of ^{131}I-MIBG therapy. Moreover, recommendations point that ^{131}I-MIBG infusion should last for longer than one hour in order to avoid metaiodobenylguanidine side effects. ^{131}I-MIBG may also be used for the treatment of other similar tumours such as paraganglioma, pheochromocytoma, medullary thyroid cancer, and carcinoid tumours. These tumours have a response rate of 30-75%, indicating high efficacies [9].

Targetted radionuclide therapy and lymphoma treatment

In the 2000s, two major targeted radionuclide therapeutic agents were introduced for lymphoma treatment to reduce the number

of deaths resulting from low-grade lymphoma that is difficult to treat with chemotherapy techniques. These agents include I-131 tositumomab and Y-90 ibritumomabtiuxetan and they have been demonstrated to yield 50-80 percent response rates. I-131 tositumomab has an IgG2a murine anti-CD20 antibody (tositumomab), while Y-90 ibritumomabtiuxetan has murine IgG1 anti-CD20 antibody (ibritumomab), the difference between the two agents is their differential linkage to the radionuclide [10]. By targeting CD20 antigens, these agents deliver the respective radionuclides mature Blymphocytes, pre-B lymphocytes, and B-cell non-Hodgkin's lymphoma, and thus it ends up inducing apoptosis, antibody-dependent cytotoxicity, and complement-dependent cytotoxicity after the formation of the antibody-antigen immune complex [11].

Yttrium-90 and liver tumours treatment

Such metastatic tumours as pancreatic carcinoma, colorectal carcinoma, neuroendocrine tumours and breast cancers also occur in the liver after metastases leading to a fatal pathological burden. However, reduction of the burden is achieved through traditional therapies with an additional administration of Y-90 microspheres for radioembolization. Radioembolization of the liver cancers with Y-90 microspheres generate between 27 and 100 percent response rates in clinical treatments [12].

Palliation of metastatic bone pain

During advanced stages of cancers, bone pain reduces the quality of life of the cancer patient to a significant extent. However, the administration of radiopharmaceuticals can palliate pain from metastatic processes. Some of the approved metastatic pain palliation radiopharmaceuticals include ^{186}Re-etidronate, ^{153}Sm-lexidronam and ^{89}Sr-chloride; their administrations result in high concentrations in bones leading to effective pain management [13].

Application of radionuclide targeted therapy in haematological malignancies

The type of radionuclide targetted therapy applied on a specific type of cancer is dependent on the type of malignancy in question. As a result, haematological malignancies require a different type of targetted radionuclide therapy from the one used for the solid tumours. In haematological malignancies, targetted radionuclide therapy is supported by three major factors. One of the reasons for the effectiveness of targetted radionuclide therapy is the expression of specific surface antigens by most cancer cell lines [14]. These antigens are absent from other tissues in the organism and thus making targetted therapies possible. Another reason for the effectiveness of this approach is the rich availability of the high-quality antibodies against antigens expressed by haematological tissues. Moreover, the effectiveness of this approach is also made possible by the high sensitivity of lymphomas and leukemias to ionizing radiation. In addition, the effectiveness of the targetted radionuclide therapy is also increased by the availability of bone marrow transplantation technologies that allow for the replenishment of the haematological stem cells after the treatment of haematological malignancies with high dose radionuclides. Some of the target antigens in targeted radionuclide treatment of haematological malignancies include CD45, CD66, CD33, CD5, CD25, and the most commonly targeted CD20. 90Y and 131I have the greatest potential for application as radionuclides in targeted radionuclide therapy. Moreover, some of the common haematological tumours treated using targetted radionuclide therapy includes T-cell leukemias, chronic lymphocytic leukemia, and Hodgkin's lymphoma [15].

Application of radionuclide targeted therapy in solid malignancies

Unlike the treatment of haematological tumours with targetted radionuclides which is highly efficacious, the treatment of solid tumours has low efficacies and is thus challenging. This challenge is presented by the inability of the ionising particles to penetrate the tumour body leading to their localization in the periphery as well as low doses in the tumour parenchyma. In targetted radionuclide therapy of solid tumours, the cells lying on the surface of the tumour body have the same structure and function and as a result, their destruction does not always result in the complete destruction of the tumour. Besides, the conditions inside of the tumour are hypoxic and do not permit the formation of reactive oxygen species which increases the damaging potential of the therapeutic agent. However, this problem can be addressed by the use of multi-step pre-targetted radionuclide therapy, which enhances exposure to tumour radiation and therapeutic selectivity [16].

Some of the successful applications of targetted radionuclide therapy of solid tumours include colorectal carcinoma, solid neuroendocrine malignancies, castration-resistant prostate cancer, metastasizing melanoma, pancreatic tumour and stage-IV melanoma, amongst others. The treatment of colorectal carcinoma involves the use of I-131-conjugated anti-CEA antibodies, and it produces up to 68 months median survival time. The application of anti- PSMA antigen antibodies with Lu-177 radionuclides offer a successful treatment of castration-resistant prostate cancer produces a successful therapy with a median survival time of 10 months, while the application of anti-NG2 with Bi-213 produces a long-lasting effect in stage IV melanoma treatment. For the metastatic melanoma, the survival time increases by nine months after administration of anti-NG2 antibodies conjugated to Bi-213 radionuclide, but the application of DOTATE in conjugation with Lu-177 produces a complication-free stable disease course in 46 percent cases [17].

Advantages and disadvantages of targetted radionuclide therapy

One of the advantages of targetted radionuclide therapy is that Auger

electron, alpha particle, and beta particle emitters are effective therapeutic particles as they can localize the delivery of cytotoxic ionizing radiation [18]. By linking the emitters to biological agents, localized treatment can be achieved because of the high affinity of some elements for some organs and organ systems. As a result, the therapeutic capability of these agents provides a localized killing of specific tissues and cells. Another advantage of the application of targetted radionuclides in cancer therapy is their large-scale availability [19]. Once a specific radionuclide is approved for use as a radiopharmaceutical, it becomes subject to large-scale production in the laboratory making it readily available for a wide scale application. Another advantage of targetted radionuclide therapy is a high specificity and selectivity for the target cell types [20]. Targetted radionuclides are linked to such biological components as antibodies which are specific for certain receptors expressed on cancer cells. As a result, when introduced into the body they become attached to the target cells where radionuclides decay to emit beta particles, alpha particles or Auger electrons, which kill the antibody-associated cancer cells. The mechanism leads to a selective killing of the tumour [21].

On the other hand, this therapeutic technique carries several significant disadvantages which limits its application in treating humans. One of the disadvantages of targetted radionuclide therapy is the shortage of radionuclides. For example, iodine-124, zirconium-89, astantine- 89, bromine-77 and copper-67 are in short supply because of their high requirements of high-energy/complexity accelerators for production and this limits their availability in contrast to radionuclides produced by the small cyclotrons in PET centres. This limitation of radionuclide supply also limits the advancement of research and development in radiobiology and radiochemistry. Amongst those listed above, only yttrium-90 and iodine- 131 are available for clinical use, but their availability is low. Another disadvantage of targetted radionuclide therapy is resistance. By being a biologically determined process, targetted radionuclide therapy is limited by resistance because some tumours might lack the receptor subtype leading to the inability to offer effective treatment. For example, a tumour may exhibit a variant subtype of somatostatin receptors leading to resistance to somatostatin-active radionuclides. Another limitation is a mutation that can lead to resistance as well. For example, mutation of somatostatin genes will result in loss of efficacy of somatostatin-targetted radionuclides [22].

CONCLUSION

Traditionally, radiotherapy has been utilized for cancer treatment to suppress and kill the cancerous cells. There are several disadvantages of this techniques including the unnecessary side effects and killing of the normal cells. Targeted radionuclide therapies are emerging as personalized medicine targeting only the receptor specific defective cells leading to minimize the side effect of the treatment along with maximizing the efficacy. This main advantage makes this as a treatment of choice for the patients in which it has proven benefits benefits over the conventional treatment. We are hopeful that with upcoming research this may well be the future direction of medicine.

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