



## Coping with ch14.18

### Part 1: Background

Since 2009, “ch14.18” has been part of the standard care for high-risk neuroblastoma patients treated at Children’s Oncology Group (COG) institutions. ch14.18 is a monoclonal antibody designed to bind to neuroblastoma cells and stimulate the patient’s own immune system to target and kill the cancer. As of this writing in 2012, the antibody treatment is the intended last phase in the COG front-line protocol, after chemotherapy, surgery, stem-cell transplant and radiation, for high-risk patients who meet the criteria to qualify for it.

Coming at the end of an already long cancer treatment, and given the very specific institutional guidelines for its administration, the start of ch14.18 therapy feels like a new phase of treatment for most neuroblastoma families. Furthermore, patients undergoing ch14.18 can experience short-term side effects that are very different from those during prior treatment. As a result, coping with ch14.18 can be unsettling until a couple of rounds are behind you.

The purpose of this chapter is to provide a general summary of the ch14.18 treatment. It contains information from families who have already experienced it, so that patients embarking on the treatment can have some idea about what lies ahead -- e.g., a sense of the scheduling, the various side effects other patients have experienced, and what coping mechanisms have helped others while undergoing this therapy.

One patient’s individual experience with ch14.18 can be very different from others undergoing the same treatment. Questions about ch14.18 should be discussed with the patient’s medical team, who are the primary source of guidance about every aspect of the patient’s disease and treatment. However, we hope the following information will help you know what questions to ask your medical team and a little more about what to expect during this stage of high-risk neuroblastoma treatment.

### Development of the ch14.18 Treatment

Neuroblastoma can elude the immune system by using a number of tactics. Specifically, it is able to suppress the immune system’s capacity to identify and destroy cancer cells. If the patient’s body is to play a role in killing the neuroblastoma cells, the immune system needs some help in its ability to locate the cancerous cells. Helping the immune system find the neuroblastoma cells is the purpose of the ch14.18 therapy.

ch14.18 is a type of “monoclonal antibody” (mAb). The ch14.18 treatment is called an “anti-GD2” treatment because the ch14.18 antibody targets a substance on the surface of neuroblastoma cells called GD2. ch14.18 is a protein which has been designed to bind to the GD2. Once the ch14.18 binds to the GD2, it sends a signal to the body that tells the immune system a foreign substance has been found which needs to be killed. This then stimulates a response from the body’s own immune system to kill the neuroblastoma cell,<sup>1</sup> which is why the ch14.18 treatment is referred to as “immunotherapy.”

The “ch” in ch14.18 refers to the term “chimeric” and means that the antibody has been created from two different sources – in the case of ch14.18, mouse and human cells (25% mouse, 75% human). In contrast, the first monoclonal antibodies used in neuroblastoma treatment were developed using

cells solely from mice and are described as being “murine” based.<sup>2</sup> The original form of ch14.18 was called 14.G2a and was 100% murine. The movement to create a more “humanized” version was due to the body’s ability to create an antibody response to the murine-derived antibodies, thus rendering them less effective or even ineffective in some patients. (You will hear this response referred to as a “HAMA” or “human anti-mouse antibody” and as “HACA” or “human anti-chimeric antibody.”) Creating a “more human” and less “foreign” version of the antibody reduced the chances of the body developing a resistance to the therapy.

14.G2a and ch14.18 have been administered by COG institutions since 1989 and ch14.18 continues to be tested to determine its efficacy.<sup>3,4,5,6,7,8</sup> In March 2009, COG revealed the preliminary results of the phase III trials of ch14.18. Independent review of the research data confirmed that high-risk neuroblastoma patients treated with the combination of ch14.18, cytokines (IL-2 and GM-CSF), and isotretinoin (Accutane) showed increased survival rates over those patients who were treated with isotretinoin alone. All randomization in the trial was stopped and ch14.18 was made the new standard of care for high-risk neuroblastoma at COG institutions.<sup>9,10</sup> As of this writing in 2012, the ch14.18 study is administered as part of the COG ANBL 0032 protocol (with no randomization). For high-risk neuroblastoma patients to qualify for this treatment, they must meet specific eligibility criteria (see Appendix A of this chapter). As in all clinical trials, parental consent and signatures are required before the therapy begins.

ch14.18 treatment is also administered at some institutions in Europe. In November 2009, the International Society of Paediatric Oncology - Neuroblastoma (SIOPEN) amended its study to include ch14.18 with or without subcutaneous IL-2. GM-CSF is not available in Europe and is not a part of the ch14.18 treatment there.

For other information about the role of monoclonal antibodies in the treatment for high-risk neuroblastoma, see Chapter 2, **“Understanding the Basics of Frontline Treatments—Overview of High Risk Treatment.”**

## **Part 2: ch14.18 Treatment Protocol**

### **Administration & Timing and Other Agents**

ch14.18 is the last phase of therapy in the full front-line treatment protocol at COG institutions for high-risk neuroblastoma. According to protocol, ch14.18 must begin by day 100 after autologous stem cell transplant (if a patient is enrolled in a tandem transplant treatment, the 100-day count begins after the second stem cell transplant). ch14.18 is administered over 5 courses, approximately once per month over five months. It is given in conjunction with either GM-CSF or Interleuken-2 (IL-2), agents known as “cytokines” that work to stimulate the immune system once the ch14.18 attaches to any neuroblastoma cells. Each round of immunotherapy is followed by 2 weeks of Accutane treatment at home. The roles of these agents are briefly described below:

#### **GM-CSF:**

GM-CSF (“Granulocyte-macrophage colony-stimulating factor”) is a protein produced in the body in small amounts under normal circumstances. GM-CSF is a cytokine that stimulates the body to produce white blood cells that the body uses to fight infection, i.e., granulocytes (neutrophils, eosinophils, and basophils) and monocytes. GM-CSF can be made in the laboratory and given to patients in higher doses than the human body would normally produce. GM-CSF accelerates the production of certain white blood cells that, with the ch14.18, can boost the body’s capacity to kill neuroblastoma cells. The generic name of GM-CSF is Sargramostim and its trade name is Leukine

(Genzyme Corporation). In comparison, G-CSF is also a colony-stimulating factor; however, it only activates the production of granulocytes (and stem cells).

### ***Interleukin-2 (IL-2):***

Interleukin-2 (or Aldesleukin-2) is a type of protein molecule and is similar to a substance made in the body to help white blood cells fight infection. IL-2 activates and enhances the growth of certain cells, specifically T-cells and Natural Killer Cells (NK cells), which are able to kill cancer cells in the body. IL-2 is produced in the laboratory and is given to the patient in much higher doses than the body can produce. There is evidence from laboratory tests that IL-2 improves the anti-cancer effect of monoclonal antibodies. COG's ANBL 0032 prescribes ch14.18 and the two cytokines as a package, and thus it cannot be determined from this study if IL2 or GM-CSF makes ch14.18 more effective. One goal of the SIOPEX study mentioned above is to determine if IL-2 is able to enhance the effectiveness of ch14.18 in human patients.

### ***Isotretinoin (Accutane, 13-cis-retinoic acid):***

Isotretinoin, which is usually referred to as "Accutane", is derived from vitamin A. It encourages immature neuroblastoma cells to stop dividing and proliferating, and ultimately die. For information about Accutane in the treatment for neuroblastoma, see Chapter 3, "**Coping with Accutane.**"

### **Treatment Schedule**

ch14.18 is administered as a daily IV infusion for four consecutive days per course, during a one-week hospital admission. In courses 1, 3 and 5, GM-CSF is also given, and is administered over two weeks, one during the week in hospital for the ch14.18 infusion. In courses 2 and 4, IL-2 is given for 4 days during the week prior to receiving ch14.18 as well as during the week of the ch14.18 infusion. Each round is generally followed by two weeks of Accutane treatment. Assuming the criteria for continuing in the protocol are met, each remaining course of ch14.18 begins the week after finishing the two-week Accutane regimen.

The specific schedule for the ch14.18 treatment varies in its details from institution to institution, and also according to the particular patient's situation. We have outlined a typical schedule below to give an overview of what you might experience.

#### Courses 1, 3, and 5 (with GM-CSF):

The chart below shows the days on which each agent is administered in courses 1, 3 and 5 of the ch14.18 treatment.

Treatment schedule for Courses 1, 3 and 5:

<b>Day</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>13</b>	<b>14-23</b>
GM-CSF	x	x	X	x	x	x	x	x	x	x	x	x	x	x	
ch14.18				x	x	x	x								
cis-RA											x	x	x	x	x

#### **Prior to starting courses 1, 3, and 5:**

- Prior to each course, there will generally be a clinic visit that includes a physical exam, blood work, and a urine sample.
- GM-CSF injections are started three days before the ch14.18 infusion begins. The first GM-CSF injection is typically done in clinic and the patient is monitored for allergic reaction. If there are no concerns, the remaining injections may be done at home (i.e., by the family and/or in-home nursing services).
- The patient is typically admitted to the hospital on Sunday evening or early Monday morning. Special arrangements for the admission day/time can usually be made with your individual hospital to take into account distance to travel and any other factors.
- Once the patient is admitted, blood work is done. Prior to starting each course of immunotherapy, a blood transfusion may be ordered to “top up” the patient depending on the hemoglobin or hematocrit level. For example, in some institutions blood transfusions are given at any time during the antibody treatment if the hematocrit level is below 0.3. In terms of the hemoglobin value, a transfusion may be ordered if it is under 10. [Please note that there are variances in how blood counts are calculated between different hospitals in different countries. As an example, a hemoglobin value of 10 in the USA is equal to a hemoglobin value of 100 in Canada. Please be sure to clarify with your care team.] If a blood transfusion is needed, the patient might be admitted the night before the start of the treatment, so that he/she can be transfused overnight.
- If needed, the dressing over the patient’s CVL/port is changed prior to the start of ch14.18.

**On each day of the ch14.18 infusion:**

- The patient’s weight is measured.
- A saline bolus is given.
- The GM-CSF injection is given 1 hour prior to starting the ch14.18 infusion.
- Benadryl is administered to help prevent allergic skin reactions (Hydroxyzine or Ranitidine may also be prescribed if Benadryl alone is not sufficient to control the allergic reaction), and acetaminophen is given to help prevent fevers.
- ECG leads and an oxygen saturation probe (pulse oximeter) are put on the patient.
- A bolus of pain medication is given (i.e., morphine, hydromorphone, fentanyl, etc.) and a continuous pain medication infusion is started (see below for more on pain control).
- The ch14.18 infusion is started via IV at half of the target infusion rate for approximately 30 minutes to 1 hour. It is then taken to the full target infusion rate as long as there are no concerning issues (more on this below). The target IV infusion time for ch14.18 is 10 hours; however, this may be longer if the ch14.18 needs to be paused due to concerning symptoms (more on this below).
- For the first hour of the infusion, vitals are taken every 15 minutes and then every hour until the ch14.18 infusion finishes.
- The IV flush for the ch14.18 takes anywhere from 2-3 hours.
- The patient’s weight is measured at the end of the day.

- The infusion of pain medication(s) is typically continued for 2-3 hours once the ch14.18 finishes. After this, it is possible to wean the patient off of the medication(s) gradually over a number of hours. You may need to work closely with your care team to determine the best pain control plan for the patient (more on this below).

**Upon the completion of the five days of ch14.18:**

- Discharge may occur on the Friday or Saturday of the same week provided there are no sustained complications (e.g. fever).
- GM-CSF injections continue until day 14 and may be given at home if the patient does not experience significant allergic reactions.
- There is generally a clinic visit immediately after each course with a physical exam and blood work. A urine sample must also be provided for a urinalysis prior to starting Accutane.
- Accutane (13-cis-retinoic acid) is taken orally by the patient on days 10 through 23.
- Additional clinic visits for blood work may be necessary.

Courses 2 and 4 (with IL-2):

In the case of courses 2 and 4 of ch14.18, a daily schedule similar to the above is followed, but no GM-CSF is given. Instead, IL-2 is administered by continuous IV infusion for 4 days (ninety-six hours) during the week prior to receiving ch14.18, and again for 4 days during the week of infusion of ch14.18. As described above, the patient must be admitted for the week of ch14.18. Some institutions choose to give the first week of IL-2 in an outpatient setting and others require the patient to be admitted. If the IL-2 is given as an outpatient, generally the first dose is given in clinic with close observation, and if tolerated well, the remaining three days of the IL-2 only infusion are given at home via a CADD pump. If the patient is admitted for the two weeks, some hospitals give patients a weekend pass to leave the hospital if there are no concerning issues. Similar to the other courses, Accutane is taken by the patient for 14 days at the completion of courses 2 and 4.

The following chart shows the days on which each agent is administered in courses 2 and 4 of the ch14.18 treatment.

Treatment schedule for Courses 2 and 4:

Day	0	1	2	3	4-6	7	8	9	10	11-13	14	15	16	17	18-27
IL-2	x	x	X	x		x	x	X	x						
ch14.18						x	x	X	x						
cis-RA											x	x	x	x	x

**For the 4 days (96 hours) of the IL-2 infusion:**

- Cap change or needle change may be done prior to starting the IL-2 infusion since it runs continuously over 96 hours.
- The patient's weight is measured.

- The IL-2 IV infusion is started (1ml/hour) using a CADD pump (a continuous ambulatory delivery device).
- Vitals are usually checked at the typical 4-hour interval unless the patient develops any symptoms of concern.
- The patient's weight is measured at the end of the day.

**On each day of the ch14.18 infusion:**

- The ch14.18 infusion is administered as outlined above, with the exception that it is infused concurrently with IL-2 instead of GM-CSF.

**Infusion Rates, Lines and Ports****Infusion Rates**

Each day's infusion of ch14.18 must end within 20 hours. If the infusion is not finished at the 20-hour mark, the infusion will be stopped and the remaining ch14.18 from that day will be discarded. The target infusion time is around 10 hours.

The ch14.18 infusion may be paused at any time and the rate can be slowed if side effects occur and cannot be controlled (potential side effects are discussed below). It is not uncommon for the infusion to be slowed, especially in the first courses. If side effects occur during an infusion, a "wait and see" approach may be taken the following day of the infusion by starting back up at the full rate and decreasing again if necessary. In particular, if the patient contracts an infection during the administration of the antibody (i.e. positive blood culture), the infusion is required to be stopped for that round of treatment.

Similarly, in courses 2 and 4, it is possible to either reduce or stop the IL-2 infusion if side effects occur and are difficult to control. The patient can continue the ch14.18 treatment even if the IL-2 has been stopped.

**Lines and Ports During ch14.18**

A distinctive aspect of the ch14.18 treatment is that it requires several types of infusions, often simultaneously: there is the antibody itself, the IL-2 cytokine in courses 2 and 4, and medications for pain and any other side effects. For this reason, double-lumen central lines or double-sided ports are very helpful. However, circumstances can develop where even a double-lumen line is not sufficient for the number of medications needing access. For example, while ch14.18 is being infused, it must have its own line into the body—it cannot be mixed with anything else. In courses 2 or 4, IL-2 is running continuously for 96 hours on another line. IL-2 is not compatible with all medications; for example, it can be infused with Morphine, but not with Fentanyl. If the situation arises where there are not enough lines, a temporary line—PIV/PICC, femoral or jugular—may have to be placed.

It is recommended that you consult in advance with your medical team about these issues.



### **Part 3: Side Effects**

Most patients experience some side effects during the ch14.18 treatment, although generally, these occur only during treatment and subside soon after it concludes. Some patients will “perk up” within hours of the completion of the infusion whereas others may take a day or more to feel well again. To date, there are no known long-term side effects associated with ch14.18.

Although side effects vary greatly from patient to patient, some of the effects that have been experienced for each of ch14.18, IL-2 and GM-CSF are summarized below. We have also included information from parents and patients on possible ways to cope with various side effects. Of course, what soothes one patient may not give comfort to another, and parents and medical staff may have to experiment to discover the best coping mechanisms for the patient. Also, different institutions may have individual approaches to addressing various side effects.

We have also included a list of less likely and rare effects (from COG) in Appendix B. Keep in mind that the patient is very unlikely to experience these more severe side effects.

As with all aspects of neuroblastoma treatment, the potential side effects of the ch14.18 therapy and the patient’s specific situation must be discussed with your medical team.

#### ***Likely Side Effects of ch14.18***

Many side effects of ch14.18 are “minor”; however, the treatment does come with warnings about the potential for more serious side effects. As a result, immunotherapy is only administered in an in-patient setting and it is not uncommon for the treatment to be given in the ICU or PICU (depending on hospital policy). In many cases, the patient will also have one-on-one nursing care while the ch14.18 is infusing. This allows for better monitoring of vital signs, patient supervision and access to specialized equipment and staff, during what is still a relatively novel treatment.

**Pain:** The most common side effect associated with antibody treatment is pain. Patients most 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 patients experience some degree of pain; however, the severity will vary greatly from patient to patient. Oncologists often point out that the presence or lack of pain is **not** indicative of how well the ch14.18 treatment is working.

Given that pain is expected, IV pain medications (e.g., morphine, hydromorphone, fentanyl, etc.) will run continuously while ch14.18 is being infused. Additional boluses may be required to address more severe or breakthrough pain. If the pain is not sufficiently controlled by traditional 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. For example, since the pain may be “neuropathic” (i.e., caused by the stimulation of the nerve cells during the treatment), it may be possible to use other drugs such as ketamine or gabapentin in conjunction with the opiate drugs to better control the neuropathic pain.

Parents and patients often find it very helpful to discuss the options for pain control with their medical team (and a pain team if available) before the treatment starts. You may wish to double check that all pain medications are accurately included in the patient’s care plan/medical orders. These orders should include the dosing for the continuous infusion of the pain medication(s), the dosing of any additional pain boluses that may be needed, and any other methods of pain control that are prescribed. Having all of these orders determined ahead of time means that the patient will not have to wait to get the pain control and relief needed. Another matter to confirm in advance is

how the pain medications will be tapered off once the infusion is complete, so that there is no confusion at the end of the day when the ch14.18 infusion has finished. In many cases, the IV pain medications are kept running for at least 2 hours after the completion of the antibody infusion.

As a general rule, it is necessary to address the pain quickly to get it under control as soon as possible. The longer any pain is allowed to build, the harder it may be to get it under control. With each ch14.18 infusion, you will get a better handle on how to help the patient deal with the pain, the right times to give a specific pain medication bolus, and whether the dosing of the pain medications needs to be changed in any way. Some patients experience the first wave of pain approximately 2 hours into the antibody infusion. Administering a bolus of pain medication at the point right before the patient generally feels the first peak of pain may be a helpful measure.

Some patients may also have residual pain for a day or so after the ch14.18 infusion is complete. It may be necessary to administer pain medication at home to help the patient deal with any remaining pain from the therapy. Confirm in advance that you have all of the proper pain medications at home and have the necessary scripts/refills.

The high doses of opiates for pain control can carry their own set of side effects, and it is important to speak with your medical team about these and be informed in advance. For example, higher doses of hydromorphone can cause respiratory challenges. Additionally, many opiates can cause constipation.

**Constipation:** If the patient is prone to constipation, it may be necessary to start some sort of proactive intervention in advance of treatment week to help guard against constipation once the pain medications are started. Or, it may be best to take a wait-and-see approach, but be ready to deal with this side effect if it occurs. There are many different interventions that can be utilized to help ease the discomfort of constipation. The following are some that have worked for various patients:

Osmotic Laxatives:

- Lactulose
- Magnesium Hydroxide/Milk of Magnesia
- Polyethylene Glycol/Peg Flakes (Miralax)
- Senokot
- Sorbitol

Lubricants:

- Mineral Oil

Osmotic Enemas:

- Sodium Phosphate Enema
- Glycerin Suppository

Dietary:

- Increased dietary fibre (i.e., through foods or supplements such as Benefibre)
- Increased fluid intake

**Allergic Skin Reactions:** One response to the ch14.18 infusion may be an allergic reaction of the skin. In some patients the skin may become inflamed and red, or rashes and hives can appear, and the patient may experience great discomfort from the associated itchiness of the reaction. The patient's breathing may be affected, since hives can arise in the throat. The allergic skin reactions can vary from minor to severe, or may not appear at all. Allergic reactions are typically managed with antihistamines such as Benadryl, and others such as Hydroxyzine or Ranitidine may be added if



Benadryl alone does not control the reaction. During the ch14.18 infusion, antihistamines may be given around the clock for the entire four days to help manage allergic skin reactions.

It is important to monitor the patient's skin closely during the infusion for spreading redness, a change in the look of the allergic reaction, the presence of hives, and other concerning skin symptoms. Allergic skin reactions can occur quickly and escalate rapidly in severity during the course of the ch14.18 infusion. If found, they should be brought to the attention of your medical team immediately.

**Nausea:** ch14.18 may cause nausea for some patients. If the patient experiences nausea during the treatment, anti-emetics such as Zofran (ondansetron) may be helpful. If the patient is not able to eat at all during the treatment, you may consider having TPN (total parenteral nutrition) run by IV overnight when the antibody is not infusing. Once the infusion of ch14.18 is stopped for the day, some patients feel significantly better and may eat then.

**Blood Pressure Changes:** Before the ch14.18 infusion begins, the patient's "normal" blood pressure is established and used as a baseline for determining the hypotensive and hypertensive blood pressure values. If the patient's blood pressure reaches a reading that is too low (hypotensive/hypotension), the antibody infusion may be paused and the patient assessed. If intervention is required to help raise the blood pressure, a saline bolus or medication (e.g., dopamine, phenylephrine, etc.) may be administered. If the patient's blood pressure reading is too high (hypertensive/hypertension), the antibody infusion may be paused and the patient examined to determine if medical intervention is required (e.g., nifedipine, amlodipine, etc.). A rise in blood pressure could also be caused by excess fluid retention, which may be addressed using diuretics (see next paragraph for more on this).

**Fluid Retention:** Another common side effect of ch14.18 therapy is fluid retention. Some patients do not experience this, whereas fluid retention may become a challenging side effect to manage for others. Throughout the treatment, the medical team monitors the patient's fluid "ins and outs" to calculate fluid balances. Patients are also weighed twice a day since there are often incalculable losses such as sweating, so keeping track of the patient's weight acts as an additional check. If it appears that the patient needs help removing the excess fluid from his or her system, medications such as furosemide (Lasix) may be ordered. Other possible medications include albumin, spironolactone and Mesna. The managing of fluid balances during the antibody infusion is a delicate matter. ch14.18 can cause low blood pressure, and removing fluids from the body can cause the blood pressure to drop even lower, sometimes creating a serious concern for the patient. Thus, the decision to intervene with medications to lower the fluid balance is made very carefully by the medical team. Typically, medications like Lasix are not given to the patient until the infusion has finished; e.g., they may be given overnight to help bring the balance back into line before the next day of the treatment begins.

If a patient has a past history of fluid retention and an inability to handle excess fluids, it is important to establish a plan with the medical team before the antibody therapy begins. The patient's past experience with fluid retention will be invaluable in helping the medical team understand the warning signs to look out for and set the criteria for medical intervention.

**Fever:** During ch14.18, some patients may become febrile. High-grade (likely) and low-grade (less likely) fevers are a common side effect of immunotherapy and patients are often started on Tylenol as a pre-medication before a high temperature reading appears. The onset of a fever typically necessitates the start of antibiotics, which means more medications being given through the lines. If this occurs, discuss the options for antibiotics with your medical team. For example, giving an

antibiotic orally or by tube means that medications already running through the lines do not have to be paused. If fevers are an issue, it is suggested that flexible ice packs be available in the freezer and cold washcloths be on-hand to help with lowering the patient's body temperature.

**High Heart Rate:** Fever, pain, anxiety, and overall discomfort may cause the patient to have a high heart rate. It may be necessary to deal with all of these side effects to help bring the heart rate under control. If this side effect is experienced, the ch14.18 and/or the IL-2 infusion(s) may be paused or stopped for a period of time to give the patient a rest and help bring their heart rate into a more comfortable range.

**CVL/Port Dressing Issues:** If the patient experiences allergic skin reactions and fevers, the combination of skin irritation and perspiration from the high temperatures may require frequent dressing changes over the CVL/port. It is possible that traditional dressings (e.g., Tegaderm) may not properly stick to the skin and the dressing itself may contribute to the irritation. If necessary, ask the Dermatology department to recommend a topical cream (e.g. corticosteroids such as hydrocortisone, betamethasone, etc.). In addition, they may be able to suggest a different type of dressing (e.g., Mepilex, Primapore, etc.) or even different types of tapes/adhesives (e.g., Mepitac tape).

### ***Likely Side Effects of IL-2***

Many of the likely side effects of the IL-2, which are listed below, are similar to those brought on by the ch14.18. Please see the previous section for more detail and suggestions for managing some of these side effects.

- Fever and chills (i.e., shaking).
- Flu-like symptoms: headache, tiredness, aches and pains.
- Diarrhea.
- Loss of appetite.
- Weakness and fatigue that is not alleviated by rest.
- Mild drop in blood pressure.
- Rashes and itching.
- Fluid retention (usually in the lower legs) that can increase weight.
- Increased levels of creatinine in the blood (which could indicate kidney damage).
- Temporary decrease in urine output (which could indicate that the kidney(s) are not functioning normally).
- In the blood, elevation of certain enzymes and bilirubin that is found in the liver.
- Increase in eosinophils (a white blood cell type) that can be associated with allergic reaction.
- Increase in the number of white blood cells in the blood.
- A drop in platelet count.

### ***GM-CSF Injections and Likely Side Effects***

Injections:

GM-CSF may be provided to you in a pre-mixed (liquid) or raw (powder) form, and in both cases it must be stored in the refrigerator at all times. If GM-CSF is provided to you in the powder form, you must prepare the drug prior to the injection. Follow the instructions given to you by your care team and/or pharmacist. When mixing the GM-CSF it is essential to swirl the liquid in the vial gently to make sure that the powder properly dissolves, but do not over agitate the mixture.

#### Injection Tips:

- It may be possible to use an insuflon catheter to give the GM-CSF injections. This saves having to poke the patient every day. An insuflon needs to be changed every 5-7 days, or earlier if there is a reaction to the injections.
- If an insuflon cannot be used, it may be beneficial to rotate injection sites. This is particularly important if the patient reacts in any way to the GM-CSF injections. Since a reaction may include tenderness and swelling, you may not want to give the injection in the arms during the days of the ch14.18 infusion since the patient's blood pressure is taken on a very frequent basis. The inflation of the blood pressure cuff over top of an injection site on the arm may cause discomfort.
- If the GM-CSF must be injected without an insuflon, you can consider placing an EMLA or topical analgesic cream on the skin for about an hour before the poke. This will help to numb the area and make the actual injection less painful for the patient. However, if the act of putting an EMLA on causes additional anxiety for the patient, then this may be counterproductive.
- The GM-CSF may be injected slowly or quickly, depending on the preference of the patient. Tapping on the skin slightly above the needle while the GM-CSF is being injected, or a light massaging of the area after the injection is done, may also help ease any discomfort.

#### Likely Side Effects of GM-CSF

GM-CSF can cause a local reaction at the injection site such as swelling, redness, warmth, and/or tenderness to the touch. If any of these occurs, it is very important to speak with your medical team so that the severity of the reaction can be monitored. This allergic response to the GM-CSF is typically addressed by giving the patient Benadryl (pre- or post-injection). If the reaction worsens, there may be cases where the oncologist decides to suspend, postpone, or even discontinue the injections. A patient's ability to tolerate GM-CSF may change over time, so it is advisable to continue to watch for possible side effects. For example, in the first two courses of GM-CSF injections no side effects may be observed, but they might appear in the last course.

It is very important to keep a record of the patient's white blood cell counts. In the ANBL 0032 protocol, if the white blood cell count goes above 50,000 (or 50 depending on how it is calculated), the GM-CSF injections must be put on hold. If there are a number of injections remaining for the patient, it is likely that blood work will be monitored closely to see if the GM-CSF injections may be restarted. If they are resumed, it is possible that the dosing of the GM-CSF may be changed (e.g., cut in half).

If there are any changes to the dosing of the GM-CSF, or if the GM-CSF must be stopped due to white blood cell counts jumping too high, this alone will not prevent the ch14.18 therapy from proceeding.

Other likely side effects of GM-CSF are:

- Headache.
- Bone, muscle, and joint pain.

- Fever and chills.
- Rash and itchiness.
- Feeling uncomfortable, tired, and/or unwell.

#### **Part 4: Summary**

ch14.18 is still a relatively new type of treatment, one requiring new insights and coping measures. The first round of antibody will likely be difficult because it is an unknown quantity. What side effects will the patient experience? What medications and procedures will best enable the patient to cope with any discomfort or medical issues? If something is not working, what needs to be changed? As is stated so often about this disease and its treatment, each patient is different, and you should be prepared to adjust coping measures accordingly.

The good news is that most families find that as ch14.18 becomes familiar to them, and as the most effective coping strategies for the patient are determined, each course of ch14.18 generally feels smoother. However, if you feel something is not as it should be with any aspect of the patient's experience during ch14.18 treatment, it is important to express your concerns immediately. Do not hesitate in asking for another opinion, paging the staff doctor, or getting a specialist team involved. Your instincts and knowledge of your child will be invaluable during this stage of neuroblastoma treatment.

For many patients, side effects of ch14.18 are manageable and limited to the days of actual treatment. There is little or no impact on blood counts and hence none of the neutropenia and opportunistic infections associated with some chemotherapy. Patients are usually able to resume a normal schedule in between the courses of ch14.18. Therefore, during this stage of treatment families may feel that they are beginning the transition back to the life that was interrupted when neuroblastoma was diagnosed, and they can see an end to a long treatment pathway.

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with any comments*

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## **Immunotherapy Appendix A**

### **Qualifying for ch14.18 Immunotherapy**

All eligibility requirements are required to be taken literally and cannot be waived in any situation. The following are the requirements for ANBL0032, current as of August 2010 (<http://clinicaltrialsfeeds.org/clinical-trials/show/NCT01041638>):

- Enrollment on A3973, ANBL0532 or ANBL00B1 is not an eligibility requirement for ANBL0032.
- Patients must be diagnosed with high-risk neuroblastoma.
- Must be younger than 40 years of age at diagnosis.

- Must have completed intensive induction therapy
- It must be no more than 9 months from the date of starting the first induction chemotherapy after diagnosis to the date of the autologous stem-cell transplant. (For tandem transplant patients, it is the date of the first stem cell infusion.)
- Prior to autologous stem-cell transplant, patients must meet the International Neuroblastoma Response Criteria (INRC) for complete response (CR), very good partial response (VGPR), or partial response (PR). The following are the particulars on the bone marrow response:
  - o Less than or equal to 10% tumor seen on any sample from bone marrow aspirates and biopsies (bilateral).
  - o If no tumor is seen in the prior bone marrow, and then the patient has equal to or less than 10% tumor in their bone marrow aspirates and biopsies (bilateral) done prior to the autologous stem cell transplant, these patients will still be eligible.
- Tests to determine residual disease must be performed (CT or MRI, MIBG Scan, bone marrow biopsies and aspirates, and blood and bone marrow samples).
  - o If there is still residual disease before radiation, re-evaluation must be performed no sooner than five days post the completion of radiation. Patients with residual disease are eligible and a biopsy is not required.
  - o Patients must not have progressive disease except for the bone marrow response outlined above.
- Patients must be enrolled in the study before treatment can begin. The treatment must begin no later than ten calendar days once the patient is enrolled in the study.
  - o Ideally enrolled between day 56 and day 85 after stem cell infusion (if tandem transplant, from date of second stem cell infusion).
  - o Must be enrolled no later than day 100 after stem cell infusion.
  - o Enrollment occurs after completion of radiation and assessment tests.
- Patients must not have received prior anti-GD2 antibody therapy.
- Must have Lansky or Karnofsky Performance Scale score of greater than or equal to 50.
- Must have a life expectancy of greater than or equal to two months.
- Must have adequate organ function.
  - o Hematological: Phagocyte count (APC = neutrophils + monocytes) is at least 1000/uL
  - o Renal: Creatinine clearance or radioisotope GFR greater than or equal to 70 mL/min/1.73m<sup>2</sup> or serum creatinine based on the following:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
Greater than or equal to 16 years	1.7	1.4

- o Hepatic: Total bilirubin less than or equal to 1.5 x normal, and SGPT (ALT) less than or equal to 5 x normal. VOD (veno-occlusive disease) should be stable or improving if present.
- o Cardiac: Shortening fraction of greater than or equal to 30 by echocardiogram. Or, ejection fraction greater than or equal to 55 by gated radionuclide study.

- Pulmonary: FEV and FVC greater than 60% of predicted by pulmonary function test. If a patient is not able to do a pulmonary function test, there must be no evidence of dyspnea at rest and no exercise intolerance.
- Central Nervous System: If a patient has seizures, these must be well controlled with anticonvulsant medications. CNS toxicity must be less than grade 2.
- Written or informed consent must be provided by the parent or legal guardian.
- Female patients must have a negative pregnancy test. If patients are of childbearing potential, they must agree to use effective birth control. Patients who are lactating must stop breast-feeding.
- No prior anti-GD2 antibody therapy, no prior vaccine therapy, no concurrent immunosuppressive drugs, no concurrent cytokines or growth factors, and no other concurrent anticancer therapy.

## **Immunotherapy Appendix B**

### ***Less Likely and Rare Side-Effects of ch14.18:***

Most side effects of ch14.18 treatment are “minor.” However, the treatment does come with warnings about the potential of more serious side effects, and while they are unlikely, it is important to be alerted to them. Given the possibility, albeit remote, of such side effects, and due to the fact that ch14.18 is a relatively new treatment, it is not uncommon for immunotherapy to be administered in the ICU or PICU at some institutions. A patient may have one-on-one nursing care during immunotherapy, if advisable for the specific situation.

#### Less Likely Side-Effects:

- Severe allergic reaction which could be life threatening (i.e., low oxygen levels in the blood, hives, tongue swelling, fever, etc.).
- A moderate rise or fall in blood pressure that requires intervention.
- Nausea, vomiting, and diarrhea.
- Low level of albumin in the blood.
- Inability to stay awake or be woken up.
- Weight loss or gain.
- Allergic reaction causing fever, aches, pains in the joints, skin rash, and swollen lymph glands.
- Increased levels of creatinine in the blood (i.e., kidney damage).
- In the blood, an elevation of a certain enzyme that is found in the liver.
- Fluid retention, specifically in the legs and arms.
- A drop in platelets.
- Issues with nerve function that may cause tingling, numbness, muscle weakness and pain.
- Drooping of the eyelids, blurred vision, dilated pupils (increased sensitivity to light, or the inability of the eye to react to bright light).
- Clotting of the central line.

#### Rare Side-Effects:

- Severe increase in blood pressure that requires intervention.

- 
- Severe allergic reaction, specifically in the mouth and throat which would make it hard to breathe.
  - Irritation of the small airways in the lungs that causes coughing and wheezing.
  - Seizures.
  - Rapid heart rate.
  - Chest pain that could mean heart damage.
  - Sudden stopping of the heart or breathing.
  - Vascular (capillary) leak syndrome that can result in dangerously low blood pressure. This can lead to organ failure and must be treated immediately. Symptoms include pale skin, a fast weak pulse, fast shallow breathing, low total blood amount, and low blood pressure.
  - Severe rashes which can cause a breakdown of the skin and damage to mucous membranes.
  - Bleeding disorder.
  - Swelling in the back of the eye caused by increased pressure in the brain.
  - Damage to the optic nerve.

### ***Less Likely and Rare Side-Effects of IL-2:***

#### Less Likely Side-Effects of IL-2:

- Nausea and vomiting.
- Low levels of certain salts in the body.
- Change in the normal acid levels in the blood.
- Vascular (or capillary) leak syndrome.
- Irregular or rapid heartbeat and chest pain.
- Dizziness.
- Cough and runny nose.
- Headache.
- Enlarged abdomen and weight gain.
- Pain in the abdomen and other parts of the body.
- High blood sugar level.
- Mood changes (i.e., depression, irritability, anxiety, mood swings, etc.).
- Aches and pains in the muscles and joints. Feeling tiredness, and not sleeping well.
- Inflammation and/or sores in the mouth.
- Severe rashes creating skin breakdown.
- Infections caused by bacteria, virus, and fungus.
- Blurred vision.
- Flushing and redness of the skin causing a feeling of warmth.
- Fewer white blood cells in the blood.
- Decrease or increase in thyroid hormones.

#### Rare Side-Effects of IL-2:

- Severe allergic reaction causing difficulty breathing, drop in blood pressure, and irregular heart beat.
- Heart attack or severe pain in the chest (angina).
- Inflammation of the heart muscle that could lead to heart failure.
- Severe drop in blood pressure.
- Decrease in the ability of the blood to clot.
- Bleeding that can occur in the head, stools, nose, urine, and other part of the body.
- Seizures.
- Loss of consciousness (coma).
- Inflammation of the colon leading to diarrhea.
- Inflammation of pancreas causing pain.

- Severe kidney damage which could be permanent.
- If the patient has an autoimmune disease, IL-2 can make this worse (i.e., lupus, rheumatoid arthritis, etc.).
- Damage to lungs causing shortness of breath.
- Sudden death.

***Less Likely and Rare Side-Effects of GM-CSF:***Less Likely Side-Effects of GM-CSF:

- Abdominal/stomach pain and/or cramps.
- Weakness.
- Loss of appetite.
- Nausea and/or vomiting.
- Diarrhea.
- Sweating.
- If the GM-CSF is given directly into a vein, this may cause the vein to become inflamed.
- Redness, pain, and swelling at the injection site.
- Weight gain.
- A drop in platelet count.
- In the blood, an increase in certain enzymes or bilirubin which could indicate liver irritation or damage.
- Elevation of the creatinine level in the blood (could indicate kidney damage).
- Fluid retention (typically in the lower legs).

Rare Side-Effects of GM-CSF:

- Severe allergic reaction causing shortness of breath, low blood pressure, and rapid heart rate.
- Severe reaction causing shortness of breath, low blood pressure, high heart rate, fever, feeling warmth and back pain, which may only occur with the first dose and not with subsequent doses.
- Abnormally rapid heart rate.
- Leakage of fluid into the lungs which may cause difficulty breathing and/or puffiness in the legs, arms and other areas of the body. Could also include weight gain and a drop in blood pressure.
- Inflammation of the lungs creating pain and shortness of breath.
- Build up of fluid around the heart creating pain.