

THE ROAD AHEAD:

NEW TREATMENT PERSPECTIVES FOR CML PATIENTS

Carson Jacobi Pattillo Our next teacher for this evening is Carolyn Blasdel. Carolyn Blasdel is an oncology certified nurse and earned her Masters of Arts degree in psychosocial nursing at the University of Washington, Seattle. She received her Bachelor of Science in Nursing at the University of Maryland, Baltimore. Carolyn has been a Clinical Research Nurse and Study Coordinator at the OHSU Cancer Institute Center for Hematologic Malignancies for five years. She works closely with Dr. Druker. In that position, she provides nursing care for patients with chronic myeloid leukemia. In addition, she has been Nurse Coordinator for Phase I and II trials for Gleevec® (imatinib mesylate). Her previous experience includes a position as a Clinical Research Nurse and Study Coordinator at Don & Sybil Harrington Cancer Institute in Amarillo, Texas for nine years. She has held past positions in administration, teaching, and hospital nursing.

**Carolyn Blasdel,
RN, MA, OCN**

Thank you all and *The Leukemia & Lymphoma Society* for letting me talk to you tonight about side effects of treatment for chronic myeloid leukemia. Drugs commonly used for chronic myeloid leukemia treatment include Gleevec, interferon, Hydrea® (hydroxyurea capsules USP), Aranesp® (darbepoetin alfa), arsenic trioxide, and other investigational agents, and transplant. Transplant side effects would be a talk in and of itself, so I won't cover that tonight.

Gleevec, also known as imatinib mesylate, has become the standard of care. It is generally very well tolerated, but side effects vary from person to person. I have patients who have almost no side effects, but for others, they can be significant and fairly serious. With proper management it is very rare that patients have to discontinue Gleevec permanently. It is important to let your health care provider know of your side effects. If we don't know about them, we can't help you.

Effects of Gleevec on Bone Marrow

As Dr. Druker has already mentioned, lowered blood counts are a therapeutic effect. If the absolute neutrophil count is below 1,000 or platelets are below 50,000, we may need to temporarily stop the Gleevec. The normal cells in your bone marrow usually recover over time, so you have to stop Gleevec less and less. Occasionally, a dose reduction of Gleevec is required. Mildly low counts (white counts of 2,000-3,000, or platelets of 75,000-125,000) are not a concern, so you needn't be fearful when you see those lows, "L's", on your lab reports.

THE ROAD AHEAD:

NEW TREATMENT PERSPECTIVES FOR CML PATIENTS

Carolyn Blasdel,
RN, MA, OCN

In particular, we watch the absolute neutrophil count (ANC). If you don't know how to find that on your lab report, ask your oncology nurse and he/she can explain it to you. Extensive instructions on managing low counts and side effects are all on the Gleevec.com website, particularly in the section for health professionals. There is a lot of good, new information there and I encourage you to pursue that.

Decreasing Gleevec dosages to less than 400 mg is generally not advisable, although in a few cases, 300 mg may be okay. This slide shows how Gleevec makes the blood count go down. In chronic myeloid leukemia, the majority of hematopoiesis (making blood cells) is contributed by these pH- positive cells. When you take Gleevec, the red leukemia cells are wiped out, and there are only a few normal cells remaining in the bone marrow. In more advanced disease, the normal cells have been crowded out by the leukemia, so when you first start Gleevec, there are just not enough cells. This is called myelosuppression (low blood count).

Anemia means low red blood cell count. Anemia can cause fatigue, headaches and shortness of breath, along with other symptoms. Procrit® (epoetin alfa) or Aranesp are usually effective and we use them a lot. These drugs may need to be used on an ongoing basis until the marrow recovers. You can gradually use less and less as the counts improve. The goal is to keep the hemoglobin above 12. Some people like to get up to around 13 or 14. People have asked me if you become addicted or develop a tolerance to Procrit or Aranesp. The answer is "no." Once your marrow recovers you can get off of it. A few people have trouble getting off because their marrow has been greatly affected by the leukemia or their prior treatment.

Neutropenia is a low white count. If the ANC is less than 1,000 we normally hold the Gleevec temporarily. This gives the count time to recover and then we start back up again. We also may consider using GCSF or pegfilgrastim, which is Neulasta™ (pegfilgrastim) so that you can stay on Gleevec if your physician wants to treat you more intensively.

If the neutrophil count is less than 500 you are at higher risk for infection. Remarkably, we have had very little trouble with ANC's between 500 and 1,000.

Thrombocytopenia is low platelets. This can cause excessive bruising or bleeding and there is no effective drug available to treat that. If a platelet count is less than 50,000, Gleevec is temporarily held to allow them to recover. Also, if you are being treated more aggressively, your physician may let your platelets go

THE ROAD AHEAD:

NEW TREATMENT PERSPECTIVES FOR CML PATIENTS

Carolyn Blasdel,
RN, MA, OCN

down to about 20,000 and you will still do fine. Then we stop them. If your platelets go below 10,000 or you have bleeding and bruising, then transfusions are available.

Common Gleevec Side Effects

Hair

A few patients have had hair loss or thinning hair. It is important to remember that this has many other causes, including side effects from other drugs including Neupogen. Hormonal changes, aging, and stress can cause it also. Some people have had thicker hair on Gleevec. Interestingly, people with gray hair have had their hair darkened by Gleevec. This only happens in about 10% of cases.

Eyes

Swelling around the eyes (periorbital edema)—one of my patients calls it “pig-eye.” This is probably the most common Gleevec side effect. Excessive tearing is common. Blurry vision with tearing happens. Also, bleeding into the whites of the eyes (sub-conjunctival hemorrhages) occurs. A blood vessel breaks and you feel a stinging pain. There is bright red blood in the white of the eye. It’s very scary looking, but it is not serious. To treat this we use artificial tears, even when you are having excessive tearing. Using additional tears can help keep the eyes washed out. Prescription steroid eye drops has been helpful for some people. If you are having a lot of trouble with tearing, I encourage you to see an ophthalmologist so that he/she can look to see if any mechanical problems can be corrected. There is no treatment needed for sub-conjunctival hemorrhages. The body absorbs the blood on its own and the eye will return to normal without any permanent damage.

Swelling (Edema)

In addition to the eyes, swelling can happen in the hands, feet and legs. It is important to avoid high salt or sodium foods. Keep sodium intake to less than 2,400 mg/day. Be careful with prepared canned foods and restaurant foods. Diuretics can be prescribed if absolutely necessary, and we usually use thiazide. Edema around the eyes tends to be worse in the morning and so patients have found that doing early morning exercise helps reduce this swelling. Plastic surgery has been used to treat edema, especially below the eyes, in a few severe cases.

THE ROAD AHEAD:

NEW TREATMENT PERSPECTIVES FOR CML PATIENTS

Carolyn Blasdel,
RN, MA, OCN

Nausea and Vomiting

These do occur with Gleevec, especially at first before you learn how to take it. It is very important to take Gleevec after a substantial meal. It is also important to drink at least 8 ounces of water afterwards. You do not want the pills to get stuck in your esophagus where they can cause irritation. It may be helpful to divide the dose; for example, you can split the dose into two 300 mg doses if you are on 600 mg/day. You can usually decrease nausea and vomiting with this approach. Anti-nausea medicines are available if necessary. Recently, I've been getting questions about the new dose formulations because Gleevec is now available in a 400 mg tablet and a 100 mg tablet. A few people report more problems, particularly with the 400 mg dose. This may be because it's concentrated. And this is all the more reason to be sure to eat plenty of food before taking the Gleevec, and drink it with plenty of water. If the 400 mg tablets are problematic, ask the doctor to give you the 100 mg tablets and you can split those up if you need to.

Heartburn and GERD

If you already have heartburn or GERD it will probably get worse on Gleevec because Gleevec does irritate the stomach. Avoid over-eating, spicy foods, decrease caffeine and alcohol. Remain two hours upright either sitting or standing after taking Gleevec. You can also try Pepcid®, which is available over the counter. In addition, some people take Maalox® or Mylanta®. These should not be taken within two hours of taking Gleevec. If you need something stronger, there are prescription drugs available. We have had good luck with Nexium® and there are other proton pump inhibitors that your doctor may prescribe.

Diarrhea

Increased volume and soft stools are common in patients on Gleevec. Watch for sorbitol, mannitol, and xylitol. These are sugar substitutes, sugar alcohols used in diet foods and gums. In sensitive individuals, even small amounts can cause diarrhea or make it worse. We have found that Imodium® AD works best on Gleevec diarrhea. This is available over the counter or you can buy a less expensive generic brand. Some patients will take 1/2 or one Imodium per day to prevent the diarrhea. It is important to control the diarrhea because persistence can cause the loss of electrolytes, particularly potassium and phosphorous. Metamucil® or Fibercon® also help. They thicken watery stool and give it more bulk. If you are sensitive to lactose or milk products, try Lactaid®. You can also buy milk that has already been pre-treated with Lactaid. Lactose intolerance can

THE ROAD AHEAD:

NEW TREATMENT PERSPECTIVES FOR CML PATIENTS

Carolyn Blasdel,
RN, MA, OCN

also cause gas. If you are experiencing gas, cut back on milk. Try an over-the-counter drug called simethicone. Acidophilus has also helped some people. It is present in live cultured yogurt; you can buy it in a health food store in capsules. If you have been on a lot of antibiotics, it helps restore the normal bacteria in the intestinal tract.

Muscle Cramps

These are pretty common, usually in the hands, feet or calves. Taking calcium in divided doses of approximately 500 mg each, taken two to three times a day, often helps them. Low potassium can also contribute to muscle cramps. If you are on a diuretic, this should be monitored.

Joint and Bone Pain

This can happen, especially when patients are first on Gleevec. It can be quite severe, but it usually [indiscernible] within days, and in a few patients it goes on for weeks. Anti-inflammatory drugs such as Celebrex®, ibuprofen in moderation (as this can affect liver enzymes and cause upset stomach), are helpful. Rarely have short-term narcotics been needed.

Skin Problems

There are several common problems from Gleevec. They include rashes, dry skin, fragile skin that tears easily, changes in pigmentation (skin gets lighter in color) and easy-to-sunburn skin. Hydrocortisone cream helps in most cases of bothersome or itchy rashes. If it is not strong enough, prescription steroids such as triamcinolone cream can be used. Claritin®, which is an oral antihistamine can be used. Also, Zyrtec® and Benadryl®, diphenhydramine, are helpful. The problem with Benadryl is that it makes people drowsy and it severely impairs driving ability. It is helpful to keep skin well-moisturized. Eucerin®, Aquaphor®, or AmLactin® are helpful.

For some people rashes come and go, while for others they can be constant. Occasionally someone gets a severe rash that requires oral steroids and then holding Gleevec. It is then restarted while tapering the steroids.

Fatigue

This is often due to anemia. In 25% of people, no cause is identified. Moderate exercise, starting gradually, is often helpful. Many studies on cancer survivors show that instituting a moderate exercise program is very helpful. It is also important to rest before you are exhausted; otherwise it takes longer to recover. People who already have fatigue and then go out and Christmas shop for 12

THE ROAD AHEAD:

NEW TREATMENT PERSPECTIVES FOR CML PATIENTS

Carolyn Blasdel,
RN, MA, OCN

hours to the point of exhaustion can take 3 to 4 days to recover. It may also seem obvious, but it is important to get enough sleep, and studies have shown over and over that most of us don't get enough.

Weight Gain

This has been a problem for some people. Weight loss is quite common before diagnosis and once Gleevec stops white cell production, the metabolic rate drops quickly. If you eat the same amount with a lower metabolic rate, you will gain weight. Some patients also report increased appetite on Gleevec. Watch calorie intake, portion sizes and get more exercise.

Drug Interactions

There are many drug interactions. Gleevec is metabolized by CYP3A3/4 pathway, as are many other drugs. You must always check with your pharmacist or doctor before starting new drugs, as there are many interactions.

The interactions also include over-the-counter drugs. You must be careful with Tylenol®, also known as acetaminophen, as many cold and flu remedies contain this and you may not realize how much you are actually taking. Try not to take more than two grams, 2,000 mgs per day. Cimetidine, St. John's wort, and many other drugs interact with Gleevec. Use caution with other drugs that irritate the stomach such as Advil® (ibuprofen). Those people on Coumadin®, or warfarin, require close monitoring, as Gleevec can change the dose requirements. Gleevec also interacts with almost all anti-seizure medications, which requires special management. Never take Gleevec with grapefruit because it can unpredictably increase blood levels of Gleevec.

Interferons

They can cause fever, chills and flu-like symptoms, fatigue, depression (which can be severe), skin rashes, weight loss, loss of appetite and numbness and tingling in the hands and feet. It is important to let your provider know if you have numbness or tingling as continuation for a long enough time may make it permanent after discontinuing the interferon. To manage side effects, it is helpful to take it at bedtime so that you sleep through the worst of it. You can also take Tylenol, drink plenty of fluids. Anti-depressants may be necessary, as would support groups and counseling. Frequently dose reduction may be required with interferons.

Fever and chills usually get better after the first few doses, but other side effects tend to get progressively worse over time, such as fatigue. Some people report memory and concentration problems.

THE ROAD AHEAD:

NEW TREATMENT PERSPECTIVES FOR CML PATIENTS

Carolyn Blasdel,
RN, MA, OCN

Ara-C (cytarabine)

This is a chemotherapy drug that may be combined with Gleevec in low doses. It is also given in high doses for blast crisis but we are not covering that tonight. It can cause lowered blood count, nausea and vomiting, diarrhea, mouth sores, fever, rash, muscle and bone pain. This all requires management by your physician.

Hydrea (hydroxyurea)

This is often used to bring counts down when people are first diagnosed. It is also used when Gleevec stops working. While on Hydrea blood counts must be monitored carefully so they don't go too low. It can cause skin rashes, ulcers, nausea, vomiting and diarrhea. There is also new information for people who have been on Hydrea in the past for an extended time. There appears to be increased incidence of squamous and basal cell skin cancers. If at some point you were on Hydrea for a prolonged time, monitor your skin and if there is anything suspicious, see a dermatologist.

Arsenic Trioxide

This is one of the drugs is one of the drugs in clinical trials with Gleevec. It is given intravenously (IV) and is well-tolerated. It can have cardiac side effects, particularly prolongation of QT intervals, low potassium and magnesium, increased blood sugar (hyperglycemia), low blood counts, edema (fluid retention), peripheral neuropathy, numbness and tingling, and changes in liver function tests. This is managed with electrolyte replacement, careful monitoring of labs and EKG, monitoring daily weights. Diuretics may need to be prescribed. Dose adjustments may need to be required.

If you need more help, there is more help at The Leukemia & Lymphoma website, as well as at Gleevec.com. There is a very good article by Dr. Michael Deininger in the *Journal of Clinical Oncology*, which goes over all the side effects. If your physician is unfamiliar with Gleevec and you are not able to manage the side effects, ask for a referral to someone with more experience. Thank you.

THE ROAD AHEAD:

NEW TREATMENT PERSPECTIVES FOR CML PATIENTS

Carson Jacobi Pattillo Thank you, Carolyn. Carolyn provided very important information for patients to understand the side effects of Gleevec for the treatment of their chronic myeloid leukemia. There are two important publications to note in the packets you were given for this meeting: "Understanding the Importance of Blood and Marrow Testing during Treatment of Chronic Myeloid Leukemia." Also, "Living with Chronic Myeloid Leukemia, Managing the side Effects." Both publications are from *The Leukemia & Lymphoma Society*. It also explains some of the terminology that Dr. Druker used, such as cytogenetic testing and Philadelphia chromosome.