50 FAQ

Frequently Asked Questions On CML

English

The Max Foundation
www.themaxfoundation.org

Friends of Max
www.friendsofmax.info

The Max Foundation

www.themaxfoundation.org

www.friendsofmax.info

Address:

Secom Business Centre
A Block-Basement, Shiv Sagar Estate
Dr. Annie Besant Road, Worli
Mumbai Maharashtra - 400 018

Tel.: 91 (22) 6660 3320 / 21
Fax: 91 (022) 6660 3322 / 24952970
Office M: 91 (0) 9833565479

50 FAQ

Frequently Asked Questions On CML

Specially put together for
Friends of Max

By

Prof M B Agarwal, MD
Dept of Haematology, Bombay Hospital, Mumbai

About the author

Prof. M.B. Agarwal, MD, MNAMS is Head, Department of Haematology, Bombay Hospital Institute of Medical Sciences, Mumbai.

He is President Elect - Indian Society of Haematology and Transfusion Medicine, President - Mumbai Haematology Group.

He is also Hon. Professor, Department of Medicine, Lokmanya Tilak Medical College, Sion, Mumbai.

He practices at Ashirwad Haematology Centre, Dadar, Mumbai. He is actively involved in research and management of patients with chronic myeloid leukaemia and other haematological diseases for last 30 years. He is a teacher par-excellance for which he was rewarded with "Best teacher's award" by J.N. Medical College, Belgaum, Karnataka. He has also been a recipient of over 10 prestigious orations. He has extensively published his research in both international and national journals. He looks after a significant number of CML patients under GIPAP through Novartis and Max Foundation and has been actively involved with Max Foundation for last 8 years.

Our grateful thanks to Dr. Agarwal for his invaluable contribution to The Friends of Max in the form of this Booklet.

Q. 1 What is Leukaemia?

Leukaemia is blood cancer. Our bone marrow produces blood and blood cancer begins from the bone marrow. There are three types of blood cells and Leukaemia is cancer of the white blood cells.

Q. 2 What is Chronic Myeloid Leukaemia and how common is it?

There are four main types of leukaemia. Two of them are acute and two are chronic. The Acute Leukaemias are Acute Myeloblastic Leukaemia (AML) and Acute Lymphoblastic Leukaemia (ALL) while the Chronic Leukaemias are Chronic Myeloid Leukaemia (CML) and Chronic Lymphocytic Leukaemia (CLL). Acute leukaemia develops quickly while Chronic Leukaemia develops slowly. In CML, white cells are present in excess. Their production goes out of control. These cells fill the bone marrow and also come out in the blood.

CML is the commonest blood cancer in India and other Eastern countries. CLL is the commonest blood cancer in Western countries.

Q. 3 What is the age at which CML occurs?

In India, most commonly, CML affects the age group between 30-60 years. In the Western world, it affects the age group between 50-70 years. Rarely, it can occur in children and very old persons as well. It affects both males and females.

Q. 4 Is CML a genetic disease? If I have it, will my children have higher chance of getting it?

No. CML is not a genetic disease. Children or any other member of the household has no higher chance of getting it. CML is not inherited.

Q. 5 Is CML a contagious disease? Can it spread to my spouse, parents or children?

No. CML is not an infection and hence it is not a contagious disease. It cannot spread to other members in the house.

Q. 6 Why did I get CML? What are the risk factors?

The exact answer to your question is unknown. In Japan, after the atom bomb explosion at Hiroshima and Nagasaki, a large number of affected individuals developed CML after a few years. Hence, there is a role of radiation. A nuclear accident can result into CML. However, in routine civil life, the reason one gets CML still remains under research. During the course of day to day living there is no way one would be exposed to the kind of radiation that would result in CML.

Also, exposure to certain chemicals, especially benzene over a period of time can result in blood cancers including CML. Benzene is a chemical in petrol and used in the rubber industry. However, exposure to petrol etc. in routine civil life cannot produce CML.

Q. 7 What is the Philadelphia chromosome?

We have 23 pairs of chromosomes (genetic material). In CML, the genetic material from chromosome 9 and 22 get translocated resulting into a shortened chromosome 22. This produces a new gene called bcr-abl. This shortened chromosome 22 was first detected in 1960 by scientists in the city of Philadelphia. Since then, the so called Philadelphia chromosome has been shown to be a consistent finding in patients of CML. This is of diagnostic importance.

Q. 8 Was I born with Philadelphia chromosome?

No. One is not born with the Philadelphia chromosome or bcr-abl gene. It develops later on. Bcr-abl leads to excessive production of an enzyme (protein) called Tyrosine Kinase (TK) which causes increase in white cells.

Q. 9 What are the symptoms of CML?

CML may not have any symptoms as it develops slowly. Many patients are diagnosed during routine blood tests carried out for one reason or the other.

Symptoms of CML are vague. Tiredness, weight loss, excessive sweating, fullness in the left upper part of the stomach , discomfort or lump in the same region and feverish feeling may occur. These symptoms are very common while CML is rare.

Once the disease is advanced (for example after few years into blastic phase), there can be anaemia (lack of blood) leading to pale appearance, bruises on the surface of the skin due to bleeding , infection leading to fever and development of glands in the neck or at other areas (lymphadenopathy).

Q. 10 How is CML diagnosed?

Usually, CML is suspected because of enlarged spleen (lump in the left upper part of stomach). The GP or your family physician, in such cases would ask for blood counts which in turn may show an increase in white cell counts. Please remember that the increase in white cells most commonly occur also due to infections causing fever, cough and diarrhoea etc. Hence, one should not get unduly worried just because the white cells are more.

Subsequently, the haematologist or medical oncologist will look at the type of blood cells and also carry out bone marrow examination looking for the presence of Philadelphia chromosome or bcr-abl gene which will confirm the diagnosis.

Q. 11 Cancer has stages. Does CML also have stages?

Chronic Myeloid Leukaemia has phases i.e. chronic phase, accelerated phase and blast phase. These phases may be loosely called stage I, II and III or early, intermediate and late.

Most of the patients are diagnosed in the Chronic phase or early phase itself. The disease remains stable for years during which there are not many complaints and one can work normally. It is during this phase that the treatment is started which is usually in the form of oral pills (Glivec-Imatinib) taken daily. No one requires hospitalization in the Chronic phase. During this phase, there are very few or no blast cells in the blood or marrow.
The next phase is the Accelerated phase which can sometimes develop very rapidly. In this phase, there are more blasts in the blood or marrow. The patient feels more weak and tired. He may also develop fever (infection) or bleeding. Spleen becomes larger and may stop responding to treatment.

Subsequently, the Blast phase develops. This is like acute leukaemia. Here, the number of blasts in the blood or marrow is maximum. Patient becomes very weak and often requires blood transfusion and even hospitalization.

Q. 12 How is CML treated?

Treatment of CML depends on its phase. We will first discuss the treatment of Chronic Phase as most of the patients present in this phase. The standard-of-care today is Glivec (Gleevec, Imatinib mesylate), an oral pill. This is made by Novartis and has been made available for patient care since the last 6 years through their Glivec International Patient Assistance Programme (GIPAP). The usual dose is a single pill of 400 mg once a day. This has made almost all previous treatments as second-line therapy. Most of the patients respond to this treatment extremely well. They also tolerate it very well. Such patients should continue to take it for their whole life, without any interruptions. The dose should not be reduced without the treating physician's / specialist's advice and one should also not take it intermittently as both these activities reduce drug efficacy.

Usually the pill is taken after 30-60 minutes of a major meal, often the night time meal - dinner. It should be taken with a glass of water. This minimizes stomach intolerance. However, one can take it after lunch or even breakfast. The occasional patient may require a pill to prevent nausea. In this situation, Tab. Domstal is prescribed 30 minutes before Glivec.

Q. 13 How is Glivec available?

Glivec is available in the form of tablets. There are 2 strengths i.e. 100 mg and 400 mg. The 100 mg tablets are orange in colour and round in shape. The 400 mg tablets are orange in colour but oval in shape. Availability of Glivec in 2 strengths gives lot of flexibility to the treating doctor who can prescribe any desired dose i.e. 300 mg, 400 mg, 600 mg or 800 mg etc. It must be remembered that any dose less than 300 mg/day is ineffective. Even children often require at least 300 mg of Glivec. This is despite their weight being less.

Q. 14 Can I split daily dose of Glivec into twice a day?

There are patients who just cannot digest 400 mg of Glivec at a time. For such patients, 200 mg of Glivec can be prescribed twice a day. For this purpose, Glivec is also available in tablet strength of 100 mg. There are patients who can tolerate 300 mg of Glivec and not 400 mg. Such patients are treated with 300 mg/day. This may be as good as 400 mg/day. Any dose less than 300 mg/day is ineffective in long run and must be strongly discouraged.

Q.15 Do some patients require higher doses of Glivec i.e. 600 mg or even 800 mg daily?

Yes. You are right. Once Glivec therapy is started, its efficacy has to be judged periodically. Usually, clinical examination to see the disappearance of enlarged spleen, CBC to see normalization of white cell count followed by cytogenetic and molecular tests are done at periodic intervals. The physician decides whether the response with 400 mg/day of Glivec is satisfactory. If not, the dose is increased to 600 mg or even 800 mg daily. It is not easy to tolerate higher doses and motivation on the part of the patient plays a major role. This does not mean that 600 mg or 800 mg daily is a better dose for every patient of CML. This dose is needed only by a few. Research is on to assess whether such higher doses are superior. Unless that is proved, 400 mg/day remains the standard dose.

Q. 16 How does Glivec work?

As was stated earlier, CML is associated with occurrence of an abnormal chromosome - Philadelphia chromosome. This chromosome contains a faulty gene called bcr-abl. This gene produces an abnormal version of a protein, an enzyme called tyrosine kinase (TK). Under normal circumstances, the TK protein helps in controlling cell growth and division. In CML, TK is defective. It passes abnormal signals resulting into continuous division of white cells.
Glivec is a small molecule which works by targeting the faulty TK enzyme. It sticks to it and prevents it from stimulating the white cells to multiply. Therefore, Glivec is called Tyrosine Kinase Inhibitor or TKI. As it targets the faulty TK, it is also called targeted therapy. As it blocks the “grow” signal, it is also known as “signal transduction inhibitor”.

Q.17 What are the common side-effects of Glivec?

The common side-effects of Glivec are rare. Very few patients find it tough to take Glivec. The occasional person may develop stomach disturbances i.e. loss of appetite, nausea, vomiting, diarrhoea etc. Some patients complain of body pain affecting muscles, bones and joints. Many patients develop swelling around the eye or feet. Some get puffiness of the face and experience weight gain of 2-3 kg due to water retention. It is also common to loose skin pigmentation and one appears fair. Unfortunately, this loss of pigmentation can be occasionally patchy which makes the patient uncomfortable. Most of these symptoms which have been discussed are considered minor side-effects and medically unimportant. They can be tolerated by the majority of patients . Antidotes to take care of nausea, vomiting, diarrhoea and analgesics to control body pain can be used. Similarly, diuretics which remove water from the body through excessive

urination can be of help in decreasing facial swelling and oedema of feet. Nothing can be done about skin depigmentation. Once again, motivation is important in accepting these minor side-effects as Glivec is the best treatment at the moment.

Q.18 Are there any serious side-effects of Glivec?

Although rare, the occasional patient can get a serious side-effect of Glivec. In the first few months, some patients have significant drops in their blood cell counts i.e. white cells, platelets and haemoglobin (Hb). To detect this early, the physician usually orders blood counts frequently in a patient who has newly been put on Glivec therapy. This is important and must not be avoided.

If the white cell counts are very low, the Glivec dose is reduced to 300 mg/day. There is an injection called G-CSF (Granulocyte-colony stimulating factor) which can be taken under the skin to stimulate white cell production. Unfortunately, this injection is expensive and costs Rs.1500/- to Rs.2000/-. It may have to be taken very often and hence many patients find it financially difficult. It is better not to reduce Glivec dose to less than 300 mg/day. If required, Glivec may be stopped totally till the counts improve.

Similarly, if Hb counts drop to a very low level i.e. below 7 g/dl and the patient is feeling weak, he can be given another injection called Erythropoietin or EPO, once again, under the skin. This is also expensive and hence one often resorts to blood transfusion support (packed cells), especially in India.

Lastly, if the platelets drop to a serious level (below 50,000/cmm), one often stops Glivec as there is no drug to push the platelet up. Platelet transfusion is another way to handle this situation; however, they are also expensive and have to be given very often, sometimes even twice a week.

Q. 19 Can the drop in blood counts occur at anytime throughout my life?

No. Most of the patients face this problem only in the first few months of Glivec therapy. Once Glivec therapy has been given for a few months, the leukaemic clone in the marrow is suppressed and the normal clone takes over. Subsequently, it is uncommon for the blood counts to drop.

Q.20 Does Glivec affect my vital organs e.g. liver?

Yes. Occasional patients have developed jaundice secondary to Glivec induced damage to the liver. This is rare. Sometimes it has happened if patient takes paracetamol (crocin, metacin) to control fever as Glivec and paracetamol interact. Majority of such patients are taken off Glivec for a short period and the treatment can be reintroduced after few weeks. Some patients need a small dose of steroid to take care of this side-effect.

Q.21 Is Glivec harmful to the heart?

Certain reports appeared two years ago suggesting that Glivec may be harmful to the heart. MD Anderson Hospital at Houston, Texas, USA, carefully reviewed the medical records of a large number of patients during last 6 years. The study confirmed that Glivec has no significant toxicity to the heart. However, those elderly patients who have a pre-existing ischaemic (coronary) heart disease, hypertension, diabetes, advanced atherosclerosis etc. should undergo periodic cardiac evaluation, approximately once a year.

Q.22 Does Glivec decrease blood calcium? I have read this somewhere. Will this make my bones weaker?

Following treatment with Glivec, almost 50% of patients have reduced calcium and phosphate levels in blood. It has been shown that Glivec significantly modulates bone turnover resulting in an increased bone mass and lowered S. calcium level. Hence, it is unlikely that Glivec will make the bones weak. Rather, it is thought that Glivec may be useful in diseases where there is bone loss (osteoporosis and osteomalacia). Overall there is no significant clinical impact and regular monitoring of calcium or assessment of bone density is not routinely required.

Q.23 Can I become pregnant during Glivec therapy?

No. Glivec therapy is considered teratogenic. If Glivec is taken during pregnancy, you may get a defective child with congenital malformations. Also, premature deliveries, abortions and miscarriages etc. are also common during Glivec therapy. Almost 50% of pregnancies result in poor outcome due to one or the other reason. At the same time, it has happened that few women have continued Glivec during pregnancy and delivered a normal healthy baby. Still, it is strongly recommended that one does not go for pregnancy during Glivec therapy.

Q.24 If I want to have a baby, can I stop Glivec until I conceive and deliver?

No. This is not recommended as Glivec is not a cure. Most of the women relapse with their CML if they stop Glivec during pregnancy. The long-term outcome of such relapses is not clear. It is possible that stoppage of Glivec for 9-12 months may lead to poor outcome in the long-term.

Q.25 I am a male patient and I am on Glivec. If I desire to be a father, can I continue Glivec?

Although, we do not have hard core data to answer your question, in general, Glivec should not be continued even in males as it could have effect on sperms leading to defective babies.

Q.26 Can I breast-feed my baby during Glivec therapy?

Probably yes. Studies have been done to show that although Glivec is secreted in milk, the levels are very low and may not be harmful to the baby. We still do not have any clinical study to support a positive reply.

Q.27 Besides clinical check-up and CBC, are there any sophisticated tests required to monitor the control of CML during Glivec therapy?

Yes. You have to periodically undergo certain tests to assess the control of your leukaemia at the cytogenetic or molecular level. You have to understand 3 terms i.e. karyotyping, FISH and PCR.

Q.28 What is karyotyping?

Karyotyping is conventional cytogenetics. As was stated earlier, chronic myeloid leukaemia is characterized by the Philadelphia chromosome. This is present in the bone marrow cells in all patients. It is usually studied by a technique called karyotyping where marrow is aspirated from the hip bone (posterior superior iliac spine) under local anaesthesia and subjected to culture. After a few days, chromosomes (genetic material inside the cell) are studied with the help of a microscope to look for Philadelphia chromosome. At least 20 cells are studied.

Once the treatment is started, this test can be carried out at periodic intervals to assess the response. Majority of the patients show substantial decrease or total absence of the Philadelphia chromosome within a year or two of starting Glivec therapy.

Q. 29 Bone marrow examination is painful. Is it really necessary?

Yes. Bone marrow examination, despite local anesthesia, is painful. However, a lot of information is obtained by carrying out this test at periodic intervals. It helps in knowing the cytogenetic response to Glivec therapy. It also helps in detecting whether a patient of CML is developing accelerated phase or blast phase. Sometimes, additional chromosomal abnormalities develop and they are fore-runners in suspecting worsening of the disease.

Having said that, many consultants do not do bone marrow test very often. This is because, certain sophisticated techniques like FISH and PCR when applied to blood, can give most of the information that one will obtain from marrow sampling.

Q.30 What is FISH?

FISH stands for fluorescence in situ hybridization. This is another type of cytogenetic test. For doing this, the bone marrow sample is not necessary. It can be done from a blood sample. The blood sample is mixed with a substance that attaches itself to the Philadelphia chromosome present inside your blood cells. This substance fluoresces (or in simple words - glows). This fluorescence can be seen by a special microscope. This makes it easier for your doctor to assess the control of your disease without resorting to bone marrow examination.

Q.31 What is PCR?

PCR stands for polymerase chain reaction. It's a highly specialized molecular test which has extraordinary sensitivity. It can tell you whether there is slightest trace of disease remaining. There are patients who have complete haematological response (i.e. no symptoms, no enlarged spleen, normal blood counts) and normal cytogenetics, however, PCR still shows that there is

residual disease. Today, this test is performed on a blood sample every 3-6 months to know that Glivec is working and the response is not lost.

Q.32 Where can I get the FISH or PCR tests done ? Are all the laboratories the same ? How much do these tests cost?

FISH and PCR tests are not widely available, especially with reliable quality. However, majority of larger cities in the country have one or more laboratories doing these tests. FISH is more widely available than PCR and it is cheaper as well. However, it is not a replacement for PCR and the decision should be left to the doctor concerned. Usually, FISH costs Rs.3000/- to Rs.4000/- while PCR costs Rs.5000/- to Rs.6000/-. Most of the major cancer hospitals, other large sized community hospitals, major oncology clinics, major haematology clinics and certain large private laboratories are doing these tests.

Q.33 What about newer tyrosine kinase inhibitors (TKI) i.e. Dasatinib (Sprycel) and Nilotinib (Tasigna)? I understand that these are even more effective than Glivec.

For most of the patients, Glivec is the first and the best line of therapy. It is effective in majority of the patients and the effect continues for years. We already have over 6 years' data in thousands of patients worldwide confirming that Glivec is effective and free from toxicity for most.

Still there are a handful of patients for whom an alternative treatment is needed. These are patients where either Glivec fails to control the disease or after initial good response, the drug becomes ineffective. Such patients may show presence of bcr-abl gene or Philadelphia chromosome in increasing amount by PCR, FISH or karyotyping. Sometimes even the blood counts tell you that the disease is not responding.

Also, there are patients who have side-effects due to Glivec and some of these side-effects are unacceptable.

Such patients, fortunately, have alternative second generation TKI and the two drugs which are US-FDA approved and have now become available are : Dasatinib by the name Sprycel and more recently Nilotinib by the name Tasigna. Dasatinib is 300 times more powerful than Glivec while Tasigna is 25 times more powerful than Glivec.

Q.34 If these drugs are more powerful, why should I continue to take Glivec?

You are quite right. It is possible that in future, your doctor may offer you Sprycel or Tasigna as the first-line treatment. However, so far, they have only been approved by US-FDA (Food and Drug Administration) for patients who are refractory to Glivec or who cannot tolerate Glivec. Although, these 2 drugs are more effective, they are also a bit more toxic. While both Sprycel and Tasigna can cause significant drop in blood counts i.e. haemoglobin, white cells and platelets; they also produce some unusual side-effects. Sprycel can cause water accumulation in the body especially around the lungs, what is called pleural effusion. Tasigna on the other

side can cause jaundice and can also raise blood sugar, lipids and affect pancreas.

We have used Glivec for 6 years and we know its effect and toxicity much better than Dasatinib and Tasigna which have only been licensed for patient's use for less than 1-2 years. As these drugs have different toxicities, there is a vision of combining them in lowered tolerable doses but this is under research.

Q.35 Can I be cured of CML by drug therapy?

Usually, Glivec therapy does not cure CML. Most of the patients do very well, but, have to take Glivec daily, probably lifelong. It is believed that the same will be proved with Dasatinib and Nilotinib (Sprycel and Tasigna). As of today, it is difficult to visualize that someone can be cured of CML by drug therapy.

Q.36 If not drug therapy, can I be cured by any other technique?

Yes. One such modality of treatment which can cure a patient of CML is bone marrow transplantation (BMT).

Q.37 What is bone marrow transplantation?

BMT is a procedure of replacing the abnormal stem cells or the cancer stem cells in the bone marrow with healthy stem cells. This was a popular and curative treatment for CML prior to availability of Glivec.

In BMT, healthy stem cells are obtained from a donor and infused in the patient's body. Before this is done, patient's own diseased, abnormal and cancerous stem cells have to be destroyed by chemotherapy and/or radiotherapy.

Q.38 Can anyone donate a marrow for me?

No. Marrow has to be obtained from a donor whose immune system is similar to that of the patient. Medically, it is called HLA (Human Leukocyte Antigen) typing. This is a special test, very different from the blood group. Both patient's blood sample and the donor blood sample are tested by a technique called “tissue typing”. This is also a PCR based test. Chance of getting a matched donor is highest from your siblings i.e. your own brothers and sisters. In some families, if there is consanguinity (i.e. when parents are related to each other or belong to the same family), even other members may get matched.

In the western world, there is bone marrow registry. Millions of people are tissue typed and their data is stored in the registry. This allows you to pick up a donor who matches with you, although, he is not related to you. It is difficult and expensive to maintain such registry and hence in India, the registries are few and contain data from limited number of donors. Hence, to get an unrelated donor matched with you, is a rarity.

Q. 39 If I have a matched donor, can I be cured by transplant?

There are other issues as well. BMT can fail (in other words, your body may reject the bone marrow) and the patient who receives BMT can die. Although the procedure is becoming safer and safer, 10% or even more patients can still die. Besides, bone marrow can react with the patient's body and produce what is called graft vs host disease (GVHD). This is a serious matter which can once again, either become fatal (acute GVHD) or produce another chronic disease called chronic GVHD which very troublesome.

In addition, to go through BMT, you have to be relatively younger. It is difficult to tolerate a procedure like BMT after the age of 50 or 60. You also have to have excellent body's health i.e. good condition of heart, kidney, liver, lungs etc.

It is from all these angles that although BMT is curative, it is now offered only to those who do not respond to drug therapy or are not able to tolerate drug therapy.

Q.40 What is the cost of bone marrow transplantation and Where is bone marrow transplantation available in India?

Bone marrow transplantation costs approximately Rupees Ten Lakhs. However, it is a one time expenditure and if you are cured, there may be no more expenses. As against this, although, drug therapy is cheaper, it may be lifelong. In addition to the drug cost, there are expenses towards laboratory tests etc. Fortunately, because of Novartis' GIPAP donation programme and The Max Foundation , its administrator , most of the patients in India and for that matter many countries in the world, have access to Glivec at no cost cost.

Bone marrow transplant is available at a few centres in this country. The major centres are Tata Memorial Hospital-Mumbai, Christian Medical College-Vellore, Apollo Hospital-Chennai, AIIMS-Delhi, R & R Hospital Delhi . Besides these, there are few more centres in Mumbai, Pune, Delhi, Hyderabad, Bangalore, Chennai.

Q.41 If I am very young (24 years old), I may have to take Glivec therapy for 60 years while BMT may cure me totally.

Yes. You are right and therefore, younger patients are often transplanted, especially if they are uncomfortable with lifelong drug therapy. Also, complications of BMT in younger patients are less.

Q.42 I was transplanted 3 years ago. However, my CML has comeback.

Yes. The disease can relapse. This can be treated by putting patient back on TKI i.e. Glivec etc. Alternatively, patient can receive an immunological treatment what is called DLI (donor lymphocyte infusion). Here, a particular type of blood cell called lymphocytes are taken out from the marrow donor and infused into the patient. This has often resulted in cure. Lastly, a second transplant can also be done. All these, I must say, are complicated treatments and applicable to a few patients.

Q.43 Although I am 60 years, I was told that I can undergo transplantation using a newer technique called mini-transplant or reduce intensity transplant.

Yes. There is a special type of BMT which can be tolerated by aged patients. This is under research and available in India.

Q.44 What about interferon therapy?

Interferon is a natural substance which exists in our body to fight infections. A man-made interferon called Interferon alpha has been used for treating chronic myeloid leukaemia - chronic phase. It was the best drug before Glivec was invented. Interferon alpha prevents leukaemia cells from multiplying. It also stimulates the body's immune system to kill the leukaemic cells. Many patients responded well to this treatment. In fact, approximately one in five patients responded so well that the cytogenetic tests for Philadelphia chromosome became negative. However, interferon has been a toxic treatment with lot of side-effects and is very difficult to tolerate. It produces fever, significant body pain and what is called flu-like symptoms. In addition, as the diseases progresses, interferon stops working.

Today, interferon is used rarely in only those cases where TKI and BMT are not the options.

Q.45 What about chemotherapy?

Chemotherapy was used in treatment of CML prior to Glivec, other TKI, interferon alpha and bone marrow transplantation. One of the oldest chemotherapeutic drug was Busulphan, which though, controlled the disease and relieved symptoms, could not prolong life. It was also toxic leading to deficiency of blood cells, lung damage and darkening of skin.

Subsequently, hydroxyurea was used for over 2 decades as a safe and effective treatment for CML. It controlled the disease and got rid of the symptoms, however, it failed to substantially prolong the life.

The third chemotherapeutic drug which was used extensively is cytosine arabinoside. It was usually given in combination with interferon alpha.

Today, none of the chemotherapeutic drugs are used as preferred drugs in the treatment of CML.

Q. 46 We have recently heard about homoharringtonine (HHT).

HHT is an injection which is obtained from a Chinese plant. It has been researched both in China and in the United States. Given intravenously, it is an effectively treatment in patients of CML. It has been shown to work in all phases of the disease i.e. chronic, accelerated and blast. It is initially given as a continuous I.V. infusion over 24 hours. Subsequently, one can switch to a subcutaneous route twice daily for 14 days per month and at a later stage, 7 days per month. Usually, 4-6 courses are administered. It can also be combined with another cytosine arabinoside. It is relatively cheap. It is bone marrow toxic and can produce drop in normal blood counts.

Q.47 Can drugs be given in combination to treat Chronic Myeloid Leukaemia?

Yes. When individual drugs are ineffective or they cannot be tolerated in the usually recommended dose, doctors often resort to combination therapy where two or more drugs are combined to achieve better results. Sometimes, to reduce the side-effects, the dose of individual drugs is reduced. Overall, combination therapy for CML is experimental and not routine.

Q.48 What is accelerated phase and how is it treated?

Some of the patients progress and develop a large spleen which does not respond to standard treatment. Others may develop significant drop in haemoglobin or platelet count. There are some who show rising WBC count which is refractory to treatment. Sometimes, presence of abnormal cells in the blood or marrow helps in suspecting accelerated phase. Lastly, when bone marrow is tested for cytogenetics (karyotyping), it may show certain chromosomal changes over and above Philadelphia chromosome. This is how doctor diagnoses accelerated phase.

It is not easy to treat accelerated phase of CML and there is no standard treatment. Depending upon the individual patient's health, doctors resort to higher dose of Glivec, interferon alpha with or without chemotherapy, chemotherapy alone or even bone marrow transplantation. The most important aspect of treatment of accelerated phase is to improve the quality of life. This is done by releiving symptoms and also by giving blood transfusion, platelet transfusion and antibiotics.

Q. 49 What is blast phase?

When CML becomes refractory to treatment, it converts into acute leukaemia. This is called blast phase. It is diagnosed by the presence of increased number of blast cells in the bone marrow or peripheral blood. Once again, there is no standard treatment of blast phase and doctors individualize the treatment. The methods used are same as those described under accelerated phase.

Q.50 What is my life expectancy ? How long will I live?

If you take Glivec properly and if you respond to it adequately, life expectancy may be normal. However, if Glivec is not working or you are not able to take it due to one reason or the other, CML can progress and enter into accelerated or blast phase which are dangerous.

Glossary of commonly used terms

Allogeneic Stem Cell Transplantation.

Anemia. A decrease in the levels of hemoglobin in the blood.

Antibiotics. Drugs that are used to treat infections caused by bacteria and fungi. Penicillin is one type of antibiotic.

Antibodies. Proteins made by plasma cells in the blood. Antibodies help to fight infection in the body.

Blast cells. Early bone marrow cells.

Bcr-Abl. A gene and also a protein created by the translocation of Chromosomes 9 and 22

Bone Marrow. The soft, spongy tissue found in the center of most large bones that produces the white cells, red cells and platelets

Bone marrow aspiration. A procedure to remove marrow cells so that they can be examined to see if they are normal. A liquid sample of cells is taken from the marrow and then the cells are looked at under a microscope.

Bone marrow biopsy. A procedure to remove marrow cells and examine them to see if they are normal. A very small amount of bone filled with marrow cells is taken from the marrow, and the cells are looked at under a microscope.

CBC. Complete Blood Count

Chemotherapy or drug therapy. Treatment with chemical agents to treat CML and other diseases.

Chromosomes. Any of the 23 pairs of certain basic structures in human cells. Chromosomes are made up of genes. Genes give the instructions that tell each cell what to do. The number or shape of chromosomes may be changed in blood cancer cells.

Differential Count. A test that measures the relative numbers of white blood cells (WBCs) in the blood; it also includes information about abnormal cell structure and the presence of immature cells (Blasts or myeloblasts)

FISH. The short name for a test called “fluorescence in situ hybridization.” This is a test to measure the presence in cells of a specific chromosome or gene. This test can be used to plan treatment and to measure the results of treatment.

Hematocrit. The amount of blood that has red cells.

Hematologist. A doctor who treats blood cell diseases.

Hemoglobin. A protein in red cells that carries oxygen. A blood test can tell how much hemoglobin you have in your blood.

HLA (Human Leukocyte Antigens) Typing. A blood test that determines a person's compatability for purposes of a bone marrow or stem cell transplant based on the types of antigens present

Immune response. The reaction of the body to foreign material. Examples of foreign material are an infection-causing microorganism, a vaccine or the cells of another person when those cells are used for an allogeneic stem cell transplant.

Immune system. Cells and proteins in the body that defend it against infection. Immunoglobulins. Proteins that fight infection.

Immunotherapy. The term for treatments that can boost the body's immune system.

Karyotype. A map of the 46 human chromosomes of a cell. There are 22 matched pairs and the sex chromosomes, shown as a separate pair (XX for females or XY for males).

LFTs. Liver Function Tests. A group of blood tests that can help to show how well a person's liver is working. LFTs include measurements of albumin, various liver enzymes (ALT, AST, GGT and ALP), bilirubin, prothrombin time, cholesterol and total protein. All of these tests can be performed at the same time

Leukemia. A cancer of the marrow and blood.

Lymphocyte. A type of white cell that is part of the immune system and fights infection.

Marrow. The spongy material in the center of bones where blood cells are made.

Oncologist. A doctor who treats people who have cancer.

Pathologist. A doctor who identifies diseases by studying cells and tissues under a microscope.

PCR. The short name for a lab test called “polymerase chain reaction,” a very sensitive test that can measure the presence of a blood cancer cell marker in the blood. PCR is used to detect blood cancer cells that are below the level of detection by cytogenetic tests (for example, FISH).

Plasma. The liquid part of the blood.

Platelet. A type of blood cell that helps prevent bleeding. Platelets cause plugs to form in the blood vessels at the site of an injury.

Red cell. A type of blood cell that carries oxygen to all parts of the body. In healthy people, red

cells make up almost half of the blood.

Relapsed CML. CML that responded to treatment but then returned.

Remission. No sign of the disease and/or a period of time when the disease is not causing any health problems.

Resistance. When a drug does not work or stops working.

Stem cell. A type of cell found in marrow that makes red cells, white cells and platelets.

Tyrosine kinase inhibitor (TKI). A drug that blocks cell growth. Gleevec (Imatinib), Sprycel (Dasatinib) and Tasigna (Nilotinib) are TKIs that are used to treat CML.

SOME WEBSITES THAT MAY BE OF HELP IN ACCESSING INFORMATION

www.cancer.gov

www.leukemia-lymphoma.org

www.cancer.org

www.ncrn.org.uk

www.cancerworld.org

www.medterms.com

www.cmlhealthcare.com

www.cmlsupport.org.uk

www.newcmldrug.com

www.cmlsupport.com

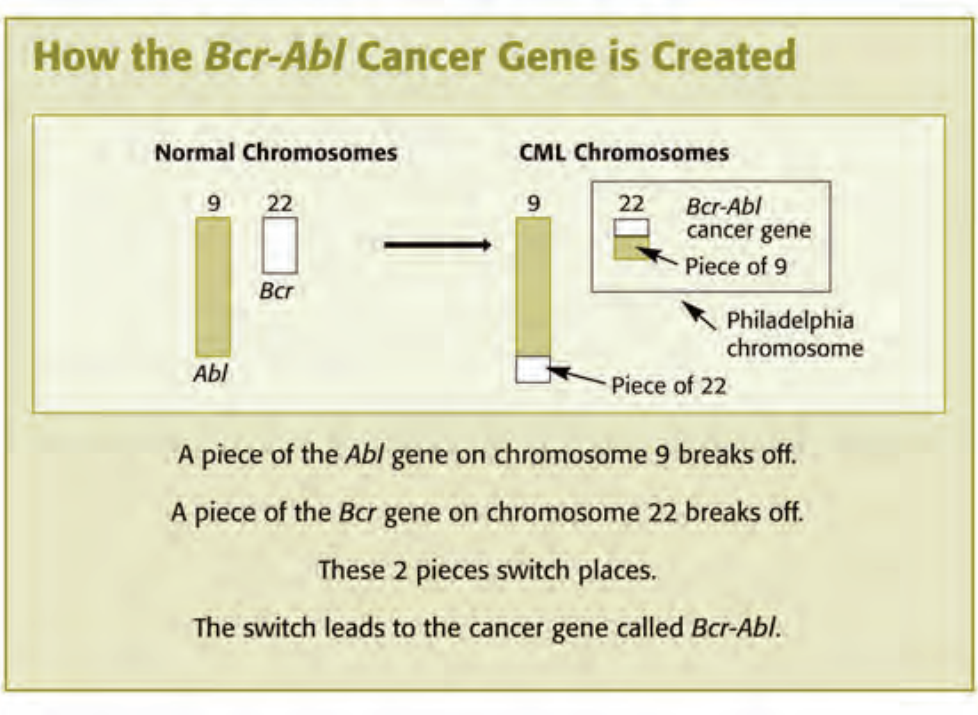
www.cmladvocates.net

www.gistsupport.org

www.gistsupportuk.com

Chronic myelogenous leukemia (CML)

Chronic myelogenous leukemia: A chronic malignant disease in which too many **white blood cells** belonging to the myeloid line of cells are made in the bone marrow. CML patients have what is called the "Philadelphia Chromosome" (Ph chromosome). Chromosomes are structures in the cells that contain genes. Every cell with a **nucleus** has **chromosomes**. Genes give instructions to the cells. The Ph chromosome is made when a piece of chromosome 22 breaks off and attaches to the end of chromosome 9. A piece of chromosome 9 also breaks off and attaches to the end of chromosome 22. The break on chromosome 9 involves a **gene** called Abl. The break on chromosome 22 involves a gene called Bcr. The Bcr and Abl genes combine to make the CML-causing gene called the **Bcr-Abl cancer gene**.



Phases of CML

There are three phases of CML:

- The chronic phase
- The accelerated phase
- The blast crisis phase

Chronic Phase CML

Most patients are in the chronic phase of the disease when their CML is diagnosed. In this phase, CML symptoms are milder. **White cells** can still fight infection. Once patients in the chronic phase are treated, they can go back to their usual activities.

Accelerated Phase CML

In the accelerated phase, the patient may develop **anemia,** the number of white cells may go up or down, or the number of platelets may drop. The number of **blast cells** may increase and the **spleen** may swell. People with accelerated-phase CML may feel ill.

Blast Crisis Phase CML

Patients with blast crisis phase CML have an increased number of blast cells in the **marrow** and blood. The number of red cells and platelets drops. Patients may have infections or bleeding. They may also feel tired and have shortness of breath, stomach pain, or bone pain.

Signs and Symptoms

People with CML may not have any symptoms at the time of diagnosis. They may be diagnosed following a medical examination for another condition or as part of a periodic checkup. CML **signs and symptoms** tend to develop gradually. Some signs and symptoms of CML are:

- Tiring more easily
- Shortness of breath doing usual day-to-day activities
- Pale skin color
- Enlarged **spleen** leading to a "dragging" feeling on the upper left side of the abdomen
- Night sweats
- An inability to tolerate warm temperatures
- Weight loss.

Many of the signs and symptoms for CML are common to other illnesses. Most people with these signs and symptoms do not have CML.

Diagnosis

The **diagnosis** of CML is usually made with information from blood and bone marrow tests.

Blood Tests

The testing for CML includes blood cell counts and a blood cell examination.

- Blood cell counts. The doctor orders a test called a complete blood count to check the numbers of blood cells. With CML, the red cell count is lower than normal. The number of white cells is higher than normal and may be very high. The number of platelets may be higher or lower than normal.

- Blood cell examination. The cells are stained (dyed) and looked at (dyed) and looked at with an instrument called a light microscope. A person with CML has a small number of developing cells called "blast cells" in his or her blood. Blast cells are not found in the blood of healthy individuals.

Bone Marrow Tests and Cytogenetic Tests

Some signs of CML do not show in blood tests. The doctor has to look at a small number of cells (a sample) from the marrow. The samples of cells are obtained with tests known as a **bone marrow aspiration** and a **bone marrow biopsy.**

Samples of marrow cells are examined under a microscope. This is called a cytogenetic analysis. The examiner looks at a map of the chromosomes in the cell. The map is called a "karyotype." The Ph chromosome in a CML cell can be detected on the karyotype.

FISH or fluorescence in situ hybridization is a special test used to detect CML cells that may not show up on a standard cytogenetic test for the Ph chromosome. A PCR test can be done on cells from blood or marrow.

PCR also known as Polymerase Chain Reaction is a very sensitive test that can detect CML cells that are not found by the FISH test. This test can detect a very small number of CML cells. A PCR test can be done on cells from blood or marrow.

NOTES

NOTES

NOTES

NOTES

Acknowledgments

We are grateful to Ishani Munshi of Friends Of Max for her sensitive portrayal of spring and hope depicted on the cover as well as K. Alexander Nadar & Dhananjay Ashtaputre of Point Blank Advertising Pvt Ltd for their professionalism and attention to detail in designing the booklet.