Nanotechnology in cancer therapeutics

New insights on an old disease

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ABSTRACT

The field of cancer therapeutics is rapidly evolving. Of particular interest is the potential for nanotechnology to overcome one of chemotherapy's biggest barriers: targeted drug delivery. Owing to the sheer small size of nanoparticles, the opportunity arises for chemotherapy to be administered much more accurately to cancer cells while sparing healthy adjacent tissues. In this article, we review the various tools in nanotechnology that have emerged as candidate delivery systems for chemotherapeutic agents. We discuss the ways in which nanotechnology has been demonstrated to eradicate cancer cells and comment on both successes and current limitations.

INTRODUCTION

Cancer dates back to the time of Hippocrates, who described it using words like *carcinos*, Greek for crab or crayfish. The oldest known description of a surgical procedure for cancer was developed in Egypt and thought to originate from approximately 1600 BC; the papyrus made note of 8 ulcerations of the breast treated via cauterization and concluded that "there is no treatment" for the disease.¹

At the turn of the 20th century, William Stewart Halsted, professor of surgery at Johns Hopkins University, developed the technique of radical mastectomy,¹ which became the mainstay of breast cancer treatment until the mid-1970s, when less disfiguring procedures were found to be equally effective and carry less complications.

The evolution of cancer surgery mimics that of both radiation therapy and chemotherapy. Radiation therapy began with the discovery of primitive X-rays but today, we have at our fingertips the services of computed tomography (CT) and magnetic resonance imaging (MRI) to more accurately locate tumours and determine the required dose of radiation. Chemotherapy can be traced back to the use of mustard gas in chemical warfare during World War II and presently, oncologists are equipped with a wide array of chemotherapeutic drugs including alkylating agents, antimetabolites, and vinca alkaloids, to name a few.

With further development of combinational chemotherapy and radiotherapy, the field of cancer therapeutics began to flourish at an exponential rate. Nonetheless, the lack of target specificity of anticancer agents (ie their relative inability to accurately distinguish between normal and cancerous cells) remains a nagging problem in the field of cancer medicine.² The birth of nanotechnology, which involves the synthesis of materials and devices to manipulate matter at an impressively small scale, presents the opportunity for chemotherapy to be more accurately delivered to target tissues, thereby minimizing collateral damage to the surrounding tissues.² Here, we discuss the principles, successes, and limitations of nanotechnology as it relates to cancer medicine.

NANOTECHNOLOGY IN DRUG DELIVERY

Various tools in nanotechnology have been explored with respect to their potential roles in cancer medicine; these include liposomes, nanotubes, dendrimers, and many others, each with their own unique characteristics. For example, nanotubes, which are carbon cylinders composed of benzene rings, can enter the cell via different methods, including passive diffusion and endocytosis.³ Further, their dynamic chemical properties are conducive to the manipulation of their solubility so that drugs contained within the tubes can be released at a specified rate. Alternatively, liposomes, which can form lipid bilayers, are able to carry both hydrophilic and hydrophobic molecules simultaneously, and are therefore attractive vehicles for combinational drug therapy.⁴ Furthermore, the newest classes of dendrimers, characterized by their tree-like branches around an inner core³ that provide vast amounts of surface area for drug attachment,⁵ have been modeled to carry a therapeutic drug, a diagnostic agent, and an active targeting molecule all in a single dendrimer.⁴ Evidently, nanotechnology, involving the synthesis of various nanoparticles of different shapes and behaviours, can open a wide avenue of possibilities in terms of achieving targeted drug delivery.

There are several ways in which the use of nanotechnology has been demonstrated within the realm of cancer medicine. They include (but are not limited to): (1) intracellular chemotherapeutic delivery, (2) photothermal ablation of tumour cells, and (3) gene therapy.⁶⁻⁸

Intracellular chemotherapeutic delivery takes advantage of angiogenesis. Angiogenesis is one of the hallmarks of cancer that involves the formation of new blood vessels through which tumour cells cultivate themselves by taking nutrients and oxygen from surrounding cells. As a consequence of their rapid, uncontrolled growth, angiogenic blood vessels form irregularly and are leakier than normal healthy vasculature.^{5,9} Pores in these vessels range from a few hundred nanometers to several microns in diameter, while their size reaches only 2 to 6 nm in normal vessels. Since nanoparticles are within 10 to 300 nm in diameter, they are the perfect size for penetrating tumour cells through their blood vessels without considerably entering healthy tissues.⁹ This Trojan horse method presents an attractive means of minimizing damage to surrounding cells.

Photothermal ablation exploits the fact that normal cells undergo apoptosis at approximately 46°C while cancer cells typically do so at about 42°C.¹⁰ Several studies have used gold nanoparticles that are tuned to be excited only at certain ranges of light, thereby eliminating targeted tumour cells while sparing the neighbouring healthy cells.¹¹

The use of nanotechnology in gene therapy has the potential to overcome limitations of current methods, such as reducing the health risks associated with efforts relying on viruses. In a recent

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study,¹² nanoparticles consisting of a synthetic delivery system (described in detail elsewhere) along with small interfering ribonucleic acid (siRNA) were successfully designed to reduce the expression of RRM2, an established anticancer target.

SUCCESSES TO DATE

Currently, there are two notable nanotech reformulations of existing chemotherapeutics that have been approved by the US Food and Drug Administration: (1) Abraxane, an albumin-bound reformulation of paclitaxel, a mitotic inhibitor, and (2) Doxil, a nano-sized liposome encapsulating doxorubicin, an anthracycline antibiotic.

Since 2005, Abraxane has been used for the treatment of metastatic breast cancer for women who failed to respond to first-line treatment for metastatic disease and for whom standard, anthracycline-containing therapy was contraindicated.¹³ It is an antimicrotubule agent that prevents depolymerisation of microtubules, thereby inhibiting their normal dynamic reorganization as required for cellular function.¹³ Abraxane has been shown to confer fewer toxic side effects and greater antitumour activity than its non-nanotech counterpart.¹³ Furthermore, this reformulation eliminates the requirement for premedication in anticipation of hypersensitivity reactions, reduces infusion time, and allows for the use of standard infusion equipment for its delivery.

Doxil was originally approved for its use in HIV-related Kaposi's sarcoma.¹⁴ Its application has now extended to the treatment of ovarian cancer and multiple myeloma. Compared to previous standard therapy involving doxorubicin or bleomycin and vincristine, Doxil was found to be more effective in the treatment of advanced Kaposi's sarcoma.¹⁴ In fact, Doxil confers other significant benefits over standard therapy, including better overall quality of life, reduced disfiguring quality of indicator lesions, and improved pain control and energy.¹⁴

CURRENT LIMITATIONS

While nanotechnology has opened up a window of endless and exciting possibilities into cancer therapeutics, it has its limitations. Perhaps the most significant obstacle yet to be entirely overcome is the biosafety issue of nanoparticles. This is primarily due to a host's complex immune response to invading nanoparticles. Further investigations with respect to the distribution, metabolism, excretion, pharmacokinetics, and pharmacodynamics of nanomedicines need to be carried out if nanotechnology is to become the mainstay of chemotherapy.¹⁵

Issues with regards to costs and environmental safety are also important to consider. For instance, both Abraxane and Doxil are priced at more than ten times the cost of their non-nanotech counterparts, and while they have been demonstrated to markedly improve quality of life as they are less toxic to healthy tissues, neither has been proven to significantly increase survival.⁹ Additionally, although nanoparticles appear to impose no immediate threats to human or environmental health, long-term investigations assessing risks due to chronic exposures have yet to be undertaken. Of particular concern is the early observation that some nanoparticles seem to persist in the environment for longer than others,

which underlines the importance of thorough risk assessment and management.¹⁶ The field of cancer therapeutics will only continue to expand and evolve, and while nanotechnology could be the long-awaited promising breakthrough, we are simply grazing the tip of the iceberg of its true therapeutic potential.

REFERENCES

1. American Cancer Society [Internet]. Atlanta: American Cancer Society; c2013. The history of cancer; c2013 [cited 2013 May 16]. Available from: <http://www.cancer.org/cancer/cancerbasics/thehistoryofcancer/>
2. Misra R, Acharya S, Sahoo SK. Cancer nanotechnology: application of nanotechnology in cancer therapy. *Drug Discov Today*. 2010 Oct;15(19-20):842-50.
3. Parhi P, Mohanty C, Sahoo SK. Nanotechnology-based combinational drug delivery: an emerging approach for cancer therapy. *Drug Discov Today*. 2012 Sep;17(17-18):1044-52.
4. Alexis F, Rhee JW, Richie JP, Radovic-Moreno AF, Langer R, Farokhzad OC. New frontiers in nanotechnology for cancer treatment. *Urol Oncol*. 2008 Jan-Feb;26(1):74-85.
5. Kim KY. Nanotechnology platforms and physiological challenges for cancer therapeutics. *Nanomedicine*. 2007 Jun;3(2):103-10.
6. Kawasaki ES, Player A. Nanotechnology, nanomedicine, and the development of new, effective therapies for cancer. *Nanomedicine*. 2005 Jun;1(2):101-9.
7. Ferrari M. Cancer nanotechnology: opportunities and challenges. *Nat Rev Cancer*. 2005 Mar;5(3):161-7.
8. Bourzac K. Nanotechnology: carrying drugs. *Nature*. 2012 Nov;491(7425):S58-60.
9. Grossman JH, McNeil SE. Nanotechnology in cancer medicine. *Phys Today*. 2012;65(8):38-42.
10. van der Zee J. Heating the patient: a promising approach? *Ann Oncol*. 2002 Aug;13(8):1173-84.
11. Jabir NR, Tabrez S, Ashraf GM, Shakil S, Damanhour GA, Kamal MA. Nanotechnology-based approaches in anticancer research. *Int J Nanomedicine*. 2012;7:4391-408.
12. Davis ME, Zuckerman JE, Choi CH, Seligson D, Tolcher A, Alabi CA, Yen Y, Heidel JD, Ribas A. Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. *Nature*. 2010 Apr;464(7291):1067-70.
13. Petrelli F, Borgonovo K, Barni S. Targeted delivery for breast cancer therapy: the history of nanoparticle-albumin-bound paclitaxel. *Expert Opin Pharmacother*. 2010 Jun;11(8):1413-32.
14. Duggan ST, Keating GM. Pegylated liposomal doxorubicin: a review of its use in metastatic breast cancer, ovarian cancer, multiple myeloma and AIDS-related kaposi's sarcoma. *Drugs*. 2011 Dec;71(18):2531-58.
15. Nie S. Understanding and overcoming major barriers in cancer nanomedicine. *Nanomedicine (Lond)*. 2010 Jun;5(4):523-8.
16. Pautler M, Brenner S. Nanomedicine: promises and challenges for the future of public health. *Int J Nanomedicine*. 2010 Oct;5:803-9.