Stem cell transplantation (SCT) has been used as a treatment for cerebral ALD since the early 1980s. It is used in children or adolescents with early stage disease, preferably when this can only be detected on MRI scanning and before the onset of neurological signs. Although some progression may occur in the first or second year after transplant, disease progression is often prevented in such boys.

By contrast, transplants have no role in boys with advanced or rapidly progressive cerebral disease: the drugs used during transplant, or other complications of the transplant procedure, may even speed up disease progression. For example, results are very poor in those boys transplanted when their performance IQ has deteriorated to less than 80. The results are also often poor in boys with even quite minimal neurological signs detectable at the time of transplant.

There is also no proven role for SCT in preventing progression of AMN or neurological problems in carrier females. Use in AMN patients may change if long term follow-up of boys transplanted for cerebral disease suggests that transplantation has prevented the appearance of AMN.

Haemopoietic Stem cells & Microglial Cells

Haemopoietic stem cells are those derived from the blood or marrow system. Suitable sources of stem cells are:

(1) bone marrow from children or adults
(2) cord blood from the placenta of a newborn baby and
(3) peripheral blood from adult donors who have been given granulocyte colony stimulating factor (G-CSF) [The G-CSF "mobilises" stem cells from the marrow into the blood]. These are called peripheral blood stem cells or PBSC for short.

Whatever the source, these stem cells can all be used to replace a person's bone marrow after this has been destroyed by chemotherapy. The donor cells growing in the marrow spaces then produce blood cells. Some highly specialised cells pass from the marrow, through the bloodstream and into the brain where they become microglial cells. This process is slow, and this may explain the "incubation period" of 12-18 months often seen before progression of the disease is arrested.

Microglia are thought to act by lowering VLCFA levels in the brain by direct cell-cell contact (although this has not been proven). This may also explain why SCT is so effective even though transplants tend not to be as effective as Lorenzo's Oil in reducing VLCFA levels. Lorenzo's Oil is usually discontinued at the time of transplant as it frequently lowers the blood platelet count, which is already severely reduced by the effect of chemotherapy on the marrow, and low platelets can lead to bleeding complications. Lorenzo's Oil is not usually reintroduced after transplant.

It should be noted that this treatment does not rely on trying to grow nerve cells from primitive blood stem cells or mesenchymal stem cells obtained from marrow or tissue: such stem cell research is only in its infancy.

Tissue Typing

This is performed on quite small volumes of blood, usually taken from the child who is to receive the transplant, their brothers and sisters (siblings) and parents. Statistically speaking, one in every four siblings should be a tissue match. However, statistics can be cruel and the author has seen many patients with four or more siblings, none of whom are matched. Younger male siblings who are asymptomatic for ALD but proven to have the disease on blood testing cannot act as donors. Girls or female relatives who are carriers often have acted as donors without any evidence that their carrier status impairs the outcome of transplant (although many find this surprising). It may be worth testing other relatives within a family where first cousin marriages have occurred as this increases the chances of other relatives (e.g. cousins, aunts, uncles) being well matched.

It is usual to test six of the tissue type proteins (antigens) when looking for cord blood matches and for ten antigens when searching for any other type of donor. Thus your doctor may talk about a cord blood being 4/6 matched (two antigen mismatched) or a marrow donor being 9/10 matched (one antigen mismatched). Transplant complications, such as graft rejection or graft versus-host-disease (see below), are more common in mismatched transplants.

Transplant Outcomes

Just under 60% of children survive to 5 years post-transplant. However, the vast majority of deaths have been due to progression of the disease rather than transplant complications, and most have occurred in children with neurological signs or symptoms having already developed by the time of transplant. These figures are also constantly improving now that it is clear that advanced ALD cannot be cured by SCT and as tissue matching and transplant technology improve. Experienced units would expect at least 90% of children transplanted from 10/10 matched bone marrow donors to be alive 3 months after the transplant (the first 3 months being the period of greatest risk). The best outcomes are obtained from matched sibling donor (MSD) transplants. Long term survival rates are more than 10% better after transplants from siblings than from unrelated donors.

Neurological symptoms or signs can be difficult to quantify accurately and can change rapidly. Harder signs are often used, such as the disease score (e.g. Loes score) on MRI scans, or IQ.

Selection for SCT

There is no absolute parameter as to who is fit or unfit for transplant and the opinions expressed are those of the author. A child presenting with neurological changes has to be considered very carefully and is best assessed by experts in this disease and its transplantation. The disease is more likely to show a rapidly progressive form in boys younger than 10 years, and referral to an expert for consideration of rapid transplantation is therefore critical for such boys.

Careful assessment by a neuropsychologist is required. They will assess both verbal and performance IQ. Performance IQ is heavily influenced by visual processing defects caused by leukodystrophy affecting the back of the brain, a very common site of damage in cerebral ALD. Falls in verbal IQ reflect changes at the front of the brain and often precede memory loss or frank dementia. Transplant doctors are very reluctant to transplant a child with a performance IQ of less than 80.

The next crucial test is an MRI scan. Children with MRI scores (Loes scores) of ≥ 9 have a very poor outcome compared with those with lesser disease. Some units will also perform an MRS scan (magnetic resonance spectroscopy, which analyses brain chemicals) at the same time. This is done during the MRI scan but allows assessment of developing leukodystrophy in areas which are not yet apparent on the MRI scan.

It is important to consider the speed of development of symptoms. Assessment should always be undertaken urgently, with investigation, tissue typing and transplant planning performed as soon as possible. Children with rapidly progressing ALD should not sit on a transplant waiting list and may need referral to another hospital if transplant cannot be performed as soon as a donor is available. However, I also believe it to be important to reconsider the decision to transplant if neurological signs develop during this planning phase.

Adolescents often have more slowly progressive disease, and may be considered for transplantation with slightly less urgency, and when slightly more symptomatic, than younger children.

The best results are obtained in children who are detected early in their disease course, i.e. those who have presented with adrenal failure (Addison's disease) or who have affected siblings. This explains the absolute necessity of testing all young males (below 40 years old) who present with Addison's Disease, as adrenal problems will be explained by an underlying diagnosis of ALD in approximately 20-50% (the incidence being higher the younger the male).

Current practice in the UK is to assess children initially using a combination of MRI (magnetic resonance imaging) and MRS. If there are MRI changes (certainly if the MRI score exceeds 3) we would recommend transplantation. If the MRI is clear, the MRS must then be scrutinised for early chemical changes.

If both MRI and MRS are clear, scans are repeated every 6 months, dropping to once a year between 10 and 15 years and stopping after that. If either or both of MRI/MRS is suspicious these scans are repeated at 3 monthly intervals, and transplant planning should commence.

In the transplant planning process many detailed assessments are required, including assessments of blood group, growth, kidney/liver/heart function and any previous viral infections. A "back-up" bone marrow harvest may be taken under general anaesthetic: this can be given back to the patient if graft rejection occurs. A Hickman catheter will also be inserted under general anaesthetic in a major vein of the neck, as this greatly reduces the number of venepunctures required for blood testing and drug administration.

The Transplant Procedure

The schedules used vary significantly between units and only general guidelines are given here to avoid confusion.

"Conditioning chemotherapy" usually lasts for 7-10 days. Most transplants until now have relied upon two drugs: busulfan and cyclophosphamide.

Busulfan is given orally or intravenously (Busulfex), typically over four days. Specific side effects include fits (usually transient and easily treated; preventative drugs are usually given), neurological deterioration in advanced ALD, veno-occlusive disease (weight gain, liver swelling and jaundice) and a high risk of infertility.

Cyclophosphamide can cause cardiac toxicity (rare at typical doses used) and bleeding from the urinary tract (haemorrhagic cystitis).

Common side effects of both drugs and the transplant process include:

Mucositis: a sore mouth and gut: strong painkillers are often required and diarrhoea is common.

Intravenous feeding (total parenteral nutrition [TPN]) or nasogastirc feeding are usually required for several weeks

Hair loss: hair regrows after blood count recovery

Low blood count: platelets are required to prevent bleeding and regular red cell transfusions to combat anaemia

Infections: very low white counts abolish most immunity to bacteria, funguses and viral infections. Patients are nursed in isolation cubicles in filtered air in order to minimise the risks. Multiple antibiotics are required to treat bacterial infections. Preventative (prophylactic) drugs against fungal and viral infection are often given, with further drugs used for treatment of specific infections if these occur.

Graft versus host disease (GVHD): termed "acute" if occurring within the first 3 months and "chronic" after that. GVHD is caused by donor cells attacking one or more of the patient's skin, gut and liver. The incidence of GVHD may be reduced by various methods which include: killing donor T-lymphocytes using drugs such as CAMPATH-1H or ATG, removing T-cells or selecting pure stem cells using magnetic beads, and using preventative drugs (cyclosporin A, mycophenolate mofetil [MMF], methotrexate, steroids). Although often successful in preventing GVHD, these drugs tend to increase the risks of graft rejection, partial chimaerism and viral infection.

Many newer drugs and combinations are being trialled, especially mixed combinations of treosulfan, melphalan and fludarabine. The aim of these is to reduce the side effects of transplant, although this might be at the cost of a lesser degree of donor cell engraftment or graft rejection.

Stem cells are infused through the Hickman catheter on day zero of the transplant. Donor white cells (neutrophils) usually appear between 14 and 21 days after transplant and G-CSF may be used to accelerate this process. Acute GVHD most commonly occurs during or soon after neutrophil engraftment. Most patients can leave isolation facilities by day +28 post-transplant provided that they have a well-recovered blood count, are off intravenous feeding and intravenous antibiotics and do not have uncontrolled acute graft versus host disease.

Chimaerism

The ideal outcome of SCT is 100% donor engraftment without graft versus host disease (GVHD), especially as the inflammation seen with GVHD may aggravate leukodystrophy. However, following chemotherapy based conditioning, especially where T-cells are killed or removed, it is common for some or many of the patient's own cells to survive, resulting in "mixed chimaerism". Thus a patient may have 95% donor chimaerism soon after transplant which subsequently wanes to anything between zero and 70% over the first year post-transplant. Although surprising, there is no evidence that long term outcome is influenced either by the percentage of donor chimaerism or by the gene carrier status of the donor. Complete secondary graft rejection (down to 0% donor cells) would almost certainly be associated with disease progression.

This lack of detailed knowledge of the mechanism and thresholds for benefit is a major problem, and an area where knowledge is badly needed in order to decide the best treatment for an individual patient. For example, it is often possible to improve 50% donor chimaerism to 100% chimaerism by administration of additional donor T-cells (donor leukocyte infusions [DLI]). However, this comes at an additional risk of GVHD which might in turn aggravate leukodystrophy.

Post-transplant Follow-Up

Follow-up decreases with time from transplant, often beginning with daily outpatient visits which reduce progressively to six monthly or annual visits if complications do not demand more frequent assessment. There are no prescribed intervals for MRI or neuropsychological assessment and due to the slow effects of transplant these investigations should probably not be performed more frequently than annually, unless demanded by an experimental protocol.

In patients with early stage disease apparent only on MRI scans there will often be some progression of leukodystophy on scans during the first 1-2 years post-transplant, but obvious neurological progression is often prevented. In those with some obvious neurological disease, progression may happen even during the transplant and stabilisation of the disease appears to be less good. The author has seen disease progression 3-4 years post-transplant in such boys, even though this may be much more slow than was expected without transplantation.

Long term follow-up is always needed after transplant, to check for any late effects of the drugs used or immune complications of the transplant.