

## Patient Information

# High Dose Chemotherapy with Melphalan and Autologous Stem Cell Transplantation (HDM-ASCT)



## *Treatment for AL amyloidosis*

AL amyloidosis is caused by the abnormal proteins, called free light chains, which are produced by abnormal cells, called monoclonal plasma cells, in the bone marrow. The chemotherapy treatment given to all AL patients is aimed at killing these abnormal cells and thereby eliminating the free light chains, which form the AL amyloid deposits in the tissues and organs. When this is achieved, the patient is said to have had a 'complete response'. In such patients, no new amyloid forms for as long as the response persists and existing amyloid deposits may slowly go away in many individuals, while organ function and clinical wellbeing improve and are maintained.

Unfortunately all the chemotherapy drugs damage normal cells in the bone marrow and elsewhere, as well as the abnormal cells which produce the amyloid forming free light chains. This is why chemotherapy has so many adverse side effects. The toxicity of chemotherapy limits the doses that can be safely given and thus its effectiveness. Many patients cannot tolerate enough treatment to obtain a complete remission and thus the best possible outcome.

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Fortunately, a treatment has been in use for many years that allows use of high dose chemotherapy with melphalan, the drug that is most effective in killing the cells that cause AL amyloidosis. Although this treatment also kills the essential normal bone marrow cells that are necessary for life, these can be replaced immediately by infusion of stem cells after the chemotherapy has been given, so that the bone marrow function is restored with the amyloid producing cells eliminated. This stem cell replacement treatment is called 'autologous stem cell transplantation' (ASCT) or just 'stem cell transplant' (SCT). It involves just collection of certain blood cells from the patient themselves and then reinfusion of these cells back into the patient after the chemotherapy dose.

The whole procedure of high dose melphalan and autologous stem cell transplantation (HDM-ASCT) provides prolonged complete responses in properly selected patients and many years with very good quality of life. A recent study of nearly 600 patients who underwent HDM-ASCT in Boston in the United States, between 1994-2012, found that many survived over 10 years and some were still in complete response 20 years after the treatment.

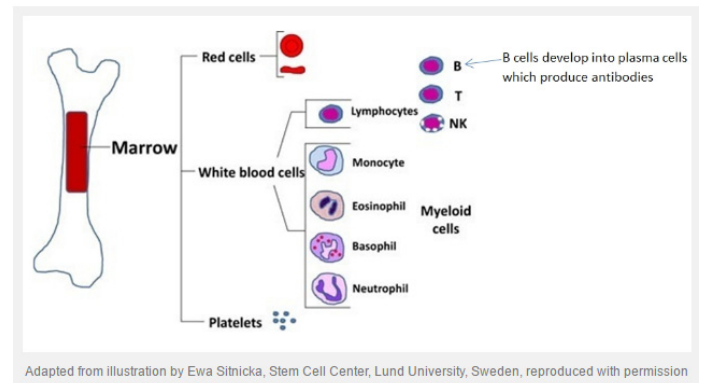
## ***Stem cell transplantation does not involve any operation or surgery***

**The word 'transplantation' is alarming to many patients because it is associated with replacement of organs like the kidney, liver and heart, involving major surgical operations. This is not the case for ASCT. The stem cells are returned in a manner similar to having a blood transfusion.**

## **What are stem cells?**

Stem cells are cells that have the capacity to produce different types of specialised cells. Many cells in our bodies have a limited lifespan, meaning that they need to be regularly replaced by new cells once that lifespan runs out. The specialised blood cells known as 'red cells', 'white cells' and 'platelets' that circulate in our bloodstream and carry out essential functions, have a lifespan of days (white cells and platelets) to months (red cells). The red cells carry oxygen round the body, the white cells fight infection and the platelets are necessary for blood clotting. They are constantly being replaced by new cells produced by the stem cells (also known as 'hematopoietic stem cells').

The formation of all new blood cells including the stem cells takes place in the bone marrow.



High dose chemotherapy can suppress all cells in the bone marrow including the normal stem cells as well as suppressing the abnormal plasma cells causing AL amyloidosis.

## ***Autologous stem cell transplantation (ASCT)***

Autologous stem cell transplantation (also known as 'stem cell rescue') is an ingenious way of working around this problem. It allows doctors to give patients the high dose chemotherapy that gives the best chance of killing all the abnormal cells that cause the AL amyloidosis. Then they can give back the stem cells which will restore all the functions of a normal bone marrow.

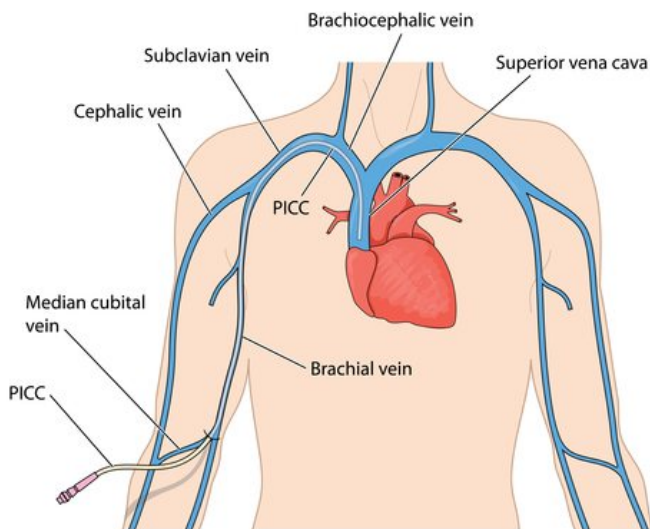
## ***HDM-ASCT- what's involved?***

### **Stage 1: Stem cell collection**

Stem cells are collected after stimulating the bone marrow to overproduce stem cells (mobilisation). This is done by administration of a small injection under the skin of granulocyte-colony stimulating factor (G-CSF) for a few days (some patient may also need an additional injection of chemotherapy). The stem cells are collected from the peripheral blood via a central venous catheter (a thin, flexible tube inserted via a needle into a vein in the arm or base of the neck or upper chest, and left in place). For stem cell collection, blood is taken from one intravenous line and passed through a so called apheresis machine, which separates out the stem cells and returns the rest

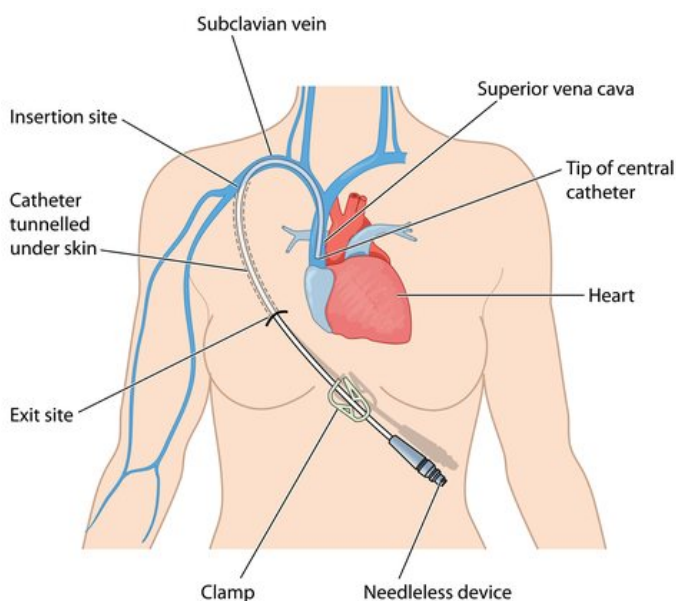
of the blood back to the body. Sometimes more than one session is required to extract sufficient stem cells. The stem cells are then preserved and frozen (they remain and can be used for up to ten years). The procedures the patient undergoes are injections of drugs such as G-CSF for several days to stimulate stem cell overproduction, insertion of the central line into the vein, and collection of the stem cells.

### PICC line inserted into an arm vein



### Central venous catheter inserted into the subclavian vein in the upper chest

*Central venous catheters may also be inserted into the internal jugular vein at the base of the neck*



## Stage 2: High dose melphalan (HDM)

Usually a few weeks after the stem cells have been harvested, the patient comes into hospital for the actual chemotherapy and transplant. At this time the patient is given the high dose chemotherapy with intravenous melphalan. This treatment suppresses all the bone marrow cells – the normal cells, as well as the abnormal plasma cells causing AL amyloidosis, and blood cell counts decrease within a few days. Melphalan may cause other side effects such as mucositis (sore mouth due to damage to the mucous membranes). Mucositis can be significantly reduced or prevented by sucking ice for an hour around the time of the infusion. This causes the blood vessels in the mucous membranes to constrict, so that less melphalan reaches them.

## Stage 3: Stem cell rescue – a ‘birthday’ for the new bone marrow

Within the next day, the patient’s own stem cells that were collected in Stage 1 are infused back into the bloodstream. This is just like a blood transfusion. No surgery is involved.

The infused stem cells then make their way to the bone marrow and grow to form the entire new marrow. It normally takes about two weeks for new blood cells to start being produced. This process is called engraftment. During this time, the blood cell counts drop to a low point called a ‘nadir’ before they start to rise as engraftment occurs. During this period, the patient is kept in isolation in order to avoid exposure to any infections until their immune system has re-established itself. Visitors are limited, diet may be restricted, and hospital staff coming in contact with the patient wear sterile gloves, masks and gowns. Most patients will get infections during this period and need antibiotics, blood or platelet transfusion.

Doctors perform regular blood tests so that they can tell when the patient’s blood cells have re-established themselves sufficiently to come out of isolation and go home.

## Stage 4: Recovery

Most patients can go home three to four weeks after the transplant. Fatigue is the major problem on discharge but that improves every week. Most patients are reasonably well in a month and all are back to normal by three months.

Doctors continue following up the patient with appropriate tests and scans, in order to check the response to treatment and monitor organ function. Recovery may take several months.

## ***Patient selection - who is likely to benefit?***

Patient selection is key to the success of this treatment. We now know that correct selection of patients avoids unnecessary toxicity from the procedure. About a fifth of all newly diagnosed patients with AL amyloidosis may be suitable for consideration for HDM-ASCT.

Assessment of the patient's overall health, including age and results of all the blood tests and imaging tests at the NAC evaluation, gives the NAC doctors a very good idea of which patients are most likely to benefit from HDM-ASCT and least likely to be endangered by the procedure. Patients with early stage disease, usually aged under 70 years, with relatively good kidney and heart function, can be potentially selected for a stem cell transplant. HDM-ASCT is more likely to be dangerous in patients with advanced stage AL amyloidosis and poor organ function, especially if the heart is affected (raised cardiac biomarkers), or if there is poor kidney function. The NAC doctors usually do not advise such patients to undergo HDM-ASCT.

If the NAC doctors recommend HDM-ASCT, it means that they think the patient is likely to derive very real benefit, hopefully for many years, and that the risk is not high. With any patient undergoing a stem cell transplant, there is a small but real risk of unexpected serious complications and a very small risk of death due a very serious complication during the transplant. Even amongst

carefully selected candidates, the risk of death from the procedure is around 5%, or may even be as low as 2% in some very good risk patients.

In recent years, it has also become apparent that some patients who are not well enough to undergo HDM-ASCT at the time of diagnosis, may improve sufficiently from a course of bortezomib-based chemotherapy that they may become eligible candidates for HDM-ASCT at a later stage.

It is crucial that HDM-ASCT for amyloidosis is carried out in centres experienced in transplanting patients with amyloidosis.

## ***Conclusions***

The attitudes to transplantation have changed over the years and we can do this far more safely than ever before. Due to out of date information, unfortunately, many patients arrive at the NAC with a wary attitude towards the possibility of stem cell transplantation. Clearly transplantation is not a procedure suitable for all. It is not considered or recommended without careful patient selection. It will be recommended if the NAC doctors believe that it gives you the best chance of a good long-term survival. When a transplant is recommended you need to be clear about the risks and benefits of the procedure. In most cases, you will need to be seen by a haematologist at one of the centres experienced in amyloidosis transplants, who will re-assess your suitability for transplantation. You and your treating haematologist, along with the team from the transplant centre, can then make a final decision to proceed. A successful stem cell transplant still remains the best available treatment for AL amyloidosis.

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