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Polymeric nanomicelles for sustained delivery of anti-cancer drugs

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ABSTRACT

In the first section of this paper, the existing and emerging nanotechnology-based cancer therapies – nanoparticles, drug conjugates, nanomicelles – are reviewed. In a second part, we present our original and unpublished findings on the sustained release of anti-cancer drugs such as paclitaxel, doxorubicin and camptothecin using block copolymer micelles [PEG-*b*-poly(dioxanone-*co*-methyl dioxanone)]. Copolymers with variable lengths of hydrophobic and hydrophilic blocks have been synthesized and successfully loaded with paclitaxel, doxorubicin and camptothecin anti-cancer drugs, with micelles size in the range 130–300 nm. Drug encapsulation efficiencies varied between 15% and 70% depending on drug and copolymer composition. The drug binding constants, which give a good insight into drug encapsulation and release, were evaluated from UV spectroscopy as we reported previously for anti-TB drugs. Through variation of the methyl dioxanone content of the copolymer, our systems can be tailored for sustained release of the different drugs.

1. Introduction

About 13% of all deaths worldwide were cancer-related in 2008 (7.6 million) and projections show that an estimated 13.1 million deaths are expected in 2030 [1]. The commonest sites of cancer, based on the latest report by the National Cancer Registry in Mauritius [2], are in males: colon-rectum (14%), prostate (10.5%), oral cancer (8%) and lung (9.6%). Among females, breast cancer (38%) is the most prevalent site of cancer followed by cancer of the uterine cervix (10%), colon-rectum (4.8%) and ovaries (5.6%).

Between 2005 and 2008, there were 2286 new male cancer cases registered and 3280 new female cancer cases. Breast cancer in females accounted for a total of 1239 new cases and childhood cancers for 96 new cases during that period. There were 1950 male cancer deaths and 1900 female cancer deaths recorded during the period 2005–2008. A list of fifty anti-cancer drugs is available in Mauritius for treating various types of tumors. These include anthracyclines, taxanes, antimetabolites, hormonal therapy drugs and platinum analogs.

In the first part of this paper, we present a mini-review of the current status of the main existing therapeutics for cancer treatment and focus on emerging nanotechnology-based therapies for delivery of anti-cancer drugs. In a second part, we present our original and unpublished findings on the sustained release of anti-cancer drugs chosen from three different classes – taxanes (paclitaxel), anthracyclines (doxorubicin) and alkaloids (camptothecin) – using block copolymer micelles [PEG-*b*-poly(dioxanone-*co*-methyl dioxanone)] as nanocarriers.

2. Cancer therapeutics

2.1. Biology of cancer

Most cancer drug development is now biology driven. In a cancer cell, several genes mutate and the cell becomes defective. There are two general types of gene mutations. One type, dominant mutation, is caused by an abnormality in one gene in a pair. An example is a mutated gene that produces a defective protein that causes the growth-factor receptor on a cell's surface to be constantly "on" when, in fact, no growth factor is present. The result is that the cell receives a constant message to divide. This dominant "gain of function gene" is often called an oncogene (onco = cancer) [3].

The second general type of mutation, recessive mutation, is characterized by both genes in the pair being damaged. For example, a normal gene called p53 produces a protein that turns "off" the cell cycle and thus helps to control cell growth. The primary function of the p53 gene is to repair or destroy defective cells, thereby controlling potential cancerous cells. This type of gene is called an anti-oncogene or tumor suppressor gene. If only one p53 gene in the pair is mutated, the other gene will still be able to control the cell cycle. However, if both genes are mutated, the "off" switch is lost, and the cell division is no longer under control.

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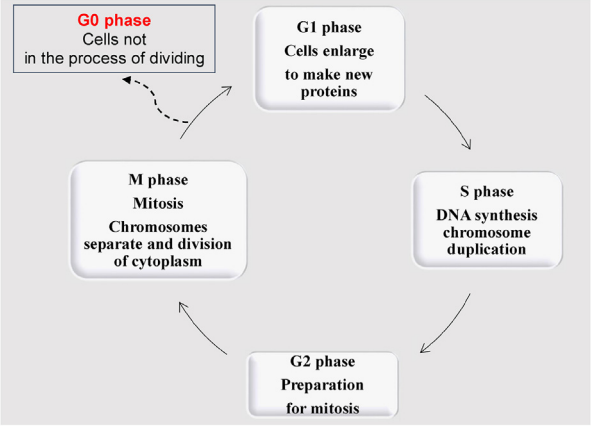


Scheme 1. Normal cell cycle depicting the different stages at which anti-cancer drugs can act, namely the G1 phase, S phase, G2 phase and M phase.

Many forms of chemotherapy are targeted at the process of cell division. The rationale being that cancer cells are more likely to replicate than normal cells. An understanding of the principles of tumor biology and cellular kinetics is helpful to appreciate the mechanisms of action of cancer chemotherapy. Advancements in knowledge about the biology of cancer cells and tumors have allowed the development of drugs which can act at specific stages of cell life (Scheme 1).

2.2. Existing therapies and limitations

Commonly used anti-cancer drugs can proceed via three mechanisms.

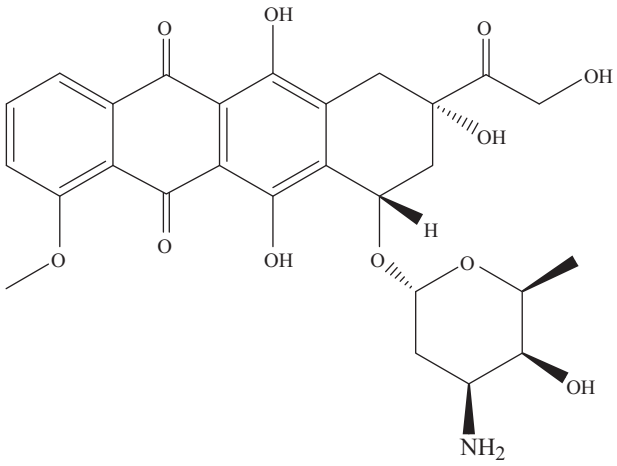
1. Damage to the DNA of the affected cancer cells. In this category are included drugs such as cisplatin, daunorubicin, doxorubicin and etoposide.
2. Inhibit the synthesis of new DNA strands to stop the cell from replicating, to prevent tumor growth (also called topoisomerase inhibitors). In this class, we can find drugs such as methotrexate, fluorouracil, hydroxyurea, and mercaptopurine.
3. Stop mitosis or the actual splitting of the original cell into two new cells to halt the progression of the cancer (also called spindle poison). Drugs such as vinblastine, vincristine and paclitaxel are found in this category.

The different classes of anti-cancer drugs are now detailed.

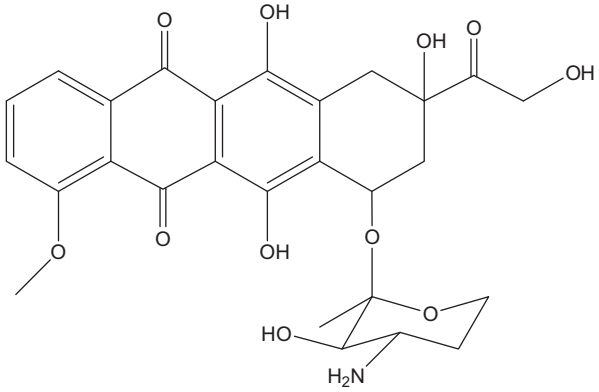
2.2.1. Anthracyclines

Anthracyclines are derived from *Streptomyces percetus var. caesius* bacteria and include drugs like doxorubicin, epirubicin and daunorubicin (Fig. 1). They are chemically similar, with a basic anthracycline structure containing a glycoside bound to an amino sugar, daunosamine.

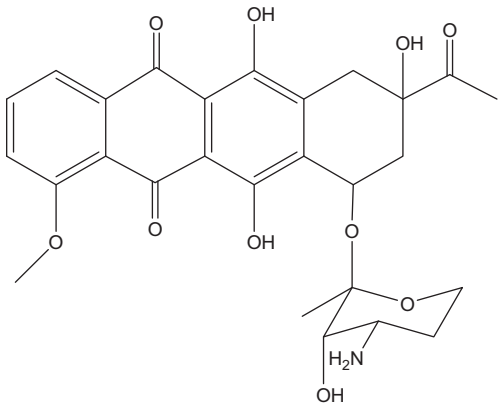
They act by (i) inhibiting DNA and RNA synthesis, thus preventing the replication of growing cancer cells (ii) inhibiting topoisomerase II, thus blocking DNA transcription and replication (iii) creating iron-mediated free oxygen radicals that damage DNA and cells membranes. They are often used alone or in combination with cyclophosphamide as first line chemotherapy for breast cancer [4]. Anthracyclines present high cardiotoxicity, limiting their use. Oxygen free radical formation from reduced doxorubicin intermediates is thought to be a mechanism associated with cardiotoxicity. Doxorubicin has an initial distribution half-life of 5 min [5].



Doxorubicin



Epirubicin



Daunorubicin

Fig. 1. Structure of anthracyclines: doxorubicin, epirubicin and daunorubicin.

2.2.2. Taxanes

Taxanes were originally derived from natural sources and include drugs like paclitaxel and docetaxel (Taxotere) (Fig. 2). They are referred to as mitotic inhibitors as they disrupt microtubule function, thereby inhibiting cell division. They are prescribed for the clinical treatment of various types of tumors but toxicity and side effects are also serious drawbacks of taxanes. Docetaxel is less