AN INVESTIGATION INTO THE POTENTIAL USE OF NANOTECHNOLOGY IN THE DETECTION AND TREATMENT OF BRAIN TUMOURS

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ABSTRACT

Brain tumours are unusual in that their removal can cause significant damage to such a delicate organ; in addition to the dangers of using chemotherapy or radiotherapy that come with any cancer. Nanotechnology provides a significant possibility of reducing these risks to provide a much more effective treatment of the cancer. This paper focuses on how recent developments in nanotechnology can be successfully applied in the detection and treatment of brain tumours in addition to the issues surrounding it.

INTRODUCTION

The NHS describes brain tumours as "a growth of cells multiplying in an abnormal, uncontrollable way in the brain".[1] This simple definition gives little indication of the complexity of the issues surrounding brain tumors or the debilitating effect they can have on sufferers or their families. About 4,500 people in the UK are diagnosed with a tumour originating in the brain every year, in addition to those whose cancer spreads to the brain form other areas.[2] Brain tumours affect all ages, they are the leading cause of cancer death in children under 20, ahead of the much more publicised leukaemia. [3]The survival rate for those with malign tumours is shockingly small, only around 15% will survive beyond the first five years – however it is important to remember that each of the 100 types of brain tumour will have a very different outlook depending on the location and size of the tumour. An aggressive grade 4 astrocytoma (a form of the most common brain tumour, gliomas) gives a life expectancy of less than a year, while almost 85% of those diagnosed with a pituitary tumour survive past 5 years.

Such discrepancies owe much to the complicated nature of the brain: with over 10 billion neurones and 50 billion other types of cells, the brain is responsible for both involuntary and voluntary body functions. As can be seen in Figure 1[4], different areas of the brain are responsible for different functions. This is why the location of a tumour is so important. If in a non-functional area of the cerebrum, surgery becomes much more possible. However, surgery in the primary motor area, for instance, carries significant risks of damage to a patient's motor skills[5].

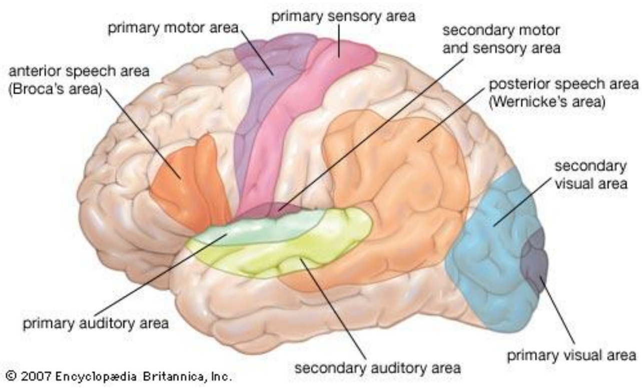

Figure 1: Image of a human brain illustrating the functional areas of the cerebrum

For brain tumours, the outlook is largely dependable on whether it is operable. If not, they can be very difficult to treat using radiotherapy or chemotherapy alone. Radiotherapy needs to be targeted precisely at the tumour, yet can still cause significant damage to surrounding brain tissue. Chemotherapy currently carries significant side effects; perhaps the best known of these are hair thinning and fatigue. However, chemotherapy has far more serious side effects: one form, vincristine, can cause loss of fertility and a drop in white blood cells causing increased risk of infection, to give one example[6].

This is where the recent advancements in nanotechnology give hope to brain cancer patients. Since the discovery of buckminsterfullerene by Kroto, Smalley and Curl in 1985[7], the possibilities of this hollow spheroid for medicine have been have been greatly explored – mostly its potential as a drug carrier system. While our current treatments are likely to damage the surrounding brain tissue and often don't eradicate the cancer fully, the small size of the nanoparticles allows treatments to be targeted directly at the tumour and penetrate deeper. Indeed, nanotechnology is already in use to treat other forms of cancer.

One example of this is Doxil[8], currently used to treat cancers including AIDS-related Kaposi's sarcoma, breast cancer and ovarian cancer. This is composed of the drug doxorubicin encapsulated in a STEALTH® liposome. By enclosing the doxorubicin in these lipid spheres, they drug is able to get close to the tumour and work more effectively against the cells. ABRAXANE®, another cancer drug using nanotechnology, although this uses albumin, a protein, to deliver the drug, showed similar success: nearly doubling the tumour response rate in clinical trials[9]. Although both of these drugs carry the same type of side effects as regular chemotherapy, the incidence is greater reduced and it can be expected that with further research and trials this would improve further. Recent research (Jan 2011) by Stephen Lippard and his team at MIT and Brigham and Women's hospital has shown that the use of nanotechnology to transport the conventional cancer drug Cisplatin can help reduce the drug's potentially severe side effects, including kidney and nerve damage. Since only one-third of the amount normally was needed to achieve exactly the same reduction in tumour size, the mice didn't experience the normal level of side effects[10].

DISCUSSION

Identification

The first problem with treating brain tumours actually lies in identifying them as cancerous; they are typically difficult to see. Can nanotechnology resolve this issue, allowing earlier identification of the cancer and consequently faster treatment? One research team at the University of Washington have successfully used nanotechnology to illuminate cancerous brain tumours and their results have been published in the journal Cancer Research in Aug 7 2009[11]. The team leader, Miqin Zhang injected fluorescent nanoparticles into the blood stream and the consequent illumination of the tumour is illustrated in Figure 2. This demonstrates the ability of nanoparticles to cross the blood-brain barrier (an extremely impermeable barrier intended to protect the brain for infection) without damaging it, but also has many other possibilities. "If we can inject these nanoparticles with infrared dye, they will increase the contrast between the tumour tissue and the normal tissue. So the nanoparticles enable surgeons to see the boundary more precisely," said Zhang; this will help avoid the severe cognitive problems explained in the Introduction of this paper. Zhang also emphasized that nanoparticles could improve the resolution of a magnified image by a factor of 10 or more. This could become significant as smaller tumours become detected – allowing earlier treatment.

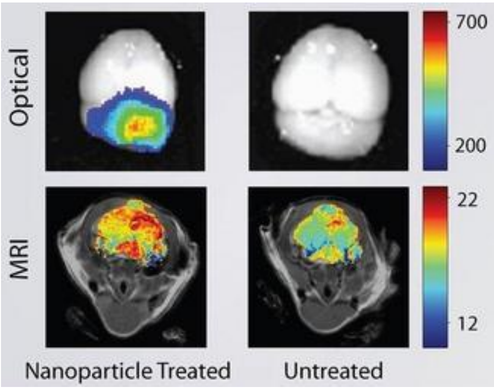

Figure 2: Comparison of treated and untreated brain tumours

Yet another incidence where nanotechnology was shown to be instrumental in detecting the primitive stages of cancer came from Shan Wang's team of Stanford researchers in 2009[12]. They have developed a biosensor chip using nanotechnology that is capable of detecting up to 64 different proteins present in the primitive stages of cancer. These magnetic-nanosensors use nanoparticle tags that fit specific antibodies, in order to detect the relevant antigens shed by the cancer cells. Since new sensors are up to 1000x more sensitive than the present detectors used, the researchers were able to detect tumours in mice long before the levels of "cancer proteins" would normally be high enough to detect as well as finding the sensor equally effective in all types of biological fluid.

Such research shows the possibilities of using nanotechnology to overcome this hurdle in treating cancer cells. Should cancer cells be detected and treated earlier, the tumour would have had less opportunity to invade the surrounding tissue. Both this and the pressure inside the skull would have had a smaller opportunity to cause lasting damage. In addition to this, by providing a clear boundary between the cancerous cells and the normal tissue it makes surgery easier and reducing the risk of causing significant damage to any surrounding neurones and therefore impairing cognitive function.

Delivery of medicine

The main advantage of using nanotechnology to treat brain tumours is that it can be used to create drug carriers to deliver medication directly to the tumour, preventing healthy tissue from being harmed. Yet it should also be emphasised that they prevent degradation of the drugs in the body, enhance the absorption of the drugs into the cancerous cells and allow better control over the distribution of drugs.

The current nano-carrier based drugs, described in the Introduction, are reliant on passive targeting through “enhanced permeability and retention” i.e. nanoparticles’ ability (largely due to their small size) to escape through blood vessel walls into tumours and accumulate there. However, what this paper believes would be more effective would be use of active targeting, based on the molecules expressed in their cell surface, this would use the same principles as of the magnetic-nanosensors explained above. Once the cancer cells are recognised, the nano-particles can bring the drugs into the cancerous cells and release the drug there – this would allow greater tumour reduction with lower doses of the drug and minimize the interaction of the chemotherapy drugs with the surrounding tissue[13].

Current research into using nanotechnology to deliver medicine

This method of using nanotechnology to deliver drugs was further investigated by Adam Mamelak who led a team of researchers at the Cedars-Sinai Medical Center, Los Angeles (2006) [14]. The team developed a synthetic form of a peptide, TM-601 (Fig 3), based on chlorotoxin found in the venom of the Giant Yellow Israeli Scorpion to target glioma, a particularly aggressive form of brain tumour. This is a particularly good example of how active targeting can be carried out as TM-601 seeks out and selectively binds to glioma cells in the way this paper describes. Transmolecular Inc. ran a trial where 18 patients with malignant glioma who had undergone surgery to remove it, had a small catheter (tube) inserted into the cavity of the former tumour. When the patients received a dose of the 131I-TM-601 through the catheter directly into the cavity two weeks later, the dose had very few adverse side effects. By using magnetic resonance imaging, scientists showed that in two patients the TM-601 had caused the tumours to disappear completely.

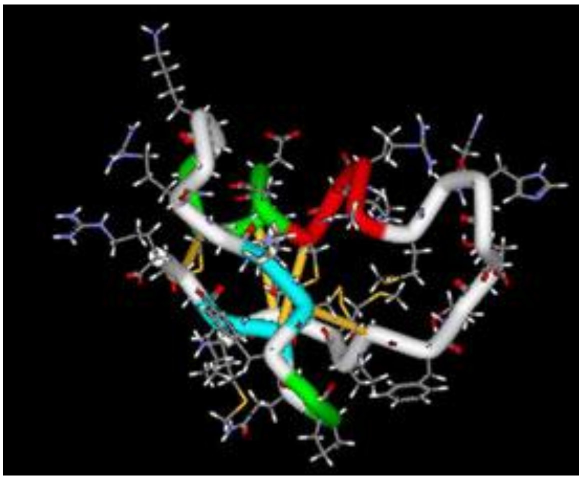

Figure 3: 3D structure of TM-601, used to target brain tumours

Pin-Yuan Chen of Chang Gung Memorial Hospital in Taiwan and his team (Aug 2010)[15] took a different approach, using ultrasound to increase the permeability of the blood-brain barrier in rats and allow greater quantities of nanoparticles to diffuse through. What was different about these nanoparticles, however, is that they were magnetic. By using an external magnetic field, the researchers were able to increase the concentration of nanoparticles in specific areas of the brain (Fig4). This localization of nanoparticles has the usual effect of reducing doses and therefore side effects. However, this paper believes that this research highlights yet

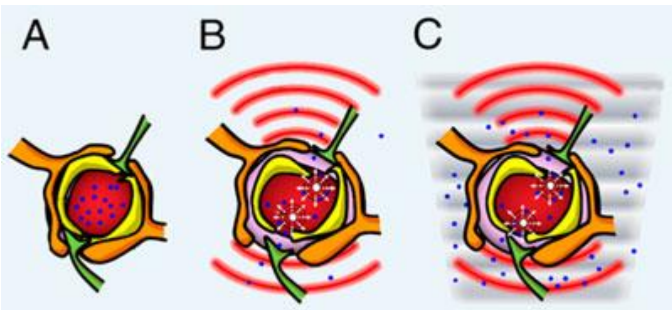

Figure 4: Represents the increasing concentration of nanoparticles as ultrasound then magnetic field are used

another important benefit of using nanotechnology. Scientists found that the magnetic particles show up on magnetic resonance imaging (MRI) scans. Therefore, doctors would then be able to track how each individual tumour responded to the treatment and how fast the rate of reduction was progressing. This paper theorises that this could become of great importance due to the fact that tumours are not typical: the different structures of each form of brain tumour may affect their response rate to the drugs and monitoring this could greatly improve a patient's outlook.

Nanoshells

A more unusual way of using nanotechnology to treat brain tumours moves away from conventional chemotherapeutics, instead physically destroying the cancerous cells from within. For this, it would require a form of nanotechnology called nanoshells. These can absorb light of different frequencies in order to generate heat. Scientists have been able to direct these nanoshells to the tumours via active targeting and apply low frequency light. Once absorbed by the nanoshells, it causes high levels of heat to selectively kill the cancer cells.[16]

Although research into this area seems currently limited, this paper is confident about its potential. Since traditional chemotherapy are drugs are not used, it would not be associated with the same severe side effects experienced currently – making the treatment far less debilitating for the patient. Additionally, through the use of active targeting and selective application of the light, healthy cells are not damaged. This could have significant repercussions for treating brain tumours, as the risks of damaging brain tissue are greatly reduced.

Surgery

One final way that this paper envisages nanotechnology being used to treat brain tumours is in surgery. This suggestion remains purely theoretical, but the belief is that by using surgical tools on a molecular level, surgery would become far more precise in removal of brain tumours with limited damage to the surrounding area. This would be of particular value with the highly invasive brain tumours who spread greatly into surrounding tissue. [17]

Additionally, nanotechnology is already being developed to assist surgery. The work of Zhang and her team has already been mentioned in this paper under Identification, yet Chun Li's research team at the University of Texas[18] are developing the use of nanotechnology using a slightly different approach. They are using near-infrared emitting nanoparticles to outline the margins of a tumour and guide the surgeon. What is different about this research team is the presence of Eastman Kodak who is developing practical ways to use these images in a real operation. This research provides an example of the advancements of nanotechnology past theoretical uses, such as nanotools, and into the practical. Such a development as Kodak is working on could be extremely significant.

Ethicality and safety concerns

It is nanoparticles ability to cross the blood-brain barrier with such ease that makes it so effective in transporting medicine. However this also raises questions about where the nanoparticles can travel and what damage they can cause: the blood-brain barrier is after all meant to protect the brain from infection. Eva Oberdörster, Ph.D., at the Southern Methodist University in Texas, found that fish exposed to fullerenes experienced extensive brain damage after just 48 hours[19]. This raises questions towards the safety of using nanoparticles as living cells much more readily take them up. Nanomedicine has developed so rapidly that concerns are increasing in regard to the relatively unexplored toxicity of the nanoparticles and what dangers they carry. This is why the Nanotechnology Characterisation Laboratory (NCL) is currently working closely with researchers to test toxicity of nanoparticles and advance our understanding.[20]

Unlike an area such as stem cells, nanoparticles carry little religious or moral contention. The main area of controversy from this perspective would be the extensive use of animal testing by a variety of research teams. However, this paper would argue that the vast benefits of more efficient treatment of the tumours outweighs the possible hurt to any animals used. Arguments following the discarding of existing pharmaceuticals may frighten drug companies, but they are unlikely to hold much significance for the general public or existing brain tumor patients.

It is important to remember that research into using nanoparticles to treat brain tumours still has many years to go and during this time the dangers of nanotechnology should most definitely be fully investigated. However, once you consider the significant benefits of using nanotechnology in this area it becomes clear that its potential is currently far more significant than any surrounding concerns.

CONCLUSION

Brain tumours are one of the most difficult forms of cancer to treat with one of the worst outlooks. Research into the use of nanotechnology is growing, with scientists approaching from all different areas. So much of its potential still has to be explored – yet so does its risk. Nanotechnology has grown so fast that it is important to remember that so much is not yet fully understood.

Yet this paper believes that all this current research can only give hope. The increased effectiveness of chemotherapeutic drugs when given with nanoparticles is extraordinary. Nanotechnology can allow more precise surgery in such a delicate organ. Tumours can be identified and treated much earlier on. There is even the possibility of moving away from the chemotherapeutics we currently rely on and using new, extremely effective treatments such as nanoshells that do not seem to carry the same side effects.

Most of this research still has many years to go, but this paper would argue that its impact will become more than considerable. By using nanotechnology most of the complex issues surrounding treatment of brain tumours, such as the side effects and the risk of impairing cognitive function, are all greatly reduced, as well as proven effectiveness in reducing tumour size. Once this further research is completed, this paper believes that nanotechnology will transform how brain tumours are treated. By allowing more specific targeting of the tumours and minimising damage to the surrounding tissue, perhaps nanotechnology will be the key to changing the survival rate for the better.

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