Advanced Drug Delivery Reviews 62 (2010) 203–230

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Improving the efficacy of combined modality anticancer therapy using HPMA copolymer-based nanomedicine formulations ☆

Twan Lammers *

Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Sorbonnelaan 16, 3584 CA, Utrecht, The Netherlands
Department of Innovative Cancer Diagnosis and Therapy, Clinical Cooperation Unit Radiotherapeutic Oncology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany
Department of Experimental Molecular Imaging, Aachen University (RWTH), Pauwelsstrasse 20, 52074 Aachen, Germany

ARTICLE INFO

Article history:
Received 2 October 2009
Accepted 12 November 2009
Available online 4 December 2009

Keywords:
Cancer
Drug targeting
Nanomedicine
HPMA copolymers
Polymer–drug conjugates
Polymer therapeutics
Chemotherapy
Radiotherapy
Surgery
Photodynamic therapy
Hyperthermia
Combined modality anticancer therapy

ABSTRACT

Copolymers based on *N*-(2-hydroxypropyl)methacrylamide (HPMA) are prototypic and well-characterized polymeric drug carriers that have been broadly implemented in the delivery of anticancer agents. HPMA copolymers circulate for prolonged periods of time, and by means of the Enhanced Permeability and Retention (EPR) effect, they localize to tumors both effectively and selectively. Because of their beneficial biodistribution, and because of the fact that they are able to improve the balance between the efficacy and the toxicity of chemotherapy, it is reasonable to assume that HPMA copolymers combine well with other treatment modalities. In the present review, efforts in this regard are summarized, and HPMA copolymers are shown to be able to beneficially interact with surgery, with radiotherapy, with hyperthermia, with photodynamic therapy, with chemotherapy and with each other. Together, the insights provided and the evidence obtained strongly suggest that HPMA copolymer-based nanomedicine formulations hold significant potential for improving the efficacy of combined modality anticancer therapy.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "HPMA Copolymers: 30 Years of Advances".

* Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Sorbonnelaan 16, 3584 CA, Utrecht, The Netherlands.
E-mail address: t.lammers@uu.nl.

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doi:10.1016/j.addr.2009.11.028

1. Introduction

1.1. Cancer and cancer therapy

Cancer is a complex disease. Not only is it difficult to understand and to treat cancer, it is even difficult to define cancer. Cancer is an umbrella term, used to describe a large number of different disease states all characterized by excessive cell growth. This rapid and uncontrolled cellular expansion results from (a series of) inherited and/or acquired genetic and epigenetic changes, giving rise to a phenotype which I) is self-sufficient in providing growth signals; II) is insensitive to anti-growth signals; III) has limitless replicative potential; IV) evades apoptosis; V) induces angiogenesis; and VI) stimulates invasion and metastasis [1]. Cancers generally develop gradually, from relatively slowly growing benign lesions, to millimiter-sized non-vascularized nodules, to vascularized in situ tumors, to rapidly expanding primary tumors, to tumors infiltrating neighboring tissues, and to metastatic lesions developing in distant organs. Cancers kill by colonizing and damaging the tissues in which they develop, and by disrupting vital organ functions. Cancer affects hundreds of millions of people worldwide, and it accounts for eight million deaths annually [2].

Treatments for cancer generally rely on (combinations of) surgery, radiotherapy and chemotherapy. To a lesser extent, also hormone therapy, hyperthermia, immunotherapy and stem cell therapy are used. The success rate of anticancer therapy strongly depends on disease stage at the time of diagnosis. If detected early, many malignancies can be treated relatively well, using surgery to locally remove as many tumor cells as possible. If tumors cannot be resected, or if only part of the lesion can be removed surgically, radio- and chemotherapy are used. Depending on the nature, location and stage of the malignancy, various different types of radio- and chemotherapy can be administered. Radiotherapy can be given as external beam radiotherapy, as brachytherapy and as radio-immunotherapy. Brachytherapy relies on the local (i.e. intratumoral) implantation of sealed seeds loaded with radionuclides, and radio-immunotherapy relates to the intravenous injection of radionuclide-labeled antibodies, which selectively bind (and kill) cancer cells. The most effective (and by far most often used) form of radiotherapy is external beam radiotherapy. External beam radiotherapy relies on the use of an external (i.e. extracorporal) source of radiation, such as a linear accelerator, or cesium- or cobalt-containing devices. By means of multi-leaf collimators and computers, the generated rays of photons (or particles) can be delivered to tumors with extremely high levels of spatial specificity. By at the same time administering radiotherapy in fractions (i.e. at low doses, on every weekday, for several consecutive weeks) and from various different angles (i.e. intensity-modulated radiotherapy), damage to tumor cells can be optimized, while toxicity towards healthy tissues can be attenuated. Radiotherapy is an effective means for treating various different types of tumors, but there are also cases in which it is not very helpful, e.g. in case of hematological malignancies, in case of radioresistant cancers, and in case of metastases. Radiotherapy is used in about 50% of all patients, and it is often combined with surgery and with chemotherapy.

As opposed to radiotherapy, chemotherapy is generally administered systemically. It can, however, also be given locally (i.e. intratumorally), for instance in case of aggressively growing brain tumors, like glioblastoma. Systemic chemotherapy is used to treat inoperable tumors, secondary malignancies, radioresistant tumors, circulating tumor cells and metastatic lesions. It is generally combined with surgery and with radiotherapy, and in such settings, it is given either as adjuvant chemotherapy (after surgical and/or radiotherapeutic intervention; to remove residual tumor cells and to avoid recurrence), or as neoadjuvant chemotherapy (prior to surgery and/or radiotherapy; to reduce tumor masses). Routinely used chemotherapeutic agents include the intercalating agent doxorubicin, the alkylating agent cisplatin, the microtubule inhibitor paclitaxel and the antimetabolite gemcitabine. Such prototypic anticancer agents all inhibit cell growth by inhibiting processes involved in DNA duplication and cell division, and they are therefore only able to discriminate between tumor cells and healthy cells on the basis of their proliferative index. Consequently, 'classical' chemotherapeutic drugs not only kill cancer cells, but essentially all rapidly dividing cells, and besides in tumor growth inhibition, their intravenous administration generally also results in bone marrow depression, in damage to the gastrointestinal mucosa and in death of hair cells.

1.2. Molecularly targeted therapeutics

Significant progress has been made over the years in understanding the principles of malignant transformation and tumorigenesis. These improved insights into the genetic and (patho-) physiological processes contributing to cancer have resulted in the development of several novel (classes of) anticancer agents. Such 'targeted therapeutics', like the growth factor receptor inhibitor Herceptin, the proteasome inhibitor Velcade, the histone deacetylase inhibitor Vorinostat and the anti-angiogenic agent Avastin, all more selectively interfere with certain 'hallmarks of cancer' [1], like with the overexpression of growth factors and growth factor receptors, with the altered balance between apoptosis and anti-apoptosis, with the numerous genetic and epigenetic changes that are present in cancer cells, and with the development of a dense vascular network, needed to provide tumors with oxygen and nutrients. By means of their pharmacologically and/or physiologically more optimal mechanism of action, such 'molecularly targeted therapeutics' have been shown to be able to more preferentially kill cancer cells, both in vitro and in vivo, and to improve the balance between the efficacy and the toxicity of systemic anticancer therapy [3–5].

An important but often neglected property that such second-generation therapeutics share with their first generation DNA-damaging counterparts, however, is that upon intravenous administration, their pharmacokinetics and their tissue distribution tend to be far from optimal. Because of their low molecular weight, for instance, the vast majority of routinely used anticancer agents are rapidly cleared from the circulation (by means of renal filtration), and they do not accumulate well in tumors and in tumor cells. Also, because of their small size and their (generally) high hydrophobicity, drug molecules often have a large volume of distribution, and they tend to accumulate in (and cause