# Clinical trials launched for treating most aggressive brain tumor with personalized cell vaccines

November 30 2009

The University of Navarra Hospital (Spain) has launched a series of clinical trials in order to assess the efficacy of an immunotherapy treatment. This approach involves the application of personalised vaccines —produced from healthy and tumour cells from the patient him or herself— and designed to combat glioblastomas, one of the most aggressive and frequent malignant tumours. The new therapy is administered to participating patients combined with the standard, first-line treatment involving surgical extirpation of the tumour followed by radiotherapy and chemotherapy treatment with temozolomide. The Hospital is currently the only centre in Spain undertaking a study of this nature, and for which it has recently received authorisation from the Medication Agency of the Spanish Health Ministry. It is planned to involve a sample of 37 patients for the research.

The trials have been devised and developed by the Neuro-oncology and Cell Therapy Areas of the University of Navarra Hospital, in collaboration with the Centre for Applied Medical Research (CIMA) through the Scientific and Technological Institute (ICT) of the same university. The investigation has received funding from FIS (Health Research Fund) announcement by the Ministry of Health for financing the development of non-commercial pharmaceutical drugs.

In essence, the production of the personalised vaccines is carried out at the University of Navarra Hospital's Cell Therapy Good Manufacturing

Practices Laboratory, where tumour proteins are processed and then combined with immune system cells obtained from the patient's blood, which are taught how to organise an immune response to the tumour. These prepared items are frozen and then administered to the patient as vaccines over the following months, in combination with conventional therapy.

It should be recalled that an immunotherapy treatment with similar characteristics was developed over two years ago by a research team at CIMA and the University of Navarra Hospital. In that case, the procedure was based on the production and administration of idiotype vaccines and personalised for patients with first relapse follicular lymphoma. The trials demonstrated clinical efficacy on managing to change the progress of the illness.

## More than 2,400 new cases each year in Spain

The glioblastoma is the most common malignant tumour of the brain. The rate is about 6 cases for every 100,000 inhabitants per year, which means that in Spain 2,400 new cases appear every year. There is no effective treatment currently, making it one of the ten tumours causing the greatest number of deaths annually. In concrete, patients with a glioblastoma, and who have been treated with the standard procedure, have an average survival period of between 12 and 15 months. Nevertheless, in the few cases studied worldwide, a number of patients undergoing immunotherapy have survived longer, the average rate being more than 30 months.

## Basis of the trials

The basis of the trials developed by the Hospital is the hypothesis that the immune system of each person is capable of recognising and

destroying tumour cells. This ability lies in the fact that tumour cells have surface markers different from those of healthy cells, to the point where the organism itself can detect these makers and produce antibodies and cell toxicity against incipient tumour cells. However, when the tumour has grown, the immune system is incapable of controlling it.

In this way, the new treatment currently being tested by the University of Navarra Hospital is trying to load the dendritic cells, responsible for directing and co-ordinating the immunity of the organism, with undesired tumour antigens, so that the cells of the immune system are activated and the body's defences are aimed at the remains of the tumour at a time when tumour cells are scarcer, i.e. after the extirpation of the tumour and the application of radio-chemotherapy.

## Multidisciplinary work

Current treatment of these tumours requires a multidisciplinary approach, which is why, the Area de Neuro-oncology, integrating doctors from various specialities involved in the diagnosis, treatment and monitoring of cerebral tumour patients, has been created. These trials involve close co-operation and co-ordination between the Area de Neuro-oncology Area and the Cell Therapy Area, with the direct intervention of specialists in Neurosurgery, Oncology, Radiotherapeutic Oncology, Pathological Anatomy and Cell Therapy.

## Criteria for selection of candidates

Patients complying with the necessary requirements for participating in the clinical trials are those suspected of having a glioblastoma, having had an examination carried out using magnetic resonance. Also possible candidates are those with a diagnosis of recently confirmed

glioblastoma, subsequent to an analysis of a tumour biopsy.

An essential condition is also that patients have not previously received any kind of an treatment for glioblastoma, except a biopsy or an partial extirpation surgery. The compliance with this premise is necessary as, for the production of the personalised vaccines, the greatest quantity possible of the tumour tissue must be obtained. Moreover, the extirpation of the tumour should be undertaken in the most complete possible manner, given that it has been demonstrated that, the cases in which the immunotherapy has proved effective are those in which wide-ranging extirpations have taken place.

## Total extirpation with fluorescent microscope

The few studies carried out to date about treatment of glioblastomas with immunotherapy has demonstrated that the residual tumour causes the tumour cells to impede a positive response by the autologous vaccines (produced with the patient's own tissue). In order to achieve that the immunotherapy treatment be the most efficacious possible, the Hospital has a fundamental tool in the operating theatre - the fluorescent microscope -, with which the percentage of tumour extirpation has increased enormously.

In concrete, the surgical fluorescent microscope has enabled specialists at the Hospital to reach the total extirpation of glioblastomas in more than 80% of the cases operated over the last two years. After the extirpation, the tumour tissue obtained has to be sent - in conditions of maximum sterility - directly to the Pathological Anatomy Laboratory to corroborate or contradict the diagnosis. If the tumour is confirmed to be a glioblastoma, the tumour tissue is then transferred to the Cell Therapy GMP Laboratory at the Hospital for its processing and the subsequent obtaining of personalised vaccines produced with the tissue of each patient taking part in the clinical trials.

# Production of personalised vaccines

The personalised vaccines are produced in the Cell Therapy GMP Laboratory at the University of Navarra Hospital given its advance therapy medication nature and having to be produced under correct manufacturing norms. They are treated as individualised (personalised) units of medication, each being produced by the combination of two elements obtained from the patient him or herself: the dendritic cells (of the immune system) and the tumour cells (obtained and processed from the tumour itself).

The dendritic cells are obtained by a process known as leukapheresis which involves the separation and extraction of white blood cells from the rest of the patient's blood, and returning it to the organism.

After the pheresis and by means of immunomagnetic selection, monocytes are obtained - a type of white blood cell the function of which in the body is to pass to the tissues, converting themselves into dendritic cells and capture antigens (molecules capable of triggering an immune response), amongst these tumoural antigens. Once captured, the dendritic cells teach the lymphocytes (the cells responsible for immune responses) to recognise cancer cells and destroy them at any point of the organism. This immunomagnetic procedure involves adding a small metal ball to some antibodies specific to the monocytes. When these antibodies adhere to the monocytes, it only needs the application of a magnetic field to achieve the separation and extraction of the monocytes from the rest of the white blood cells.

Once the monocytes are selected, they are cultured for eight days - at the same Cell Therapy Laboratory, under similar conditions to those of the organism itself. After this period of culture, the monocytes, to which cytokines have been added (regulatory proteins of the immune system cells), change into dendritic cells, fundamental for the l functioning of

this immune system.

## Processing the tumour

To obtain the second component - the tumour cells - in suitable conditions, the process known as "tumoural lysis" is s necessary - requiring the tumoural mass to have been extracted, analysed and transferred under conditions of maximum sterility. To this end it is necessary that, after surgical extirpation, the processing of the tumour take place rapidly in the GMP laboratory. The tumoural lysis involves decomposing or breaking up the tumour cells through a procedure of freezing, de-freezing and irradiation. From this process a suspension of the proteins of the tumour is obtained in sufficient quantity to produce a dozen vaccines.

Once the proteins from the glioblastoma are obtained, these are incubated with the immune system dendritic cells in order to be processed and the components of the tumour proteins placed in their membrane. In this manner the vaccine is produced, in such as way that, when the patient is injected, the lymphocytes of the blood will detect the tumour particles in the membrane and generate an immune system response against the cells of the glioblastoma.

## Vaccines combined with standard treatment

In total, it is expected that, for each patient, about twelve personalised cell vaccines will be mad at the Cell Therapy Laboratory. Over the period of time of the treatment, the vaccines are conserved frozen in the laboratory.

The usual treatment for these tumours involves extirpation by surgery, followed by a combination of radio and chemotherapy of five weeks and

then between six and twelve cycles of chemotherapy (administered once every four weeks). The cell vaccines are administered by intradermally simultaneously with these treatments, once a month at first, then bimonthly and the final dose every three months.

Source: Elhuyar Fundazioa