Nanotechnology and the treatment of cancer

Perla Astudillo
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Recent successful medical trials of a cancer treatment involving the use of "nanotechnology" may open up important new avenues for the diagnosis and treatment of other cancers and diseases.

Nanotechnology is a broad term covering the building of structures and "machines" on an atomic or molecular scale—in the range from 1 to 100 nanometres. A nanometre is one billionth of a metre or about the size of 10 hydrogen atoms. The techniques range from various chemical and biological processes used to "construct" structures—in some cases atom by atom—to the etching methods used to produce computer chips.

The field of nanotechnology has over the last decade or so been surrounded by considerable hype. Some of the visions of what is possible in medicine conjure up the Science Fiction classic film *Fantastic Voyage* where tiny submarine ships were injected into the body and travelled through the bloodstream to eradicate foreign bodies. The reality is more prosaic, but the potential is nonetheless exciting.

Many of the standard radiation and drug therapies now used to treat cancers can have serious side effects. The use of radiation and chemicals to kill fast-growing tumour cells inevitably affects and kills other cells in the body. Nanotechnology offers the possibility of far more precisely localising the treatment and thus minimising the damage to healthy tissue.

In early April, the nanotechnology company pSivida announced the very promising results of the Phase 2 clinical trials of its product "BrachySil" for patients with liver cancer.

BrachySil is a tiny structure about one-millionth of a metre in size and made up of modified particles of silicon impregnated with the radioactive isotope of phosphorus 32P. Unlike other radiation treatments that involve focussing beams of radiation on tumours, BrachySil is injected directly into the cancer using a fine gauge needle. By using 32P, the radiation is limited to a range of just 8 millimetres, resulting in the killing of tumour cells rather than healthy tissue.

For several years, doctors have been using a similar technique known as brachytherapy—injecting radioisotopes directly into tumours. The difficulty was that the injected material would not remain in the cancer, but would over time be carried to other parts of the body. The advantage of BrachySil is that its silicon structures, while small, prevent the radioisotope from leaking away.

The result is that the dose of radiation is focussed very precisely on the tumour itself. The silicon eventually breaks down and is excreted. 32P, which has a half-life of 14 days, eventually decomposes to stable isotopes or is excreted. Because the treatment is localised, the side effects are likely to be less than other forms of brachytherapy. None have been observed to date, although the long-term impact of the treatment is not known.

BrachySil consists of tiny pockets made up of silicon microparticles. The pores or holes in the silicon pocket are the size of about 10 atoms. Radioactive phosphorus is bombarded into the structure. Because of its method of delivery of radiation doses, the treatment may well be applicable to a broader range of cancers than other forms of brachytherapy, which is currently limited to prostate and liver cancers.

The clinical trial of BrachySil was undertaken at the Singapore General Hospital beginning in mid-2004. It involved eight patients suffering from primary liver cancer (where the tumours have not spread to a secondary site). They were given CT scans before and after the injection of BrachySil to determine the impact on the tumours and were monitored for possible side effects.

After 12 weeks of the treatment, smaller tumours were completely eradicated. The most extraordinary finding, however, was that all tumours were reduced by

an average of 80 percent—a result not seen in other treatments. After the trial results were announced, the company received a flood of inquiries and was forced to announce on its website that testing was still in its early stages.

Worldwide, liver cancer is not one of the most prevalent cancers. Nevertheless, more than half a million new cases are diagnosed every year—some 45 percent of them in China. Causes of liver cancer include infection by parasites such as the Chinese liver fluke. Liver cancer can also be related to hepatitis, exposure to radiation and to the irritant Polyvinyl Chloride.

An article published in the British scientific journal *Nature* in March entitled "Cancer Nanotechnology: Opportunities and Challenges" provided an overview of the diverse array of nanodevices and their possible application. These included "nanovectors" to provide the targetted delivery of anticancer drugs as well as "nanowires" and "nanocantilever arrays" for the early detection of pre-cancerous and malignant lesions.

Many of the devices are still in the process of development, but some are being used or, like BrachySil, are in the testing process. The earliest known application was the use of "liposomes" or small spheres that have been used to treat cancers such as Kaposi's sarcoma for about 10 years. They are now being used in cases of breast cancer and ovarian cancer.

"Nanovectors" are generally made up of three basic parts: a core; the contents which may be a specific drug or chemical used for imaging; and a surface coating. The coating is needed both to target cancerous tissue and to prevent the body's own defence mechanisms from engulfing and destroying the nanovector.

In 2003, US scientists developed a "nanoshell" made up of a silica core and a thin gold metal shell modified to strongly absorb near-infrared (NIR) light. The nanoshells were injected into mice, which were then exposed to a safe dose of NIR radiation causing cancer cells to die. Magnetic Resonance Imaging (MRI) scans enabled the scientists to monitor exactly where the nanospheres were located and thus successfully target cancer cells.

Scientists have also built nanoshells to deliver small precise doses of drugs to tumours. It is hoped that such techniques will be able to avoid many of the serious side effects that are associated with current chemotherapy.

At the end of March, scientists at the Institute of Bio-engineering and Nanotechnology in Singapore published their findings on the use of polymer nanoparticles to deliver anti-cancer drugs directly to diseased tissue. The results showed that the technique applied to mice was effective in conveying the drug doxorubicin to breast tumours. The scientists hope that clinical trials will follow in the next five years.

The nanoparticles were tagged with biological signals to enable them to hone in on the cancer cells. This was achieved by modifying the particles to be sensitive to both temperature and pH. The tumour cells, which are characteristically slightly acidic, caused the nanosphere to "deform" and release the drugs at the exact site of the cancer cells. The outer shell was also coated with bioactive compounds to protect the particle from degradation and digestive fluids.

Nanoparticles have also been modified to provide better cancer detection. Researchers at Washington University School of Medicine demonstrated that very small human melanoma tumours growing in mice—that are not discernible using a direct MRI scan—would "light up" and be easily located some 30 minutes after the mice were injected with specialised nanoparticles.

Stanford University nanotechnology expert Stephen Quake has predicted within a decade that the diagnosis and treatment of cancers and other diseases will be "carried out automatically, in a few seconds or minutes, on a just a handful of cells or their contents". While the prediction may turn out to be overly optimistic, there is no doubt that nanotechnology may well open the way for a new generation of cancer treatments that are more effective and less damaging than those currently available.