Manual of information for adult patients with acute lymphoblastic leukemia (ALL)

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Introduction and objective of this manual

Acute lymphoblastic leukemia (ALL) is a severe blood disease caused by uncontrolled proliferation of immature cells, known as lymphoblasts, in the bone marrow. Although the diagnosis of this disease has a great physical and emotional impact on you and those around you, you should be aware that there are currently many therapeutic tools which enable an increasingly greater percentage of patients to be controlled and even cured. The objective of this manual is NOT to substitute the work of the medical team who attends you in regard to being the only source of information of your disease, but rather it is to provide complementary information to help you understand aspects related to the diagnosis and treatment of ALL and to even facilitate communication with your physician. Please read the manual carefully. However, you should remember that the best information is provided by the members of the medical team caring for you. Do not hesitate to ask and request information about any aspect related to the diagnosis, prognosis or treatment of your disease.

What is acute lymphoblastic leukemia?

Acute leukemias are uncontrolled proliferations of malignant, immature cells (known as blasts) of the hematopoietic system. In the hematopoietic system, different types of blood cells are developing from one basic cell type (pluripotent stem cell, which is located in the bone marrow). The blood cells develop step by step, becoming more and more mature. Only at the end of their development, they are ready to play their role in immune defense. Sometimes the regularly mechanisms of this system are failing. In contrast with chronic leukemias, acute leukemias usually develop in only a few weeks and rapidly lead to the appearance of symptoms, severe in some cases, making diagnosis and rapid treatment extremely important. There are two large groups of acute leukemias: acute lymphoblastic leukemias (ALL) and acute myeloblastic leukemias (AML) and within each of these two large groups there are numerous subtypes based on the characteristics which each malignant immature cell has. In the cases of acute lymphoblastic leukemia (ALL), the immature cell which multiplies uncontrollably is the precursor of the lymphocytes (known as lymphoblasts). The lymphocytes are a type of blood cells which make up part of the immune system and are mainly localized in the bone marrow, the blood, the lymph nodes and the spleen. As a consequence of this uncontrolled multiplication of the lymphoblasts the following occurs:

An alteration in the normal process of manufacturing the remaining blood cells (platelets, red and white cells or leukocytes), which may thereafter lead to hemorrhages, anemia, and the ease of having infections of any type, respectively.

Infiltration of other organs in the body by these cells which may alter their function and increase their size, particularly of the lymph nodes, the spleen and the liver. However all other organs may be involved.

Causes of acute lymphoblastic leukemia

The uncontrolled proliferation of abnormal cells (blasts) which takes place in ALL is the result, as in other types of cancer, of alterations in the mechanisms of control and regulation of cell growth and differentiation. These mechanisms are regulated by genes (fragments of the chromosomes of the cells formed by DNA which contain the information on all the functions that each cell type carries out). The alteration in these genes leads to their transformation into malignant cells by mechanisms which we only partially understand. At present there are very specific techniques such as conventional cytogenetics, in situ hybridization or molecular biology techniques which make it possible to study the genes and chromosomes. In this way alterations which help to make the diagnosis and classify the type of ALL may be detected and treatment may be administered on the basis of these findings. The causes as to why these alterations in the genes and chromosomes of the cells are produced and lead to the appearance of the ALL are not completely understood. It is thought that both genetic and environmental factors (for example, ionizing radiation or toxic substances such as derivatives of benzol and pesticides) and even infections (as in some viruses) may play a role. Some known carcinogenic substances such as tobacco and alcohol do not increase the risk of ALL. However, in most cases it is not possible to discover the cause of the leukemia. Although some genetic abnormalities are found in leukemias, it is important to emphasize that ALL is not a hereditary disease. In addition, as ALL is not an infectious disease, there is no risk to transmit the disease.
Types of acute lymphoblastic leukemia

Many types of ALL may be differentiated based on the characteristics the lymphoblasts have on microscopic observation: the presence or absence of surface cell markers and the presence of gene and chromosome alterations. Therefore, the classification of the type of ALL requires the use of several complementary techniques including:

- **Morphology** (observation of the cells under the microscope)
- **Cytochemistry** (staining of the cells with specific stains)
- **Immunophenotyping** by flow cytometry (detection of proteins in the membrane of the lymphoblasts by antibodies)
- **Cytogenetics** or in situ hybridization (detection of specific alterations in the chromosomes of the lymphoblasts)
- **Molecular biology** (detection of alterations in the genes of the lymphoblasts)

Establishing the specific type of ALL is a fundamental step for deciding the most adequate treatment and predicting response to the treatment as well as determining the prognosis of the disease. At the end of the 1990’s, the World Health Organization (WHO) created a classification which incorporated the knowledge of flow cytometry and cytogenetics to the classical classifications determined by cell morphology (the appearance of the cells). This classification may be seen in table 1.

There is also a classification which is frequently used in practice which is based on the immunophenotype of the lymphoblasts when analyzed by flow cytometry. This technique consists in confronting the lymphoblasts with different antibodies which thereby allows us to know the presence or absence of different proteins on the surface and the interior of the cells. Table 2 shows this classification according to the immunophenotype.

Table 1: Classification of acute lymphoblastic leukemia (ALL) by the World Health Organization (WHO)

<table>
<thead>
<tr>
<th>SUBTYPES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemias</td>
<td>B-precursor leukemia</td>
</tr>
<tr>
<td></td>
<td>T-precursor leukemia</td>
</tr>
<tr>
<td></td>
<td>Burkitt cell leukemia</td>
</tr>
</tbody>
</table>

Table 2: Immunologic classification of the ALL (EGIL criteria)

<table>
<thead>
<tr>
<th>TYPE AND SUBTYPE</th>
<th>FREQUENCY Children/Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B cells ALL</strong></td>
<td></td>
</tr>
<tr>
<td>Pro-B or pre-pre-B</td>
<td>5 % / 20 %</td>
</tr>
<tr>
<td>Common</td>
<td>60 % / 40 %</td>
</tr>
<tr>
<td>Pre-B</td>
<td>15 % / 10 %</td>
</tr>
<tr>
<td>Mature B</td>
<td>2-3 % / 5 %</td>
</tr>
<tr>
<td><strong>T cell ALL</strong></td>
<td></td>
</tr>
<tr>
<td>Pro-T</td>
<td>15 % / 25 %</td>
</tr>
<tr>
<td>Pre-T</td>
<td></td>
</tr>
<tr>
<td>Cortical thymic</td>
<td></td>
</tr>
<tr>
<td>Mature thymic</td>
<td></td>
</tr>
</tbody>
</table>

**ALL**: acute lymphoblastic leukemias

**EGIL**: European Group for Immunologic Classification of Leukemias

By using these methods, the disease ALL can be divided in two main groups and two further groups of smaller size:

- **B-Cell ALL (B-ALL)**: As you will see (Table 2), there is a large group of ALL, the B-cell ALL (characterized by the presence of characteristic markers of normal B lymphocytes on the surface of the cells) which make up 75 % of the total number of ALL cases.
- **T-Cell ALL (T-ALL)**: The other large group of ALL is the T-cell ALL (characterized by the presence of characteristic markers of T lymphocytes on the surface of the cells) which make up 25 % of the cases of ALL.
There are two special types of ALL which are clearly differentiated from the remaining types by their characteristics. As you will see later, the treatment of these forms of ALL is very different from the remaining subtypes of ALL:

**The ALL with Philadelphia chromosome (Ph' ALL)** corresponds to a type of ALL in which there is an interchange of genes between chromosomes 9 and 22 (two genes denominated BCR and ABL). This alteration leads to the production of abnormal proteins which are involved in the development of this type of leukemia. The Ph'ALL is more frequent in older adults (although it may occur at any age). The response to conventional chemotherapy is not good, but in recent years specific drugs, which inhibit the formation of the anomalous protein, have been developed which has improved the results of treatment and the prognosis of the this type of ALL. The Ph' ALL sometimes constitutes the final phase of a disease known as chronic myeloid leukemia in which this chromosomal alteration is also detected.

**Burkitt's ALL** corresponds to a type of ALL in which there is an alteration between chromosomes 8 and 14. This subtype of ALL which is also named mature B-ALL represents less than 5 % of the ALL cases. It also requires different treatment from the remaining ALL but, contrary to the previous case, the response to chemotherapy is, generally, good.

### Symptoms of acute lymphoblastic leukemia

The symptoms and signs of ALL are derived from the infiltration of the bone marrow and other tissues and organs as a consequence of the uncontrolled multiplication of the lymphoblasts (leukemic cells). On occasions, however, leukemia may be detected by accident when having analysis for any other reason but its presentation is normally accompanied by other symptoms, with the following being of note:

#### Constitutional symptoms

These are symptoms derived from an alteration of the general status perceived as a sensation of not feeling well and generally include:

- **Tiredness** (which, in medical terms, is called asthenia) produced by the anemia due to the decrease in the production of red blood cells by the bone marrow.
- **Loss or a decrease in appetite** (called anorexia)
- **Loss of weight**
- **Fever**, which may be observed in half of the patients and may be due to both leukemia itself as well as the presence of a simultaneous infection (due to a decline in the production of white blood cells or leukocytes by the bone marrow).
- **Osteoarticular pain**: observed in one third of the patients (particularly in children).

#### Symptoms derived from the infiltration of blasts in the bone marrow

- **Hemorrhages**: These are due to the decrease in the production of platelets (the elements in the blood responsible for blood coagulation) by the bone marrow. These hemorrhages are normally mild and usually affect the skin and the mucosa (for example, in the mouth where small vesicles with blood are formed, in the mucosa of the nose, the bladder or the rectum, among other areas).
- **Infections**: These usually appear because of the decrease in the production of leukocytes with normal function. Infections may appear in any organ or system (for example, in the lungs which may cause pneumonia, in the urinary tract and other zones) and are manifested by fever, among other symptoms.
- **Anemia**: Due, as stated previously, to the decrease in the production of red blood cells thereby producing tiredness, paleness and weakness.

#### Symptoms derived from tissue and organ infiltration

- **Enlarging of the lymph nodes**, spleen and liver: due to the infiltration of blasts into these organs.
- **Infiltration of the nervous system**: although infrequent, lymphoblasts may sometimes reach the brain and spine or the meninges (the membranes covering the brain and the spine). When this occurs the patients may notice:
  + Paralysis of the cranial nerves (the nerves which control the movements of the eyes and the face muscles, among other things): which may lead to double vision, eyelid drooping, deviation of the corner of the mouth and other symptoms.
+ Alterations in the perception of sensitivity (numbness of the chin or other areas of the body).
+ Headache (cephalea) with or without vomiting.

Infiltration of other tissues (skin, mucosa, testicles or breasts): these are not frequent at the time of ALL diagnosis, although they may be observed in cases of relapse of leukemia.

Other symptoms

Some types of ALL produce special symptoms. For example, ALL which originates in the T lymphocyte precursors (T-ALL) more often affect males than females and in more than one half of the cases a tumor in the mediastinum (the space of the thorax between the lungs) is found. On the other hand, mature B-ALL or Burkitt’s leukemia may be accompanied by a large tumor in the abdomen in addition to tan increase in the size of the liver and the spleen.

Diagnosis of acute lymphoblastic leukemia

As in most diseases, the diagnosis is first carried out by interrogating the patient and performing a physical examination in search of the symptoms and signs described above.

To confirm the definitive diagnosis of ALL it is necessary to do only a few tests. Although these tests are practically without risk, they may or may not be a little bothersome. These tests consist in a blood analysis, bone marrow aspirate (also called myelogram) and a lumbar puncture.

The blood analysis usually shows:

- Anemia (reduction in red blood cells and hemoglobin count)
- Thrombocytopenia (reduction in the number of platelets)
- Leukocytosis (rise in the number of leukocytes) and less frequently leukopenia (reduction in the number of leukocytes).

The bone marrow aspirate or myelogram consists in doing a puncture of the bone, generally in the sternum or the posterior iliac crest, with local anesthesia, and thereafter extracting a few milliliters of blood from the medulla of the bone. By microscopic examination of the medullar blood the doctors will try to identify the lymphoblasts which usually make up more than 20% of all the cells of the bone marrow. In addition to identifying the lymphoblasts by morphology (by microscopy), other complementary techniques described above (cytochemistry, flow cytometry, cytogenetics and molecular biology) should be undertaken. In this way physicians are able to determine the type of ALL and establish the most adequate treatment.

Lumbar puncture: This is a puncture performed in the area of the back, at the height of the last lumbar vertebrae which may be carried out with the patient being seated or laying on his/her side. The technique is similar to that used to give epidural anesthesia. A needle is introduced into the space located between two vertebrae and a few milliliters of cerebrospinal fluid (the fluid which surrounds the brain and spine) are withdrawn. This fluid is always examined when making the diagnosis of ALL to see whether it contains lymphoblasts. If so, chemotherapy may be directly administered into the nervous system to destroy these lymphoblasts (made by several of these punctures). If the fluid is normal, preventive chemotherapy is also administered into the nervous system, although less often. The secondary effects of this procedure include headache which may last a few days later but is easily controlled with analgesics.

Treatment of acute lymphoblastic leukemia

What does the treatment consist in?

The treatment of ALL is based on the administration of chemotherapy, that is, drugs which have the capacity of destroying the tumor cells (the lymphoblasts). Nonetheless, the treatment to be administered will depend on the specific type of ALL in addition to other important factors such as the age of the patient or the simultaneous presence of other diseases (for example, cardiac or pulmonary diseases). Moreover, together with chemotherapy, other aspects are important such as the need for blood or platelet transfusions or the administration of antibiotics or other drugs needed to control the complications and the secondary effects derived from chemotherapy. It may be a normal practice in some countries to request written authorization from the patient to administer the treatment or to do tests and explorations such as the placement of a venous catheter or to perform a biopsy.
In general, the treatment requires the placement of a central venous catheter (a tube of flexible material inserted into one of the large veins, generally the jugular or the subclavian vein) through which all the treatments may be administered and the blood analysis may be extracted when necessary, thereby avoiding the bother derived from the multiple venous punctures.

In general lines, the treatment has several phases in all the types of ALL. The first phase is known as induction treatment, the second is intensified treatment (also known as consolidation) and the third phase is maintenance treatment. In some types of ALL there is a high risk of relapse and after the consolidation phase it may be necessary to perform a transplantation of hematopoietic progenitors (also known as hematopoietic stem cell transplantation, HSCT). The global duration of all the treatment (including all the phases) is lengthy and may last up to 2 years. Some of the phases are administered under hospital admission with rest periods of 1 to 3 weeks between each cycle. During these rest periods the patient may remain at home. It is very important to follow strictly the treatment plan, and not prolong breaks between cycles. The maintenance phase is usually done completely on an outpatient basis. Table 3 shows the main drugs used in the chemotherapy usually given for the treatment of ALL. Likewise, table 4 shows a list of drugs for the treatments of ALL which are still under study.

Below you will find a brief description of each of the phases of treatment:

### Table 3: Chemotherapy drugs used in the treatment of ALL

<table>
<thead>
<tr>
<th>Chemotherapy drugs</th>
<th>Other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>L-asparaginase</td>
</tr>
<tr>
<td>Cytarabine or ara-C</td>
<td>6-mercaptopurine</td>
</tr>
<tr>
<td>2-Chlorodesoxiadenosine</td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Teniposide</td>
</tr>
<tr>
<td>Etoposide</td>
<td>6-thioguanine</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>Vindesine</td>
</tr>
<tr>
<td>Iphosphamide</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Other drugs under study for the treatment of acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
</tr>
<tr>
<td>Aminopterine</td>
</tr>
<tr>
<td>AMN107</td>
</tr>
<tr>
<td>BMS 354825 (dasatinib)</td>
</tr>
<tr>
<td>Clofarabine</td>
</tr>
<tr>
<td>Liposomal daunorubicin</td>
</tr>
<tr>
<td>Liposomal vincristine</td>
</tr>
<tr>
<td>Forodesine</td>
</tr>
<tr>
<td>Imatinib</td>
</tr>
<tr>
<td>Nilotinib</td>
</tr>
<tr>
<td>Dasatinib</td>
</tr>
<tr>
<td>Nelarabine</td>
</tr>
<tr>
<td>PEG-Asparaginase</td>
</tr>
<tr>
<td>Rituximab</td>
</tr>
<tr>
<td>Trimetrexate</td>
</tr>
</tbody>
</table>

**Induction to remission:** Several chemotherapy drugs are administered over a period of 4 – 5 weeks. Aplasia is generally produced during the chemotherapy, that is, a lack of production of leukocytes, platelets and red cells because the chemotherapy does not act only on the lymphoblasts but rather also decreases normal cells in the bone marrow. The objective of induction treatment is to reduce the number of lymphoblasts in the bone marrow to less than 5 %, which is known in medical terms as “complete remission”. To do this, once the induction period is finished, when the blood analysis shows that the leukocytes, platelets and red blood cells begin to increase, another bone marrow aspirate is taken to determine the number of lymphoblasts left. If the reduction does not reach the percentage above, the administration of chemotherapy may be prolonged a little longer until remission is achieved. A bone marrow aspirate is also usually performed in the middle of the induction phase to follow the response to
treatment in case it is necessary to increase the dose of chemotherapy in order to achieve greater efficacy.

**Intensification/consolidation:** This consists in the administration of several short cycles of chemotherapy (of one week approximately, separated by 2 to 3 weeks) involving drugs at high doses. In many cases different drugs from those administered in the induction phase are given with the aim of ensuring the remission obtained, eliminating residual leukemic cells.

**Maintenance treatment:** This is administered over a prolonged period of time (between 18 – 24 months). It involves a combination of oral drugs every day (generally mercaptopurine) and once a week (methotrexate). In some types of ALL short cycles of reinforcement chemotherapy may be interspersed during the maintenance phase.

**Prophylaxis** in the central nervous system: As of the possibility of the lymphoblasts arriving to the nervous system, it is necessary to administer small doses of chemotherapy directly to the nervous system by lumbar punctures (known as intrathecal chemotherapy). Several punctures are normally made throughout the treatment period. When injecting the chemotherapy a few milliliters of cerebrospinal fluid are taken to observe whether there are lymphoblasts. In some hospitals, cranial radiotherapy are also given together with the intrathecal chemotherapy as a method of preventing the involvement of the nervous system by the leukemia.

**Hematopoietic stem cell transplantation (HSCT):** This procedure is only used in some types of ALL with a high risk of relapse and is usually performed after the consolidation phase. It lasts approximately 4-6 weeks and is done under hospital admission. The greatest possibilities of success are produced when therapy is able to eliminate most of the malignant cells (that is, when the patient has achieved complete remission) prior to undertaking the transplantation. The HSCT consists in the administration of a chemotherapy treatment, generally also associated with radiotherapy, followed by the administration of hematopoietic progenitor cells. Chemotherapy and radiotherapy attempt to completely eliminate the malignant cells (lymphoblasts). However, this treatment not only eliminates the abnormal cells but also the normal cells (healthy) of the bone marrow. Therefore, hematopoietic progenitor cells are administered to counteract the toxic effects of the chemo and radiotherapy on the bone marrow and allow its regeneration. The HSCT may be autologous (if the hematopoietic progenitor cells are from the patients themselves) or allogeneic (if the hematopoietic progenitor cells are from a donor, generally a compatible relative or a compatible voluntary anonymous donor from the donor registry, or units of umbilical cord blood). Allogeneic transplantation is associated with greater complications than the autologous procedure, although, in contrast, it may provide greater probabilities of cure of the disease. The type of transplantation to be performed in each patient (autologous or allogeneic) is decided by the medical team based on some characteristics such as the type of disease, age, the general status of the patient and the availability of a compatible donor. Therefore, if the type of ALL carries a high risk of relapse, the compatibility of the patient with his/her brothers and sisters may be determined early after the induction phase by analysis of HLA molecules (made by a simple blood analysis). If no relative is compatible, a voluntary donor is looked for through the world registries of bone marrow donors or compatible units may be obtained in the umbilical cord blood banks. For obtaining the hematopoietic progenitor cells, there are currently three fundamental methods: progenitors from peripheral blood, from bone marrow, and those from umbilical cord blood. The choice of the method depends on centre experience and donor preference. Today the most frequently used are those from the peripheral blood since they are the easiest to obtain (do not require hospital admission) in addition to other advantages with respect to the other progenitors (bone marrow and cord blood). To obtain the progenitors from the blood the patient (or donor if it is an allogeneic transplantation) is connected to a automatic cell separation machine which separates the stem cells (progenitors) from the remaining cells in a process known as apheresis. The necessary cells are usually collected within a few hours and they are usually frozen until the time of transplantation and the donor/patient may afterwards return home.

**Clinical trials:** Under certain circumstances the medical team may ask you to participate in a clinical trial aimed to improve the treatment results, and therefore to sign a written authorization.

As already mentioned, in addition to chemotherapy treatment, other complementary or support treatments are important because they help to control the secondary effects and complications. These complementary treatments include the following:

- Transfusions of red blood cell concentrates to treat anemia.
- Transfusions of platelets to control bleeding or to avoid this happening (for example when the platelet count is very low as a consequence of the chemotherapy).
- Antibiotics and antifungal drugs: these drugs are used to fight against the infections produced by bacteria and fungi, respectively.
- Colony growth factors (G-CSF): these are substances which are subcutaneously injected after finishing chemotherapy to stimulate the production of leukocytes and avoid, as far as possible, the risk of infection.

- **Steering Committee:** Rüdiger Hehlmann (Coordinator), Ute Berger (Scientific Network Manager), Marie C. Béné, Alan Burnett, Guido Finazzi, Christa Fonatsch, Eliane Gluckman, Nicola Gökbuget, David Grimwade, Torsten Haferlach, Michael Hallek, Jörg Hasford, Dieter Hoezler, Per Ljungmann, Thomas Müller, Dietger Niederwieser, Steven O’Brien, Hubert Serve, Bengt Simonsson, Theo J. M. de Witte
Hydration: large quantities of liquids are administered to the patient to protect the kidney and avoid the possibility of this or other organs being damaged by the chemotherapy treatment and by the release of toxic products produced after the destruction of the malignant cells.

Mouth washes: during the administration of chemotherapy, especially during the period of aplasia, tooth brushing is not recommended since it may favor bleeding of the gums and the passage of germs in the mouth to the blood with the consequent risk of infection. Mouth washes with different types of antiseptic products are therefore recommended.

What complications and secondary effects does the treatment have?

Most of the complications are due to the administration of chemotherapy which, in addition to provoking the destruction of abnormal cells (lymphoblasts), affects the production of the remaining blood cells and other tissues and organs. Most of these complications are reversible and may be successfully treated. The following are some of these complications:

- **Nausea and vomiting:** These are directly provoked by the chemotherapy but, fortunately, today there are drugs which largely control these symptoms.
- **Anemia:** This is caused by the deficit of red blood cells and produces weakness and fatigue. Each patient tolerates this differently but transfusions of packed red blood cells will probably be required on several occasions.
- **Bleeding:** The decrease in the production of platelets increases the risk of bleeding. The blood analysis carried out throughout the treatment period will determine the number of platelets and platelet concentrates will be transfused if the numbers are low.
- **Infections:** The decrease in the number of white blood cells increases the risk of infections of any type and localization. Infection is manifested by fever, among other symptoms. Therefore, if the patient presents fever during the treatment blood and urine or other types of cultures will be obtained, together with a chest X-ray on many occasions, and antibiotic treatment will be immediately started.
- **Mucositis:** Small ulcers may develop in the mouth and the intestine (known as mucositis) and cause pain when eating food and diarrhea, respectively. These ulcers are also due to the reduction in the number of leukocytes (white blood cells) and the effects of chemotherapy.
- **Alopecia:** The administration of chemotherapy is the cause of alopecia (hair loss) which is transitory and hair is recovered within a few months after finishing the treatment.
- **Permanent sterility:** Chemotherapy does not normally produce permanent sterility, although it is practically inevitable in the case of patients who later receive hematopoietic progenitors. Therefore, to preserve fertility, semen may be cryopreserved for men or ovarian tissue or fertilized eggs may be frozen for women.
- **Alterations of other organs:** In some cases chemotherapy may affect the function of different organs and systems, such as the heart, the liver or the peripheral nerves which may compromise the continuation of chemotherapy treatment or may require a modification in the dose or the elimination of the drug causing the toxicity.
- **Emotional problems:** These are derived from the impact of the diagnosis and the treatment of this severe disease in both the patient and the relatives and social environment. Many hospitals have specialists in psychology and psychiatry who may provide advice and help the patient and relatives confront the disease better.
- **Fatigue:** After therapy, some patients report on extreme tiredness and inability to function due lack of energy. This symptom, called “fatigue” may be acute or chronic. The causes of fatigue are not definitely known, but there are many chemical, physical, and behavioral factors that are thought to cause it.

With regard to work, the patient normally remains off work during the treatment, but may return to work on finishing treatment based on his/her general status and the activity the work involves.

What results does treatment provide?

In some cases, a relapse of leukemia may be possible on completion of the treatment. However, the longer the time after the termination of treatment, the lower the possibility this will occur. This is why periodic controls are carried out during several years. In the case of relapse, the medical team will indicate the available therapeutic options. Despite all the complications, an ever increasing number of patients are disease free in the long-term and only require periodic controls throughout their lifetime. In children the global rate of cure from ALL is around 70 %, while being 35 % to 40 % in adults. In any case, these results depend on the subtype of ALL, as well as the
presence of determined prognostic factors such as age, the existence of particular chromosomal alterations, the speed of treatment response, and the degree of elimination of the occult disease (also known as residual disease).

Treatment of two special forms of acute lymphoblastic leukemia

**Acute lymphoblastic leukemia with Philadelphia chromosome and acute Burkitt’s lymphoblastic leukemia**

**In ALL with Philadelphia chromosome (ALL Ph’+)** the recent appearance of drugs specifically aimed to block the particular enzyme responsible for this type of leukemia has changed its prognosis. These drugs (for example, imatinib mesylate) are administered in combination with conventional chemotherapy. Since they are new drugs, the long-term results are still not precisely known (although they appear to be clearly better than those of conventional therapy alone) and they have, up to now, only been administered in clinical trials. Therefore, since, in many cases, they are not officially approved by healthcare institutions, you will probably have to sign an informed consent form (written authorization) to receive the drugs. Moreover, in this type of ALL allogeneic HSCT is indicated when remission is achieved, since the risk of relapse with chemotherapy alone is high.

**Burkitt’s ALL** also requires a different treatment from that of other types of ALL and includes cycles with high doses of chemotherapy (especially with methotrexate and cytarabine, in addition to other drugs) achieving long lasting remissions in more than 50% of adults. These results may improve with the addition of monoclonal antibodies such as rituximab to each cycle of chemotherapy. Therefore, in this type of ALL HSCT is not generally indicated when remission is achieved. Transplantation is reserved for patients who present relapse of leukemia or who do not satisfactorily respond to treatment at the beginning.

Treatment of relapse

Relapse of leukemia indicates that the treatment administered did not completely eliminate the leukemic cells. The manifestations of relapse may be similar to those at the initiation of ALL or may occur with different symptoms (for example, relapse only in the nervous system). Bone marrow aspiration tests are necessary to determine if there is isolated relapse in the bone marrow or there are other sites of relapse. Whatever the localization of the relapse, chemotherapy will most likely have to be given again. In addition to some aspects such as the time which has passed since finalizing the previous treatment until the relapse (the prognosis is generally better with a late relapse, that is, years after having finished the treatment, than an early relapse of only a few week or months after), the localization, previous treatment administered, and the general status of the patient should be taken into account. A relapse means that the leukemia has a high risk of presenting successive relapses in the future. Therefore if necessary, and if the patient can tolerate it, more vigorous chemotherapy treatments and probably an allogeneic transplantation (if there is a compatible donor) are performed. It is also important to think about treatment with new drugs under evaluation in clinical trials.

Controls after treatment, long-term effects of acute lymphoblastic leukemia and quality of life

The controls that are made after finishing the treatment will normally be undertaken on an outpatient basis. The periodicity and the type of controls vary based on the patient, the complications and the secondary effects presented, as well as the type of treatment administered (transplant, chemotherapy alone, etc.). A physical examination, blood analysis and a revision of the treatment, if necessary, will be made on each appointment. On occasions, other explorations will be requested such as bone marrow aspiration. The quality of life of the patient may be more or less affected depending on the treatment and the complications presented.

In patients who undergo a hematopoietic stem cell transplantation, if there are no serious complications, the patients may return to their normal life after a period ranging from 6 to 12 months. The most frequent problems noted by the long-term survivors are emotional, followed by fatigue, eye problems, sleep disorders and difficulties in concentration and the memory. In addition to these problems, the following are also relatively frequent:

**Persistence in a loss of appetite**, due to an alteration in saliva secretion and the senses of taste and smell or the taking of some drugs such as cyclosporine A (a type of medication used to prevent and treat “graft versus host disease”, which is a frequent complication of allogeneic transplantation in which the

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progenitor cells transplanted react against the donor cells and lesions are produced in different organs and tissues).

**Cataracts** are a relatively frequent problem and generally appear 5 years after the transplantation or later, especially if total body radiation has been administered during the conditioning or if prednisone has been given over a long period of time.

**Hormone disorders**, especially hypothyroidism (decrease in the function of the thyroid gland which may require substitutive treatment with medication) and early menopause (which may be solved by the administration of substitutive hormone treatment which, although does not restore fertility, prevents the development of the symptoms of menopause such as flushes, dry skin and mucosas, and a decrease in sexual desire).

**Sterility** is practically inevitable after transplantation. This is why the fertility preservation techniques mentioned before are undertaken.

In exceptional cases, a second neoplasm or cancer may appear which, in general, does not usually appear until several years after transplantation.

The possibility of a relapse of leukemia which is less probable with the passing of time after the transplantation. In the case of relapse, the medical team will indicate the therapeutic options available.

In the patients who only receive chemotherapy the long-term complications are less frequent and recovery is more rapid because of the lower intensity of treatment received and these patients are able to return to normal activity within a shorter period of time. In addition to the already mentioned emotional problems and fatigue or disorders in sleep, concentration and memory, we should add a greater incidence of cataracts (because of the prolonged administration of corticoids) or the always present possibility of relapse of leukemia (also lower the longer the time that has passed since the completion of treatment). To the contrary, sterility and other hormonal problems are generally transitory. Some patients may develop osteonecrosis (loss of intact and healthy bone tissue in articulating joints) of the hip, shoulder, or other articulated joints.

**Coping with acute lymphoblastic leukemia**

Receiving the diagnosis of ALL is mostly a shock. It often causes severe emotional distress and it is quite possible, that you will feel helpless and desperated. Maybe you ask yourself “Why does this happen to me?”

The following suggestions may help you to be able to adjust to the diagnosis:

- **Try to get information** (just like you do now).
- **Talk to someone**: It can be very much helpful to share your fears and problems. You should talk to some particular persons. This can be one (or more) member(s) of your family, relatives and/or friends. If you decide not to do so, you may can get emotional support from self-help groups.
- **Share your thoughts and fears** with the medical team caring you and never do hesitate to ask any question.
- **Listen and follow the recommendations of your physician**.
- **Always take care of yourself**. Try to eat the right food to get strength, get your rest and stay away from people having a cold or flu.

After your treatment: Watch yourself carefully and **do not hesitate to contact your physician** if any of the named symptoms appear. For example, if you develop fever you should go and visit your doctor. He will check the underlying causes and this clearly can also be a regular infection.

**Glossary**

- **Alopecia**: is one of the secondary effects of the administration of chemotherapy which consists in the transitory and reversible loss of hair.
- **Anorexia**: loss of appetite
- **Apheresis**: process of collection of hematopoietic progenitors from peripheral blood by a cell separator. This is the most commonly used method at present to obtain “stem cells” before performing hematopoietic progenitor transplantation.
- **Bone marrow**: tissue that fills the space or the cavity located in the interior of the bones and constitutes the site where the different types of blood cells (leukocytes, platelets, and red blood cells) in addition to other types of cells are produced.
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- **Bone marrow aspirate or myelogram**: bone puncture generally performed in the sternum or the posterior iliac crest with local anesthetics after which a few milliliters of medullar blood is withdrawn.

- **Bone marrow biopsy**: similar exploration as the above in that a small fragment of bone tissue is extracted, generally from the posterior iliac crest.

- **Central venous catheter**: tube of flexible material with two or three entry ports or lumens which is inserted into a thick vein (generally the jugular or subclavian vein) for the administration of chemotherapy, transfusions, antibiotics and other types of medication which may be needed during treatment.

- **Clinical trial**: study to determine the superior efficacy of new treatments in comparison with known treatments. To be able to participate in a clinical trial and receive these new treatments it is obligatory to sign an authorization known as informed consent.

- **Cyclosporin A**: this is a type of medication that is administered to patients who have undergone allogenic hematopoietic progenitor transplantation with the aim of avoiding the so-called graft versus host disease.

- **Ecchymosis**: small, superficial hemorrhage of the skin

- **Echocardiogram**: this is an echography which allows the visualization of the cardiac chambers and the functioning of its walls and valves. This test is normally carried out before initiating chemotherapy treatment. In some cases it may be substituted by an isotopic ventriculography which also measures heart function although by a different method.

- **Flow cytometry**: laboratory technique used to know the immunophenotype of the leukemic cells.

- **Hematopoietic progenitors**: commonly known as “stem cells”. They are the cells responsible for the production of all the types of cells in the blood and the immune system.

- **Hematopoietic stem cell transplantation**: consists in the administration of a chemotherapy treatment, often associated with radiotherapy, followed by the administration of hematopoietic progenitor cells (cells responsible for the production of blood cells, commonly known as “stem cells”). Chemotherapy and radiotherapy reduce/eliminate the tumor or the number of malignant cells. However, this treatment not only eliminates abnormal cells but also normal (healthy) cells of the bone marrow. That is why, the hematopoietic progenitor cells are then administered with the aim of counteracting the toxic effects of chemotherapy and radiotherapy on the bone marrow and allow regeneration. Hematopoietic progenitor transplantation is therefore not a classical surgical intervention.

- **HLA**: molecules located on the surface of the cells which define the compatibility between individuals when performing hematopoietic progenitor transplantation.

- **Immunophenotyping**: technique for the study of cells based on confronting antibodies directed against proteins present on the surface or in the interior of the cell.

- **Informed consent**: authorization requested from the patient (generally written) for the administration of some treatments.

- **Intrathecal chemotherapy**: chemotherapy administered directly into the nervous system by lumbar puncture or with a small device connected directly to the nervous system (Ommaya reservoir).

- **Isotopic ventriculography**: exploration in which a substance (isotope) is intravenously administered and which allows the evaluation of the function and contraction capacity of the heart. This test is normally performed before initiating chemotherapy treatment. In some cases this procedure may be substituted by an echocardiogram which also measures heart function although by a different method.

- **Karyotype**: analysis of the chromosomes of the leukemic cells

- **Lumbar puncture**: puncture between two vertebrae at the height of the last lumbar vertebrae which may be performed with the patient seated or laying on his/her side for the administration of intrathecal chemotherapy.

- **Lymphoblast**: malignant leukemic cell, precursor of the lymphocytes which multiples uncontrollably in acute lymphoblastic leukemia.
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- **Mucositis**: clinical picture consisting in the appearance of small ulcers in the mouth and the intestine due to the decrease in the number of leukocytes (white cells) and the effects of chemotherapy treatment and which are manifested with pain when eating and diarrhea.

- **Parenteral nutrition**: intravenous alimentation administered to some patients in whom normal alimentation is impeded.

- **Petechias**: hemorrhagic spots on the skin. They generally indicate that the platelet count is very low and platelet transfusion may be necessary.

- **Prednisone**: is a type of corticoid drug administered to patients as part of the treatment for acute lymphoblastic leukemia (particularly during the induction phase).

- **Residual disease**: quantity of malignant cells remaining after the administration of a treatment. To determine this, very different specific laboratory techniques may be used.

### Sources of information

Below you will find some addresses of interest from which more information may be obtained:

**European LeukemiaNet**
http://www.leukemia-net.org

**Website of information for the patient from the National Cancer Institute**
http://www.nic.nig.gov/cancertopics/types/leukemia
http://www.cancer.gov/cancertopics/coping (Coping with cancer)

**European Blood and Marrow Transplantation**
http://www.ebmt.org

**Spanish Association of Hematology and Hemotherapy**
http://www.aehh.org

**Leukemia & Lymphoma Society**
http://www.leukemia-lymphoma.org

**Massachussets General Hospital Cancer Center**
http://www.massgeneral.org/cancer

**Deutsche Leukämie- und Lymphomhilfe e. V**
http://www.leukaemie-hilfe.de

**Polish Adult Leukemia Group:**
http://www.polg.pl

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