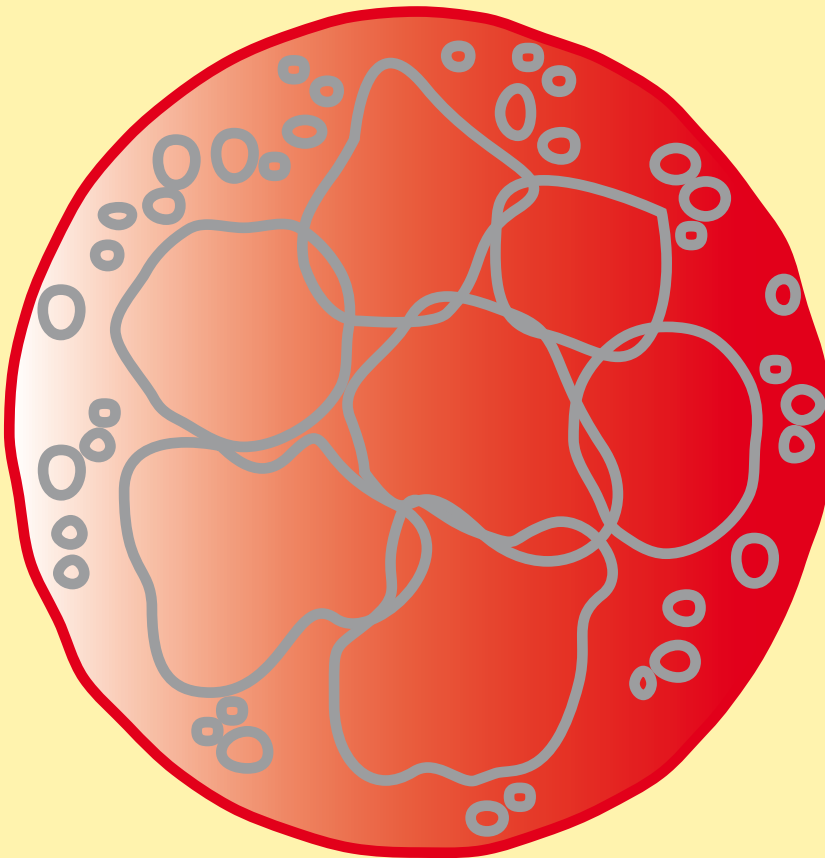


Bone Marrow and Stem Cell Transplantation (BMT) — for children and adults



The diagnosis of a blood cancer can be a devastating event for patients, families and friends. It is therefore vital for everyone to have access to reputable and understandable information to help cope with the illness. Whenever possible our booklets are written in line with national guidelines for the treatment of patients with a blood cancer. The information in our booklets is more detailed than in many others but is written in a clear style with all scientific terms explained for the general reader.

We recognise that the amount and level of information needed is a personal decision and can change over time. Particularly at the time of diagnosis, patients may prefer less detailed information. A number of alternative sources of information are available which complement our publications.

The booklets in this series are intended to provide general information about the topics they describe. In many cases the treatment of individual patients will differ from that described in the booklets.

At all times patients should rely on the advice of their specialist who is the only person with full information about their diagnosis and medical history.

For further advice contact the clinical information team on 020 7269 9060.

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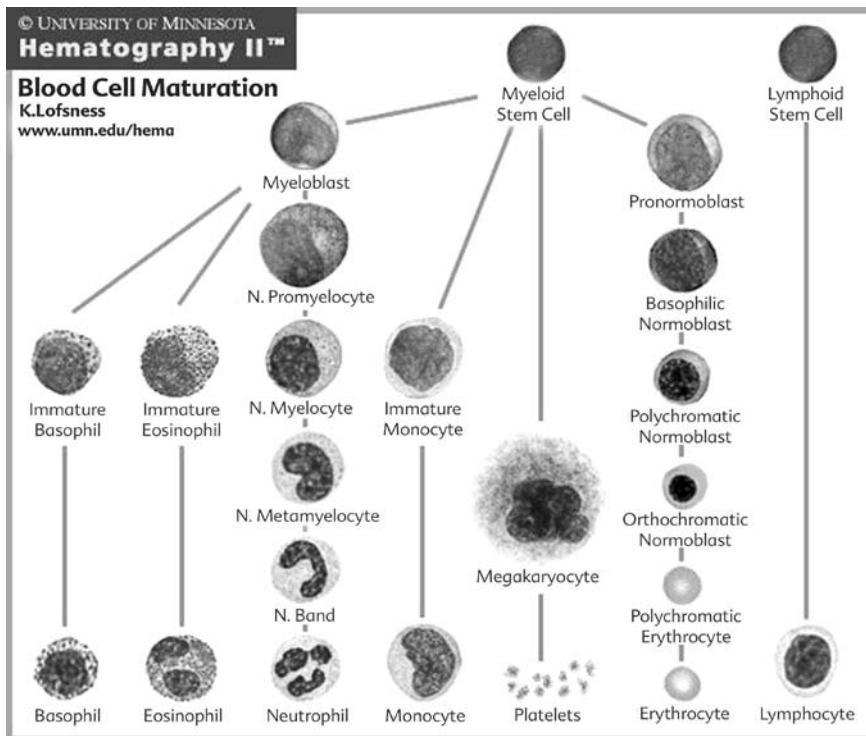
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Bone marrow and stem cell transplants

Bone marrow and blood cells



Origin of the different types of blood cells from bone marrow stem cells.

Bone marrow is a spongy tissue found within bones. All blood cells are produced within the bone marrow. To sustain the necessary levels of blood cells the bone marrow of an adult must produce about three million red blood cells and 120,000 white blood cells every second.

All these cells originate from a small population of stem cells. Less than one in 5,000 of the marrow cells is a stem cell. As well as producing mature blood cells stem cells have the remarkable ability to reproduce themselves. This maintains the pool of blood forming stem cells throughout life.

Production of blood cells

Normal bone marrow produces three types of blood cells: red and white cells, and platelets. Red blood cells contain a protein, called haemoglobin, which carries oxygen to the body tissues. A lack of haemoglobin is called anaemia and causes fatigue after gentle exercise, general weakness or tiredness and shortness of breath. Red blood cells survive for about four months (from the time they are produced in the bone marrow).

Platelets circulate in the blood and are important following an injury, because they are involved in forming blood clots to prevent continued bleeding. A shortage of platelets can cause bruising and bleeding from minor wounds and from the gut, mouth and other sites. Platelets usually live for about eight days (in the blood circulation).

There are several different types of white blood cell, which co-operate to protect the body against infection with bacteria, viruses, fungi and parasites. One of the most important types of white blood cell, responsible for general defence against infection, is the neutrophil.

Lymphocytes are another specific type of white blood cell. They are responsible for the production of antibodies and have other important functions within the immune system. Some specialised lymphocytes may live for many years, unlike other white blood cells, which live only for hours or days.

Lymphocytes are able to recognise cells foreign to the body and trigger a response by the immune system to eliminate them. This process may also

be triggered by a stem cell transplant and without careful matching may lead to serious complications. Both the production of blood cells and maintenance of the correct numbers are controlled by chemicals called growth factors.

Several types of growth factors have now been produced in the laboratory and can be used in the treatment of blood disorders and to assist in collection of stem cells for transplantation.

The bone marrow cannot carry out its normal function if it is affected by cancers of the blood (e.g. leukaemias or myeloma), or invasion by cancerous cells from tumours elsewhere in the body.

Radiation therapy and most drugs used to treat cancer will also damage the marrow because of the enormous rate of blood cell production. If the marrow is irreversibly damaged by disease or treatment the only curative option is a stem cell transplant.

Stem cell transplants and the immune system

The immune system has evolved to protect the body against foreign invaders. These may be bacteria, parasites, fungi or viruses. Unfortunately, the immune system cannot recognise transplanted stem cells from a donor as beneficial and there is a need to minimise the patient's reaction against the incoming bone marrow graft. However, at the same time, the incoming immune system may act beneficially in helping to destroy residual leukaemia cells in the patient.

The main cells of the immune system are lymphocytes, which can be classed into several types, and monocytes. The major types of lymphocytes are:

- B cells, which mature into plasma cells that secrete antibodies, the proteins that recognise and attach to foreign substances known as antigens. Each type of B cell makes one specific antibody, which recognises one specific antigen.

- T cells which directly attack infected, foreign, or cancerous cells. T cells also regulate the immune response and work primarily by producing proteins called lymphokines.
- Natural killer-cells (NK cells) produce powerful chemical substances that bind to and kill any foreign invader. They attack without first having to recognise a specific antigen.

What is a stem cell transplant?

Stem cell transplantation (SCT) is the term now used in preference to bone marrow transplantation (BMT).

When a patient's bone marrow fails to produce new blood cells, for whatever reason, he or she will develop anaemia, be prone to frequent, persistent infections and may develop serious bleeding problems. Anaemia can be treated reasonably well with blood transfusions. However, white cells cannot be effectively transfused and the short life-span of platelets limits the effectiveness of platelet transfusions. If normal blood cell production cannot be restored, and the bone marrow failure is very severe, patients will inevitably die of infection or bleeding.

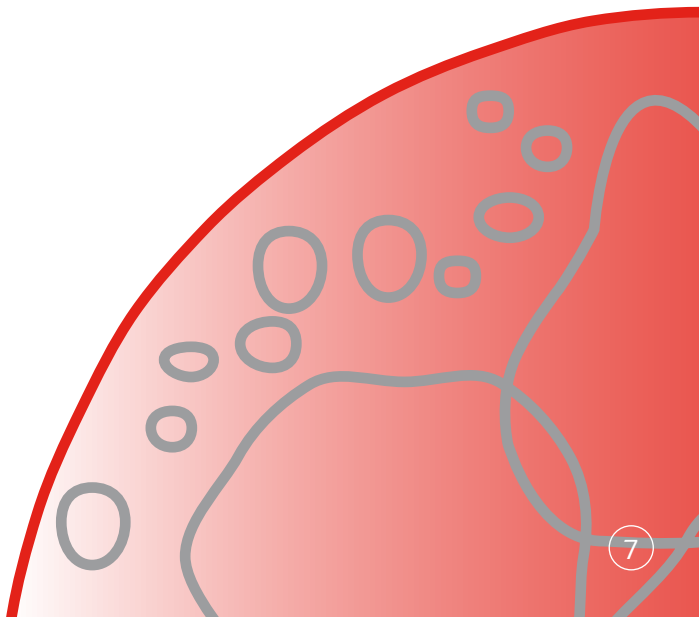
In order to restore blood cell production, a patient may be given healthy stem cells. These may be the patient's own stem cells which were collected either prior to the disease or before intensive treatment started. This is known as an autologous transplant or an autograft. If healthy stem cells cannot be obtained from the patient they may be from a donor (e.g. from a brother or sister or an unrelated person). This is particularly beneficial in eliminating malignant disease from the marrow. A relatively new source of stem cells is the blood from the umbilical cord and placenta of a newborn infant. However, the number of stem cells obtained this way is lower than that obtained from an adult donor. At present this form of transplant is mainly used for children.

Any form of transplant from a donor is called an allograft or an allogeneic transplant. The best match in terms of tissue typing (explained later) is an identical twin. This is called a syngeneic transplant. If a family member of the patient provides stem cells they are known as a related donor. The most common donor is a brother or sister of the patient, but occasionally a parent or child may be suitable. This form of transplant is only feasible for about

one in three patients who have a sibling or, rarely, a parent with a matching tissue type. Less closely related kin are rarely a match so they are not usually tested. If no related donor is available, it is necessary to search for a matched unrelated donor.

The major limitation of stem cell transplantation is the ability of the patient to withstand the high doses of chemotherapy and radiotherapy that are typically given before the transplant. Unfortunately, many of the conditions for which a donor stem cell transplant is the only curative option mainly affect older patients. An autologous transplant is generally considered to be less dangerous than an allogeneic transplant, and therefore the upper age limit at most centres is about 55 years for the latter and between 60 and 70 years for an autologous transplant.

Apart from the age, the patient's general health will be considered in order to decide their eligibility for a transplant. If a patient has other illnesses for example heart disease, it is unlikely that they will withstand the intensive chemotherapy and radiotherapy (also called conditioning treatment) that is needed to prepare the patient for the transplant. Therefore such patients may not be eligible for a transplant regardless of their age.



Why are stem cell transplants needed?

There are three situations in which patients may require a stem cell transplant. Two of these relate to failure of the bone marrow to produce blood cells while the third offers an opportunity to cure an otherwise incurable inherited disease.

Stem cell transplants are predominantly used as part of the treatment for certain types of malignant diseases, mainly leukaemia, lymphoma or myeloma which involve the bone marrow. Of almost 18,500 stem cell transplants carried out in Europe in 1998, 13,750 (75%) were for leukaemia or one of the related blood cancers. Over 95% of all donor transplants were performed for patients with leukaemia, lymphoma, or aplastic anaemia.

Almost all cancer drugs and all but very localised radiotherapy damage normal tissues as well as cancer cells. This damage particularly affects cells lining the gut, the skin, hair follicles and the bone marrow stem cells. Most affected tissues can recover completely, given time. The bone marrow stem cells are particularly vulnerable and may be irreparably damaged by high-dose treatment or radiotherapy. The availability of a stem cell transplant will allow a patient to receive intensive treatment for their disease even though this will destroy normal marrow function. The transplanted donor marrow also helps to eliminate the leukaemia. This is called the 'graft versus leukaemia' (GvL) or 'graft versus tumour' effect. Transplants can also be performed to allow administration of intensive therapy for other forms of cancer.

A less common indication for a stem cell transplant is failure of the bone marrow without obvious cause which is a condition called aplastic anaemia¹. Although this condition can be treated with drugs, which suppress the activity of the immune system, this approach does not appear to restore the marrow to function completely normally. A donor stem cell transplant may therefore be recommended for young patients with severe disease who have a well-matched family donor. A stem cell transplant may also be the only curative option for patients with certain inherited conditions, particularly severe forms of thalassaemia and immune deficiencies.

¹ Aplastic anaemia is a rare but serious disorder, which may lead to complete failure of the bone marrow to produce blood cells. There is a separate publication on aplastic anaemia available from Leukaemia Research.

Source of stem cells

Bone marrow

Until recently, bone marrow was the only source of stem cells for transplantation. The procedure for obtaining bone marrow is known as harvesting and is carried out under general anaesthetic. The risk of this procedure is very small and the procedure has been carried out on a very large number of volunteer donors with no serious side-effects.

About one litre of bone marrow is collected from the bones of the pelvis by inserting a special needle a number of times and drawing off marrow. This represents a small proportion of the donor's marrow and it is replaced very quickly. It is common practice to take a unit of blood from the donor a week before the donation and to transfuse this after the donation to replace lost blood volume. Using the donor's own blood completely eliminates any slight risk of transfusion-borne infection. The donor is able to leave hospital the day after making a donation. There is usually some soreness but most people are able to resume work within a few days and are completely back to normal in a week or two.

In the case of an autologous bone marrow transplant, patients act as their own donors and the procedure is identical to that outlined above. The marrow can be frozen and stored for months or even years. This is often done with bone marrow collected from a patient in the chronic phase of chronic myeloid leukaemia or with indolent lymphoma. Both of these diseases may undergo a transformation to a more aggressive form. An autograft at this stage using the stored stem cells may be capable of reversing this transformation. In acute leukaemia, harvesting marrow during remission (that is when the disease has responded to treatment) offers the possibility of an autograft, should the disease return.

Peripheral blood stem cells

There are small numbers of stem cells in the circulating blood in healthy people. These are known as peripheral blood stem cells (PBSC). Normally there are insufficient numbers of these to harvest them from the blood. The use of PBSC for transplantation became practical when it was discovered that it was possible to mobilise stem cells from the bone marrow into the peripheral blood. There are a number of ways in which this can be achieved. Growth factors, which are natural substances that control the production of blood cells, can increase the numbers of stem cells in the blood. For healthy donors growth factors may be given as an injection. Donors may experience a degree of bone pain as a side-effect but this is usually easily controlled with non-prescription painkillers. For patients receiving treatment for cancer, growth factors can be given together with a dose of chemotherapy.

Stem cells are obtained from the blood circulation by passing the donor's blood through a machine. The machine will collect the blood cell population that contains the stem cells. The remainder of the blood is returned to the patient or donor. This process is called leukapheresis. It usually requires about two sessions of two to three hours on successive days and is less invasive than bone marrow harvesting. No anaesthetic is needed which means that leukapheresis can be done as an outpatient procedure. Any potential donor will be given detailed information on the procedure and on related risks by the transplant team.

Leukapheresis is much less inconvenient for the donor than a bone marrow donation. To avoid the risk of infection all the sections of the machine which come into contact with the donor's blood are disposed of after use.

Most patients who receive peripheral blood stem cell transplants spend a shorter time in hospital, compared to those who receive a bone marrow transplant, and are at less risk of complications because both their white blood cell and platelet counts return to normal more rapidly.

Cord blood

Normally, after a baby has been delivered the placenta and the umbilical cord are examined for any abnormality and then discarded. Blood vessels in the umbilical cord contain only blood from the baby because the mother's blood cells do not cross the placenta. It should be emphasised that the stem cells are not collected from the baby but from the blood of the cord and the placenta, materials which are normally discarded. Careful studies have shown that the procedure carries no risk of harm to the baby or the mother.

The harvesting of cord blood stem cells provides a valuable clinical resource, which is otherwise wasted. For this reason banks of frozen cord blood donations have been established in a number of countries including the UK. The reduced number of stem cells in a single donation has largely limited the use of cord blood transplants to children. In most cases these have been from a brother or sister of the patient. At the moment there is very limited banking of cord blood cells in Britain.

A special case arises where a pregnant woman has an existing child who is affected by a condition which requires a stem cell transplant e.g. leukaemia or aplastic anaemia. In this case the obstetrician and the specialist treating the affected child should discuss whether special arrangements can be made to collect cord blood stem cells from the present pregnancy.

There are several commercial organisations which offer to harvest and store cord blood stem cells on a long-term basis. Most experts do not recommend this as an option. The probability of a child requiring the use of its own stored stem cells is extremely low. For a child with leukaemia it may be undesirable to use their own stored stem cells because there is evidence that their cord blood may contain stem cells with the same genetic abnormalities which originally contributed to the development of their leukaemia. There is further information on this topic at the Leukaemia Research website at www.lrf.org.uk

Type of transplant

Autologous transplant

For some patients it may be possible to use their own bone marrow or peripheral blood stem cells. This is known as an autologous transplant (autologous means ‘related to self’). This form of transplant can be used for patients with chronic leukaemia, lymphoma and myeloma. Trials are still continuing for other conditions such as acute leukaemia and solid tumours.

One of the benefits of autologous transplantation is that there is no need to search for a related or unrelated donor. Family size and the pattern of inheritance of tissue types mean that only about 30% of patients have a perfect match from an immediate relative. Of the remaining 70%, many will not be able to find a matched donor in the unrelated volunteer donor panels. In cases where a donor is found the process may take many months during which time their disease may progress.

Stem cells collected for an autologous transplant may be contaminated with tumour cells that may cause a relapse (return of the original disease) after treatment. This is particularly likely when the transplant is being performed for leukaemia, lymphoma or myeloma. It may be possible to remove, or to reduce the number of malignant cells, by special techniques prior to the transplant. This is called purging and is done in one of two ways. The first is by isolating the stem cells and giving this enriched population to the patient. This is called positive selection. The other approach is to use selective treatments to remove the malignant cells from the marrow harvest before the stem cells are returned to the patient. This is called negative selection.

The two methods can be used on the same marrow or stem cell harvest. Development of very sensitive tests for the detection of minimal numbers

of malignant cells has improved the ability to assess the success of purging techniques. It remains to be proven whether or not removing contaminating tumour cells reduces the risk of relapse after treatment. A significant limitation to the use of positive or negative selection is that both approaches reduce the number of stem cells available for transplant. If a stem cell collection contains small numbers of cells it may not be feasible to carry out purging.

The risks directly associated with the transplant procedure (infection, graft failure or rejection) are lower for an autologous transplant but the risk of the original disease returning (relapse) is greater. The greater risk of relapse is almost certainly due to the absence of a graft versus leukaemia effect, which is described below. The greater relapse rate can also be due to residual tumour cells, which were not removed by purging.

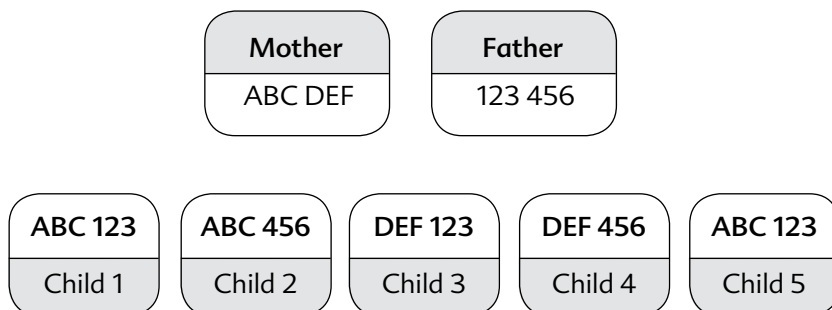
Allogeneic (donor) transplant

Any transplant in which the stem cells comes from a donor is called an allogeneic transplant. It is necessary for the stem cells to be collected from a donor whose tissue type closely matches that of the patient. Even in this situation, the tissue types are unlikely to be identical because there are other minor tissue type markers, which influence the immune reaction between donor and patient.

The body can distinguish between its own tissues (not to be attacked) and foreign or non-self cells (which are to be attacked and destroyed). This is done by detecting specific markers on the surface of cells. The most important markers are called human leukocyte antigens (HLA)³. There are six major HLA-markers, three inherited from each parent. The three markers that are inherited from each parent as a 'packet' are called a haplotype. In the diagram, ABC, DEF, 123 and 456 each represent a haplotype. A child receives one haplotype from each parent as shown. Because the HLA-markers are inherited in this way, for any one sibling (brother or sister) there is about a 25% chance

³ Links to websites offering more detailed accounts of the HLA system can be found on the Leukaemia Research website at: www.lrf.org.uk

of a full tissue match, a 25% chance that they will share no markers and a 50% chance that they will share half their markers. This assumes that the parents do not have any haplotypes in common. If they do, the chance of a match will be higher.



In this diagram child 1 is assumed to be the transplant candidate. Child 2 and child 3 each share half the markers therefore they are 50% matches. Child 5 shares all six markers and is a full tissue match.

It is necessary to have a good tissue match in order to minimise the risk of graft rejection. The match will never be perfect except in the case of identical twins because of the way in which the tissue types are inherited. A non-identical sibling who matches for the six main markers is also likely to match on most of the minor tissue type markers. This makes a matched sibling donor a better choice than an unrelated donor who matches on all six main markers.

An allogeneic transplant contains immune cells from the donor. These will recognise the cells of the recipient as ‘foreign’ and will attack them. This causes a condition called graft versus host disease (GvHD), which may be severe and may even be life-threatening. There is also a beneficial aspect to this immune response by the donor cells the same process will destroy residual leukaemia cells very effectively. This is known as the graft versus leukaemia effect (GvL). Many clinical trials are seeking to achieve the maximum GvL-effect with the minimum of GvHD.

GvHD can be a serious complication of stem cell transplantation. Attempts have been made to prevent GvHD but this was found to lead to an increased rate of relapse (return of the original disease). This was shown to be due to the loss of the GvL-effect and confirmed the importance of GvL in a successful stem cell transplant.

A procedure called donor lymphocyte infusion (DLI) exploits the graft versus leukaemia effect for treatment of patients who have relapsed following an allogeneic transplant. Lymphocytes are harvested from the original donor and transfused into the patient. DLI has become the treatment of choice for patients who relapse following allogeneic transplantation. This technique has proved to be most effective in treating relapses in patients with chronic myeloid leukaemia. DLI is less effective in other conditions but may still be of benefit.

Related donor

⚡ HLA identical

A transplant between identical twins is called a syngeneic transplant. Such transplants are extremely rare. Since the donor and recipient are genetically identical there is minimal risk of graft rejection. There is no graft versus host disease and therefore likely to be little or no graft versus leukaemia or lymphoma effect. The usual type of related donor is a matched sibling (brother or sister). Where a sibling is completely matched they are known as an HLA identical donor. The average family size means that about one third of patients will be fortunate enough to have a well-matched brother or sister to act as a donor.

⚡ Haplotype identical

It is possible that patients without a matched sibling may be able to use a half-matched family member. This is known as a haplotype identical match. In general, haplotype identical transplants are between partly matched brothers and sisters or a parent and their child. The number of stem cells available means it is more common for the parent to be the donor.

Whether a haplotype identical donor is acceptable depends largely on how well the remaining markers are matched. Some mismatches are more significant than others.

Occasionally, particularly in ethnic groups in which cousin/cousin marriages are common, there may be a good tissue match with an aunt, uncle or cousin.

Unrelated donor

∴ Volunteer donor

For patients who lack a related donor it may be necessary to look for a matched unrelated donor (MUD), also known as a volunteer unrelated donor (VUD). The probability of finding a suitable donor depends on a number of factors including the rarity of the patient's tissue type. There are now several million volunteers around the world who have been tissue-typed as potential bone marrow donors and in theory this should help up to 70% of patients to find a suitable donor. Unfortunately, practical problems such as tracing donors, their availability for marrow donation and the donor's age and their own health status mean that only about 10% of searches result in a transplant.

In all bone marrow registers the majority of potential donors are from the Caucasian population. This means that there are particular difficulties in finding donors for patients from non-Caucasian ethnic groups because some tissue types are rare within the Caucasian population. Ethnic minorities are under-represented on donor registers, which makes it difficult to find suitable donors for patients within certain ethnic groups.

The closeness of a match needed for a good result depends on which particular tissue markers are identical or non-identical. For some markers, it may be possible to accept a degree of mismatch and so improve the chances of finding an acceptable donor. The older the patient the greater the need for close matching since graft versus host disease tends to be more common and severe with increasing age.

∴ Cord blood

There are now cord blood banks in many countries. There are over 75,000 units of cord blood stem cells available worldwide and to date over 1,500 transplants have been carried out using cells from these banks, primarily for the treatment of blood cancers. The results of these transplants confirm the theoretical prediction that cord blood stem cells need not be as closely matched as bone marrow or peripheral blood stem cells to ensure a successful outcome. However, the low number of stem cells in a single donation compared to an adult stem cell donation has largely restricted these transplants to children. Research is being directed towards overcoming this restriction in order to extend this option to adult patients.

The transplant procedure

Prior to a transplant patients will receive a conditioning regimen of drugs and/or radiotherapy, in order to destroy the bone marrow cells. This is called myeloablation. In the case of a donor transplant this is necessary to prevent rejection of the donor cells. This stage cannot be omitted even in patients with aplastic anaemia in whom the marrow has already failed otherwise there is a high risk of graft rejection. Conditioning for an allogeneic transplant is typically either with busulphan and cyclophosphamide or with cyclophosphamide and total body irradiation.

For many patients who are older and/or have other illnesses this procedure is too stressful and therefore they are unable to receive a donor transplant. A reduced intensity conditioning (RIC) stem cell transplant, sometimes known as a 'mini-transplant' or as 'transplant-lite', is a recent innovation and may offer an alternative to this group of patients. It uses lower doses of drugs and radiation to suppress the patient's immune response sufficiently to allow donor cells to become established. There is usually a stage during which the patient has a mixture of their own and donor marrow cells. This is called mixed chimaerism. This can be followed by full chimaerism, which means the complete replacement of patient marrow with donor marrow.

Despite the reduced intensity of pre-transplant treatment, the toxicity of this procedure remains relatively high compared to chemotherapy alone. Reduced intensity conditioning transplants extend the possibility of allogeneic transplantation to a wider patient population but will not be appropriate for all patients.

For autologous transplants the problem of rejection does not arise but conditioning regimens are still used to eliminate any residual diseased marrow. A regimen called BEAM is frequently used. This is a combination of several drugs given over a period of five days. For myeloma patients, the drug melphalan is frequently used, with or without total body irradiation.

Receiving the conditioning regimen

Often high-dose chemotherapy is used, given intravenously. For this reason a tube called a central venous line is placed under the skin of the chest and into a vein. This is often done in the operating theatre where an X-ray machine can be used to ensure it is correctly inserted. Local painkillers and a sedative are given as necessary to ensure that the procedure is not painful. The central venous line removes the need for the patient to have repeated injections into veins in the arms during the course of treatment. Also blood samples can be taken from the line for laboratory tests. The line remains in place until the treatment is finished. It is possible to wash and shower as normal. One effect of chemotherapy is nausea but with current anti-sickness drugs this is now rarely severe.

Total body irradiation

This is not necessary for all patients but may offer a treatment advantage for some. It is important to calculate the dose accurately and this is done by a specialist radiologist. There are a number of side-effects associated with radiotherapy. These will vary depending on the exact type of treatment and will be discussed in detail by the specialist. In order to reduce these side-effects radiotherapy is given in split doses or fractions. The exact number of fractions given depends on the procedures practised in the treatment centre but often a fraction is delivered in the morning and another in the late afternoon/evening for several days. The treatment is not painful at the time it is administered. It is necessary to keep still in front of the beam of radiation. A special support is prepared to help the patient remain in exactly the right position.

Receiving the transplant

The bone marrow or blood stem cell transplant is given very simply in the same way as a blood transfusion into the central line. Once the blood-producing stem cells are in the circulation, they find their own way to the sites in the bone where the new marrow will establish itself. Regular post-transplant blood counts will indicate when new white blood cell and platelet production has started. This confirms that the transplant has been successful. For peripheral blood stem cell transplants it normally takes about two weeks for the blood count to improve to the point where the patient can go home. This process takes about twice as long following autologous and allogeneic bone marrow transplants. It takes up to two years for bone marrow function to fully recover.

Growth factors

A natural substance called G-CSF (granulocyte-colony stimulating factor) is produced in the body to control the production of white blood cells. G-CSF can now be produced in the laboratory and can be given by injection to stimulate blood cell production or to mobilise stem cells into the blood. G-CSF accelerates the recovery of the bone marrow and stimulates the production of normal granulocytes and monocytes after a transplant. It may also help to reduce the risk of infection.

Risks of transplantation

Allogeneic transplants

∴ Graft versus host disease (GvHD)

With improved tissue-typing methods (which have reduced the risk of graft failure or rejection) and better supportive care for patients with infections, graft versus host disease has become the major life-threatening risk following an allogeneic transplant. GvHD occurs when the donor's immune system attacks the patient's body. It mainly affects the tissues of the skin, the liver and the gut. A distinction is made between acute and chronic graft versus host disease, which is to some extent arbitrary, and based on a time-point of 100 days post transplant. There are significant differences in the behaviour of acute and chronic GvHD and the division is clinically useful. For example, the lungs may also be affected in chronic graft versus host disease.

Acute graft versus host disease

When GvHD occurs within the first 100 days after transplant it is termed acute GvHD. This form typically causes a severe rash and may also attack cells in the liver and gut leading to nausea, vomiting, diarrhoea and jaundice.

Factors known to increase the risk of acute GvHD include:

- Increasing age of the patient or donor
- A donor who had been pregnant in the past
- Any donor who had received a blood transfusion
- Reduced doses of immunosuppressive drugs post-transplant
- Less exact tissue match between donor and recipient

Acute GvHD can be classified as grade I to grade IV on the extent and severity of the condition. Grade I may require no treatment, although some centres

recommend treatment if the transplant is from an unrelated donor. Grade II or higher is considered moderate to severe and always requires treatment. Moderate to severe acute GvHD is a serious and potentially life-threatening complication of allogeneic stem cell transplantation.

Acute GvHD can be prevented by giving more intensive treatment to suppress the immune reaction post-transplant but this increases the risk of serious infections. Removal of a particular type of lymphocyte from the graft has also been shown to reduce the risk of acute GvHD but this increases the risk of graft rejection, serious infections and of relapse.

Once moderate to severe acute GvHD has been diagnosed the first choice of treatment is usually steroids (prednisolone) to increase the level of immunosuppression. If this is unsuccessful then a drug called Atgam™ (antithymocyte globulin) may be used to reduce the numbers of T lymphocytes which play a key role in causing and sustaining graft versus host disease.

Chronic graft versus host disease

Chronic GvHD can present in many different ways. In the majority of cases it affects the skin. It can also affect the lungs, liver and immune system. It may resemble certain auto-immune diseases, which may confuse the diagnosis. Chronic GvHD may present in patients in the absence of acute GvHD ('de novo onset'), in patients who had acute GvHD which resolved fully ('quiescent onset'), or following persistent acute GvHD ('progressive onset'). It may develop at any time from three months post-transplant to six months after the end of immunosuppressive treatment. Known risk factors are:

- Increasing age of the patient or donor
- Prior acute GvHD
- Donor lymphocyte infusion (DLI)
- Infection with the Herpes zoster virus (HZV), the cause of chickenpox and shingles

The treatment of choice for most patients with chronic GvHD is with high-dose steroids (prednisolone). If the patient has poor-risk features such as progressive onset chronic GvHD, low platelets, or jaundice then ciclosporine or a drug called tacrolimus may be used alongside prednisolone. Limited chronic GvHD (in skin, liver or both) has a good prognosis. If the condition is more widespread then the long-term outlook is poorer. The commonest cause of death related to chronic GvHD is infection and patients will usually receive multi-drug antibiotic therapy in an attempt to prevent this complication.

Other complications

Once pre-transplant conditioning has finished, any nausea will soon clear up. Almost all patients develop a sore mouth and it can be difficult to swallow. This is controlled with mouthwashes or injections of painkillers. It is important for the patient to have painkillers when the mouth starts to get sore in order to make mouth-care more tolerable. Candida (fungal) infections of the mouth are also common and are prevented or treated with mouthwashes and tablets. Diarrhoea is a frequent side effect of the conditioning regimen but may also be associated with graft versus host disease. Invariably patients develop temperatures that are associated with infections and need early treatment. Patients may become short of breath. If this happens the doctor must be informed so that chest X-rays can be arranged.

Infections

Infections are frequent in the immediate post-transplant period. These may be bacterial, viral or fungal infections. In all cases where infections develop they are difficult to treat because the patient is not producing white blood cells, particularly neutrophils which guard against bacterial infections.

Strict anti-infection precautions are taken. Patients may be kept in special isolation units, be given antibiotics by mouth or via the central line to reduce the risk of bacterial, fungal or viral infections. Specially treated food may be required and it may be necessary to sterilise everything that comes into contact with the patient. During this period visitors may be restricted in the amount of time they can spend in the patient's room. The use of growth factors to speed up the grafting process has reduced the length of time such precautions are necessary.

The much earlier recovery of the neutrophil count in patients receiving peripheral blood stem cell transplants reduces the risks from infection and, in some centres, these patients do not require isolation nursing and are cared for on the open ward.

If an infection does happen it will be treated very promptly with the most suitable antibiotics or anti-fungal drugs. The majority of patients who develop an infection can be successfully treated.

Cytomegalovirus (CMV) is a particularly important cause of illness after allogeneic transplants. It can inhibit bone marrow activity and most importantly cause a widespread pneumonia, which can be fatal. Antiviral drugs, especially ganciclovir are given.

Bleeding

There is a risk from internal bleeding during the period before the platelet count recovers. This can be guarded against with platelet transfusions. The introduction of peripheral blood stem cell transplants has reduced the length of time the platelet count takes to recover to normal and so lessened the risk from bleeding. A growth factor that stimulates platelet production has been developed but results from clinical trials have not been promising and therefore this is not in routine use.

Anaemia

Inevitably, during the transplant procedure, the patient will fail to produce enough red blood cells and will therefore become anaemic. This is monitored by regular blood counts and is treated with blood transfusions.

Mucositis

Almost all transplant patients experience sores in their mouths and/or gut, called mucositis. These are caused when chemotherapy or radiotherapy damage the rapidly dividing cells that form the lining of the digestive tract. The more intensive the conditioning treatment is the more likely the patient is to develop mucositis, and the more likely it is to be severe.

Mucositis leaves the patient vulnerable to infection so anti-bacterial and anti-fungal preparations such as mouthwashes may be prescribed to reduce the risk.

Graft failure

A serious complication of transplantation is failure of the stem cells to re-populate the bone marrow cavities. This means that new blood cells are not produced in sufficient numbers. This failure of engraftment can affect the platelets, white cells and red cells to varying degrees. Rarely, there is total failure of engraftment with none of these cells being formed at all. Total failure to engraft will lead to the death of the patient, unless a further transplant is possible.

Graft failure may result from immune rejection, which is most likely when there is a poor match between the tissue types of the donor and the recipient. Although most cases of graft failure appear to be caused by an adverse immune reaction, it is clear that this is not the only cause. There are rare instances of an autograft failing in which there is no possibility of a tissue-type mismatch.

It is recognised that the number of stem cells in the graft strongly affects the risk of graft failure. The number of stem cells can be assessed before the conditioning regimen begins and provided this is done, the risk of graft failure for this reason is very small.

Lung damage

A frequent serious complication is a lung condition called interstitial pneumonitis. This can occur both as an early and as a late complication. It may be the result of chest infections particularly caused by cytomegalovirus or *Pneumocystis carinii*. In many instances there is no obvious cause. Quite a high proportion of cases of lung damage will respond to steroid treatment.

Many patients, even without graft versus host disease, develop a lung condition called interstitial fibrosis, which may cause abnormal lung function tests but has little or no impact on day-to-day activities. Patients should not assume that an abnormal lung function test result indicates that they have serious lung problems. If concerned, they should discuss the situation with their specialist.

Veno-occlusive disease⁴

High-dose chemotherapy and/or radiation, which are given during the conditioning phase of a stem cell transplant, may cause a liver complication known as veno-occlusive disease. Veno-occlusive disease happens when blood vessels within the liver become clogged and swollen. The liver's ability to carry out its normal functions of breaking down toxic substances, drugs and waste products is impaired. The liver may swell as a consequence and kidney function may be affected leading to water retention. In severe cases of veno-occlusive disease fluid may enter the abdominal cavity (ascites) or the lungs may be affected. Liver damage resulting from mild or moderate veno-occlusive disease is usually reversible.

Severe veno-occlusive disease is potentially fatal.

⁴ Veno-occlusive disease may be abbreviated in clinical use as VOD.

Cataracts

One of the major long-term complications of receiving radiotherapy is the risk of developing cataracts in the lens of the eye. Patients will be monitored for this and if cataracts develop the patient will be referred to an ophthalmologist for treatment.

Impaired reproductive ability

Virtually all patients who undergo an allogeneic stem cell transplant will be permanently sterile. This is particularly so if total body irradiation is used. In children, growth and sexual development may also be affected.

Autologous transplants

The risks are less than those associated with an allogeneic transplant. The introduction of peripheral blood stem cell transplants has reduced the risk of side-effects even further. Infections are still a problem after autografts but the precautions that are taken do not need to be as stringent as for an allogeneic bone marrow transplant. However, patients are still kept in isolation for a short period of time.

There is a very small risk of failure of engraftment. It is recognised that the number of stem cells in the graft strongly affects the risk of graft failure. The number can be assessed before the conditioning regimen begins and provided this is done the risk of graft failure for this reason is very small.

Discharge from hospital is usually possible about three weeks after the transplant. However, it can take up to three months before the patient feels completely well.

Outcome of treatment

The likelihood of success for a bone marrow or stem cell transplant depends on the disease being treated, the source of the stem cells and the general fitness of the patient before the procedure.

In some conditions such as chronic myeloid leukaemia, myelodysplasia or severe aplastic anaemia it may be the only treatment that offers the prospect of cure. In others, like childhood acute leukaemia, it is reserved for a minority of patients with a less than average chance of responding well to conventional treatment.



Supportive care

Various aspects of the management of patients having a bone marrow transplant are special and thus not standard for other hospital patients.

These mainly apply to the critical period between the destruction of the diseased bone marrow and the restoration of normal blood cell production by the new stem cells. During this period patients are at particular risk of infection. Details of supportive care may differ from hospital to hospital. Patients will normally be provided with detailed advice on diet and precautions against infection.

Helping others

The British Bone Registry is always looking for new bone marrow donors to help save the lives of people who desperately need a transplant.

Sometimes an appropriate donor can be found within the patient's immediate family as it is more likely that their 'tissue type' will match. However, only 30% of donors are found this way, which is why the British Bone Marrow Registry is always looking for new bone marrow donors.

It is your genes that determine your tissue type. But there are other factors that determine the probability of finding a compatible tissue typed donor for a patient.

- Could you join a bone marrow donor registry?
- Are you aged between 18 and 49 years old and in good general health?

If the answer is yes to these questions, you may be able to save a life by registering as a volunteer bone marrow donor.

You can find out more by visiting the National Blood Service website at <https://secure.blood.co.uk/bonemarrow.asp>

Information for parents



Introduction

This section of the booklet has been written for parents of children who are expected to have a stem cell transplant. There are important differences between stem cell transplants for an adult and a child. This section of the booklet will explain some of the key issues specific to childhood transplants.

The booklet does not give detailed information on ward procedures, drugs used and staff roles because these will differ between treatment centres and it is usual for transplant units to provide detailed handouts to parents.

The overall success rate for stem cell transplants in children is higher compared to adults. However it is important to understand that there are still significant risks to the procedure and not all transplants are successful. The prevention and treatment of transplant-associated infection has improved greatly; this means that the greatest risk from stem cell transplants for children is acute graft versus host disease (aGvHD — see page 22). This may occur in the first 100 days after the transplant and is the most common cause of transplant-related deaths. The chronic form of graft versus host disease is very uncommon in children, however when it does happen it can affect joints and be disabling. A great deal of research in the transplant field is directed towards understanding and controlling graft versus host disease.

If a child has cancer which does not involve the bone marrow, it may be possible to collect (harvest) a child's own stem cells from peripheral blood or bone marrow before high dose anti-cancer treatment and then return them when the treatment is complete. This type of transplant is called an autologous transplant and is typically undertaken in certain types of solid tumours in children.

When a transplant is being done for a disease which affects the bone marrow, it is usually necessary to find a healthy donor who is a match for the patient. This means the donor has a similar tissue type and so a strong immune reaction between the cells of the donor and the patient is minimised to reduce the risk of GvHD. A donor transplant may be done for patients who do not have cancer but whose bone marrow is not working properly (e.g. thalassaemia, sickle cell disease, aplastic anaemia) or whose body chemistry is not working properly (inborn errors of metabolism). This type of transplant may be done for children who have very rare conditions which means that their immune system does not work.

Finding a donor

Whatever the source of stem cells, it is crucial that they are a good tissue-match for the patient. If not, there is a higher risk of the transplant either being rejected or causing severe GvHD. The best donor choice is a fully tissue-matched brother or sister (ie a sibling). The next best choice would be a fully matched family member. If no family member is a suitable match, an unrelated donor may be used. A partially matched donor will only be used if the need for a transplant is urgent and no fully matched donor is available. In this case, the same order of preference applies – first choice is a matched sibling, then a matched related donor and the last choice would be a matched unrelated donor.

One of the main differences between adult and child transplants is that a child is more likely to receive stem cells collected from donated cord blood. This may be from a matched sibling or saved from an unrelated volunteer. If no fully matched stem cells are available, from either a related or unrelated donor, then a partially matched cord blood may be preferable to partially matched adult donors. It is possible to accept a slightly poorer tissue match for a cord blood because partially matched cord bloods are less likely to cause severe graft versus host disease than adult bone marrow. The limiting factor in cord transplants is often the amount of stored cells available hence its use is most common in smaller children. Some transplants have been carried out using cords from two separate donors.

Half-Matched (Haploidentical) Transplants

A parent will always be at least a half-match to each of their children (this is called a haploidentical match: haplo- means half)⁵; sometimes a parent will be better than a half-match, because some of their tissue-type genes match with the other parent. This means that all patients who have at least one

⁵ See page 12 for an explanation of tissue types and how they are inherited.

parent alive will have a potential donor available. Because of the way in which tissue types are inherited, there is a 50% chance a brother or sister (sibling) will be haploidentical. This also means that there is a 25% chance of being a full match and a 25% chance of no tissue types matching.

There have now been many successful haploidentical transplants, mainly to children, but there is a higher risk of infection and severe graft versus host disease.

In summary, this table shows the usual order of preferences for a possible donor. However, individual patient circumstances may alter some of these preferences and it is important to discuss these issues with doctors undertaking the transplant.

Choice	Family donor	Unrelated	Unrelated cord
1 st	Matched sib or cord		
2 nd	Fully matched	10/10	6/6
3 rd	5/6	9/10	5/6 or better
4 th	4/6 or less		4/6 or less
5 th	Haploidentical		

10/10 indicates that each of ten genes matches; 5/6 indicates five genes match and one differs

The scores refer to the number of tissue type genes that the patient and donor have in common.

When a haploidentical donor is used it is necessary to remove donor white blood cells called T lymphocytes to avoid complications resulting from the incomplete match. This is called T cell depletion. It means that there is a higher risk of transplant rejection or the return of the cancer. To reduce these risks, patients receive more intensive pre-transplant treatment (conditioning). There may also be slower recovery of the immune system following the transplant, which means a greater risk of infection.

Special consideration for child donors and patients

The donor

If a child is receiving a transplant from a brother or sister in most cases the donor will also be a child. The welfare of a child donor is of particular importance because consent usually has to be given on the child's behalf. In the UK when a donor is under 16 years of age, even if the parents have given consent, it is also a legal requirement for the Human Tissue Authority (HTA) to give permission for the procedure. If they conclude it is against the interests of the donor they will refuse permission. For a very young child, although the procedure will be explained in as much detail as the child can understand, the only consents required are those of the parents and the HTA. For an older child, the procedure will only go ahead if both the child and the parents have given informed consent. There is no fixed age for this; the test is whether the child is old enough and mature enough to understand the nature of the consent they are giving.

Peripheral blood stem cells are not normally collected from child donors, as this requires the use of growth factors to mobilise stem cells from the bone marrow into the circulation. Although this is thought to be safe, there is very little experience of use of growth factors in healthy children and there are rightly concerns that there may be as yet unknown very long-term side effects including a chance of developing blood cancer in later life. Bone marrow is harvested from a child donor under a general anaesthetic by inserting a needle into the pelvis and sucking out marrow. The child normally recovers quickly, going home within 24 hours and usually being back at school two or three days later. There are no expected long-term side effects.

A potential donor is likely to spend time with a child psychologist, who can assess how much the child understands of the process and identify any

possible difficulties that might arise. A play specialist may also help the child to understand the various procedures involved. Where there are several siblings, it is very important that parents consider the feelings both of the chosen donor and of the other children. For example, they may already be feeling guilty if they are jealous of a sibling who then falls ill. It is difficult, but parents must try to make sure that the donor does not feel responsible for the outcome and that other siblings do not feel less valued because they were unable to help. The child psychologist can help with these family issues.

The patient

How much a child understands of the transplant process depends on the individual child's age and maturity. Older children may have firm views on whether they are prepared to undergo high intensity treatment followed by a transplant. If the procedure is strongly recommended but the child is reluctant to give consent, a child psychologist may be able to help. In the case of younger children, both the child psychologist and the play specialist will be very actively involved in preparing the child for the transplant.

The patient may receive full-body irradiation before the transplant and this involves remaining still throughout the procedure. A young child will probably be given a general anaesthetic whereas an older child will usually manage with support and reassurance. Although no one else can be in the room during the radiotherapy, it may be possible for the parent to talk to the patient on an intercom and there is usually a video to watch.

Following the transplant, there is a period during which the child effectively has no immune system. During this time it is necessary to protect the child from the risk of infection; units have different isolation policies and this will be discussed in detail with you all before the transplant. How long this isolation is necessary for will depend largely on how quickly the new marrow is established and produces disease-fighting white cells.

The transplant team will be keen to see a return to normal life, including school or pre-school, as soon as possible. It is very unlikely that this will be possible any earlier than three months after the transplant. For children of school age, it is very important to maintain the link with school activities. They will not be able to have visits from children (other than brothers and sisters) whilst they are being nursed in isolation, but sending work from school and regular messages to and from classmates can all help to ease the eventual return to school. A child who has received a transplant is likely to have problems with fatigue for some months. The return to normal activities, at home or outside may need to be phased in, to allow for this. If returning to school, it may be possible to gradually increase the numbers of hours up to a full school day, or at junior school especially, there may be a quiet area where the child can have a rest during the day.

It is important to prepare information for the school on what special needs the child may have and on what to do if the child falls ill during the school day⁶. The most important consideration is the risk of infection and often children are still taking medicines to guard against bacterial or fungal infections when they return to school. It is critical to ensure that the school or pre-school is aware that the child may be endangered if exposed to chickenpox or measles. Both teachers and parents of other children in the school/pre-school must be made aware that it is vital to inform the family of the transplanted child if any other child has, or has been in contact with, either of these infections.

Sometimes a child will return to school with a central line still in place. If this is the case, the hospital will offer advice on what special precautions are necessary. The school staff should be aware of what restrictions on activities may be necessary; it is also necessary to make sure that designated first-aiders within the school know what to do if a line is displaced. A child who has a line in place may have problems of self-image; teachers and other staff should

⁶ See "Pupils with Cancer – A Guide for Teachers" www.royalmarsden.org.uk/teachersguide

be aware of this and should discuss any concerns with parents. Children will always notice that a pupil has been off for some time and has now returned. It will be a matter for discussion between parents and the school whether the whole school or just classmates should be told why the child has been away and how much information should be given. It is usually best to fully inform the other pupils what has happened; this should be at a level suitable to their age. One of the reasons is that pupils who are aware of what has happened are likely to be supportive and even protective of their classmate. Giving information will also allow teachers to explain that leukaemia (and other cancers) cannot be “caught” and to explain any special arrangements that are needed. Many units have specialist nursing staff who will help in this whole process of getting back to a normal life.

Complications of stem cell transplants

Complications of stem cell transplants may be divided into short term and long term, although there is considerable overlap.

Short term

When a transplant has been done to treat cancer, return of the original disease (relapse) may happen but this is rarer in children compared to adults.

Fortunately, transplant failure (rejection) is a rare complication in children. However, when this does occur it is a very serious situation and the specialists will discuss treatment options with the parents. The risk of graft versus host disease is generally lower in children but causes similar problems of skin rash, gastrointestinal disturbance and liver dysfunction as outlined in the main section of this booklet.

Long term

When a child receives a successful transplant, doctors hope and expect that the child will live for many years. This makes it particularly important that children should be followed up carefully to identify any delayed effects there may be from the transplant or related treatment.

The Childhood Cancer and Leukaemia Group (CCLG) carries out research into the long-term effects of cancer treatment in children, including after stem cell transplantation. The CCLG web site provides very detailed information and advice on follow up after a transplant. This can be found at www.cclg.org.uk/public/followup/PracticeStatement/index.html.

Even for children who have been transplanted for non-malignant disease, this site will give valuable information on the effects of the transplant itself.

Sadly one of the most common long-term side effects is infertility and growth impairment because of the drugs and radiotherapy used before the graft. The risk of infertility is very high in grafts for leukaemia but is not always seen in some other disorders such as aplastic anaemia. Again, this risk should be discussed with the transplant team prior to going ahead. Older children should be involved in discussion of this issue and on very rare occasions sperm banking or egg collection may be possible; for children who undergo a transplant while too young to understand fertility this should be discussed at some point during follow-up. The appropriate age to initiate such discussions will vary from child to child and should be agreed between the family and the follow-up team.

Immunisation

The advice given in this section is based on a report by the Royal College of Paediatrics and Child Health⁷ however a child's specialist may recommend changes to these recommendations, based on their clinical judgement.

After a successful stem cell transplant, the patient has a completely new immune system and so they will have lost any immunity they had due to previous vaccination or exposures to infection. This means that any vaccinations they have already received will need to be repeated.

After a donor transplant, the patient may benefit from the donor's immunity to infection, but this does not last very long. The exact programme of vaccinations and their timing may vary between transplant units.

The type of donor will influence the timing of re-immunisation; if the donor is a brother or sister, it is recommended to commence the programme at one year after transplant; in all other cases not until 18 months have passed. In either case it is also necessary that:

- There is no evidence of active chronic GvHD, and
- The child has been off **all** immunosuppressive treatment (e.g. steroids, cyclosporine A) for **at least six months** (12 months before administering any live vaccines), and
- The child has been off intravenous immunoglobulin (IVIg) for **at least three months**.

Patients with chronic GvHD not receiving IVIg can be given non-live vaccines although response may be poor.

The vaccinations recommended are listed on the web site at:

www.cclg.org.uk/public/followup/PracticeStatement/APPENDICES-e.pdf.

⁷ Skinner R, Cant A, Davies G, Finn A, Foot A (2002) Immunisation of the immunocompromised child, Best Practice Statement, London: Royal College of Paediatrics and Child Health.

Summary

Stem cell transplants are performed for a number of reasons in children. Although children have a higher chance of complete success than adults, there are still risks attached to the procedure, and the long-term side effects may be more severe than with other forms of treatment.

If the donor is a brother or sister, he or she is likely to be around the same age as the patient. This will mean that both the donor and the patient are likely to need support from child psychologists and the family may need a great deal of support. The hospital will provide expert help in preparing the patient and the donor for the transplant.

Although the outcome of a stem cell transplant in a child is more likely to be successful than for an adult, it is still important not to underestimate the impact of the procedure on the child. Adults commonly take at least a year to return to normal life after a successful transplant; although a child may recover more quickly physically, they may need support for a long period after this. A child of school age may need special help both in coping with long-term effects of treatment and to catch up from any missed education.

Notes



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Childhood Acute
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