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Neuroblastoma - Childhood - Treatment Options [1]

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ON THIS PAGE: You will learn about the different ways doctors use to treat children with this type of cancer. To see other pages, use the menu on the side of your screen.

In general, cancer in children is uncommon, so it can be hard for doctors to plan treatments unless they know what has been most effective in other children. That?s why more than 60% of children with cancer are treated as part of a clinical trial. Clinical trials [3] are research studies that compare the best proven treatments available (standard treatments) with newer approaches to treatments that may be more effective. Clinical trials may test such approaches as a new drug, a new combination of standard treatments, or new doses of current therapies. Studying new treatments involves careful monitoring using scientific methods, and all participants are followed closely to track their health and progress.

To take advantage of these newer treatments, all children with cancer should be treated at a specialized cancer center. Doctors at these centers have extensive experience in treating children with cancer and have access to the latest research. A doctor who specializes in treating children with cancer is called a pediatric oncologist. In many cases, a team of doctors treats a child with cancer; this is called a multidisciplinary team [4]. Pediatric cancer centers often have extra support services for children and their families, such as child life specialists, nutritionists, physical and occupational therapists, social workers, and counselors. Special activities and programs to help your child and family cope may also be available.

Descriptions of the most common treatment options for neuroblastoma are listed below. Treatment options and recommendations depend on several factors, including the size and location of the tumor, whether the cancer has spread, the risk classification [5], possible side effects, family preferences, and the child?s overall health. The treatment is tailored according to the risk group the tumor has been assigned, including additional types of therapy. Your child?s care plan may also include treatment for symptoms and side effects, an important part of cancer care. Take time to learn about all of your child?s treatment options and be sure to ask questions about things that are unclear. Also, talk about the goals of each treatment with your child?s doctor and what your child can expect while receiving the treatment. Learn more about making treatment decisions [6].

Surgery

Surgery is the removal of the tumor and surrounding tissue during an operation. A surgical oncologist is a doctor who specializes in treating cancer using surgery. If the cancer has not spread, surgery can sometimes be used to remove the entire tumor. However, most neuroblastoma is not found until after the cancer has spread. In that situation, the doctor removes as much of the tumor as possible during surgery. If the tumor cannot be completely removed, the child may receive radiation therapy or chemotherapy (see below) to kill the remaining cancer cells.

The doctor may also remove lymph nodes on both sides of the abdomen to look at them under a microscope to see if there are cancer cells. The doctor may also take a biopsy of the liver to find out if the disease has spread to the liver. Talk with your child?s surgeon about the possible side effects of the surgery and how they will be relieve or managed. Learn more about cancer surgery [7].

Even if a tumor cannot be removed because of its location, a surgical biopsy (see Diagnosis [8]) may still be done to determine the type of tumor.

Chemotherapy

Chemotherapy is the use of drugs to destroy cancer cells, usually by stopping the cancer cells? ability to grow and divide. Chemotherapy is given by a pediatric oncologist or a medical oncologist, a doctor who specializes in treating cancer with medication.

Systemic chemotherapy is delivered through the bloodstream to reach cancer cells throughout the body. Common ways to give chemotherapy include an intravenous (IV) tube placed into a vein or muscle using a needle or in a pill or capsule that is swallowed (orally). A chemotherapy regimen (schedule) usually consists of a specific number of cycles given over a set period of time.

Most children with neuroblastoma will need to have chemotherapy. Chemotherapy may be used as the primary treatment for neuroblastoma, or it may be given before surgery to shrink the tumor or after surgery to kill any remaining cancer cells. Occasionally, a single drug is given, but most often, a combination of drugs is used.

Children with intermediate-risk neuroblastoma often receive the following drugs:

- Carboplatin (Paraplatin)
- Cyclophosphamide (Neosar)
- Doxorubicin (Adriamycin)

Children with high-risk neuroblastoma often receive the following drugs:

- Cyclophosphamide
- Ifosfamide (Ifex)
- Cisplatin (Platinol)
- Vincristine (Vincasar)
- Doxorubicin
- Melphalan (Alkeran)

- Etoposide (VePesid, Toposar)
- Topotecan (Hycamtin)
- Busulfan (Busulfex, Myleran)
- Carboplatin (Paraplatin)
- Chimeric 14.18 antibody
- Cytokines (GM-CSF and IL2)
- Isotretinoin

The side effects of chemotherapy depend on the individual and the dose used, but they can include fatigue, risk of infection, nausea and vomiting, hair loss, loss of appetite, and diarrhea. These side effects usually go away once treatment is finished. The severity of the side effects depends on the type and amount of the drug being given and the length of time the child receives the drug.

Learn more about chemotherapy [9] and preparing for treatment [10]. The medications used to treat cancer are continually being evaluated. Talking with your child?s doctor is often the best way to learn about the medications prescribed for you, their purpose, and their potential side effects or interactions with other medications. Learn more about your prescriptions by using searchable drug databases [11].

Radiation therapy

Radiation therapy is the use of high-energy x-rays or other particles to destroy cancer cells. A doctor who specializes in giving radiation therapy to treat cancer is called a radiation oncologist. The most common type of radiation treatment is called external-beam radiation therapy, which is radiation given from a machine outside the body. A radiation therapy regimen (schedule) usually consists of a specific number of treatments given over a set period of time. Side effects from radiation therapy may include fatigue, mild skin reactions, upset stomach, and loose bowel movements. Most side effects go away soon after treatment is finished.

Because radiation therapy can sometimes cause problems with the normal growth and development of a child?s brain and the ovaries (in girls) or testicles (in boys), the doctor may choose to treat the cancer in another way.

Learn more about radiation therapy [12].

Stem cell transplantation/bone marrow transplantation

A stem cell transplant is a medical procedure in which diseased bone marrow is replaced by highly specialized cells, called hematopoietic stem cells. Hematopoietic stem cells are blood-forming cells found both in the blood stream and in the bone marrow. Today, this procedure is more commonly called a stem cell transplant, rather than a bone marrow transplant, because it is the blood stem cells that are typically being transplanted, not the actual bone marrow tissue.

Before recommending transplantation, doctors will talk with the patient about the risks of this treatment and consider several other factors, such as the type of cancer, results of any previous treatment, and patient?s age and general health.

There are two types of stem cell transplantation depending on the source of the replacement blood stem cells: allogeneic (ALLO) and autologous (AUTO). AUTO transplants are most often used for children with high-risk neuroblastoma.

In an AUTO transplant, the patient?s own stem cells are used. The stem cells are obtained from the patient when he or she is in remission from previous treatment. The stem cells are then frozen until they are needed, usually after the high-dose treatment (explained below) is completed.

The goal of transplantation is to destroy cancer cells in the marrow, blood, and other parts of the body and allow replacement blood stem cells create healthy bone marrow. In most stem cell transplants, the patient is treated with high doses of chemotherapy and/or radiation therapy to destroy as many cancer cells as possible. This also destroys the patient?s bone marrow tissue and suppresses the patient?s immune system. After the high-dose treatment is given, blood stem cells are infused into the patient?s vein to replace the bone marrow and restore normal blood counts. Different combinations of high-dose chemotherapy have been used before the stem cells are infused, and the best combination has not yet been determined. Recent research suggests that busulfan (Busulfex, Myleran) and melphalan may cause fewer side effects and may also be more effective than carboplatin, etoposide and melphalan. The Children?s Oncology Group [13] is currently testing the safety and efficiency of busulfan and melphalan in a clinical trial.

In stem cell transplantation, the replacement cells engraft (begin to make new blood cells) and turn into healthy, blood-producing tissue in 10 days to three weeks. Destroying the patient?s own marrow reduces the body?s natural defenses, temporarily leaving the patient at an increased risk of infection. Until the patient?s immune system is back to normal, patients may need antibiotics and blood transfusions, and they need to follow certain safety restrictions provided by the health care team to help avoid infections.

In an AUTO transplant, there is little risk of tissue rejection because the replacement stem cells are the patient?s own cells. However, there is a risk in an autologous transplant that some of the cells that are put back into the patient could still be cancerous. Learn more about stem cell and bone marrow transplantation [14].

Retinoid therapy

Retinoids are substances that are similar to vitamin A. They are thought to help some cells mature into normal cells. When chemotherapy no longer works for some tumor cells, 13-cis-retinoic acid (RA) or isotretinoin has been given to children with high-risk neuroblastoma after completion of consolidation therapy, which is treatment given after the initial treatment. A Children?s Oncology Group study showed that when children who were in remission following stem cell transplant were given RA, their risk of recurrence was reduced.

Immunotherapy

Immunotherapy, also called biologic therapy, is designed to boost the body?s natural defenses to fight the cancer. It uses materials made either by the body or in a laboratory to bolster, target, or restore immune system function.

G_{D2} is a compound on the surface of cells, called a disialoganglioside, that is found in large amounts in most neuroblastomas. G_{D2}-targeted treatments using a variety of monoclonal antibodies have been effective to treat patients with recurrent neuroblastoma. A monoclonal antibody is a substance made in a laboratory that acts like the antibodies the body?s immune system naturally makes to fight diseases such as a tumor.

The Children's Oncology Group has used antibody therapy combined with cytokines (chemicals released by cells that help control the immune system) and retinoid therapy (see above) for patients with high-risk neuroblastoma that responded to induction (first) chemotherapy and who have had a stem cell transplantation without the neuroblastoma growing or spreading. In a recent clinical trial, children received either RA alone, or RA plus cytokines and a specific type of monoclonal antibody. The patients who received the monoclonal antibody lived longer and had fewer recurrences. Immunotherapy is now a part of the standard treatment for patients with high-risk neuroblastoma. Learn more about immunotherapy [15].

Targeted delivery of radionuclides

A radionuclide called ^{131}I MIBG is being researched to treat neuroblastoma. ^{131}I MIBG has led to responses in about 30% of children with recurrent neuroblastoma. Based on how efficient this drug is in the setting of recurrence, a new clinical trial has been opened by the Children?s Oncology Group to test ^{131}I MIBG combined with high-dose chemotherapy and stem cell transplantation in patients newly diagnosed with high-risk disease.

Remission and the chance of recurrence

A remission is when a tumor cannot be detected in the body and there are no symptoms. This may also be called ?no evidence of disease? or NED.

A remission can be temporary or permanent. This uncertainty leads to many survivors feeling worried or anxious that the tumor will come back. While many remissions are permanent, it?s important to talk with your doctor about the possibility of the tumor returning. Understanding the risk of recurrence and the treatment options may help you feel more prepared if the cancer does return. Learn more about coping with the fear of recurrence [16].

If the tumor does return after the original treatment, it is called a recurrent or relapsed tumor. It may come back in the same place (called a local recurrence), nearby (regional recurrence), or in another place (distant recurrence). If there is a recurrence, the tumor may need to be staged again (re-staging) using the system described in stages and risk grouping [5].

When this occurs, a cycle of testing will begin again to learn as much as possible about the recurrence. After testing is done, you and your child?s doctor will talk about the treatment options. Often the treatment plan will include the therapies described above such as surgery, chemotherapy, and radiation therapy but may be used in a different combination or given at a

different pace. Your child?s doctor may also suggest clinical trials that are studying new ways to treat this type of recurrent tumor.

The treatment of recurrent neuroblastoma depends on where the tumor recurred and how aggressive the new tumor is. While there are treatments that work well for patients with low- and intermediate-risk disease who have a recurrence where the original tumor started, treating recurrent high-risk neuroblastoma is difficult. Neuroblastoma comes back in more than 50% of children with high-risk disease. Over the past several years, more new treatments and combinations have been developed for these patients:

- **Chemotherapy.** The drugs topotecan and irinotecan (Camptosar) are often used early when there is a recurrence. Topotecan works better when combined with low-dose cyclophosphamide. The combination of irinotecan and temozolomide (Methazolastone, Temodar) has few side effects. This chemotherapy treatment regimen has been evaluated in a Children?s Oncology Group study, and it works well for some patients with recurrent neuroblastoma.
- **Targeted delivery of radionuclides.** As explained above, radionuclides have been attached to MIBG, as well as somatostatin analogs (substances similar to a specific hormone produced by cells) and anti-G_{D2} antibodies. Early studies looking at combinations of radio-labeled MIBG and radiation sensitizers like irinotecan or histone deacetylase inhibitors like vorinostat (Zolinza) are ongoing. Radiosensitizers are drugs that make tumor cells more sensitive to radiation therapy, making radiation therapy more effective.
- **Immunotherapy.** A special molecule combined with an antibody directed against the G_{D2} and interleukin-2 (IL2; a substance that can be used to boost the immune system) as well as other monoclonal antibodies directed against the G_{D2} antigen are being evaluated for patients with recurrent neuroblastoma. The combination of the immune-modulating agent lenolinomide and chimeric anti- G_{D2} is currently being tested in an ongoing Phase I clinical trial. Vaccines against tumor cell DNA, function, and structure, as well as use of immune cells created in the laboratory that can destroy tumor cells, are also being researched.
- **Retinoids.** Fenretinide works against neuroblastoma in a laboratory, even when other retinoids do not. Research shows that the drug has few side effects. Newer versions of this drug are being created to make it easier to give this medication to young children.
- **Angiogenesis inhibitors.** Anti-angiogenesis therapy is focused on stopping angiogenesis, which is the process of making new blood vessels. Because a tumor needs the nutrients delivered by blood vessels to grow and spread, the goal of anti-angiogenesis therapies is to ?starve? the tumor. Research is focuses on stopping vascular endothelial growth factor (VEGF) from working, which is needed for blood vessels to form.
- **Tyrosine kinase inhibitors.** Tyrosine kinase inhibitors are drugs that block cell communication and can stop tumor growth. Drugs that inhibit ALK, a tyrosine kinase that is mutated in some types of neuroblastoma and in some patients with familial neuroblastoma, are being tested in clinical trials. Other tyrosine kinase inhibitors that are being tested in clinical trials include inhibitors of the epidermal growth factor receptor (EGFR) and the insulin growth factor 1 receptor (IGR1R). These receptors help tumor cells grow and blocking them may slow or stop neuroblastoma growth.
- **Aurora kinase inhibitors.** Aurora A kinase helps cells divide early on and is found in all cells that are dividing. Aurora kinase inhibitors are drugs that block this protein, stopping or slowing the cells from dividing. Research on these drugs is ongoing.

- **Other treatment options.** Demethylating drugs such as decitabine (Dacogen) are currently being studied. Histone deacetylase inhibitors, substances that can prevent a tumor from growing and spreading, have also shown some promise as a treatment for neuroblastoma. At least three histone deacetylase inhibitors are now being studied in clinical trials for patients with refractory solid tumors, which are tumors that remain after the initial treatment. The New Approaches to Neuroblastoma Therapy (NANT) Phase I Consortium has a number of open clinical trials testing new treatments for children with relapsed or refractory neuroblastoma (www.nant.org [17]). Several studies are testing combination therapy that includes biologic agents plus chemotherapy.

When a child has a recurrent tumor, family members often experience emotions such as disbelief or fear. Families are encouraged to talk with the health care team about these feelings and ask about support services to help them cope. Learn more about dealing with cancer recurrence [18].

If treatment fails

Although treatment is successful for the majority of children with cancer, sometimes it is not. If a child?s cancer cannot be cured or controlled, this is called an advanced or terminal cancer. This diagnosis is stressful, and it may be difficult to discuss. However, it is important to have open and honest conversations with your child?s doctor and health care team to express your family?s feelings, preferences, and concerns. The health care team is there to help, and many team members have special skills, experience, and knowledge to support patients and their families.

Parents or guardians are encouraged to think about where the child would be most comfortable: at home, in a home-like setting elsewhere, in the hospital, or in a hospice environment. Hospice care is a type of palliative care for people who are expected to live less than six months. It is designed to provide the best possible quality of life for people who are near the end of life. Nursing care and special equipment can make staying at home a workable alternative for many families. Some children may be happier if they can arrange to attend school part-time or keep up other activities and social connections. The child?s health care team can help parents or guardians decide on an appropriate level of activity. Making sure a child is physically comfortable and free from pain is extremely important as part of end-of-life care. Learn more about caring for a terminally ill child [19] and advanced cancer care planning [20].

The death of a child is an enormous tragedy, and families may need support to help them cope with the loss. Pediatric cancer centers often have professional staff and support groups to help with the process of grieving. Learn more on grieving the loss of a child. [21]

The next section helps explain clinical trials, which are research studies. Use the menu on the side of your screen to select About Clinical Trials, or you can select another section, to continue reading this guide.

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