The Potential of Ultrasound Technology and Chemotherapy Carriers in Breast Cancer Treatment

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Introduction

Cancer is one of the deadliest diseases of the twentieth and twenty-first centuries, claiming the lives of millions of people worldwide. In the United Arab Emirates (UAE), approximately 39 of every 100,000 people are diagnosed with cancer yearly. According to the Health Authority Abu Dhabi (HAAD), Cancer has been reported as the third most leading cause of death in Abu Dhabi (HAAD, 2014). 1768 new cancer cases were reported to the Abu Dhabi Central Cancer Registry in 2014, with breast cancer representing the leading cause of death among other types of cancer in women (see Figure 1).

The cumulative probability of breast cancer incidence in the UAE has increased sharply over the past three decades, being 2% in 1980, 2.4% in 1990, 3.9% in 2000 and 5.2% in 2010 (Forouzanfar et al., 2011). Mammogram breast cancer screenings detect cancer at a very early stage, up to two years before the patient can feel the lump in the breast. In the UAE, there is usually a significant increase in mammogram intake during the month of October, which is recognized internationally as breast cancer awareness month, and is when mammogram screenings are widely offered. However, these numbers drop for the rest of the year and screening is opportunistic rather than regular. Generally, a large number of...
breast cancer cases in the UAE are discovered beyond the early stages of the disease due to lack of knowledge about breast cancer, cultural beliefs, and deficient coverage of screening programs (Elobaid et al., 2016). These factors lower the chances of early detection of the disease and increase the need for an effective treatment.

Chemotherapy is an effective method of cancer treatment, including for breast cancer. However, the high toxicity of this treatment limits the drug dosage that can be administrated (Malam et al., 2009). The chemotherapy drugs eliminate cancer cells that are rapidly dividing, but these drugs are not able to differentiate between the cancer cell and a normal cell. This leads to the well-known, negative side effects of this treatment, such as hair loss, fatigue, nausea, and a weakened immune system. These harmful side effects need to be addressed in order to improve the quality of life of the patients treated in the UAE and around the world, in addition to enhancing the outcome of the treatment.

The Ultrasound in Cancer Treatment Research Laboratory at the American University of Sharjah was established in 2012, with the goal of creating a better and more patient-friendly chemotherapy treatment by decreasing the side effects of conventional chemotherapy. This is achieved by encapsulating high dosages of the chemotherapeutic drug inside a small capsule in the nano-size range (nanoparticles). When injected into the bloodstream, large numbers of the nanocarriers will accumulate in the cancer site exclusively. Ultrasound can then be applied externally on the cancer site; enhancing the release of the drug from the nanoparticles as well as eliminating the cancer cells without interacting with and harming the healthy cells.

In this policy paper we focus on breast cancer, which, according to the statistics mentioned above, poses a significant risk to the UAE’s female population. This paper introduces the traditional methods used in breast cancer treatment, describes the chemotherapeutic agent we use in our lab and its side effects, and outlines the benefits and limitations of both components of our drug delivery system (i.e., ultrasound and nano-carriers). The paper concludes with a summary of the implications of using nano-carriers in breast cancer treatment and gives policy recommendations related to furthering cancer research for the benefit of UAE citizens, residents, and those impacted by breast cancer around the world.

### Traditional Methods of Breast Cancer Treatment

Cancer refers to the abnormal cell growth in which unhealthy/mutated cells live longer than intended and multiply in an uncontrolled manner (Kerr et al., 1994). In some instances, cancer cells migrate to other healthy organs and start to grow in their new location(s), a phenomenon referred to as metastasis. Such malignant tumors feed off resources that healthy cells need to survive, eventually causing a variety of health problems, which may lead to death (Seyfried & Huysentruyt, 2013). Surgery, chemotherapy, and radiation are traditional treatments that are widely used in breast cancer treatment. However, each of these treatments/procedures carry the risks of complications and side effects, as shown in Table 1 (McKnight, 2003; Nieder et al., 2000; Newman, 2014).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Method</th>
<th>Usage and Outcome</th>
<th>Possible Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Removal of part of the breast (conserving surgery) or removing the entire breast (mastectomy).</td>
<td>Cures the cancer before it spreads to other organs around the breast.</td>
<td>Bleeding, damage to nearby tissues, and infections.</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Radiation beams are delivered to the tumor from various angles.</td>
<td>Used after treatment to destroy possible cells left untreated.</td>
<td>Fatigue, nausea, hair loss, and skin changes.</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>A single drug (or a combination of drugs) is injected into the vein or can sometimes be taken as pills.</td>
<td>Used to eliminate cancer cells entirely or shrink the tumor to be removed surgically later.</td>
<td>Hair loss, fatigue, nausea, skin changes, weakened immune system, and infections.</td>
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Table 1. Overview of breast cancer treatment methods and their side effects
Chemotherapy for Cancer Treatment

Doxorubicin (DXR) is one of the most widely used anti-cancer agents in clinics and treats both solid and hematological (blood) cancers (Patel & Kaufmann, 2012). Breast cancer treatment may involve the use of either pure DXR or a mixture of DXR and other chemotherapeutic drugs. Although DXR is effective in disrupting the growth of cancerous cells, it can also have an adverse influence on healthy cells in the patient’s body. These unwanted effects can be mild, and can get better with time, or can be severe, and worsen over the course of the chemotherapeutic treatment. Below are some of the most common side effects experienced by cancer patients, some of which are general side effects of chemotherapy, while others are specific to DXR (Partridge et al., 2001; Carvalho et al., 2009).

- Pain at the injection site;
- Hair loss from the head and body; occurs 10 to 14 days after chemotherapy;
- Mouth pain or open sores (ulcers) in mouth;
- High sensitivity to sunlight; dark lines might appear on the skin;
- Nausea and/or vomiting for several days in addition to diarrhea;
- Low white blood cell count, increasing the risk of infection;
- Low platelet count, causing the patient to bleed and bruise easily and for longer than normal;
- High levels of uric acid, or hyperuricemia, and possible development of kidney stones;
- Low hemoglobin causing the patient to feel fatigued, may require blood transfusions;
- Facial flushing which is rare but has been reported; and
- Doxorubicin toxicity targets the heart muscles.

Since our drug delivery system entails encapsulating the chemotherapeutic agent in a package and releasing it preferentially to the diseased tissue upon exposure to ultrasound, most of the side effects listed above will be reduced, and possibly eliminated. Simply put, there will be an indirect and less concentrated effect of DXR on the healthy cells of the patient’s body, increasing the patients quality of life during treatment.

Benefits of Proposed Chemotherapy Modality

This research suggests that cancer specialists may reduce their patients’ adverse side effects through a unique form of chemotherapy treatment. In simple terms, this paper argues for the potential effectiveness of delivering chemotherapy drugs to tumors in protective barriers (through "encapsulation" in a nano-carrier) that isolate the drug from healthy tissues (Peer et al., 2007). These nanocarriers can then diffuse into the tumor site via pores and defects in the blood vessels around the tumor and accumulate in the tumor site (Hauert and Bhatia, 2014). Ultrasonic waves can then be administered at the cancer site in order to release the chemotherapy drug from its capsule. In this way, drugs (e.g. DXR) that are potentially harmful to healthy cells can be relatively restricted to the physical location of the cancerous cells. The benefits of (1) drug encapsulation and (2) ultrasound technology are discussed below.

Drug Encapsulation

Cancer patients usually experience side effects because the chemotherapeutic agent is allowed to interact with healthy as well as diseased cells. This is why our drug delivery system uses fatty acids or lipids to form a capsule around the agent. These nanostructures are called liposomes. The capsule stays intact upon injection in the patient’s body until it reaches the tumor, where it is destroyed using ultrasound, releasing its therapeutic contents in the process. Liposomes are considered safe nanocarriers due to their biocompatibility and biodegradability. According to Molinari and Bozzuto (2015), liposome-encapsulated drugs offer the following advantages over drugs given in their free form:

- Liposomes increase the solubility of the drug and hence it would be easier to administer the agent to the patient;
- Liposomes have a special structure that allows them to trap both hydrophilic (water soluble) and hydrophobic (non-water soluble) drugs, keeping them from being absorbed by the patient’s body until the capsule b (see Figure 2).
- Liposomes protect the drug from being detected and attacked by the body’s immune system.
- Liposomes increase drug’s therapeutic index. Thus, they increase the ratio of its therapeutic effects and minimize the poisonous/toxic effects on the patient’s body.
- Liposomes do not affect DXR’s therapeutic activity.
- Liposomes reduce the cardiotoxicity of DXR, DXR is known to be toxic to the heart muscle. Using a capsule to deliver DXR to the desired location will minimize the side effects.
Liposomes consist of a phospholipid bi-layer shaped as a sphere, with the hydrophilic heads of the phospholipid molecules facing the aqueous phase and the hydrophobic tails facing away from the aqueous phase. This special structure of the liposomes allows them to entrap both hydrophobic and hydrophilic drugs. DXR in entrapped inside the hydrophobic layer [Tanbour et al., 2016].

Figure 2. Liposomes structure and drug encapsulation

Ultrasound Triggering

Once at the tumor site in the breast, the chemotherapeutic drugs need to be released from their tiny capsules in order to treat the cancer cells. Several triggers have shown promise in releasing cancer-fighting agents from nano-carriers. These triggers could be internal or external and include temperature, enzymes, pH levels, and light stimuli. Our research has focused on ultrasound because it was proven effective in the rapid release of the chemotherapy drugs from the core of nano-vehicles (Martins et al., 2016; Husseini et al., 2015; Husseini et al., 2013; Husseini et al., 2010).

During ultrasound administration to the breast, a medical technician applies the sound waves to the tumor (similar to the way pregnant women can image their fetus using a sonogram). The same equipment that technicians use to image parts of the human body or to disrupt kidney stones can also be used to release chemotherapy drugs from nano-carriers. Ultrasound has the following advantages:

- The technique is non-invasive and safe to use (it is currently used to image neonatals);
- Ultrasound waves can be controlled and focused on the cancer site;
- Drugs and ultrasound work together in order to increase the efficiency of the chemotherapeutic agent;
- Ultrasound waves enhance the transport of drugs through tissues and other membranes;
- Ultrasound-induced hyperthermia (the increase of the tumor temperature above 40 °C) helps to destroy cancerous cells; and
- Since most hospitals and clinics are equipped with ultrasound imaging facilities, doctors and patients have access to the ultrasound equipment needed for this therapy. The abundance of ultrasonic equipment would also help control the costs of offering this alternative chemotherapeutic treatment.

A combination of ultrasound and DXR has shown efficacy in vivo (in animals studies) where a tumor is inoculated in the hind legs of a rat, and the latter is treated with a combination of the chemotherapy-loaded nano-capsule and ultrasound (Pitt et al., 2011; Staples et al., 2009; Staples et al., 2010) and in vitro (in test tubes where cancer cells are grown in containers) studies (Husseini et al., 2005; Marin et al., 2002; Husseini et Pitt, 2008).

Limitations of This Technology

Some limitations associated with the proposed system exist. For instance, the technique is not as effective against leukemias or metastasized cancers because the system is designed to transport anti-cancer agents to localized tumors in early stages of the disease (before the spread of cancer). Moreover, cancers of the lung, brain, and bone are not candidates for this treatment since bone tissue reflects acoustic waves and air pockets (alveoli) in the lungs scatter them. Finally, some patients may acquire a sense of inconvenience because he or she has to be connected to an ultrasonic machine for 15 to 30 minutes, 30 minutes to one hour after the administration of the encapsulated chemotherapeutic drug.
Implications of Using Nanocarriers in Breast Cancer Treatment

The long-term goal of this research is to develop a drug delivery system that reduces the side effects of chemotherapy. The combination of drug encapsulation and ultrasound triggering could limit the exposure of healthy cells to chemotherapy medicines, thus preventing the adverse side effects associated with conventional chemotherapy. The idea of modeling and controlling encapsulated drug release through ultrasound administration has shown promise for future clinical implementation (Abusara et al., 2018, Ahmad et al., 2015; Husseini et al., 2009; Husseini et al., 2007, Moussa et al. 2017, Wadi et al. 2018). Further implications include:

- Doctors and medical professionals will not require extra training because the nano-capsules will be injected in the same manner as the chemotherapeutic agents are currently administered. The ultrasound use is similar to what is practiced in imaging facilities.

- This drug delivery system has the potential to change the conversation about breast cancer treatment by reducing, and possibly eliminating, the harmful side effects of conventional chemotherapy.

- The quality of life of the patient will be improved significantly. This is because the strong chemicals employed in chemotherapy will have minimal interaction with healthy cells. Thus, many of the side effects of conventional chemotherapy will be minimized, including: hair loss, malaise, low immunity, and low energy levels. This improvement in the patients’ quality of life will also lead to an improvement in their (as well as their families’) moral, well-being, and psyche.

Recommendations

In view of the above implications, we offer the following policy recommendations related to furthering cancer research for the benefit of UAE citizens, residents, and those impacted by breast cancer around the world.

- UAE government and private funding bodies as well as charities need to support and fund biomedical research in UAE universities, like this study, which aim to improve cancer treatment and the quality of life of cancer patients. By investing in more innovative cancer research, the UAE could claim a leadership position in biomedical innovation along with the United States and Europe. Financial assistance to universities creates a supportive environment in which they can continue to research, innovate, and help breast cancer patients beat cancer.

- Encouraging and funding scientific collaborations and joint projects between researchers in UAE universities and other leading universities around the world will enhance national research on breast cancer treatment using nanocarriers.

- Organizing national and international workshops and conferences in the UAE will enhance and influence breast cancer research in the UAE, Gulf region, and beyond.

- The UAE government needs to establish a nationwide breast cancer-screening program, which runs throughout the year and not only during breast cancer awareness month. Also, creating support groups for women to help them share their doubts, fears, and experiences will improve the understanding and create greater awareness of breast cancer screening in the UAE. This will lead to earlier detection, which will considerably improve the chances of a full recovery from the disease.

- It is essential that the Ministry of Health supports and funds clinical trials. Clinical trials are critical in developing new approaches in cancer treatment such as using liposomes in breast cancer treatments. The UAE is a multinational country with expats coming from all around the world, which makes it an ideal place for clinical trials. Many pharmaceutical and biomedical research laboratories are interested in conducting clinical trials in the country. This is because of the diversity of the patients and proper regulatory guidelines and governmental policies that are aligned with global standards. In addition, investing in training medical professionals and researchers in the UAE will aid in understanding the ethical challenges associated with clinical trials especially those involving the vulnerable cancer patients.

- It is essential to establish a National Cancer Registry, for all the seven emirates, accredited by the International Agency for Research on Cancer. There is a cancer registry at present, but it covers the cancer cases only in government hospitals and not private hospitals. This will significantly reduce cancer death rates by creating efficient and targeted screening programs.
References


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