Dendritic vaccine promising for gliomas

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A dendritic cell vaccine has recently shown promise in Phase I trials for the treatment of the highly aggressive brain tumour, glioblastoma multiforme (or glioma)[1]. Scientists at the Cedars-Sinai Medical Center's Maxine Dunitz Neurological Institute (Los Angeles, CA, USA) have shown that intradermal vaccinations with peptide-pulsed dendritic cells increased the median length of survival of patients in the study from 257 to 455 days.

Glioma: the disease

Glioma is an especially aggressive tumour and patients with the disease have a poor prognosis. Current treatment consists of surgical resection followed by radiotherapy and/or chemotherapy, but still leaves patients with a median survival of <1 year[2]. Keith Black, Director of the Institute and the study's lead investigator, explains the reason for this poor response: 'The cells appear to have multiple clones, some that are sensitive to the chemotherapy and some that are not. Those that are resistant continue to grow despite chemotherapy, leading to the development of multiple drug-resistant genes.'

Other immunotherapeutic treatments for brain tumours have focused on adoptive and non-specific strategies, without the administration of an antigenic target[2,3]. However, these treatments have had limited success for glioma as the tumour cells are poor antigen presenters to the immune system. This is compounded in glioma by a downregulation of MHC antigens and B7 costimulatory molecules on the cell surface, which are required for direct T cell activation.

The vaccine

Black explained that dendritic cells were chosen for the vaccine because they are potent 'professional' antigen presenting cells, which are necessary to efficiently internalize, process and present glioma antigens to T cells[4]. As opposed to most vaccines, which are usually prophylactic, these vaccines are intended to prevent the recurrence of the cancer.

The team produces the peptide-pulsed dendritic cell vaccine by isolating the glioma cells from previously removed glioma tumours. These are then co-cultured with dendritic cells isolated from the blood, in the presence of tumour necrosis factor and interleukins, to promote both cell maturation and the presentation of the antigens on the surface of the dendritic cell. Vaccination of rat models of metastatic intracranial tumour[5] and glioma[6,7] produced complete eradication of the tumours in 60% of animals and the animals were able to mount an immune response against the tumour, both peripherally as well as inside the tumour.

Clinical trials

In Phase I trials, seven patients with glioma and two patients with anaplastic astrocytoma were given three intradermal injections, once every two weeks, of the peptide-pulsed dendritic cells and the blood was evaluated one week after each injection and 6 and 12 weeks after the last vaccination. All patients had stopped taking steroids for the period of the trial. The glioma patients were age- and gender-matched with similar levels of tumour removal and treatment as the 42 newly diagnosed glioma patients in the control group.

Out of the seven glioma patients, four exhibited enhanced cytotoxic T cell activity after vaccination, which lasted for more than 12 weeks post-vaccination. In two more patients, cytotoxicity was demonstrated both before and after vaccination, while in one further patient, no cytotoxicity was noted at any point. Four patients developed tumour progression and underwent reoperation, two of which were found to have developed significant $CD8^+$ cytotoxic and $CD45RO^+$ memory T cell infiltration in the tumour areas, as well as a limited increase in $CD4^+$ helper T cells. The other two patients who underwent reoperation displayed few infiltrating T cells of any type post-vaccination.

No serious adverse events or clinical or radiological evidence of an autoimmune reaction was seen with the administration of the autologous dendritic cells. Side effects noted included a slight fever, nausea and vomiting, and swelling of the injected lymph node. This supports previous studies using dendritic cell immunotherapy for lymphoma[8], melanoma[9], prostate cancer[10] and renal cell carcinoma[11]. These studies also demonstrated improvement in survival times and activation of the immune system against the tumour. Furthermore, in some instances, there was actually regression of the tumour. However, the team remains cautious about the lack of autoimmunity reaction, saying that continued evaluation will be necessary to determine if any crossreactivity occurs between brain tumour antigens and normal neural antigens.

Future work

These Phase I trial results suggest that this dendritic cell vaccine can induce intra-glioma T cell infiltration and generate specific immunity, providing a promising approach for glioma treatment. The vaccine has therefore now moved into a randomized double-blind Phase II clinical study of 100 patients with glioma

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and Black says that 'preliminary results look promising'.

This is the first dendritic cell vaccine to move into clinical trials, although other teams are in the preliminary stages of examining their potential use for the treatment of other cancers and diseases that activate the immune system such as multiple sclerosis. Black and colleagues are also beginning research into the use of this technique for the treatment of other types of brain tumours, especially in the paediatric population, where it is one of the leading causes of death.

Black and his team are also working to try to improve the current vaccine. 'One of the difficulties of producing a vaccine for brain tumours is that the tumours use several methods to evade the immune system, including directly killing activated T cells,' he explains. 'We are therefore trying to work out a strategy to inhibit this mechanism to make the vaccine even more effective.'

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Trojan antibiotics

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Researchers have developed a new technology to design antibiotics against drug-resistant bacteria. From the outside, the novel drugs look like conventional antibiotics, but they carry a potent bactericide hidden within their chemical structure. The lead antibiotic candidate based on this new technology, NB2001, has been shown to be effective *in vitro* and is now being tested in animal models.

According to the WHO, as many as 60% of hospital-acquired infections in the industrialized world are caused by drug-resistant microbes[1]. Bacteria have developed many tricks to resist antibiotic treatment. Often, they produce enzymes that convert the antibiotic drug into an ineffective compound and so much current research is concentrating on developing products that inhibit these resistance enzymes.

Mechanism of new technology

Scientists at NewBiotics (San Diego, CA, USA) have developed a new approach to avoiding the resistance problem by turning the production of the resistance enzyme into a therapeutic advantage as opposed to the usual mechanism of trying to inhibit the enzyme. The general approach involves first identifying the key enzymes in the infectious organisms that play an essential role in the development of drug resistance. They then modify the natural substrate of the enzyme and incorporate a potent toxin into its chemical structure. As a result, the resistance enzyme catalyses the release and activation of the toxin, causing the cell to self-destruct.

Drugs based on this Enzyme Catalyzed Therapeutic Activation (ECTA) technology are not only being developed for treatment of infectious diseases. The approach was originally invented to overcome drug resistance in cancer therapy. NB1011 is in development for the potential treatment of patients with colorectal and breast cancer that have suffered relapse with 5-fluorouracil (5-FU). Preclinical efficacy and toxicology studies look promising, and the compound is now about to enter clinical trials.

Identification of lead candidate

By comparison, the company's anti-infective programme is still in its infancy.

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