Patients with high-risk neuroblastoma are currently treated with an intensive and complex schedule of treatment including chemotherapy, surgery, ‘high-dose’ chemotherapy and stem cell rescue, radiotherapy and antibody therapy with cis-retinoic acid. If neuroblastoma comes back during or after this treatment (relapsed neuroblastoma), it may be possible to control the disease for years, although it is usually very difficult to achieve a complete cure.

The purpose of this information leaflet is to tell you about treatment opportunities that are available in the UK for treating children with relapsed or refractory (disease that isn’t responding to treatment) neuroblastoma. Choosing which treatment is right for your child will depend on a number of things including where their disease is and what treatment they have previously been given. Your child’s own doctor will be able to help you decide which the most appropriate treatment for your child is at this time.

Possible treatment options include chemotherapy, radiotherapy including molecular radiotherapy (using radioactively-labelled medicines to target cancer cells), surgery and antibody therapy (treatment that recognises and attaches to specific molecules produced by cancer cells), as well as new drugs being tested in early phase clinical trials. An early phase trial (phase 1 or 2 trial) is usually a small trial recruiting only a few patients and is often open to children with any type of cancer [1].

Chemotherapy

In most cases where the neuroblastoma is in more than one place or has returned distant to where it first started (metastatic relapse) a patient will be treated with chemotherapy. There are a number of different chemotherapy options that doctors can use to control neuroblastoma in this situation, but currently no specific chemotherapy combination has been shown to be the best. Researchers are therefore looking further into some of these combinations in the current BEACON trial.

BEACON [2]

Temozolomide, irinotecan and topotecan are chemotherapy drugs doctors have used for some time to control relapsed neuroblastoma in children, but we do not know if having combinations of drugs together is better than having temozolomide on its own. Researchers within SIOPEN (the European collaborative group for neuroblastoma research) are looking to answer this question in the current BEACON trial, a randomised Phase 2 study currently open in 7 centres around the UK (Birmingham Children’s Hospital, Leeds General Infirmary, Royal Manchester Children’s Hospital, Royal Victoria Infirmary Newcastle, Royal Marsden Hospital Sutton, Royal Hospital for Sick Children in Glasgow and Great Ormond Street Hospital London) as well as in Europe. They also want to find out if having a drug called bevacizumab can help children with neuroblastoma. Bevacizumab is a monoclonal antibody that targets the tumour’s blood supply. It is already used to treat some adult cancers and researchers are now looking to see if it works in children too.

The current aims of the BEACON trial are to find out:

- If having irinotecan or topotecan as well as temozolomide helps children and young people with relapsed or refractory neuroblastoma
- If adding bevacizumab to chemotherapy helps children and young people in this situation
- More about the side effects of the different drug combinations
In the future, testing of other combinations of chemotherapy medicines that might help to treat neuroblastoma is planned. To be able to take part in this trial at present children and young people must not have previously received temozolomide or irinotecan and must not be at risk of bleeding (as the bevacizumab could increase this bleeding risk). A computer will decide for each person taking part which of the following six treatments they will receive; this means that the treatment is decided at random rather than by families or doctors. This method is very important for ensuring that the different treatments can be fairly compared; at the moment, we don’t know whether one or other treatment arm is any better than the others:

- Temozolomide
- Bevacizumab and temozolomide
- Irinotecan and temozolomide
- Bevacizumab, temozolomide and irinotecan
- Topotecan and temozolomide
- Bevacizumab, topotecan and temozolomide

Other chemotherapy
For patients who are not eligible for the BEACON study, or who decide not to take part, chemotherapy might be given outside of a clinical trial. There are a number of possible combinations of chemotherapy medicines that might be used and at present there is no evidence that any particular combination is any better than another. The choice of medicines will be decided depending on a number of factors including what medicines a child has already received and whether there have been significant toxicities (side effects). Your child’s own doctor will be able to discuss further the possible chemotherapy combinations that might be used.

Molecular radiotherapy
Molecular radiotherapy is another way of using radiation to kill cancer cells and may have a role in treating relapsed or refractory neuroblastoma. Your child is likely to have received standard ‘external beam’ radiotherapy as part of their upfront treatment for high-risk neuroblastoma. This involves giving radiotherapy as a beam of x-rays given from outside the body. By contrast, molecular radiotherapy uses radioactive medicines that will travel to the sites of neuroblastoma around the body and deliver radiation at these areas of disease.

There are two main types of molecular radiotherapy for neuroblastoma. One technique that has been in use for many years uses radioactive mIBG. This works on the same principle as an mIBG scan that your child will probably have received during their initial treatment in that radiation is tagged onto the mIBG molecule that is taken up by neuroblastoma cells. For mIBG treatment a much stronger dose of radiation is linked to the mIBG with the aim of killing neuroblastoma cells, not just detecting whether and where they are present. mIBG therapy is only suitable for some patients and is currently available at University College London Hospital and Royal Marsden Hospital, Sutton.

An alternative form of molecular radiotherapy is being tested in the current LuDO trial.

\[ ^{177} \text{LuDO} \ [3]\]

Many neuroblastoma cells have a protein on their surface called somatostatin. This protein can be used to attract drugs that deliver radiotherapy directly to the cells. LuDO is a drug that targets somatostatin on the surface of neuroblastoma cells. It has a radioactive molecule attached to it that on finding the tumour cells kills them. Previous trials have shown that this type of treatment can help people with other types of cancer.

The aims of the LuDO trial, a phase 2 trial open at University College London Hospital, are to find out:

- If LuDO can help children and young people with neuroblastoma
- How safe it is

In order for a child or young person to be suitable for this type of treatment they must have the somatostatin receptor targeted by the therapy present on their tumour cells, otherwise it will not work. This will be checked by a special scan (Ga-DOTATATE PET/CT) similar to an mIBG scan which will be used to determine if your child can take part.
**Immunotherapy**

Doctors think that children with relapsed disease who have responded to chemotherapy and/or molecular radiotherapy and only have a small amount of remaining neuroblastoma may benefit from receiving immunotherapy, although at the moment it is not known if this will be beneficial for patients who have already received immunotherapy as part of their initial treatment for high-risk neuroblastoma.

Researchers are looking into different ways of giving immunotherapy in the current ch14.18/CHO (GD2) long-term infusion study.

**Ch14.18/CHO**

Ch14.18/CHO (also known as anti-GD2) is a monoclonal antibody that seeks out neuroblastoma cells by looking for particular proteins on their surface. We know that this antibody can help children with neuroblastoma but that it also causes severe pain often requiring morphine and meaning children have to stay in hospital whilst having this treatment. If the antibody is given more slowly over a longer period of time the pain is less.

This phase 1/2 trial is open in 7 centres across the UK (Alder Hey Children’s Hospital Liverpool, Great Ormond Street Hospital London, Bristol Royal Hospital for Children, Royal Victoria Infirmary Newcastle, Leeds General Infirmary, Royal Hospital for Sick Children Glasgow and Southampton General Hospital).

Researchers first looked at different ways of giving ch14.18/CHO over a number of days, to see if children and young people could have the treatment more comfortably and not need to be in hospital. In this first part of the trial everyone had ch14.18/CHO, a drug called aldesleukin (IL-2) and a drug called isotretinoin (which makes neuroblastoma cells less active). Aldesleukin (IL-2) may help the antibody work better against neuroblastoma but this is not definitely proven yet and results from the first part of the trial suggest that aldesleukin may cause a number of side effects. So in the second part of the trial, which is now open, half of the people taking part will have ch14.18/CHO, aldesleukin (IL-2) and isotretinoin (13 cis retinoic acid) and the other half will have ch14.18/CHO and isotretinoin (without aldesleukin).

To be considered for participation in this study your child must have already had at least one high dose treatment followed by a stem cell transplant and their disease must have responded to treatment and not be getting worse at this time. Note that patients who have already received immunotherapy with anti-GD2 antibody are currently not eligible to receive the antibody again as there is no clear evidence that re-treatment can be effective. However this situation may change when the results of additional trials are known.

**Phase 1 trials**

If your child’s disease does not respond to chemotherapy/radiotherapy/molecular radiotherapy/immunotherapy or alternatively if it responds well but has not disappeared completely, you may wish to consider a phase 1 trial. There are currently several trials open for recruitment in the UK which children with neuroblastoma can take part in. It is important to remember however that the new drugs tested in these trials have not been proven to work in neuroblastoma in children and may not help your child. These phase 1 studies are often only open at a limited numbers of centres in the UK and therefore it may be necessary to travel to another hospital to take part.

If you are considering taking part in a phase 1 trial it may be helpful to ask your doctor about whether

- there is any pre-clinical evidence exists for the treatment that is relevant to neuroblastoma, for example in laboratory studies using cells or animal models
- there have been other studies of similar drugs trialled in neuroblastoma
- the drug has been trialled in adults and if so what side effects were seen
- it will involve being away from home for a long time

Of the trials currently open, the phase 1 study of a drug called LDK378 in children’s cancers with a genetic alteration in anaplastic lymphoma kinase (ALK) (a cell surface receptor that controls cell growth) appears to hold the most promise for children with neuroblastoma. Similar drugs, such as crizotinib, have been trialled previously in neuroblastoma and showed encouraging results for those children whose tumours have ALK-mutations.
However only around 8% of children with neuroblastoma have an alteration in the ALK gene and most children will therefore not be able to take part in this study. The trial is being done to find the safe dose range and side effects of the drug, as well as how the body copes with the drug and to see if this particular drug is effective.

The future

New studies to treat neuroblastoma are continuously in development and there are several trials currently in preparation including:

- a new study called VERITAS for patients with refractory high-risk neuroblastoma that will look at the role of mLG molecular radiotherapy and high-dose chemotherapy
- a new approach to treating relapse neuroblastoma using genetically-engineered immune cells (CAR T-cells) that will hopefully open at Great Ormond Street Hospital in 2016
- a new study using anti-GD2 antibody and other medicines to treat relapsed neuroblastoma, including patients that have previously received immunotherapy

The process of opening new studies is long and complex and it is not possible to say for certain when these studies will be open or whether or not your child might be eligible until these studies are finalised and open for recruitment.

To find out more about taking part in any of these trials please refer to the web sites below.

References