Use of Nanoparticles in Fighting Cancer compared with Current Treatments

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PASS

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Abstract:

Cancer treatment has greatly improved in the last century. Cancer diagnosis is no longer a death sentence. However, cancer treatment is by no means an easy ordeal, and still involves harmful side effects and much discomfort. This paper describes some of the problems associated with cancer treatments, and suggests an alternative in nanotechnology. It demonstrates how we may advance the destruction of cancer cells using nanoparticles, and how nanotechnology is helping us on our way to the ideal treatment.

Introduction:

Nano comes from the Greek word "nanos," meaning "dwarf." One definition of nanotechnology is "the art of manipulating materials on an atomic or molecular scale especially to build microscopic devices (as robots)."[1] Devices come under the umbrella title of nanotechnology when they have been manipulated on the nanoscale. A nanometre is 1×10^{-6}m, which is approximately 1/80,000 of the diameter of a human hair, or 10 hydrogen atoms long.

One field of nanotechnology being pursued at the moment is the use of nanoparticles in cancer treatment.

Around 298,000 new cases of cancer are diagnosed every year, and 1 in 3 people will develop some form of cancer in their lifetime.[2] There are over 200 different types of cancer, with breast, lung, colorectal and prostate cancer being the most common, accounting for 54% of the incidence in 2007.

Current treatments of Cancer [3] [4]

Chemotherapy

Chemotherapy literally means drug treatment, and in the context of cancer treatment the term refers to treatment with cell killing (cytotoxic) drugs. There are more than 90 different chemotherapy drugs and treatment can be done with either one or a combination of these drugs. Whether chemotherapy is applicable to you is dependent on many things. For example:

- The Type of cancer.
- Where the cancer originated from.
- What the cancer cells look like (the grade).
- Whether the cancer has metastasized (spread).
- Your general health.

Chemotherapy can also be used with other forms of cancer treatments such as surgery or hormone therapy.

Chemotherapy destroys cancers by killing dividing cells and it does this by damaging the control centre inside each cell which controls its division or it interrupts some of the chemical processes involved in cell division and this damage causes the cells to apoptose.

The fact that Chemo kills cells that are dividing explains some of its side effects because the cancer cells are not the only cells in the body that are rapidly dividing. Other groups of cells that divide rapidly are the skin, the bone marrow, the hair follicles and the lining of the digestive system. And the damage that chemo causes to these areas causes side effects such as hair loss and anaemia. But these side effects don't usually last because after the chemotherapy has been ended normal cells can repair or replace the damaged ones causing the side effects to disappear.

Chemotherapy does have disadvantages though. For example, as can be seen above it does cause some rather unpleasant side effects. Chemotherapy is also not a universal cure as it can only fully cure some forms of cancer (for example testicular cancer and Hodgkin's lymphoma). Finally chemotherapy is an indiscriminate treatment and this means that it is not only toxic to the cancer but also to the body.

Radiotherapy

Radiotherapy is when radiation is used to treat cancers and about 40% of cancer patients are treated with radio therapy and this can be done in two ways:

- External Radiotherapy, this is when the radiation is administered from outside the body by the use of X-rays, cobalt irradiation, electrons and more rarely other sub-atomic particles such as protons

- Internal radiotherapy, this is when the radiation is administered inside the body by either drinking a radioactive liquid that is taken up by the cancerous cells or by injecting the radioactive material close to or into the cancer cells.

Radiotherapy works by causing mutations in the DNA during its replication and this will cause cells to apoptose(initiate cell death). Normal cells are also affected by radiation but they are much better at repairing themselves than the cancer cells. A course of radiotherapy will be administered over a five day period and this will normally be between Monday and Friday allowing the normal cells to repair over the weekend, but if the normal cells can't be repaired or replaced side effects can be permanent.

There are many side effects from radiotherapy and these include tiredness, anaemia, hair loss in the treatment area and skin sores but the majority of the side effects are short term and wear of within a few weeks of treatment. Another disadvantage of radiotherapy is that it can only be used to treat macroscopic tumours.

Hormone Therapy

Hormone therapies use the sex hormones produced by our body, or drugs that block these hormones to treat cancers. Only cancers that are hormone dependant can be treated in this way, so it limits their use, but cancers that can be treated in this manner include prostate, breast and endometrial cancer.

Hormone therapies work by preventing hormone dependant cancers getting the hormones they need to grow. This is done by either stopping the hormone from reaching the cancer or by stopping the production of the hormone. There are a number of different types of hormone therapy and the one that is administered depends on the type of cancer. For example some breast cancers are affected by the hormone oestrogen and progesterone, and drugs such as tamoxifen, which prevents oestrogen from reaching the cancerous cells, can be used to treat these cancers.

Hormone therapy does have its disadvantages though, and these include a large number of side effects which can be different for men and women. For example some of the side effects for women include tiredness, digestive system problems and menopausal symptoms. And side effects for men include erectile dysfunction, breast tenderness and weight gain. But the main disadvantage of hormone therapy is the fact that it has very limited uses.

Antibody Treatment

Antibody treatment is the use of antibodies to kill cancers. The antibodies can be used to make cancer cells more visible to the immune system, block growth signals, stop new blood vessels from forming and deliver radiation to cancer cells. Antibodies are very effective when treating lymphomas.

Antibody treatments do have some disadvantages. For example there are some side effects that are linked to anti body treatments such as allergic reactions, flu like symptoms, nausea, diarrhoea, skin rashes and more seriously infusion reaction, as can be seen from the Northwick park disaster. Also they are quite limited in their uses.

Surgery

Surgery is another way that cancer can be treated, this is done by removing the tumour and some of the surrounding tissue to create a 'clear margin' the surgeon may also remove the nearest lymph nodes as they may contain some cancer cells. After surgery other treatments such as chemotherapy or radiotherapy are used to help reduce the chance of recurrence. This may be done to either cure the patient, prevent the risk of cancer, to control symptoms or to prolong the life of a patient.

There are disadvantages to do with the surgery however. Firstly there is inherent risk of surgery and of being put under a general anaesthetic especially if the patient is old. Also there is there can be a large amount of trauma caused by surgery that can be very uncomfortable for a patient. And surgery is only limited to tumours that are macroscopic, and is no use at removing submicroscopic disease.

The Ideal Treatment

The Ideal cancer treatment is a treatment that will target only that cancer cells in the body and cause apoptosis to occur, thus removing many of the unpleasant side effects that are affiliated with many cancer treatments today such as hair loss and nausea which are a result of collateral damage from the treatment. Also the treatment would have to be able to get around the entire body and find all cancer cells in the body including submicroscopic deposits of cells in the body. The treatment would have to be non-toxic to normal tissue and not kill essential tissues throughout the body. Also it would only have to be administered once. Finally the treatment must be applicable to many if not all patients that have cancer so that it acts as a universal treatment.

Nanoparticles [5] [6]

Nanoparticles are being developed in two major fields of cancer treatment:

1. Magnetic Hyperthermia.
2. Drug delivery.

Magnetic nanoparticles are a class of nanoparticle that one is able to manipulate with a magnetic field, they are most commonly formed of nickel, cobalt, iron and their compounds.

Currently magnetic nanoparticles are being used as an experimental cancer treatment called magnetic hyperthermia. Magnetic hyperthermia is caused by the property that some nanoparticles possess, which enables them to heat up when they are placed in an alternating magnetic field, and this property is useful because cancer cells are slightly more susceptible to changes in temperature and therefore die with a lower temperature increase. This treatment consists of either injecting the nanoparticles into the area where there is a tumour or attaching the particle to an antibody that binds to the antigen of the cancer cell thus making the treatment much less dangerous as it poses less of a danger to the surrounding tissue.

Nanoparticles can be used in drug delivery by either attaching a cytotoxic drug to the side of the particle or by encapsulating it inside the particle. The particle can then be ingested or applied intravenously and directed to the sites of cancerous cells.

Both of these uses of nanoparticles require directing them to the cancer cells. One way of doing this is using a magnetic field to draw the particles to the site. Another is by injecting the particles directly into the site. The most promising method is by using chemical bonds (for example, a thiol-gold bond on gold nanoparticles) to attach antibodies to nanoparticles. These antibodies are cancer specific, as they correspond to proteins that present only on the surface of cancer cells, so they only target cells that present the protein, and they are also able to discover and attach to submicroscopic disease, therefore they have the ability to rid the body of all cancerous cells. But even these nanoparticles are hindered by the fact that there are concerns about the potential toxicity of the metallic elements used to synthesise the nanoparticles.

Synthesizing Nanoparticles

Many nanoparticles, including gold and iron oxide particles, which are the most widely used today, can be synthesized in water. The fact that they are water-soluble is crucial for their use in biological systems. As changes in diameter of spherical nanoparticles affect their properties, we need to ensure a narrow size distribution. Gold nanoparticles are made by reducing Au(III) salts using reducing agents (e.g. citric acid). Iron (hydr)oxide particles are formed in the coprecipitation process, where either iron hydroxides are partially oxidized, or Fe_3O_4 is converted to Fe_2O_3 in the presence of an alkali (a base in aqueous solution) and an oxidizing agent. If the size distribution of the nanoparticles needs to be narrower, then particles can be transferred to non-polar solvents and particles of the required size are obtained by size selective precipitation.[7]

Methods for particle synthesis that do not involve water include use of organic solvents, chemical vapour deposition, mechanical milling and electrical explosion, although these are more used for the synthesis of carbon nanotubes which require "dry" synthesis routes.

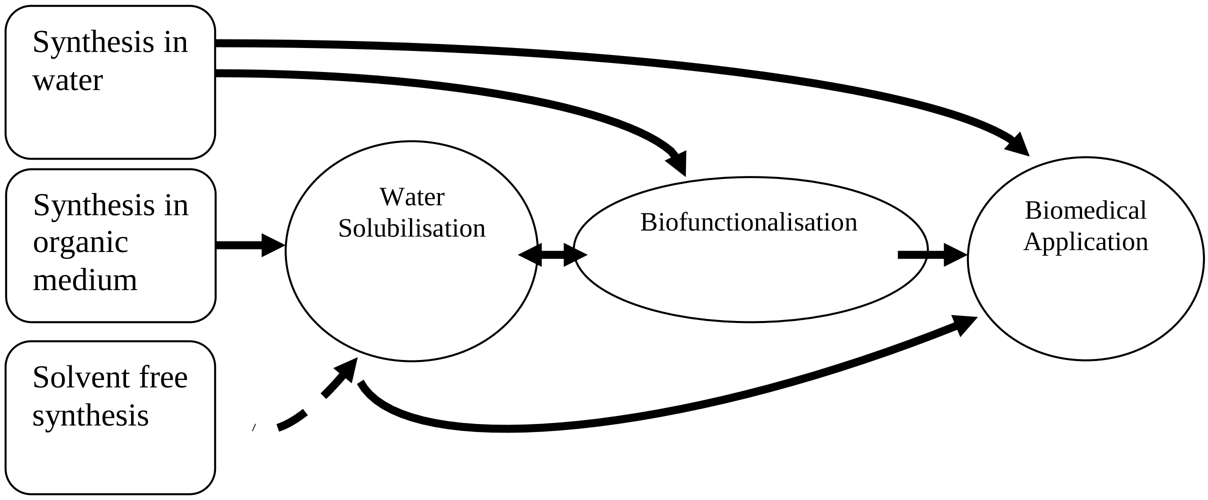

Figure 1 Synthesis processes for medically applicable nanoparticles, dotted line indicates that particles synthesized as solids are water non-soluble or may have no medical application.

Targeting Cancer Cells

The most important thing for us to make sure of at the moment is that we can target and direct our nanoparticles to only cancerous cells. To do this we designed an experiment based on one that proved that doctors at Harvard Medical School could target macrophages, key participants in atherosclerosis.[8]

An antigen that presents on the surface of several types of cancer cell, including pancreatic and colon cancer, is the carcinoembryonic antigen (CEA). So, if we attached a CEA antibody/antibody-fragment to a nanoparticle, we would expect the nanoparticle to remain at the site of the cancer once it had got there. We would therefore go through three stages of testing:

In Vitro testing:

We can develop a culture of cells presenting the CEA on the inside of a column. Then, by passing a suspension of nanoparticles along the column, half with the CEA antibody attached, and half without, we can check to see if any of the nanoparticles coming out the other end have the CEA antibody, and if any do, we can work out what percentage of the particles still have the antibody. This way, we know the efficiency with which the nanoparticles bind to cancer cells, and we can estimate how long a certain number of particles would take to all bind to cancer cells in a human body, letting us know how long before we should start magnetic hyperthermia, or how long the particles need to last before they dispense their drug load.

Animal testing:

Firstly, we would inject a small mammal, usually some species of mouse, with a cancer that presents the CEA, thus causing the mouse to contract that cancer. We would then inject the mouse with nanoparticles that had the CEA antibody attached, and trace their movements through the mouse using a PET/CT scan, comparing them to nanoparticles injected into an uninfected mouse.

Tagging the nanoparticles using a contrast agent (researchers at Yonsei University have developed a mixture of albumin and radioactive iodine coated manganese particles, for detection under both MRI and PET/CT scans[9]), we can track the progress of nanoparticles through the body. Waiting until the tagged particles stop moving, firstly we can compare where the nanoparticles end up in the infected mouse to where they end up in the uninfected mouse. Secondly, we can dissect the infected mouse to see if there are cancer deposits where the nanoparticles showed on the PET-scan.

Human testing:

Human experiments would be similar to the animal tests, injecting radioactively tagged nanoparticles with the CEA antibody attached into already infected patients. However, after the PET-scan showed the location of the nanoparticles, we would have to correspond that to the location of the cancer using an x-ray, rather than explorative surgery. This has the disadvantage that we can’t see if some of the nanoparticles had bound themselves to submicroscopic disease.

Conclusion

Nanoparticles as the Ideal Cancer Treatment

The ideal nanoparticle treatment would consist of a nanoparticle that was easy to synthesise and stable so it would be cheap to produce and it would last a long time and this would make it very widely available. It would have to be easy to administer and have very few side effects so that it would be an easy treatment to use and it would make the experience a lot easier on the patient as it would reduce the amount of stress that he or she would be put through. Most importantly it would have to only target cancer cells so as to reduce the amount of collateral damage to the rest of the body. The ideal nanoparticle would be able to be internalised into the cell to initiate apoptosis, which is a natural process with no harmful side effects, so it would make the experience better for the patient.

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Picture References:

Figure 1: Functionalisation of nanoparticles for biomedical applications
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