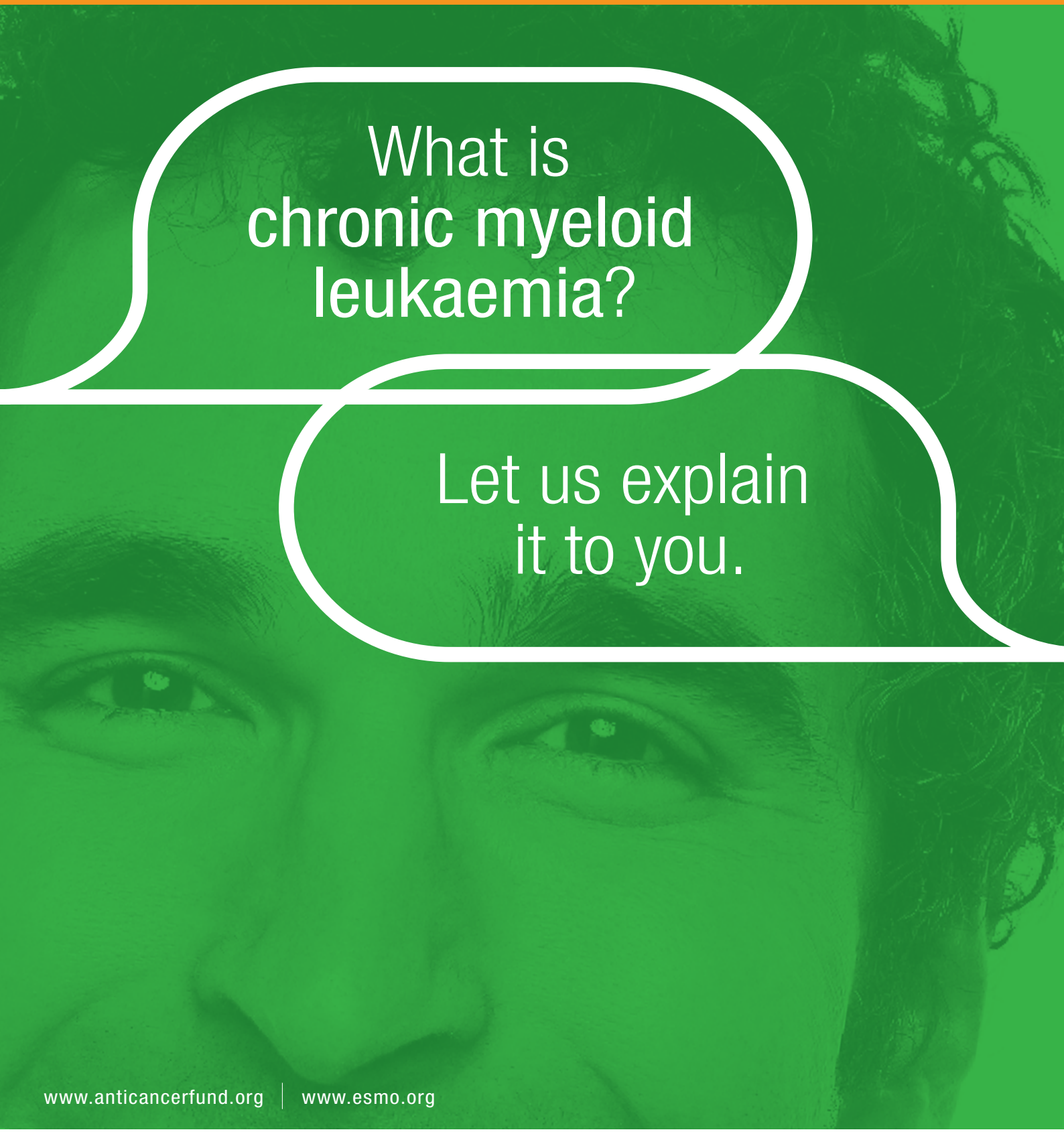
Chronic Myeloid Leukaemia



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ESMO/ACF Patient Guide Series

based on the ESMO Clinical Practice Guidelines

CHRONIC MYELOID LEUKEMIA: A GUIDE FOR PATIENTS

PATIENT INFORMATION BASED ON ESMO CLINICAL PRACTICE GUIDELINES

This guide for patients has been prepared by the Anticancer Fund as a service to patients, to help patients and their relatives better understand the nature of Chronic Myeloid Leukemia (CML) and appreciate the best treatment choices available according to the subtype of CML. We recommend that patients talk to their doctors about the tests or treatments that are needed for their type and stage of disease. The medical information described in this document is based on the clinical practice guidelines of the European Society for Medical Oncology (ESMO) for the management of Chronic Myeloid Leukemia. This guide for patients has been produced in collaboration with ESMO and is disseminated with the permission of ESMO. It has been written by a medical doctor and reviewed by two oncologists from ESMO including the lead author of the clinical practice guidelines for professionals. It has also been reviewed by patients' representatives from ESMO's Cancer Patient Working Group.

More information about the Anticancer Fund: www.anticancerfund.org

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For words marked with an asterisk, a definition is provided at the end of the document.

Table of content

This text was written by Dr Holbrook E.K. Kohrt (Anticancer Fund) and reviewed by Dr Gauthier Bouche (Anticancer Fund), Dr Svetlana Jezdic (ESMO), Dr Michele Baccarani (ESMO), Pr Martin Dreyling (ESMO) and Mr Jan Geissler (ESMO's Cancer Patient Working Group).

The current update (2013) reflects minor changes in the latest version of the ESMO Clinical Practice Guidelines. The update was done by Dr Gauthier Bouche (Anticancer Fund) and was reviewed by Dr Svetlana Jezdic (ESMO), Dr Michele Baccarani (ESMO) and Pr Martin Dreyling (ESMO).

DEFINITION OF CHRONIC MYELOID LEUKEMIA (CML)

Leukemia is a type of cancer of the blood. There are different forms of leukemia depending on what type of blood cell is affected. “Chronic” describes a gradual or slow progression, and “myeloid” denotes the origin from myeloid cells, which are immature cells that normally become mature red blood cells*, white blood cells*, or platelets*. In chronic myeloid leukemia, the bone marrow produces too many myeloid blood cells which are at various maturation stages including cells known as immature granulocytes*, metamyelocyte*, and myeloblasts*. Platelets and basophils (different myeloid cells responsible, in part, for the allergic response) are also often overproduced at diagnosis.
Excess production of myleloid blood cells in the bone marrow ultimately prevents the normal production of red blood cells, which are important in delivering oxygen to all cells in the body, and can also decrease production of platelets or thrombocytopenia*. Platelets play a critical role to stop bleeding.
Patients with chronic myeloid leukemia (CML) may be diagnosed at a routine checkup, or after seeking medical care due to lack of energy and fatigue from anemia*, or bleeding, abdominal* pain or discomfort, and rarely bruising from insufficient platelets. Enlargement of the spleen, known as splenomegaly, leads to abdominal and left chest discomfort, early satiety, or a change in bowel patterns. Other possible symptoms include fever, shortness of breath and bone pain. At diagnosis, most patients, have a white blood count (the number of white blood cells circulating in the blood) increased above normal.

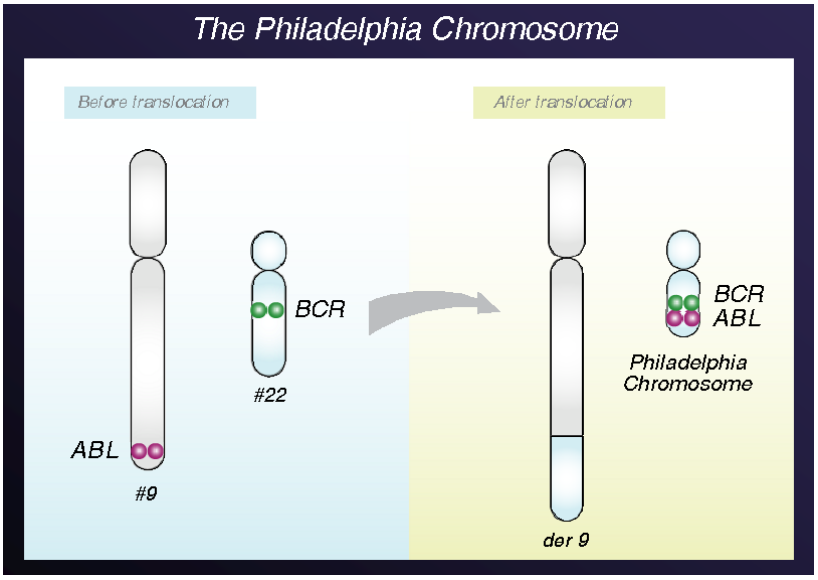
IS CHRONIC MYELOID LEUKEMIA FREQUENT?

Compared to breast cancer in women or prostate cancer in men, chronic myeloid leukemia is not common. In the European Union, 1 to 2 cases will be diagnosed among 100,000 people every year. CML is very rare in children. Its frequency increases with age. Median age of patients diagnosed with CML is around 60 years. There are no geographic differences in number of newly diagnosed cases.

WHAT CAUSES CHRONIC MYELOID LEUKEMIA?

Today, the cause of chronic myeloid leukemia (CML) is known to result from a specific genetic abnormality* which occurs in the blood stem cell*, however the cause leading to the abnormality is not understood.

This specific genetic abnormality is an abnormal rearrangement of genetic material. Two chromosomes* exchange a portion of their genes with genes on the other chromosome. This is known as a translocation. For CML, specifically, genes from chromosomes 9 are swapped with genes from chromosome 22. Translocation of the Abelson murine leukemia gene (*ABL**) on chromosomes 9 and the breakpoint cluster region (*BCR**) on chromosome 22 resulting in the Philadelphia chromosome* (translocation of chormosomes 9 and 22, t(9;22)) can be detected in 95% of patients with CML either from cells circulating in the blood or in the bone marrow.



The Philadelphia chromosome encodes a dysregulated tyrosine kinase* (an enzyme in cells), which results in an abnormal behavior of the cells affected. This includes the formation of immortalized cells, increased cell turnover and proliferation*, and abnormal cell maturation.

There are very few known risk factors* of CML, which increase the chance of leukemia occurrence, but do not necessarily lead to development of leukemia.

- Exposure to high-dose radiation* can increase the risk of CML. Atomic bomb and nuclear reactor accident survivors as well as radiology technicians prior to 1950 (when protective shielding was first introduced) are at inceased risk of developing CML.

- The risk of developing CML increases with age but as people get older the risk is still very small. CML also occurs slightly more often in men than in women.

People exposed to pesticides* or benzenes* as part of their work seem to have a moderate increased risk of developing CML.

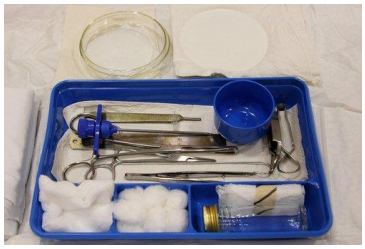
HOW IS CHRONIC MYELOID LEUKEMIA DIAGNOSED?

Chronic myeloid leukemia can be suspected in patients due to symptoms or laboratory abnormalities in patients with and without symptoms (asymptomatic*). **Symptoms and clinical manifestations** may include:

1. **Splenomegaly.** Enlargement of the spleen due to its location in the upper left abdomen*, results in abdominal discomfort, pain that radiates to the left shoulder, early satiety (inability to eat full meals), a change to bowel habits (due to obstruction of the intestines), occasionally weight gain, and the feeling of a mass extending from under the left chest into the abdomen.
2. **Fatigue.** Fatigue is a common symptom due to anemia* (a decreased red blood cell count, often measured as hematocrit* or low hemoglobin* level). Patients who are physically active may not notice the effects of being anemic until it is severe
3. **Bleeding.** Sometimes patients initially present with an elevated platelet* count. Conversely, a low platelet count due to replacement of the normal bone marrow cells with leukemic cells can be seen and may result in easy bruising, bleeding from the nose or gums, petechiae* (red spots seen on the skin commonly over the shins and ankles), and purpura (groups of petechiae resulting in larger red skin spots).

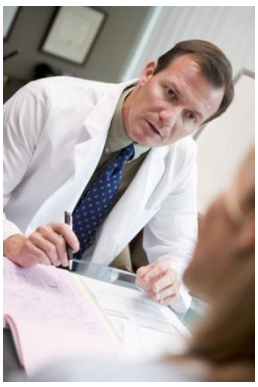
In patients who have the above symptoms a complete blood count should be done to check the three types of blood cells produced in the bone marrow: 1) white blood cells*, 2) red blood cells*, and 3) platelets*. Occasionally the first suspicion of a possible leukemia may be based on routine **laboratory** findings alone. In addition, the **complete blood count** identifies, as part of the white blood cell count, leukemia cells circulating in the blood: An increased number of white blood cells at various stages of maturation, which are proliferating* at an abnormal rate, with a disproportionate increase in basophils*, are observed in the circulation.

If a diagnosis of CML is suspected based on symptoms and the white blood cell* count, a **bone marrow biopsy*** is performed. In the majority of cases the leukemia cells, which are found on the complete blood count, can provide adequate tissue to test for the presence of the Philadelphia chromosome* (translocation of chromosomes* 9 and 22, described above). The **Philadelphia chromosome**, t(9;22) can be detected by conventional cytogenetic methods (chromosome banding analysis of marrow cell metaphases) but also by molecular techniques including polymerase chain reaction (**PCR*)**, a technique in molecular biology to amplify a single or a few copies of a piece of DNA* (deoxyribonucleic acid), and fluorescent in-situ hybridisation (**FISH*)**, a cytogenetic* technique that is used to detect and localize the presence or absence of specific DNA sequences on chromosomes. In these cases, treatment may begin prior to a bone marrow biopsy.



A bone marrow biopsy is an uncomfortable minor procedure lasting fifteen minutes. Local anesthesia* (pain-numbing medicine) is used for the procedure and sharp pain is usually not experienced. The procedure allows the pathologist* (a doctor trained in diagnosing the disease based on the appearance of cells or tissues in the microscope) to diagnose CML. The pathologist can also determine what type of CML a patient has and further identify the genetic abnormalities of the leukemia by looking closely at the chromosomes*. PCR* and FISH* tests are performed to identify the Philadelphia chromosome*.

WHAT IS IT IMPORTANT TO KNOW TO GET THE OPTIMAL TREATMENT?



Doctors will need to consider many aspects of both the patient and the leukemia in order to decide on the best treatment.

Relevant information about the patient

- Personal medical history
- Results from the clinical examination* by the doctor
- General well-being
- Typing for bone marrow transplant*. Before the development of targeted therapies* for CML, first-line therapy was bone marrow transplantation. These days, some patients with CML may require a bone marrow transplant, but usually only if they fail to respond to targeted therapy and their disease progresses. Bone marrow transplant involves using the healthy bone marrow cells of someone else to replace the patient's own, cancerous bone marrow. To prevent the donor's immune system* from damaging the patient's body (a condition known as *graft*-versus-host disease*), tissue typing must be performed to determine if a donor and a patient 'match'. This is determined by the level of resemblance of specific proteins* called Human Leukocyte* Antigen (HLA), between the patient and donor. Since the process of finding a matching bone marrow may take a few months, it is helpful to know the patient's type ahead of time. HLA typing of the sisters or brothers who are possible donors should also be performed. If siblings do not 'match', unrelated donors will be screened.

Relevant information about the leukemia

- **Staging, prognosis* and risk classification**

Unlike other cancers, which develop at a single site (such as breast cancer within the breast, or prostate cancer within the prostate) and then spread (metastasise*), malignant cells in patients with leukemia are considered to be present throughout the body at diagnosis due to their normal circulation in the bloodstream. For this reason the prognosis is not determined by the extent of spread of the disease. The stage of disease is determined by the "phase" including chronic*, accelerated, and blastic* phase or blast crisis. The majority of patients are diagnosed in chronic phase. Patients are diagnosed with accelerated phase disease if the percentage of blasts increases to 15-29% in the blood or bone marrow, greater than 20% basophils* develop in the blood, platelets* either become severely elevated or low (but not as a result of therapy), or a clonal abnormality develops in addition to the Philadelphia chromosome*. The most advanced stage of disease is blast crisis which is defined by an increase in bone marrow or peripheral blood blasts to at least 30%.

	Accelerated Phase	Blastic Phase
Blast cells*	15 – 29%	≥ 30%
Basophils*	> 20%	/
Platelet count**	< 100 x 10^9/L unrelated to therapy	/
CCA / Ph+	Present	/
Extramedullary involvement +	/	Present

* In peripheral blood or in bone marrow
CCA / Ph+= clonal chromosome* abnormalities in Ph + cells
+ Excluding liver and spleen, including lymph nodes*, skin, central nervous system (CNS*), bone, and lung.

Untreated, patients with chronic* phase CML will progress to accelerated phase in 3-5 years. Patients diagnosed with accelerated phase have a median survival of 4 to 6 months without treatment. Survival is further limited if blast* crisis occurs with a median survival among untreated patients of 2 to 4 months.

The prognosis* of a patient is best predicted by characteristics of the patient (including percentage of basophils* as well as spleen size). Multiple scoring systems using patients and disease characteristics have been developed which provide an estimate of likelihood of response to therapy and survival. When using the most up to date, EUTOS risk score, five-year, progression-free survival was significantly better in the low than in the high-risk group (90% vs. 82%), but overall survival was only slightly lower than that of the normal, healthy population.

WHAT ARE THE TREATMENT OPTIONS?

The treatment should take place only in centres used to treat CML and offering an adequate multidisciplinary* infrastructure. Whenever possible, the treatment should be offered in the form of clinical trials*.

Treatment of CML is tailored to the individuals based on phase of disease at diagnosis. Unlike solid tumors, surgical resection and radiation therapy* do not typically serve a role in the management of CML.

Treatment for chronic* phase CML

The aforementioned t(9;22) mutation results in the mutation of a tyrosine kinase. Today, all patients should first be treated with an inhibitor of this mutated* tyrosine kinase*, also known as the BCR-ABL* tyrosine kinase. Other agents, including interferon* and hydroxyurea* have a limited role in first-line therapy. Hydroxyurea is used to rapidly lower disease burden and white blood cell* counts. Imatinib* is a first generation oral, tyrosine kinase inhibitor* which achieves a 8-year overall survival of nearly 90% of patients. Second generation tyrosine kinase inhibitors, such as dasatinib* or nilotinib*, may also be considered for all patients with CML at diagnosis. Patients *should not* discontinue (stop taking) imatinib, dasatinib, or nilotinib, unless instructed to as part of a clinical trial* or in case of severe side effects. These therapies are used indefinitely as stopping their use has been shown to result in recurrence* or progression* of CML.

After initiating therapy for CML, patients should be monitored for treatment response assessment. The process of monitoring response to therapy is important to determine if an adequate response is being achieved, or if patients should be transitioned to a higher dose or different therapy. Since therapy is continued indefinitely and relapse occurs upon cessation of therapy in most patients, it is critical that the disease is closely monitored. Continued monitoring over time is needed, even in the setting of an optimal response, in order to detect and treat potential recurrence*. Specific response criteria, including optimal, suboptimal, and failure have been established to guide appropriate increase or change of therapy.

Response assessment is based on 3 levels of response: hematologic response*, cytogenetic response* and molecular response*, as described below.

- Hematologic response*
  - Assesment of hematologic response should be performed after the initiation of therapy every 2 weeks to monitor peripheral white blood cell* (WBC) and platelet* counts.
  - A complete hematologic response* (CHR) is the association of
    - a total WBC $<10\times10^9$/l,
    - a WBC formula with no present immature granulocytes* and <5% of basophils*,
    - platelets* count $<450\times10^9$/l,
    - and non palpable spleen.
- Cytogenetic response (CgR)*
  - Cytogenetics* should be monitored after 3 months, 6 months, 12 months, and 18 months of therapy with a tyrosine kinase inhibitor*. Until a complete cytogenetic

response* (CCgR) is achieved, cytogenetics should be repeated at least every 6 months.
    - A complete cytogenetic response (CCgR)is defined by the inability to detect the Philadelphia chromosome* by analyzing the chromosomes* metaphases*
    - A partial cytogenetic response (PCgR) is defined as presence of 1%–35% positive Philadelphia chromosome metaphases.
- Molecular response*
    - Monitoring of molecular response is done with PCR which quantifies the BCR-ABL/ABL anomalies
    - It should be repeated at least every 3 months until a major molecular remission* is achieved
    - Major molecular remission is defined by a PCR result with BCR-ABL/ABL <0.10% on the International Scale.
- Once both a complete cytogenetic response and a major molecular remission have been achieved, cytogenetic monitoring should be performed every 12 months and molecular monitoring by PCR should be performed every 6 months.

Patients who achieve an optimal response should continue therapy with imatinib* or the second generation tyrosine kinase inhibitor* they are currently receiving. This group of patients should only discontinue therapy in the setting of a clinical trial*.

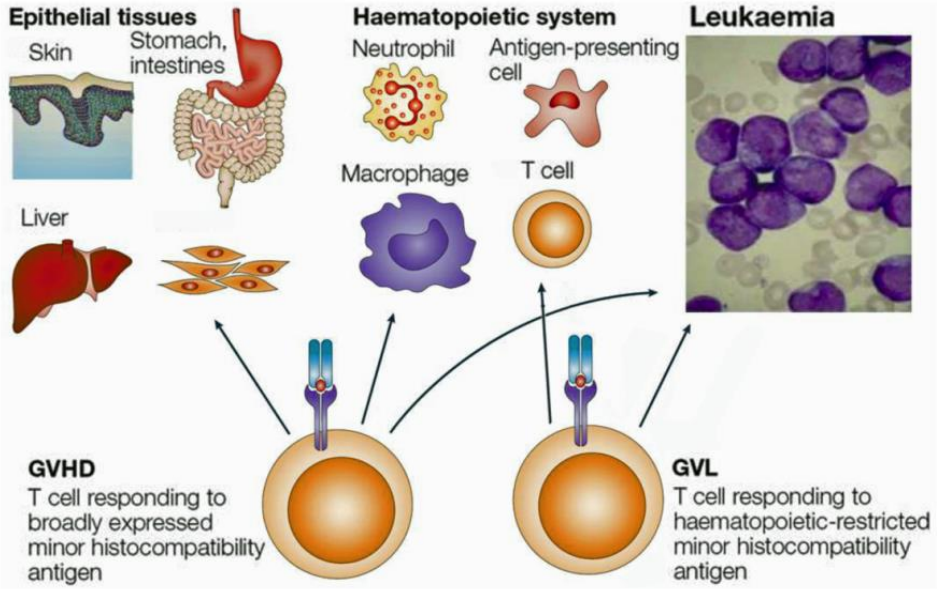
Patients with only a suboptimal response can be considered for a dose increase in their current tyrosine kinase inhibitor or a change of therapy, if they are receiving imatinib, to a second generation tyrosine kinase inhibitor.

In patients failing to respond to imatinib, the treatment should be changed to a second generation tyrosine kinase inhibitor such as dasatinib* or nilotinib. More recently, another second generation tyrosine kinase inhibitor (bosutinib) has been approved in the USA. The tyrosine kinase inhibitor ponatinib is also approved in the USA for the CML forms that have a specific mutation called T315I mutation*. A different type of drug, omacetaxine that does not belong to the class of tyrosine kinase inhibitor has also been recently approved in the USA for the treatment of cases whose CML is resistant to tyrosine kinase inhibitors. A dose increase in imatinib is unlikely to have a beneficial effect on the progressing disease. The ability to achieve a response and the duration of time a response lasts should be considered important factors when patients are being considered for allogeneic bone marrow transplant*.

Treatment for accelerated phase or blast* crisis CML

In these phases, evidence is more limited to decide which treatment option is the best. Treatment with a tyrosine kinase inhibitor can be initiated in patients who have not already been treated with a tyrosine kinase inhibitor. Change to another tyrosine kinase inhibitor or chemotherapy can be considered for patients who have already been treated with a tyrosine kinase inhibitor. However, those options are effective for only a limited time.
In these patients performing an allogeneic bone marrow transplant* remains the most valid option and should be considered. This is the process of transferring someone else's bone marrow stem cells* into the patient. The patient's white blood cells*, red blood cells*, and platelets* are replaced by the donor's cells. The donor's cells will all become part of the patient's own blood . The donor's cells can recognise the patient's cells as foreign since they are new to the patient's body, resulting in damage to the patient's own cells (this is known as *graft-versus-host disease*). GVHD typically involves the donor's T cells* contained in the graft* attaching the patient's skin, gastrointestinal tract

(mouth, stomach and intestine), and liver. These tissues express minor histocompatibility antigens* for which no match between donor and patient needs to be verified before transplantation, as opposed to major antigens. Expression of these minor antigens result in their recognition as foreign. During the same process the donor's cells also recognise the patient's leukemic cells as foreign and will destroy them, which is the main beneficial effect of a bone marrow transplant (this is known as *graft-versus-leukemia effect, GVL*). Bone marrow stem cell transplants provide an opportunity to eradicate the leukemia completely and cure the patient.



Allogeneic bone marrow transplant* is the only established curative therapy* for CML in either of these phases of disease. In order to control the pace of disease and to obtain a response prior to transplant, patients should consider a clinical trial*, a second generation tyrosine kinase inhibitor*, or conventional cytotoxic* chemotherapy*.

Treatment of resistant disease

The disease can become resistant* to treatment with a tyrosine kinase inhibitor*. Resistant disease can develop as the patient's disease progresses resulting from mutations* in the BCR-ABL* tyrosine kinase. It is important when disease progresses and therapy is either increased in dosage or changed to a different tyrosine kinase inhibitor, that mutations which lead to resistance to therapy with a tyrosine kinase are screened. In rare cases in which compliance or drug metabolism* is a question, imatinib* drug levels can be assayed from the peripheral blood. If leukemia cells present a specific mutation called T315I mutation, the patient can be treated with one tyrosine kinase inhibitor, ponatinib, which is approved only in the USA for the moment.

Treatment of patients who cannot tolerate tyrosine kinase inhibitors*

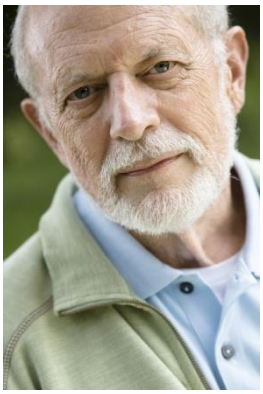
Patients who develop severe side effects because of first generation tyrosine kinase inhibitors, such as severe rash, severe edema (swelling of the legs), or fluid accumulation on the lungs should be first treated with second generation tyrosine kinase* inhibitors*. The majority of patients who cannot tolerate first generation tyrosine kinase inhibitors can be successfully treated with second generation tyrosine kinase inhibitors without side effects. To reduce the risk of side effects, the dose of second

generation tyrosine kinase inhibitors can be reduced without decreasing efficacy*. For patients who cannot tolerate three tyrosine kinase inhibitors, a new therapy, omacetaxine* was recently shown to be effective and tolerable. In rare cases, patients who cannot tolerate all tyrosine kinase inhibitors should be considered for a bone marrow transplant* from a sibling or unrelated donor.

Managing symptoms of the disease and side effects of the treatment

Leukemia and its treatment can cause severe side effects including diarrhoea, nausea, vomiting, hair loss, lack of energy, appetite, and severe infections. Effective therapies for these side effects exist and patients may expect that some of these problems can be treated.

WHAT HAPPENS NEXT?



Today, patients with CML require lifelong treatment with tyrosine kinase inhibitors*. Research is ongoing to understand if treatment can be discontinued and which patients may be allowed to discontinue the treatment. No treatment discontinuation is recommended outside clinical trials*.

Why and how do I need to be followed up by doctors?

After the treatment has been initiated, doctors will propose a follow-up* aiming to:

- detect possible progression, relapse, or return of leukemia, as soon as possible
- evaluate adverse effects of the treatment and treat them
- provide psychological support and information to enhance returning to normal life.

Follow-up visits with the doctor should include:

- History-taking, eliciting of symptoms and physical examination
- Routine evaluation of the complete blood count
- A repeat bone marrow biopsy, only in case of treatment failure, or in case of unexplained thrombocytopenia*, or if a reliable molecular test cannot be obtained*.

In general, from the third month of the treatment initiation, cytogenetics* will be repeated every 6 months until complete cytogenetic response* has been achieved and confirmed, and PCR* every 3 months until achievement of major molecular response*. Once a complete cytogenetic response has been achieved and confirmed, a cytogenetic test is recommended every 12 months, but it is not necessary if molecular testing is available and reliable. Once a major molecular response has been achieved and confirmed, a molecular test is recommended at least every six months. If the patient was high risk according to the risk score, or responded subobtimally to the therapy, more frequent monitoring may be advised. Screening for BCR-ABL mutations* should be proposed only in the case of treatment failure or suboptimal response.

Returning to normal life

It can be hard to live with the idea that the leukemia can come back. From what is known today, no specific way of decreasing the risk of recurrence* exists. As a consequence of the cancer itself and of the treatment, return to normal life may not be easy for some people. Questions related to body-image, sexuality, fatigue, work, emotions or lifestyle may be a concern to you. Discussing these questions with relatives, friends, other patients or doctors may be helpful. Support from patients organisations providing advice e.g. on managing effects of treatments, as well as psycho-oncologist services, or telephone info-lines are available in many countries.

How important is it that I take my medicine?

Only treatments that are taken can actually work. It is very important you take your medication as prescribed.

Studies have shown that patient adherence to medication varies significantly in CML patients. Especially when treated with oral drugs like in CML, it is mostly the patient's own responsibility to take the medicine as prescribed. Non-adherence - either deliberately or unintentionally - can have a significant impact on the success of therapy and the maintenance of response. CML studies have demonstrated a strong correlation between adherence levels, rates of relapse and rates of responses, as well as rate of hospitalisations. Already leaving out 1 in 10 pills has shown to have a significant impact on remission* rates.

What if the leukemia progresses or comes back?

If the leukemia progresses, such as changing from chronic* to accelerated or blastic* phase, it is called disease progression or a relapse . The treatment depends on the age of the patient, prior treatment, and possibility of a bone marrow transplant*. Specific recommendations for therapy are discussed for each phase of disease.

After obtaining a response using a second generation tyrosine kinase inhibtor*, a bone marrow transplantation is recommended in patients at accelerated or blastic phase and those with a T315I mutation*, if a sibling or unrelated donor can be identified as only a bone marrow transplant offers a chance of cure. Patients who relapse following a bone marrow transplant are usually not considered for a second transplant. Instead, donor lymphocyte infusion* with a tyrosine kinase inhibitor, or a clinical trial* are the preferred options for patients who relapse following a bone marrow transplant.

Should I consider clinical trials?

With the use of current standard therapy, including tyrosine kinase inhibitors*, the prognosis* of patients diagnosed with CML is favorable. In rare cases, the disease progresses despite the best current therapies. In such cases, the prognosis is poor and alternative therapies including clinical trials* should be considered. For this reason, doctors and scientists are exploring new therapies. Promising therapies have to be first tested in clinical trials before they are accepted and given to all patients. These clinical trials provide an opportunity to receive a new therapy before it is generally available. On the other hand, such new therapies also have some risks as the side effects are unknown. Because of these positive and negative aspects of clinical trials, it is very important that you discuss the suitability of a clinical trial with your doctor.

Where can I find a CML patient support group?

Patient advocacy groups* can help you get in touch with other patients who have CML, learn more about your disease, identify helpful information, find an experienced doctor for a second opinion, or identify clinical centers that run clinical trials*. To find a group in your country, visit the CML Advocates Network group at http://www.cmladvocates.net/members

DEFINITIONS OF DIFFICULT WORDS

Abdomen
Part of the body between the chest and hips. The muscles corresponding to this area enclose a cavity containing the stomach, intestines, liver, spleen, and pancreas. It is also known as the belly.

Anemia
Condition characterized by the shortage of *red blood cells** or hemoglobin*, the iron that contains the hemoglobin carries oxygen from the lungs to the whole body; this process is diminished in this condition.

Anesthesia
Reversible state of loss of awareness in which the patient feels no pain, has no normal reflexes, and responds less to stress, induced artificially by the employment of certain substances known as *anesthetics*. It can be complete or partial and allows patients to undergo surgical procedures, such as collecting cells from the bone marrow.

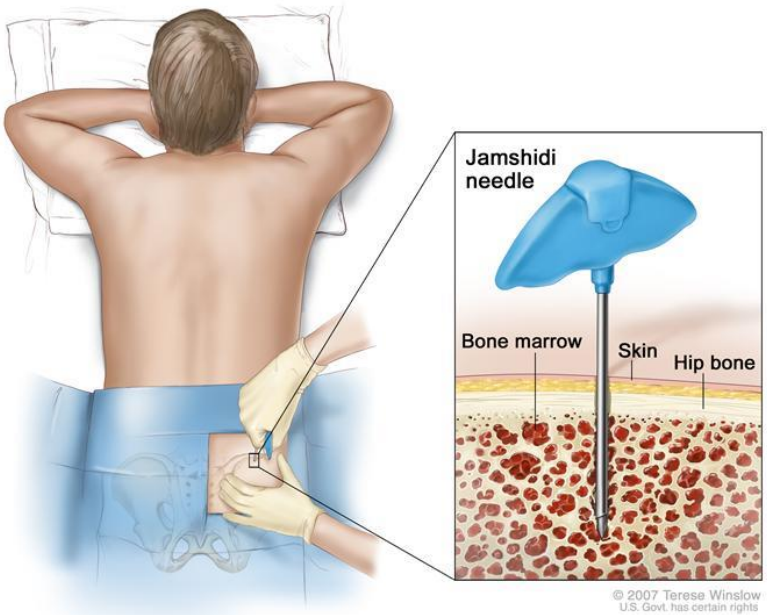
Asymptomatic
In a disease, is the absence of symptoms, such as pain, or subjective manifestations of the illness.

BCR-ABL
Translocation of the Abelson murine leukemia gene (*ABL*) on chromosomes* 9 and the breakpoint cluster region (*BCR)* on chromosome 22 resulting in the Philadelphia chromosome* (translocation of chormosomes 9 and 22, t(9;22)) can be detected in 95% of patients with CML either from cells circulating in the blood or in the bone marrow.
The Philadelphia chromosome encodes a dysregulated tyrosine kinase* (an enzyme in cells), which results in cells not dying normally, increased cell turnover and proliferation*, and abnormal cell maturation.

Benzene
A chemical that is used widely by the chemical industry, and is also found in tobacco smoke, vehicle emissions, and gasoline fumes. Exposure to benzene may increase the risk of developing leukemia.

Blast
Leukemia cells are often referred to as *blasts* as they can appear larger than normal white blood cells* found circulating in blood. The way the *blasts* look can give a pathologist* clues to help diagnose what type of leukemia a patient has.

Bone marrow biopsy
A procedure in which a small sample of bone with bone marrow inside it is removed, usually from the hip bone. A small area of skin and the surface of the bone underneath are numbed with an anesthetic*. Then a special, wide needle is pushed into the bone and rotated to remove a sample of bone with the bone marrow inside it. This procedure may be done at the same time as a bone marrow aspiration. The removed cells or tissues will be examined by a pathologist*. The pathologist may study the tissue under a microscope or perform other tests on the cells or tissue.



Bone marrow aspiration and biopsy. After a small area of skin is numbed, a Jamshidi needle (a long, hollow needle) is inserted into the patient's hip bone. Samples of blood, bone, and bone marrow are removed for examination under a microscope.

Bone marrow transplant
A procedure to replace bone marrow that has been destroyed by treatment with high doses of anticancer drugs or radiation. Transplantation may be autologous (an individual's own marrow saved before treatment), allogeneic (marrow donated by someone else), or syngeneic (marrow donated by an identical twin).

Bosutinib
A drug used to treat chronic myelogenous leukemia (CML). It is used in patients who cannot be treated with other treatment or have not gotten better afterwards. It is also being studied in the treatment of other types of cancer. Bosutinib blocks the action of BCR-ABL and other proteins, which may help keep cancer cells from growing and may kill cancer cells. It is a type of tyrosine kinase inhibitor.

Central nervous system (CNS)
The part of the nervous system that consists of the brain and the spinal cord.

Chemotherapy
A type of cancer treatment using drugs that kill cancer cells and/or limit their growth. These drugs are usually administered to the patient by slow infusion into a *vein* but can also be administered orally, by direct infusion to the limb or by infusion to the liver, according to cancer location.

Chromosome
An organized structure which encodes genes which are the body's code for characteristics such as hair color or gender. Human cells have 23 pairs of chromosomes (46 chromosomes in total). Cancer or leukemia cells often have a **chromosomal abnormality** which is a change to their chromosomes, such as a **chromosomal duplication** or an extra chromosome (47 chromosomes) or have a

chromosomal deletion or a loss of a chromosome (45 chromosomes). A **chromosomal** or **genetic inversion** is when no extra chromosomes are added or deleted, but instead a portion is backwards.

Chronic
Of long duration. When it is used to describe a disease or a condition, it means that it persists or progresses over a long period of time.

Clinical examination
The examination of the body to search for signs of disease.

Clinical response
A way of describing the response to a given treatment. It is evaluated by changes in signs and symptoms caused by the disease.

Clinical trial
A research study conducted with patients to evaluate whether a new treatment is safe (safety) and whether it works (efficacy). Clinical trials are performed to test the efficacy of drugs but also non-drug treatments such as radiotherapy or surgery and combinations of different treatments.

CT-scan
A form of radiography in which body organs are scanned with *X-rays* and the results are synthesised by a computer to generate images of parts of the body.

Curative therapy
Treatment given to a patient with the purpose of erradicating or curing the disease or injury as opossed to palliative treatment that aims to relieve the symptoms caused by them.

Cytogenetics
The study of genes and chromosomes*. Studying the changes in genes or chromosomes can determine if a cell is normal or leukemic. Some types of leukemia have common cytogenetic abnormalities (changes to genes or chromosomes) that are like a fingerprint and can tell a pathologist* which specific type of leukemia a patient has.

Cytogenetic response (CCgR)
A way of describing the response to a given treatment. For CML, it is evaluated according to the decrease of the proportion of cells that have the (abnormal) Philadelphia chromosome* in the bone marrow and blood.

Cytotoxic
Toxic to cells.

Dasatinib
Dasatinib belongs to a group of medicines called ‘protein kinase inhibitors’. These compounds act by blocking types of *enzymes* known as *protein* kinases. Dasatinib acts mainly by blocking the Bcr-Abl protein kinase. This enzyme is produced by leukaemia cells, and causes them to multiply uncontrollably. By blocking Bcr-Abl kinase, as well as other kinases, dasatinib helps to control the spread of leukaemia cells.

DNA
Abbreviation for desoxyribonucleic acid. DNA serves as the carrier of genetic information.

Drug metabolism
Process in which a drug is broken down by enzymes present in the body so it can be used by the body and expelled afterwards.

Efficacy
In medicine, the ability of an intervention, for example, a drug or surgery, to produce the desired beneficial effect.

FISH/Fluorescence in situ hybridisation
A technique used by pathologists* to identify changes to genes and chromosomes*. Unique changes to genes or chromosomes can be detected by FISH and help a pathologist to recognise what type of leukemia a patient has.

Follow-up
Monitoring a person's health over time after treatment. This includes keeping track of the health of people who participate in a *clinical study** or *clinical trial* for a period of time, both during the study and after the study ends.

Graft
Healthy skin, bone, or other tissue taken from one part of the body and used to replace diseased or injured tissue removed from another part of the body.

Granulocyte
A type of immune cell that has granules (small particles) with enzymes that are released during infections, allergic reactions, and asthma. Neutrophils, eosinophils, and basophils are granulocytes. A granulocyte is a type of white blood cell. Also called granular leukocyte, PMN, and polymorphonuclear leukocyte.

Hematocrit level
The proportion of the blood that is composed of red blood cells. It is expressed as a percentage.

Hematologic response
A way of describing the response to a given treatment. In CML, an hematologic response is complete (complete hematologic response or CHR) when it includes the normalization of blood counts, particularly white blood cells and platelets, together with the absence of blast cells or leukemia cells in the patient's blood, normalization of the spleen size and absence of signs and symptoms of CML.

Hemoglobin level
Quantitative measure of the protein called hemoglobin contained in red blood cells, it is expressed in weight (grams) by volume of blood (deciliters). Hemoglobin carries oxygen through the body.

Histocompatibility antigens
Proteins existing on the surface of nearly every cell in the body. They help our immune system to differenciate our own cells from foreign substances. They exist in large amounts on the surface of white blood cells. They are also called human leucocyte antigens (HLA).

Hydroxyurea
An anticancer drug that belongs to the family of drugs called antimetabolites.

Imatinib
Imatinib is a protein-tyrosine kinase inhibitor*. This means that it blocks some specific enzymes known as tyrosine kinases. These enzymes can be found in some receptors on the surface of cancer cells, including the receptors that are involved in stimulating the cells to divide uncontrollably. By blocking these receptors, imatinib helps to control cell division.

Immune system
The immune system is a biological system of structures and processes that protects the body from diseases by identifying and killing tumor cells and foreign invaders such as viruses and bacteria.

Interferon
A protein made by lymphocytes and involved in the communication between immune cells. A biological response modifier (a substance that can improve the body's natural response to infections and tumor cells). There are several types of interferons, including interferon-alpha, -beta, and -gamma. The body normally produces these substances. They are also made in the laboratory to treat cancer and other diseases.

Leukocyte/white blood cell
A term which is the same as a white blood cell*: cells of the *immune system* that are involved in the body's defence against infections.

Lymph node
A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Lymph nodes filter lymph and they store lymphocytes. They are located along lymphatic vessels. Also called lymph gland.

Lymphocyte infusion
Type of therapy in which lymphocytes from the blood of a donor are given to a patient who has already received a stem cell transplant from the same donor. The donor's lymphocytes may kill remaining remaining cancer cells. Lymphocyte infusion is used to treat chronic myelogenous leukemia (CML) that has come back and myeloma. It is being studied in the treatment of other types of cancer.
A lymphocyte is a type of white blood cell that is essential in the immune system. The three major types of lymphocyte are T cells, B cells and natural killer (NK) cells which all have their own roles in the immune system.

Metaphase
The phase of cell division in which the already duplicated chromosomes align along the center of the cell. Afterwards the cell will divide into two cells with the same number of chromosomes each.

Metastasise/metastasis
The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a metastatic tumor or a *metastasis*. The metastatic tumor contains cells that are like those in the original tumor.

Metamyelocyte
Type of immature white blood cell that derives from a myeloblast and that will develop into a specific category of white blood cells.

Molecular response
A way of describing the response to a given treatment. In CML, it is indicated by the negativity of a test called PCR (Polymerase chain reaction). This test is performed to confirm the absence of leukemia cells or blasts in the blood, when they are so scarce that they cannot be detected by other tests. PCR detects a substance produced by leukemia cells.

Multidisciplinary
That which covers several fields of practice or expertise. In medicine, it is defined as the combination of the knowledge and expertise of different medical and non-medical health care professionals from different disciplines.

Mutation
A change in the sequence of base pairs in the *DNA** that makes up a gene. Mutations in a gene do not necessarily change the gene.

Myeloblasts
Type of immature cell that develops in the bone marrow and will develop into a specific category of white blood cells.

Nilotinib
Nilotinib belongs to a group of medicines called protein kinase inhibitors. These compounds act by blocking types of enzymes known as protein kinases. Nilotinib acts by blocking the protein kinase called 'Bcr-Abl' kinase. This enzyme is produced by leukemia cells, and causes them to multiply uncontrollably. By blocking Bcr-Abl kinase, nilotinib helps to control the spread of leukemia cells.

Omacetaxine
Investigational anticancer drug that inhibits the formation of proteins meaning that it may slow or stop cell growth.

Pathologist
A doctor trained in diagnosing the disease based on the appearance of cells or tissues in the microscope.

Patient Advocate/ Patient advocacy group
A person who helps a patient work with others who have an effect on the patient's health, including doctors, insurance companies, employers, case managers, and lawyers. A patient advocate helps resolve issues about health care, medical bills, and job discrimination related to a patient's medical condition. Cancer advocacy groups try to raise public awareness about important cancer issues, such as the need for cancer support services, education, and research. Such groups work to bring about change that will help cancer patients and their families.

Petechiae
A small red or purple spot caused by a broken capillary blood vessel.

PCR/Polymerase Chain Reaction
A technique to determine the sequence which codes for a gene. Pathologists* use PCR to identify unique mutations* (changes to the coding sequence) which are the fingerprint for certain types of leukemia.

Pesticide
Any substance that is used to kill insects and other pests.

Philadelphia chromosome
An abnormality of chromosome 22 in which part of chromosome 9 is transferred to it. Bone marrow cells that contain the Philadelphia chromosome are often found in chronic myelogenous leukemia.

Platelet
Small cell fragments that play a fundamental role in the formation of blood clots. Patients with a low *platelet* count are at risk of severe bleeding. Patients with a high count are at risk of thrombosis, the formation of blood clots that can block blood vessels and result in stroke or other severe conditions, and can also be at risk of severe bleeding because of *platelet* dysfunction.

Ponatinib
A drug used to treat patients with CML and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL). Some forms of CML, those that have the T315I mutation, are resistant to therapies with other tyrosine kinase inhibitors such as imatinib. Ponatinib is used to treat CML with this specific mutation.

Prognosis
The likely outcome or course of a disease; the chance of recovery or *recurrence**.

Cell Proliferation
An increase in the number of cells as a result of cell growth and cell division.

Protein
Essential nutrients that are made of *amino acids*. They are essential for the functioning of many organisms including the human body. They are responsible for transport and communication between cells, for chemical changes and maintain the structure of e.g. cells.

Radiation
Can be defined as energy travelling through space. Examples of *radiation* include *UV*, and *x-rays* wich are commonly used in medicine.

Radiation therapy
A therapy in which radiation is used in the treatment of cancer always oriented to the specific area of the cancer.

Recurrence
Cancer or disease (usually auto-immune) that has come back, usually after a period of time during which the cancer or disease was not present or could not be detected. This may happen at the same location as the original (primary) tumor or at another location in the body. Also called recurrent cancer or disease.

Red blood cell
The most common type of blood cell. It is the substance that makes the blood appear red. The main function is the transport of oxygen.

Relapse
Return of the manifestations of a disease after a period of improvement. In cancer, return of the cancer after a *remission**.

Remission
A decrease in or disappearance of signs and symptoms of cancer. In partial *remission*, some, but not all, signs and symptoms of cancer have disappeared or diminished. In complete *remission*, all signs and symptoms of cancer have disappeared, although cancer still may be in the body.

Resistant (to treatment)
In medicine, describes a disease or condition that does not respond to treatment.

Risk factor
Something that increases the chance of developing a disease. Some examples of risk factors for cancer are age, a family history of certain cancers, use of tobacco products, being exposed to *radiation** or certain chemicals, infection with certain viruses or bacteria, and certain genetic changes.

(Blood) Stem cell
Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. Stem cells are distinguished from other cell types by two important characteristics. First, they are unspecialized cells capable of renewing themselves through cell division, sometimes after long periods of inactivity. Second, under certain physiological or experimental conditions, they can be induced to become tissue- or organ-specific cells with special functions. In some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues.

T-cell
A type of white blood cells (lymphocytes) that can determine whether something belongs to the body or not. They kill infected cells. They play an important role in the immune system.

Targeted therapy
A type of treatment that uses drugs or other substances, such as monoclonal antibodies, to identify and attack specific cancer cells. Targeted therapy may have fewer side effects than other types of cancer treatments.

Thrombocytopenia
The presence of abnormally few blood platelets in the blood.

Tyrosine kinase inhibitor
A drug that interferes with cell communication and growth and may prevent tumor growth. Some tyrosine kinase inhibitors are used to treat cancer.

The ESMO / Anticancer Fund Guides for Patients are designed to assist patients, their relatives and caregivers to understand the nature of different types of cancer and evaluate the best available treatment choices. The medical information described in the Guides for Patients is based on the ESMO Clinical Practice Guidelines, which are designed to guide medical oncologists in the diagnosis, follow-up and treatment in different cancer types.
These guides are produced by the Anticancer Fund in close collaboration with the ESMO Guidelines Working Group and the ESMO Cancer Patient Working Group.

For more information please visit www.esmo.org and www.anticancerfund.org

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