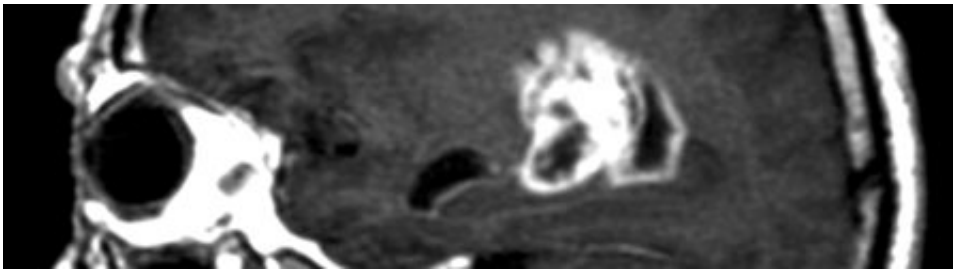
Biomaterial-delivered chemotherapy could provide final blow to brain tumors

November 12 2013



A polymer originally designed to help mend broken bones could be successful in delivering chemotherapy drugs directly to the brains of patients suffering from brain tumours, researchers at The University of Nottingham have discovered.

Their study, published in the journal *PLOS ONE*, shows that the biomaterial can be easily applied to the cavity created following brain cancer surgery and used to release chemotherapy drugs over several weeks.

The targeted nature of the therapy could also reduce the toxic effects of chemotherapy drugs on healthy parts of the body, potentially reducing the debilitating side-effects that many patients experience after cancer treatment.

Patient survival

Dr Ruman Rahman, of the University's Children's Brain Tumour Research Centre (CBTRC), who led the study, said: "Our system is an innovative method of drug delivery for the treatment of brain tumours and is intended to be administered immediately after surgery by the operating neurosurgeon.

"Ultimately, this method of drug delivery, in combination with existing therapies, may result in more effective treatment of brain tumours, prolonged patient survival and reduced morbidity."

Brain tumours are the major cause of cancer-related death in children and adults up to the age of 40. Most relapses occur when surgeons are unable to remove all of the cancerous cells during surgery – something which can be particularly challenging in very young children and babies and by the very nature of a type of adult brain cancer called glioblastoma.

Although alternative systems for delivery of drugs directly to the brain have been developed, they are used infrequently because their success has been limited. This new drug delivery system is the first that can be moulded to the shape of the brain tumour cavity and the first to deliver several different drugs over a clinically meaningful period of time.

The Nottingham polymer formulation is made from two types of micro-particles called PLGA and PEG and has been developed and patented by leading tissue engineer Professor Kevin Shakesheff, based in the University's School of Pharmacy. A powder at room temperature, it can be mixed to a toothpaste-like consistency with the addition of water.

Unique properties

The unique properties of the polymer lie in its ability to set into a rigid structure only when it reaches body temperature (37 degrees), a feature perfectly tailored for use in medical therapies. It was originally developed as a scaffold on to which new bone cells could be grown to speed up the knitting back together of broken bones.

Dr Ruman Rahman at the CBTRC and Dr Cheryl Rahman from the School of Pharmacy spotted the potential for the polymer to deliver chemotherapy drugs directly to patients' brain tumours. The work was performed at the CBTRC with neurosurgeon Mr Stuart Smith and neuro-oncologist Professor Richard Grundy. The cavity left by the removal of a tumour would be lined with the polymer while in paste form, which would start to solidify and gradually release the chemotherapy drugs after the incision has been closed. This would directly target any residual cells not initially removed during surgery.

In the lab, the Nottingham scientists were able to successfully demonstrate the slow-release properties of the material by placing paste loaded with three commonly used chemotherapy drugs into a solution of saline and measuring the quantities of the drugs given out by the material over time.

To establish whether the material itself is safe to use on patients in this form of therapy, they used it to create a 3D model onto which they were able to grow brain tumour cells and healthy brain blood vessel cells without any toxicity. They then simulated surgery on a sheep's brain from an abattoir by moulding the paste around a brain cavity and warming the brain to human body temperature to harden the polymer.

The brain was then scanned using CT and MRI technology to demonstrate that it is still possible to distinguish the polymer from normal brain tissue on a routine brain scan, an aspect crucial for doctors when dealing with follow-up care for brain tumour patients who have

undergone surgery.

Robust material

The team also dealt with concerns that the material could disintegrate and release its chemotherapy contents too quickly during the subsequent radiotherapy which many cancer patients undergo following surgery. By placing the biomaterial loaded with chemotherapy drugs into a head cavity of a medical training dummy and subjecting it to the same duration and intensity of radiotherapy used for brain tumour patients they were able to successfully demonstrate the robust integrity of the structure.

Finally they showed that a chemotherapy drug called etoposide could be effective at killing brain cancer cells in a mouse when released from the polymer formulation. The next stage of the research will be to extend the study in mice with brain tumours to test whether animals with the drug-loaded polymers survive longer. The team are also investigating the release of other chemotherapeutic drugs that hold promise, supported by a recent grant award from Sparks.

As the research used a biomaterial and chemotherapy drugs already approved for medical use, many of the usual ethical approval hurdles to allow further investigation have already been cleared.

The first clinical test, anticipated in 3 years' time, will be to devise a multi-centre phase 0 clinical trial which would involve testing the therapy on a small number of patients for whom other clinical treatments have not been successful and would otherwise only be offered palliative care.

"This is a very exciting development and holds considerable promise for the treatment of malignant brain tumours in the near future" commented

Professor Grundy, Co-Director of the CBTRC.

More information: www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0077435

Provided by University of Nottingham