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Protocol of Procedure for Autograft of Non-Cryopreserved Hematopoietic Stem Cells at the EHU of Oran (Algeria)

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Abstract

Haematopoietic stem cell (HSC) autotransplantation after therapeutic intensification consists of the administration of intensive, highly aplasitic chemotherapy followed by reinjection of an autologous graft that allows rapid haematological reconstitution. This procedure shortens significantly the duration of theoretical aplasia, and in fact, decreases the morbidity and mortality of the intensive treatment to an acceptable threshold for the patient.

Its cost has made it inaccessible in many countries, particularly in Africa where there are only six countries with 16 centers compared to 679 in Europe. In Algeria, the first HSC autotransplant was performed in 1998 at the CPMC in Algiers. Then it was at the EHU 1er November in Oran where the first autotransplant was performed in May 2009. The department of haematology and cell therapy subsequently became a transplant center with a national vocation, going from 11 autotransplants in 2009 to 150 autotransplants in 2019. This significant increase in the number of autotransplants shows that our team has been able to master the procedure with less mortality thanks to a well-coded protocol which has been improved over the years.

The objectives of my work is to share the protocol of the HSC autograft procedure which is the fruit of my experience of 4 and a half years of residency in haematology and especially of two years as a specialist in haematology and head of the autograft unit during real life in the university hospital of Oran.

Keywords: *Autologous transplantation procedure; Non-cryopreserved haematopoietic stem cells; cell therapy; lymphoma; multiple myeloma.*

Introduction

Autologous transplantation was introduced into the haematology therapeutic armory in the 1980s and has undergone numerous developments.The autograft stem cell transplantation after therapeutic intensification consists of the administration of intensive, extremely aplasitic chemotherapy, followed by reinjection of an autologous graft that allows rapid haematological reconstitution. This procedure shortens significantly the duration of theoretical aplasia, and in fact decreases the morbidity and mortality of the intensive treatment to a threshold acceptable to the patient.

HSC autotransplantation was performed for the first time in Algeria in 1998 at the haematology and cell therapy department of the CPMC in Algiers (1). Ten years later a second centre in the west of the country at the EHU of Oran performed its first autograft in May 2009(2).

Development of the procedure:

The number of autografts performed at the EHU of Oran has been increasing steadily over the last 10 years and reached its peak during my tenure, estimated at 150 autografts in 2019 compared to 11 autografts in the year of the beginning of the activity (2009), which is mainly explained by the mastery of the procedure by adapting it to the progress of the field of transplantation, the local conditions and the means available (training of the unit's team for the central venous catheter placement in the unit, which avoided the need to move patients to the dedicated intensive care unit for this purpose, shortening of the post autotransplant aplasia period by using growth factors during the aplasia period, use of preventive anticoagulation during the procedure, which clearly reduced the incidence of thrombosis(4),(5)

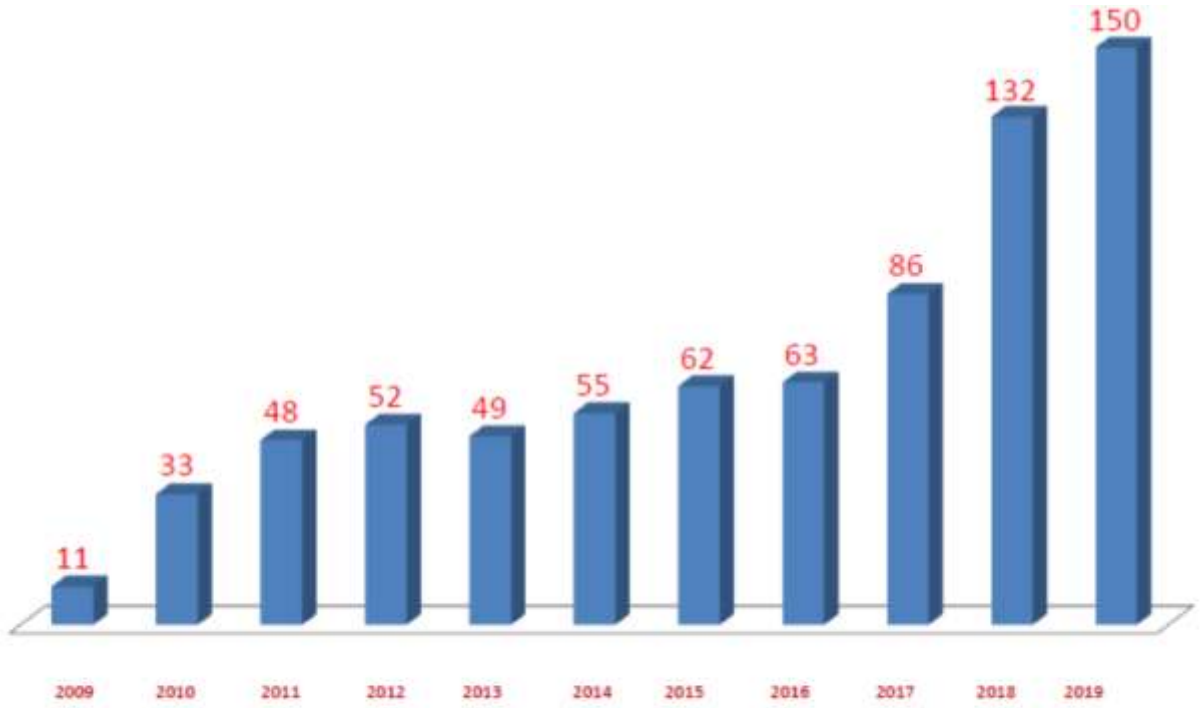


Figure 1 :Global autograft activity in EHU of Oran(2009-2019)

Eligibility for an Autograft Procedure :

- Age: Generally less than 65 years, however, in our current practice, we can autograft subjects who are older than 65 (65-75 years) (6),(7). practically we select them according to the CIRS (Cumulative Illness Rating Scale-Geriatric), this score consists in evaluating from the interrogation, the clinical examination, the pre-transplant assessment and/or the patient's file, if there is an organic impairment, Functional disorders and limitation of activities, we consider that the patient who has an age greater than 65 years is eligible for an autograft unless the CIRS-G is greater than 06, namely in our current practice we score it at 4 for all patients over 65 years.This rating is made in the context of haematological malignancies to be transplanted such as myeloma or lymphoma(8) .
- General condition: The procedure requires a good or preserved general condition with an ECOG 0 to 3, or 4 (disabled patient with a paraplegia for example, sequelae of a complication of a Myeloma), which does not prevent him from moving around with the help of a wheelchair and which can be considered as independent and capable of taking care of himself, provided that he is

rated at least 3 or more on the AGGIR autonomy evaluation scale (Autonomy Gerontological Groups Iso resources)(9)

- Pre-transplant assessment: The safe performance of the autograft, whose main risk lies in the placement of the central line and the period of aplasia, requires patient selection to minimise the risk of the procedure (10).

The pre-transplant consultation must be carried out by the referring doctor with the presence of the psychologist, where the procedure is explained to the patients, its progress, its advantages, its possible complications, and the consent to be signed by the patient (ART 44 of the Algerian deontological code), with a good interrogation, a meticulous clinical examination, and verification of the pre-transplant assessment.

The procedure requires the absence of comorbidities such as heart disease with a left ventricular ejection fraction of less than 50% or poorly balanced hypertension, poorly balanced diabetes, obstructive or severe restrictive respiratory disorders (if slight or moderate disorders, to be discussed in the transplant committee on a case by case basis), disturbed liver balance, disturbed renal balance except in the case of multiple myeloma,Even if renal clearance according to cockroft is less than 40ml/min,ASCT can be performed safely by reducing the dose of Melphalan from 200mg/m2 to 140mg/m2. Our center even participated with 21 patients out of 44 in an international prospective and observational study over a period of 2 years (2017- 2019), which proved the acceptable toxicity of the procedure and above all a good haematological and renal response post-transplantation in patients with newly diagnosed multiple myeloma with renal insufficiency (11).The patient's infectious status must also be checked in particular progressive infection (tuberculosis, hepatitis B, hepatitis C, HIV ...)

Indications

ASCT is not limited to haematological malignancies, which nevertheless constitute the main indications. Indeed, autograft may be of interest in some very specific cases of solid tumours and even in autoimmune diseases. The EBMT publishes recommendations that can serve as a basis for discussion (12). These are summarised in Figures 2 and 3,

It should be noted that in our department there is a particular indication for autotransplantation of HSC in advanced stage Hodgkin's lymphoma in first line after first line treatment for which ASCT has proven its

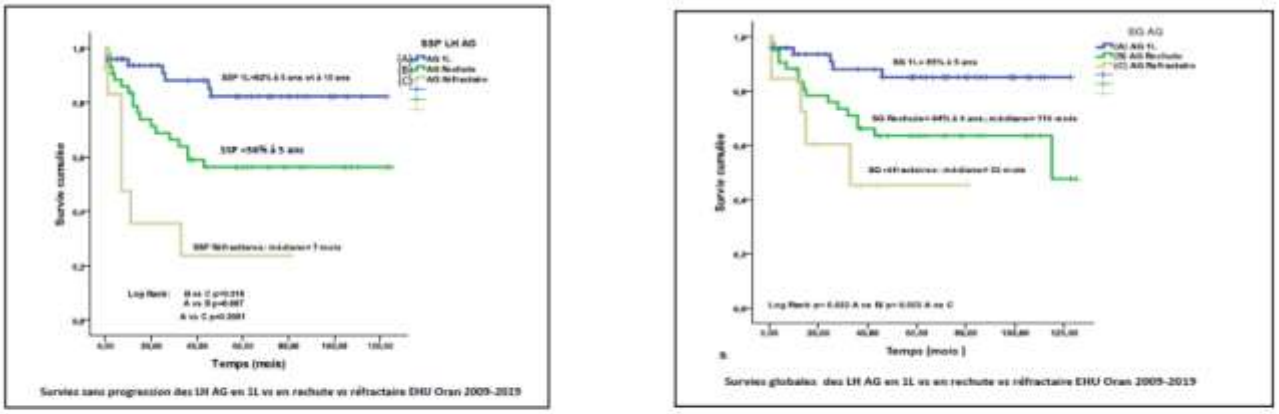
effectiveness in terms of progression free and overall survival even though it is well known that it is not recommended by EBMT.M Bekadja et al published a relevant work showing the reasons to do autotransplantation as 1st line treatment for these patients, namely that most of our patients with Hodgkin's lymphoma are diagnosed at an advanced stage and that the lack of means in our country would not allow us to catch them up correctly in case of relapse, which is an additional reason to privilege autograft after 1st line treatment if this procedure would have proved its safety and efficiency in terms of survival(13)(14). In this context we calculated the survival of our patients with autografted HL in first-line treatment (Figure 4 and 5). Our results are comparable to those of N Arakelyan et al (15) who evaluated 76 pts with high-risk HL (stages IIB, III and IV) treated with 4 cyclesof ABVD followed by BEAM and autograft intensification, in which the OS and PFS at 5 years were 86% and 75%.

Leucémies aiguës myéloïdes	
Rémission complète 1, faible risque	**Optionnel**
Rémission complète 1, risque intermédiaire	Standard de prise en charge
Rémission complète 1, haut risque	Optionnel
Rémission complète 2	Optionnel
Leucémie myéloïde chronique	Expérimental
Leucémies aiguës lymphoïdes	
Rémission complète 1	**Expérimental**
Syndromes myélodysplasiques	
Leucémie aiguë myéloïde (20–30 % blastes)	Optionnel
Leucémie lymphoïde chronique	Optionnel
Lymphomes	
LBDGC, IPI 2-3	Optionnel
LBDGC, rémission complète 2	Standard
LNH du manteau, rémission compète 1 ou 2	Standard
Lymphome lymphoblastique	Optionnel
Lymphome de Burkitt	Optionnel
LNH folliculaire de haut risque	Optionnel
LNH folliculaire, rémission complète 2 ou plus	Standard
Lymphome T	Optionnel
Lymphome de Hodgkin, rémission complète 2	Standard
Lymphome de Hodgkin réfractaire	Optionnel
Myélome multiple	Standard
Amylose AL	Optionnel

Figure 2 : Autograft indications for hemotologicak malignancies

Affections auto-immunes	Cytopénies auto-immunes	Optionnel
	Sclérodermie	Optionnel
	Polyarthrite rhumatoïde	Optionnel
	Lupus érythémateux disséminé	Optionnel
	Maladie de Crohn	Optionnel
	Sclérose en plaques	Optionnel
Tumeurs solides	Cancer du sein	Optionnel
	Tumeur à cellules germinales	Optionnel/ standard
	Cancer de l'ovaire	Expérimental
	Médulloblastome	Expérimental
	Carcinome pulmonaire à petites cellules	Expérimental
	Sarcome des tissus mous	Expérimental

Figure 3: autograft indications for non—hematological pathologies



Figures 4-5 : Progression free and overall survival of autograft HL in 1st line vs AG of R/R HL for the EHU patient series(Oran,Algeria)

The Stages of the Procedure

Hospitalization: Patients are hospitalized on D-5 AG in the autograft unit which is completely separate from the allograft unit. It complies with the recommendations of the European Bone Marrow Transplant Association EBMT(16) . It has 8 individual rooms, with individual sanitary facilities and using air sterilised by a Plasmair®(air purification device) placed in each room. Access to the patients' rooms is

through an airlock allowing for hand washing, the wearing of a mask, a gown, a cap and overshoes. One room is equipped as a dedicated operating theatre for central venous catheterization.

The medical staff consists of one assistant in Haematology and two residents. The paramedical staff consists of one nurse and one nurse's aide for 3 patient rooms providing continuous care. (Figure 6)

Screening for BMR: Triple swab (nasal, pharyngeal, and rectal) and cytobacteriological urine exam, initiated on the day of admission of the patient to screen for multi-resistant bacteria.

3-Mobilization of HSCs: This is achieved from D-5AG by one of the two types of G-CSF, originator (Granocyte®=lenograstim, Neupogene®=filgrastim)(17) and filgrastim biosimilars (Zarzio®)(18). The dose used is 15ug/kg/d for lymphoma and 10µg/kg/d for MM. Osmani et al demonstrated in his work that there is no significant difference between the two doses for the mobilization of HSCs during autotransplantation of patients with MM in a cohort of 221 pts (19). The mode of administration is in the form of subcutaneous injections, lasting 5 to 7 days depending on the number of cytapheresis sessions. The definition of HSC mobilization is established by the French health establishment (Figure 2) :Or after collection of HSC by cytapheresis(20),(Figure 7).

The definition of HSC mobilization is established by the French health establishment (Figure 8) :Or after collection of peripheral stem cells by cytapheresis(20),(Figure 9) .

In our current practice, PSC counting is only initiated for lymphomas, a circulating CD34 cell count at least equal to 20c/ul allows collection by cytapheresis. There is a possibility of autograft with failed mobilization in patients with multiple myeloma (CD34 count between 1 to 1.99 x 10.6/kg) and this is done after the agreement of the staff. (21)

Plerixa for which is a selective and reversible antagonist of CXCR4 receptors responsible for stem cell retention in the bone marrow microenvironment is used in case of mobilization failure (peripheral CD34 count<10c/µl)(22) at a dose of 0.24mg/kg 6H to 11H before the collection session(22). The use of the generic Plerixafor (Mozifor®) has not shown a significant difference in the efficiency of HSC mobilization(23). Mobilization can be performed with chemotherapy, but it is not common practice (cyclophosphamid 1.5 to 4g/m2, Ara-C HD, Etoposide...), GCSF to start on Day 4 of CHIMIO collection on Day 8.

4-Central venous catheterization: The central venous catheterization remains essential during intensifications followed by autograft of PSC of hematological malignancies (multiple myeloma, non-

Hodgkin's lymphoma, Hodgkin's lymphoma). It is considered as a key to provide a large-caliber venous access to cytapheresis by allowing the collection of HSC, as well as the infusion of venotoxic products such as chemotherapy (melphalan, etoposide, aracytine...), parenteral nutrition...), antibiotic therapy (in particular vancomycin), parenteral nutrition...The central venous catheterization is done in the autograft unit, by medical staff (assistants or residents of the unit).the type of central venous catheter used is HEMOCLAV (VYGON) with two lumens, polyurethane, multiperforated distal end and proximal end equipped with a silicone clamping area, 1 trocar needle, 1 metal guide, two lockable plugs, 2 lockable membrane plugs, 2 dilators. For the placement of the line there are several central venous access techniques used. At the level of the internal jugular vein, there are several routes that allow access to the IJV, the most widely used and easy to master is the lateral DAILY route. The patient is in a declive position, head situated in a sagittal plane, with a small log under the shoulders. The operator punctures at the level of the center of Sedillot's triangle, the needle is directed downwards, in a para sagittal plane, at an angle of 30° to the skin plane. Puncture of the vein is generally easy with the help of an echodoppler, but in the event of difficulty, another venous route can be considered, such as the subclavian or femoral route.The position of the catheter should be checked immediately after insertion. A presumption of correct position can be given by the clinic: a clear and rapid flow of the infusion fluid and a clear backflow of blood when the bottle is lowered under the bed. However, this presumption is not sufficient and a radiological check should be performed immediately. A frontal chest X-ray can be used to check both the absence of immediate complications secondary to the insertion (false route, haemothorax, pneumothorax..) and the correct position of the distal end of the catheter (junction between the superior vena cava and right atrium).

To limit the risk of thrombosis, any catheter that is not in a "central" position, i.e. at the junction of the superior vena cava and the right atrium, must be repositioned.

5-Peripheral stem cell collection: Collection is performed using a device (Figure4)that selects circulating CD34+ cells and collects them via a venous approach toa blood bag (Future Graft).

Each cytapheresis session lasts approximately two to five hours, during which more than thirty litres of blood or six times the average blood volume is processed. Collection can be done daily until the target CD34+ cell count is reached. The cytapheresis process can take from one to four days depending on the level of CD34+ cells collected. Collection of PSCs is performed from day 5 (morning) by cytapheresis (Optia® or Fresinus®) (Figure 10). The biologist counts the WBCs on an automated FNS machine, such

as Beckman Coulter®, the CMNs on a blood smear and the CD34s on a flow cytometer such as Facs cantoll® with 8 colours. It should be noted that the mortality rate during cytapheresis is very low and estimated at three deaths per 10,000(24). Hypocalcaemia is the most frequent complication which often manifests itself by tingling of the mouth, hands and feet, sometimes dizziness. To prevent this dreaded complication, the apheresis rate is reduced with an increase in the blood/citrate ratio and calcium supplementation treatment from the start of mobilization.

Citrate toxicity is a rare complication during the cytapheresis process, as citrate is an anticoagulant used to prevent blood clotting during PSC collection. Other complications, particularly ionic ones, are therefore rare.

6-CONSERVATION OF THE GREFFON: In our current practice, peripheral stem cells are not cryopreserved, they are put in the refrigerator at +4°C.(25),(26). As a preventive measure, it is necessary to ensure that the refrigerator door is well sealed, to shake the HSCs twice a day, especially for lymphomas, the conservation of HSCs in the refrigerator is durable compared to myeloma with regard to the duration of conditioning which is different between the two.

Freezing (Cryopreservation) is sometimes indicated at our level while waiting for a transplant (infectious problem, the level of CD34 collected is not reached, the case of lymphoma for example), the HSC are frozen in a freezer at -80°C with a cryopreservative such as dimethylsulfoxide (DMSO).

DMSO maintains the viability of the cell by preventing the formation of ice crystals inside the cells during storage, the disadvantage of this type of freezing, viability would only allow a storage time of a few months. The EHU has a single freezer at 80°C (Figure 11)

Freezing in liquid nitrogen at -196°C or in nitrogen vapour at 156°C is not done at the EHU of Oran due to lack of means.

7-Therapeutic conditioning: or intensification varies according to the type of malignancy to be treated: for MM the protocol used is high-dose Melphalan (140 to 200 mg/m2), for lymphomas the protocols used are BEAM or CBV, or BeEAM or EAM DZ or modified EAM (27). The schematics of the different protocols are shown in figures [12-13-14-15].

In MM the choice of Melphalan dose depends on the response in pre-transplant status, if partial response 200mg/m2 otherwise if CR or VGPR 140mg/m2(28)(29). This dose is also used for subjects over 65 years of age and with renal failure regardless of age(28). Melphalan is easily administered by diluting it in 100 ml of 9% SSI and placing it in a central venous catheter. The infusion should last 30 minutes.

For lymphoma protocols (NHL and HL) 4 protocols have been used since the beginning of autograft activity at the EHU (figure 10), the most used of which is the modified EAM of Bekadja et al(27). The Algerian or modified EAM differs from the English EAM (J Loke et al)in the dose of cytarabine is increased.In the english EAM the dose is 200mg/m2/24h D-5, D-4, D-3, D-2 (30),It 10 times less than the dose of ara-C in the modified EAM.

8-Reinjection of the graft: This is done 24 hours after the infusion of the melphalan (the duration of elimination by the renal route of the latter) and 48 hours after if renal insufficiency(31), by a simple transfusion of the graft in 20 to 30 minutes after premedication with corticosteroids and antihistamines.

9-Management of post-transplant aplasia: this is a decisive stage, during which serious complications may arise, such as metabolic disorders, mucositis, anaemia requiring transfusions of irradiated red blood cells, and severe thrombocytopenia requiring transfusions of irradiated apheresis platelet cells. Infections, in particular bacterial (E.coli, clostridium...), fungal (aspergillosis) or viral (HSV reactivation, VZV, CMV...), can lead to sepsis, requiring medical haematological resuscitation, most of the time performed in situ. In the case of septic shock, transfer to intensive care is recommended. In order to avoid these various complications, a preventive support treatment is administered as soon as the patient is hospitalized in the transplant unit.Prevention of Melphalan-type conditioning toxicity is done in two ways. Prevention of renal toxicity by hyperhydration at a rate of 3L/m2 alternating between SGI and SSI, to be started the day before conditioning until D0 AG. Prevention of digestive toxicity is done by antiemetics of the APREPITANT type (neurokinin1 receptor antagonist); EMEND® 150mg IV administered 15 minutes before the Melphalan infusion.Another anti-emetic such as SETRON.ZOPHREN® 8mg administred intravenously twice daily D1 D2 D3.Usually DEXAMETHASONE is associated with this protocol as it has proven to be effective in preventing advanced grade nausea/vomiting, administered IV 12mg D1 and 8mg D2 D3 D4. (32),(33).Severe mucositis is prevented by simple means such as intravenous cryotherapy, which consists of giving the patient small ice cubes to suck on for 10 minutes before, during and after the infusion of Melphalan(34).A per os antifungal agent such as Econazole 150mg to be sucked without

swallowing the day before reinjection until the end of aplasia(34). Mouthwash is done with Betadine® 1% or serum bicarbonate 1.4% 4 to 6 times a day.

For the conditioning of lymphomas, whether Hodgkin's or non-Hodgkin's, and more particularly BEAM or modified EAM, the same preventive measures are used as for Melphalan, including the addition of an eyewash which is an antibiotic and corticoid combination; CHIBROCADRON® and artificial tears to prevent the ocular toxicity of Cytarabine, and an H1 antihistamine; TELFAST® (FEXOFENADINE), one tablet in the evening, to prevent its cutaneous toxicity.

The prevention of infectious complications during aplasia begins with digestive decontamination. There are two types of decontamination, total digestive decontamination (aerobic + anaerobic) which requires sterile food and a sterile environment which is not done at our level. In our current practice we do partial digestive decontamination (aerobes only): to leave the barrier effect of the anaerobes requiring a protected food (not sterile), isolation and protected environment.

On the drug side, pneumocystis and opportunistic bacterial infections are prevented with BACTRIM® (SULFAMETHOXAZOLE/TRIMETHOPRIME) 400/80mg one tablet per day(35), and viral infections with ACYCLOVIR 200mg twice daily. In case of advanced mucositis, parenteral treatment can be switched to. Parenteral route.

Antithromboembolic prophylaxis is carried out with a LMWH-type anticoagulant; LOVENOX® (ENOXAPARINE) 4000IU per day by subcutaneous route, which is started 24 hours after the central line is inserted (D-1AG) until the patient is discharged from the hospital (4),(36). In the event of thrombosis, the curative dose is switched to 100IU/kg/12H with monitoring of the APTT and maintenance of platelet levels above 20 Giga/L. Furthermore, it is preferable to use TINZAPARINE in the event of thrombosis at a rate of 175IU/KG/D, which is given in a single injection per day instead of two. Unfractionated heparin (UFH) still has a place in renal failure with a cockroft renal clearance of <30ml/min because UFH is pharmacokinetically eliminated from the tissue, whereas LMWH is eliminated by the kidney (increased risk of cerebral haemorrhage).

If the patient has a femoral venous catheter, it should preferably be removed in the first few days post-transplant (D2 D3) because the length of time the central catheter is maintained is a predictive factor for thrombosis during the autograft procedure, particularly at the femoral site(4).

The prevention of haematological complications is done by blood transfusions of red blood cells and platelet cells from irradiated apheresis. Blood irradiation is done at a dose of 25-45 Gy, from D1 conditioning until 6 months after D0AG. The EHU department has a gammacell® type irradiation device (Figure 10) which enabled the staff to irradiate labile blood products on site. The transfusion threshold for haemoglobin is 8g/dL for normal subjects and 10g/dL for cardiopaths(38) and 20Giga/L for platelets. The use of growth factors of the GCSF type is done by FILGRASTIM at a rate of 5µg/kg/d at D5AG for MM and D1AG for lymphoma with the aim of shortening the duration of aplasia which means significantly reducing the frequency of severe mucositis, avoiding febrile neutropenia and its complications and the duration of hospitalisation and improving the graft take. This therapeutic approach was not considered to be predictive of thrombosis during the autograft procedure. (4). GCSF is routinely discontinued if the neutrophil count is >0.5 Giga/L.

10-Graft uptake: evidenced by neutrophil count >0.5G/L for more than 3 days without the use of growth factors and persistent platelet count >20Giga/L for at least 7 days without platelet transfusion(39).

11-Post-autotransplant follow-up: The patient, once out of the aplasia phase, without complications, leaves the transplant unit and is reviewed on a monthly basis (clinical and biological examination), then an evaluation of the haematological malignancy will be carried out at D100AG, by imaging (CT or Pet Scan for lymphoma, for example) and biology (haemogram, calcium levels, renal function, immunological assessment and bone marrow sampling to perform a myelogram and search for residual disease by flow cytometry in MM, for example). Once complete remission has been achieved, the patient is reviewed every 3 months for one year, then every 6 months thereafter.

Within the same framework, a secretariat dedicated to this follow-up has been set up. Thus, patients outside Oran are examined by their referring doctors in their haematology departments and their biological analyses are sent to us by FAX or by e-mail to the department's transplant secretariat. In this way, we remain close to our transplant patients through permanent telephone contact.

HSC mobilization	Peripheral CD34
Difficult mobilization	**< 20Cell/µl**
Sufficient mobilization	**20-40 Cell/µl**
Optimal mobilization	**> 60Cell/µl**

Figure 6: Definition of mobilization according to EFS

HSC mobilization	CD34 collected after cytapheresis
Optimal mobilization	**≥5.106/kg**
Sub optimal mobilization	**≥2.106 et <5.106/kg**
Mobilization Failure	**2.106/kg**

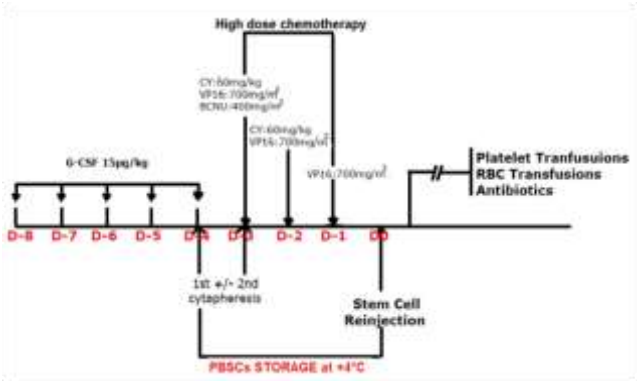
Figure 7: Mobilization according to the number of CD34 collected

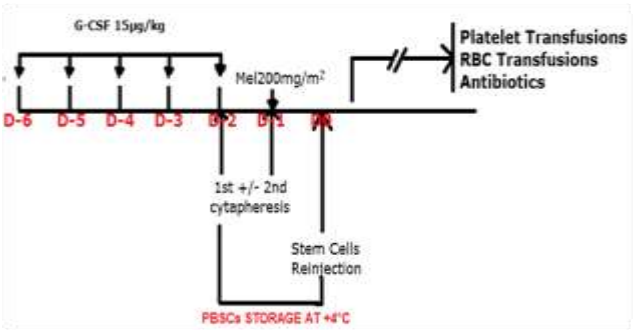
Figures 8: Autograft unit

Figure 9: Cytapheresis Room

Figure 10: Apheresis Device

Figure 11: Freezer -80°C





ProtocoleEAM	Dose	Day
Etoposide	200mg/m2	-5-4-3-2
Cytarabine	1000mg/ m2/12h	-5-4-3-2
Melphalan	140mg/m2	-1

Drugs	Dose/m2	D-
BCNU	300	-6
Etoposide	800	D-5 to D-2
Cytarabine	800	D-5 to D-2
Melphalan	140	D-2

Figures 12-13-14-15:

Conditioning for lymphomas	**Number of ASCT for HL (2009-2019)**	**Numbuer of ASCT for HNL (2009-2019)**	**Total (2009-2019)**
EAM Bekadja	**36**	**33**	**69**
BEAM	**45**	**20**	**65**
BENDA EAM	**5**	**6**	**11**
CBV	**15**	**00**	**15**

Figure 16: Conditioning protocol for autograft for lymphomas

Figure 17: Gammacell Irradiator

Figure 18: Transplant Departments in Algeria

Conclusion

Autologous stem cell transplantation has become a common practice, especially due to the relative ease of collection by cytapheresis with conventional haematopoietic growth factors (G-CSF) and new mobilizing agents such as Plerixafor.

The particularity of the center where I was trained and worked for two years as a practitioner and head of the autograft unit (from March 2019 to April 2021) is the use of non-frozen cell grafts(5) . This method is

less expensive and requires protected individual rooms and a plasmair or air purifier and a minimum of equipment (flow cytometer .a cell irradiator) (2),(3).

The idea behind the publication of this work is to share with my Algerian transplant colleagues from other transplant centers that have already started the activity (6 centers) and the next centers (4 centers) whose project is underway (Figure 9) and why not with other centers throughout the world, particularly developing countries, our protocol used at the EHU, which is effective, well codified and represents the result of 10 years of experience.

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