Clinical Oncology xxx (2013) 1–6

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Advances in Anticancer Radiopharmaceuticals

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Received 8 April 2013; received in revised form 16 May 2013; accepted 12 June 2013

Abstract

This review highlights recent progress in the development of anticancer radiopharmaceuticals. Molecularly targeted radiotherapy refers to the selective delivery of radionuclides that emit charged particles, such as α particles, β or Auger electrons, to cancer cells via a targeting vector. The discovery of new molecular targets through systems biology and other approaches has widened the scope for radiopharmaceutical development. Innovations in antibody engineering and humanisation, recombinant DNA technology, conjugation chemistry and, increasingly, nanotechnology have provided new approaches to the delivery of radionuclides to cancer cells. The increased availability of radioisotopes that have not traditionally been considered for therapy, such as α particle emitters, has also broadened the indications for targeted radiotherapy.

Key words: α Particles; β electrons; radioimmunotherapy; targeted radiotherapy; vectors

Statement of Search Strategies Used and Sources of Information

Recent relevant papers concerning advances in anticancer radiopharmaceuticals were identified using Pubmed under search terms such as radioimmunotherapy, molecular targeted radiotherapy, radionuclide therapy, alpha particle therapy, Auger electrons, pretargeting, alpharadin, zevalin, among others.

Introduction

Radioiodine was first used in the treatment of thyroid cancer in 1948. Since then the treatment of cancer through the use of systemically or locally delivered radionuclides has developed into a subspecialty of radiation oncology, often referred to as molecularly targeted or systemic radiotherapy. Just as it has affected conventional drug development, so the discovery of abundant new cancer targets has dramatically influenced the design and synthesis of new radiopharmaceuticals. These can be tailor made to seek out and eliminate cancer cells by exploiting those features that distinguish them from normal cells. It is not the aim of this article to provide a comprehensive overview of anticancer radiopharmaceuticals, but rather to highlight important examples of recent preclinical and clinical progress.

New Targets

Most currently approved radiopharmaceuticals for targeted radiotherapy (TRT) fall into two categories. The first is a class of agents that accumulate naturally in specific tissues. Examples include ^{131}I, ^{131}I-MIBG and ^{89}Sr, which are concentrated in malignant thyroid, neuroectodermal and bone tissue, respectively. The second is a group of agents designed to seek antigens on the surface of cancer cells, which being immediately accessible to circulating drugs, are easily targeted. Zevalin, for example, is a ^{90}Y-labelled, antibody-based radiopharmaceutical directed against CD20, a cell surface glycosylated phosphoprotein expressed on the surface of B cells in non-Hodgkin lymphoma. Many other antibody-based agents, directed against cell surface antigens and receptors that are overexpressed in cancer,

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0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2013.06.004

have been tested in preclinical models and, in some cases, in clinical trials [1]. For example, agents that target the epidermal growth factor receptor (EGFR) family of receptors have been investigated extensively [2]. One approach to targeting surface antigens is to radiolabel the natural peptide ligands of cancer-associated receptors. An important example, ^{90}Y-labelled octreotide (^{90}Y-DOTATOC), which targets the somatostatin receptor subtype 2, is used in the treatment of neuroendocrine tumours in some specialist centres. This general approach has been termed peptide receptor radionuclide therapy and an authoritative clinical guide for its use in neuroendocrine tumours has recently been published [3].

Although the focus in the past has been on the development of radiopharmaceuticals that bind surface epitopes, the cytoplasm and nuclei of cancer cells also harbour many potential therapeutic targets. This has driven efforts to synthesise radiopharmaceuticals capable of internalising into cancer cells and, in some cases, accumulating in their nuclei. Cell-penetrating peptides have short, arginine-rich sequences and effect internalisation into cells through direct penetration of the plasma membrane or via endocytosis. Cell-penetrating peptides are capable of carrying into cells cargoes, such as small molecules or peptides, to which they have been linked chemically or through non-covalent interactions. The trans-activating transcriptional activator of HIV protein, TAT, which includes a nuclear localising sequence, was the first cell-penetrating peptide to be identified and has been used in both conventional drug and radiopharmaceutical design [4,5]. The modification of radiolabelled antibodies by the addition of TAT peptide has allowed targeting of molecules that are located exclusively in the nucleus, such as DNA damage signalling and cell cycle control proteins, although these agents are still at the preclinical stage of development [4,6]. Similarly, the addition of nuclear localising sequence peptide to radiolabelled carrier molecules enhances nuclear uptake [7–9]. This is especially advantageous for radionuclides that emit particles of extremely short path length, such as Auger electrons, because for these delivery to the nucleus can be critical for a therapeutic effect. Another method used to promote intranuclear accumulation of radioactivity is to radiolabel a peptide ligand that normally traffics to the nucleus after interaction with its cognate receptor. This is the principle behind the design of the investigational radiopharmaceutical, ^{111}In-DTPA-hEGF, which binds EGFR [10]. The EGF–EGFR receptor–ligand complex, through the action of an nuclear localising sequence in the juxtamembrane region of EGFR, translocates to the nucleus, coming into close proximity with DNA, resulting in DNA damage and cytotoxicity [11].

In general, anticancer radiopharmaceuticals have been designed to target molecules that are overexpressed in cancer cells. However, recognition that the stroma is critically important in supporting the growth of cancers has stimulated interest in agents that are directed against elements of the tumour microenvironment. For example, radiolabelled analogues of vascular endothelial growth factor (VEGF), designed to interact with VEGFR and thereby insert radioactivity into endothelial cells in tumours, have been developed. In a recent report, a recombinant single-chain variant of VEGF, labelled with ^{177}Lu, was shown to cause cytotoxicity in murine models of human breast cancer with regression of tumour vasculature and widespread intratumoural apoptosis [12]. ^{89}Sr, ^{153}Sm and, more recently, α-emitting ^{223}Ra are radionuclides that target the bone stroma, and have been effective in the treatment of bone metastases, particularly in prostate cancer [13]. These examples suggest that the tumour microenvironment may provide a rich source of targets for future development of investigational radiopharmaceuticals.

Radionuclides: New Options

Radionuclides, such as ^{131}I, ^{90}Y and ^{177}Lu, which emit β electrons, are most widely used for TRT at present. β electrons are sparsely ionising, with linear energy transfer values of about 0.2 keV/μm, and have a range in tissue of several millimetres. One consequence of the relatively long range of β electrons is that energy is deposited in neighbouring, non-targeted cells; a phenomenon known as 'crossfire'. Although this negates the need to target every cell within a large tumour, thus addressing issues of heterogeneity of radionuclide distribution, it has the disadvantage of delivering a significant dose to adjacent normal tissues. In particular, myelosuppression due to collateral irradiation of the bone marrow has been a limitation of many radiopharmaceuticals that emit β^- particles. It has been proposed that by combining isotopes such as ^{90}Y and ^{177}Lu, which emit β electrons with a range in tissue of 12 and 2 mm, respectively, it would be possible to treat macroscopic tumours and micrometastases simultaneously. This concept has been investigated successfully preclinically *in vivo,* when ^{90}Y- and ^{177}Lu-labelled somatostain analogues were combined in a rat tumour model [14]. Although this approach is an interesting one, it has yet to be tested thoroughly in the clinical setting where the complexity of dosimetric calculations for two isotopes would be particularly challenging [15].

The use of α particle-emitting isotopes, such as ^{213}Bi, ^{211}At, ^{225}Ac, ^{227}Th and ^{223}Ra, for TRT has been the subject of intense research over the last few years. α particles, which are ^{4}He nuclei, have high linear energy transfer values (80–100 keV/μm, increasing to 300 keV/μm at the Bragg peak). Their path length is short so that they traverse, at most, a few cells from the point of decay. These properties render α-emitting isotopes ideal for treating small-volume, disseminated cancer [16]. Recently, ^{223}Ra chloride (Alpharadin) has shown efficacy in castrate-resistant prostate cancer [17]. ^{223}Ra mimics calcium and is deposited in areas of bone turnover, including sites adjacent to bone metastases, which are therefore irradiated. The bone marrow, being distant from the deposition site, is relatively protected given the short range of α particles. In the ALSYMPCA phase III trial, patients with castrate-resistant prostate cancer were randomised to receive Alpharadin or placebo. An interim analysis showed a statistically significant

Please cite this article in press as: Jackson MR, et al., Advances in Anticancer Radiopharmaceuticals, Clinical Oncology (2013), http://dx.doi.org/10.1016/j.clon.2013.06.004