What to expect with Naxitamab

The purpose of this chapter is to provide a general summary of naxitamab including what role it might play in the treatment of high-risk neuroblastoma and what to expect with it. The information is from clinicians who have treated many patients.

Naxitamab (DANYELZA®) is a humanised anti-GD2 monoclonal antibody developed for the treatment of neuroblastoma, osteosarcoma and other GD2-positive cancers. After naxitamab plus granulocyte-macrophage colony-stimulating factor (GM-CSF) was found to be effective and safe, naxitamab was granted accelerated approval by the USA Food and Drug Administration (FDA) for marketing as treatment for patients of **at least one year old with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who had a partial response, minor response, or stable disease to prior therapy**. **It is important to note that naxitamab is not indicated as a salvage option when neuroblastoma is actively progressing.**

Naxitamab targets the same molecule (GD2) as other antibodies such as dinutuximab and dinutuximab-beta (mainly used in Europe) that are part of upfront treatment for high-risk neuroblastoma. At the moment it is not clear whether one antibody is 'better' or more effective than another. Of note, naxitamab is given as a short infusion and may be administered in the outpatient setting rather than requiring hospital admission.

As an anti-GD2 antibody in combination with GM-CSF, some side-effects may be common with previous anti-GD2 therapy received as a first-line treatment. These side-effects appear to be intense over a short period of time and are likely to happen during and right after the infusions which are done on 3 days in the same week. Your team will take previous tolerance of these drugs into account when discussing treatment options and monitoring naxitamab therapy.

Your team may also consider using naxitamab in combination with GM-CSF and chemotherapy ("chemo-immunotherapy"), although at the moment these combinations are not approved by the FDA.

How was naxitamab developed and studied?

Naxitamab was first called "humanized-3F8" because it was derived from the mouse antibody 3F8 which was also effective for treatment of high-risk neuroblastoma. Humanizing 3F8 was found to have several advantages in laboratory studies compared to mouse 3F8 and other anti-GD2 antibodies. Therefore, humanized-3F8 was tested in children with resistant

neuroblastoma in a phase 1 trial. The aim was to find the highest and safest dosage. Toxicity was manageable, even with very high dosages, so the standard became 9 mg/kg/cycle, which may be better for killing neuroblastoma—although at present has not been proven and it is not known whether one anti-GD2 antibody is more effective than another. Next came phase 2 trials to define success rates using the new standard dosage plus GM-CSF among patients with resistant but not progressing neuroblastoma in bones and/or bone marrow but without soft tissue disease.

Treatment Overview

Naxitamab treatment involves a combination of the following:

- Anti-GD2 antibody (naxitamab):
Naxitamab is given as an infusion (3 mg/kg) on days 1, 3, and 5 of each treatment cycle (i.e., 9 mg/kg/cycle or ~270 mg/m^2/cycle). This infusion typically happens outpatient (in day hospital or outpatient infusion clinic).

- Cytokine (GM-CSF):
Naxitamab is used in combination with GM-CSF, by shots (subcutaneous) for 10 days: 5 days before the 1st dose of naxitamab using the GM-CSF standard dosage 250 μg/m^2/day and then stepped-up dosage using 500 μg/m^2/day for the 5 days in the week of naxitamab injections. A variation has only 3 days of GM-CSF before the 1st dose of naxitamab and daily injections continued through 2 days after the 3rd dose of naxitamab.

Typically, your child would be assessed with physical exam and bloodwork on the day the GM-CSF shots start and continued the GM-CSF shots at home.

Your child would then be seen the following week on the next Monday in an outpatient infusion clinic or day hospital, be assessed in the same way, and start naxitamab the same day along with an increased dose of GM-CSF. The next naxitamab infusions would take place on two more days the Wednesday and Friday of the same week.

For patients starting this treatment in complete remission, 5 cycles are the standard, given every 4 weeks. For patients starting with neuroblastoma in bones and/or bone marrow, once a major response is seen, 5 additional cycles are given, usually every 4 weeks but with flexibility for up to 6 weeks.

Pre-medications

To help prevent or lessen side effects of naxitamab, your child will be given medications before each dose. These are called “pre-medications” and most often include:

Medication given on the days prior to the infusion: Gabapentin is used to prevent nerve (“neuropathic”) pain and can be started 5 days before the 1st naxitamab infusion and continued for a total of 12 days.

Medications given on the day of the infusion:

- IV fluids to hydrate your child.
- Antihistamines to help prevent allergic reactions. These may include over the counter hydroxyzine, famotidine, cetirizine, or loratadine.
- Acetaminophen/Tylenol is given to help prevent and control pain or fever.
- Opioid pain medication is given by mouth prior to naxitamab (i.e. morphine, hydromorphone). This medication can be repeated orally or IV during the infusion.
- Medicines to prevent nausea and vomiting.
- Pre-medicating with steroids is allowed, at the discretion of the treating team.

Monitoring

Close monitoring during and after the infusion will include:

- Heart rate and oxygen saturation will be monitored continuously from the start if the infusion to discharge.
- Other vital signs (blood pressure, temperature) are taken at least every 15 minutes for the first hour and then every 30 minutes after infusion for 2 hours after the end of infusion.
- Monitoring of vital signs may need to be prolonged in case of fever, abnormal blood pressure, or rapid heart rate. Your child may require admission for monitoring and management of side effects.

Labs will be drawn before each naxitamab infusion in day hospital including complete blood counts (CBC), electrolyte panels (chemistry), liver enzymes and albumin levels.

Infusion

The naxitamab infusion is planned to be given over 1 hour for the first dose and between 30 and 60 minutes for the next doses.

Infusion may be paused at any time and the rate can be slowed if side effects occur (potential side effects are discussed below). It is not uncommon for the infusion to be slowed, especially on the first day of a cycle. Infusion rate can be resumed to full rate if side-effects decrease.

It is expected that ~~We expect~~ side effects to be more intense during the first infusion of the week but to lessen with the next 2 doses of the cycle. Therefore, the first day of the week is likely to have the longest stay in day hospital because of the longer time of the infusion and the possibly longer monitoring of side effects after the infusion.

Central and peripheral venous lines

The antibody treatment requires several types of IV infusions, often at the same time (the antibody itself, pain medication, and other medications used to help with side effects).

Rarely, a temporary line may need to be placed. It is recommended that you consult in advance with your medical team about what type of central line your child will have during this phase of therapy.

Likely Side Effects of Naxitamab

Most children experience several side effects during naxitamab infusions. Some of them can be severe, distressing for your child and worrisome for you. But the treatment does not have the same side effects as chemotherapy (such as low blood counts) and has rare long-term side effects.

Pain, nausea and vomiting as well as short periods with low blood-pressure are common during the infusion. Most side effects start decreasing soon after the infusion is complete, and your child will likely be able to be discharged home on the same day.

For these reasons, naxitamab is only infused by trained teams under the supervision of experienced physicians. You should expect to see a lot of health professionals in the room during the infusion including Intensive Care Unit specialists if required. Your child's vital signs and pain will be closely monitored during and for two or more hours after completion of each infusion.

To control infusion-related reactions, your child will receive premedication prior to each naxitamab infusion as well as medications as needed during the infusion.

Your child may require IV fluids to help raise blood pressure, oxygen if breathing is difficult, pain medications, and anti-allergic medications if needed. Naxitamab infusions may be paused while the team is assessing and treating side effects.

In our experience, the 1st infusion of the cycle (Day 1) comes with more rapid side effects than the next infusions (Day 3 and Day 5). Therefore, Day 1 infusion is more likely to be paused or done at a slower rate and, as a result, day hospital stay is likely to be longer on that first day.

Children are usually able to resume a normal schedule of activities in between cycles of naxitamab therapy.

We describe below the most common side effects and their management:

Pain

The GD2 antigen found on neuroblastoma cells is also on nerve cells and pain fibers. Naxitamab can cause pain when it binds to the GD2 on nerve cells and pain fibers. Children often describe this pain as centering in the abdomen, but it can also be described as tingling, burning, numbness, and general all-over body pain. Most children have some degree of pain but how much varies greatly from patient to patient.

Gabapentin is the standard medicine that will be started in advance of the cycle to try to decrease the pain. Opioid pain medications (e.g., morphine, hydromorphone) will be used prior to infusions and if needed during infusions.

If the pain is poorly controlled by the usual opiate drugs, it may be necessary to consider other options. If there is a "pain service" or "pain team" in your hospital, their expertise can help provide other options for your child.

Opiate pain medications can cause constipation or difficulty urinating., problems that might require treatment.

Allergic reactions:

Another common side effect is an allergic reaction, usually hives, redness, or swelling, with or without itching. This side effect is usually controlled with medicines called antihistamines.

Sometimes, hives or swelling occurs in the mouth or throat and causes breathing difficulties. All children receiving naxitamab should wear a pulse-oximeter to measure oxygen levels in their blood. If a child's oxygen level drops, oxygen is on hand to be given by mask. In addition, children may receive a nebulizer with medication to help treat the throat swelling or difficulty breathing. Although rare, a life-threatening allergic reaction may occur and may be treated with epinephrine injected into the muscle, often referred to as an Epi-pen.

It is important to let the medical team know if at any time during treatment ~~hc cycle~~ you notice any redness on your child's skin, such as hives (red or pink raised bumps on the skin), or if your child has respiratory signs such as shortness of breath.

Low Blood Pressure

Children receiving naxitamab may develop low blood pressure during the infusion, either as a direct reaction to naxitamab or from high levels of ~~too much~~ sedation. The low blood pressure is usually treated with a rapid infusion of intravenous (IV) fluids sometimes by using a syringe (faster effect). The naxitamab infusion may be paused while efforts are made to increase the blood pressure. When the infusion is restarted, it may be at a slower rate.

With the extra fluids, it is common for a child to appear puffy during the week of antibody therapy.

In rare situations where the blood pressure does not improve after the infusion is stopped and/or a fluid bolus is completed, medications to increase the blood pressure may be given.

High Blood Pressure

Children can develop high blood pressure (hypertension) during and sometimes after the naxitamab infusion. The high blood pressure may be due to pain and will resolve when the

pain is controlled. However, if the blood pressure remains high, the team may start medication to lower the blood pressure and may admit the child to the hospital. Blood pressure might need to be checked for 1-3 days after a cycle is completed.

A rare side effect which results from high blood pressure is posterior reversible encephalopathy syndrome or PRES. Symptoms include headache, mental confusion, and seizure. PRES does not usually cause long-lasting side effects. This is also called reversible posterior leukoencephalopathy syndrome (RPLS)

Fever

Fevers are common with anti-GD2 monoclonal antibodies and can be a sign that the immune system is activated. Children are often given acetaminophen (Tylenol) as a pre-medication before a naxitamab infusion starts. Along with other vital signs, temperature will be checked often during the infusion. The onset of a fever typically means it is good practice to draw a blood culture, sometimes with a dose of an antibiotic as a precaution, which means more medications being given through the lines. If this occurs, discuss the options for antibiotics with your medical team.

Vomiting, Intestinal Distress

Patients may experience other symptoms such vomiting, diarrhea, or constipation to varying degrees during treatment. The vomiting is more likely if the child ate a large breakfast and then becomes upset from pain caused by the infusion. Constipation can occur as a side effect of the pain medication.

Side effects in clinical trials for reference

In past clinical trials, the most common infusion-related side effects of naxitamab were:

- Pain
- Rapid heart rate
- Fever
- Skin rash
- Low blood pressure
- High blood pressure
- Cough
- Vomiting

Naxitamab in combination with chemotherapy – This regimen has not been approved by the FDA.

Some patients will benefit from combining naxitamab with standard chemotherapy regimens to enhance the effect against neuroblastoma. Naxitamab has been given and well tolerated in combination with irinotecan/temozolomide, cyclophosphamide/topotecan, and ifosfamide/carboplatin/etoposide - so-called chemo-immunotherapy.

When used in combination with chemotherapy, naxitamab is given on days 2,4,9,11 with chemotherapy being given on days 1-5 or 1-3 depending on the regimen. Since naxitamab is given on 4 days, the dosing is 2.25 mg/kg/dose for the same combined dosage of 9 mg/kg/cycle. GM-CSF starts the day after chemotherapy ends and continues through 2 days after the final dose of naxitamab.

The side effects of naxitamab do not change when chemotherapy is added. The same supportive medications are used for both the antibody treatments and the chemotherapy.

While chemo-immunotherapy can be done outpatient, but a long stay is required when both chemotherapy and antibody are given, one after the other, on the same day.

The prescribing information contains a Boxed Warning stating that naxitamab can cause serious infusion-related reactions and neurotoxicity, including severe neuropathic pain, transverse myelitis and reversible posterior leukoencephalopathy syndrome (RPLS).

Summary

Naxitamab is a relatively new drug for the treatment of neuroblastoma.

However, naxitamab can carry distressing side-effects during and shortly after infusions and requires administration by a trained team.

One patient's individual experience with naxitamab may be very different from others undergoing the same treatment and tolerance of naxitamab may be different from one infusion to another.

For more information on antibody therapy and naxitamab please contact your healthcare team.

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Any comments please contact: info@cncfhope.org

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