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Autologous Hematopoietic Stem Cell: Experience of the Hematology and Cell Therapy Department of the Grand Hôpital De l'Est Francilien (Meaux-France)

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Abstract

Introduction: *Autologous hematopoietic stem cells after therapeutic intensification is considered a standard in the management of several pathologies. The reinjection of hematopoietic stem cells associated with the use of growth factors makes it possible to significantly reduce the duration of medullary aplasia induced without completely eliminating the risk of death.*

Objective: *Double, identify the indications for the autograft and describe the complications observed during the procedure.*

Material and Methods: *Descriptive cross-sectional study carried out in the hematology and cell therapy department of the Grand Hôpital de l'Est Francilien (Meaux - France). It concerned the records of patients treated with at least one autologous hematopoietic stem cell transplant between January 2012 and July 2019 (7 ½ years). The accompanying chemotherapy and the transplantation protocols varied according to the type of hemopathy. Four parameters were analyzed: the indication, the duration of the chemo-induced aplasia, the transfusion requirements and the complications*

Results: *The study involved 114 cases for a total of 130 autografts. The average age was 56 years, with a sex ratio equal to 1.4. The main indications were : multiple myeloma (55.3%) and diffuse large B cell lymphoma (35%). The average time to retrieve an absolute number of neutrophils greater than 1.000 cells / mL was 7 days. The average recovery time for platelets greater than 50.000 / mL was 18 days. The average number of transfused erythrocyte concentrates was 2. The average number of platelet units was 4. The main complications were digestives, infectious and cutaneous. The graft-related mortality was 3.5%.*

Conclusion: *The multiple myeloma of the young subject and the diffuse large B cell lymphoma constitute the essential indications of the autograft. Oral mucositis and fever are major complications. Death due to transplantation is less than 5%.*

Keywords: *Autograft, Hematopoetic stem cells, Hemopathy*

1. Introduction

Autologous hematopoietic stem cell transplantation was developed in 1976 at Saint Antoine Hospital in Paris, France. It is considered the reference therapy for many hematological malignancies and some solid tumors [1]. There are currently nearly 20,000 operations carried out each year in Europe. Conditioning chemotherapy depends on the type of pathology to be treated. It is sometimes at the origin of a severe aplasia. The use of hematopoietic growth factors and resuscitation measures that accompany autografting reduces the duration of this aplastic anemia and therefore the mortality rate [2, 3]. This survey was conducted in the hematology and cell therapy department of the Grand Hôpital de l'Est Francilien (Meaux - France). It had a dual objective, to list the main indications of hematopoietic stem cell autograft and to describe its complications at short term.

2. Materials and Methods

This was a descriptive cross-sectional study carried out in the hematology and cell therapy department of the Grand Hôpital de l'Est Francilien (Meaux - France). It concerned the records of patients treated with at least one autologous hematopoietic stem cell transplant

between January 1, 2012 and July 31, 2019 (7 ½ years). These patients were hospitalized in sterile positive-pressure chambers. The accompanying chemotherapy and the transplantation protocols varied according to the type of hemopathy :

- Three to four cycles of induction therapy were administered prior to peripheral blood stem cell (PBSC) collection. PBSC mobilization was by granocyte-colony stimulating factor (G-CSF) injections combined with chemotherapy (cyclophosphamide for multiple myeloma or chemotherapy of hemopathy).
- The collection of the PBSC was done by cytapheresis.
- The graft was kept in liquid nitrogen (- 180 ° C) and thawing was done on the day of autografting. In order for this to be achieved, the graft richness had to be greater than or equal to 3.10^6 CD34 + cells per kilogram of the patient's weight.
- A solution of sodium bicarbonate 1.4% associated with chlorhexidine-chlorobutanol was administered in mouthwash to prevent mucositis.
- The hematopoietic growth factors used were either pegfilgrastim administered on day 2 post autograft or filgrastim administered for 5 days from day 5 post autograft. Additional injections of filgrastim were sometimes given in case of deep and prolonged neutropenia with infectious problem.
- Platelet unit transfusions were systematic in the presence of platelet counts <20.000 / mL and / or the existence of a bleeding syndrome.
- Transfusions of red cell concentrates were systematic with a hemoglobin level of less than 8 g / dl. Between 8 and 9 g / dL transfusion depended on whether or not there was evidence of clinical intolerance or comorbidity (especially cardiac).

Four parameters were analyzed: the indication, the duration of the chemo-induced aplasia, the transfusion requirements and the complications. Statistical analyzes were processed by SPSS software.

3. RESULTS

The study involved 114 cases for a total of 130 autografts.

The average age at transplant was 56 years [21 years - 70 years], with a sex ratio equal to 1.4. Twenty-eight autografts were performed in patients over 65 years of age, including 25 patients in multiple myeloma.

The indications for hematopoietic stem cell autograft are shown in figure 1. The different types of lymphoma encountered are shown in figure 2. Eighty-eight patients had one autograft. Sixteen patients had have 2 autografts. A double autograft for eleven of them (9 multiple myelomas and 2 Hodgkin's lymphoma). An autograft at diagnosis and the second for a relapse for the other five.

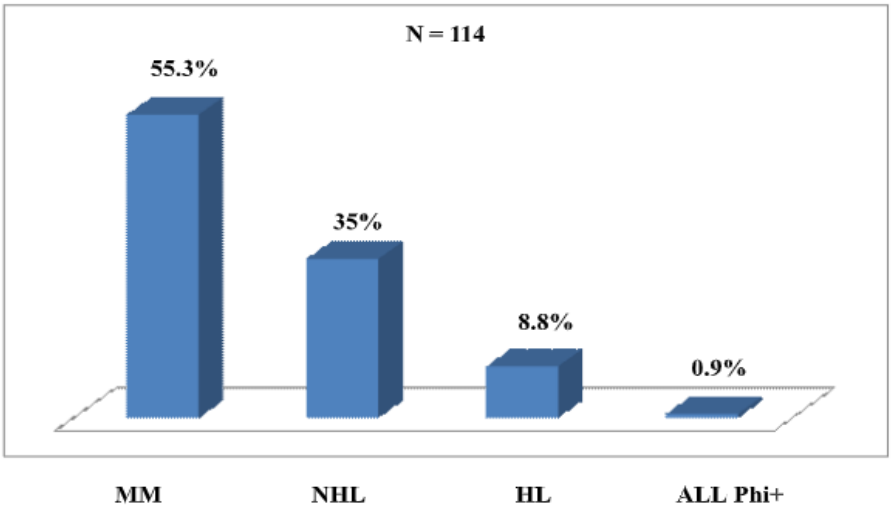

Figure1: *Indications of autologous hematopoietic stem cell transplantation at the Grand Hôpital de l'Est Francilien (Meaux), from January 2012 to July 2019.*

MM: multiple myeloma, NHL: Non Hodgkin's lymphoma (diffuse large B cell lymphoma), HL: Hodgkin's lymphoma, ALL Ph+: Acute lymphoblastic leukemia with chromosome Philadelphia positive

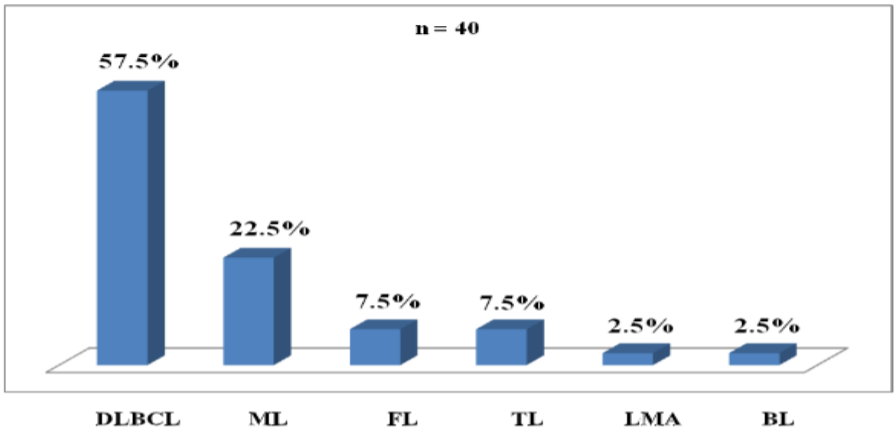

Figure2: *distribution of different types of lymphomas treated by autologous hematopoietic stem cell transplantation at the Grand Hôpital de l'Est Francilien (Meaux), from January 2012 to July 2019.*

DLBCL: Diffuse Large B Cell lymphoma, ML: Mantle lymphoma, FL : Follicular lymphoma, TL : T lymphoma, LMA : Lymphoma of marginal area, BL : Burkitt's lymphoma

The average richness of the graft was 5.6 × 10^6 CD34 + cells per kilogram of patient weight [3.6 × 10^6 CD34 cells - 17.2 × 10^6 CD34 + cells].

The average time to retrieve an absolute number of neutrophils greater than 1.000 cells / mL was 7 days [4 days - 17 days]. The average recovery time for platelets greater than 50.000 / mL was 18 days [8 days - 45 days]. Two patients did not come out of aplasia. The average number of transfused erythrocyte concentrates was 2 concentrates [0 concentrate - 15 concentrates]. The average number of platelet units was 4 units [0 units - 24 units]. Two patients had no need for transfusion.

Table1: *observed complications after autologous hematopoietic stem cell transplantation at the Grand Hôpital de l'Est Francilien (Meaux), from January 2012 to July 2019.*

Complications	Effective	Frequency (%)
Neuropsychiatric		
Confusional syndrome	2	1.4
Access manic / Depression	5	3.5
Digestive		
Diarrhea	115	88.4
Vomiting	127	97.7
Mucositis	117	90
Hepatic cholestasis	9	7
Hepatic cytolysis	3	2.1
Gastrointestinal bleeding	3	2.1
Acute cholecystitis	1	0.7
Dermatological		
Toxiderma	34	26
Immunological		
Macrophage activation syndrome	1	0.7
Vascular		
Thrombotic microangiopathy	1	0.7
Kidney		
Renal failure	2	1.4
Infectious		
Fever	99	76
Fever without bacteriological documentation	47	36
Fever with bacteriological documentation	52	40
Septic shock	11	7.7

Table2: *Frequency of main complications according to the WHO grade of toxicity after autologous hematopoietic stem cell transplantation at the Grand Hôpital de l'Est Francilien (Meaux), from January 2012 to July 2019.*

Complication	WHO Grade				
	1%	2%	3%	4%	Total N
Mucositis	25,6	22,2	27,4	24,8	117

Vomiting	26,8	40,9	27,6	4,7	127
Diarrhea	23,5	23,5	32,2	20,8	115
Toxiderma	20,6	70,6	8,8	0	34

Due to severe vomiting and / or mucositis, parenteral nutrition was introduced in 71% of cases.

In cases of infectious complication, the most frequently found germs were gram-positive cocci bacteria. *Pneumocystis carinii* and *Aspergillus fumigatus* were found in one case each. Clostridium difficile infection was found in 8% (11 cases) of patients with diarrhea. The graft-related mortality was 3.5%. Three deaths occurred within 100 days after autologous transplantation: at 4, 48 and 55 day's post-autograft, in connection with severe sepsis and multiorgan failure.

A patient with Lyell syndrome died on day 106 in a sepsis table with macrophage activation syndrome. The oldest of these patients was 62 years old. Four patients died within 12 months of the autograft either from progression of their disease (I LH and 1 MM) or from an early relapse of MM after double autograft. Five patients died beyond the 12 months post-autograft including 3 for a relapse of MM, 1 for a relapse of LH and the last of pancreatic cancer.

4. Discussion

Multiple Myeloma (MM) of the young subject and high-grade lymphomas of malignancy constitute the main indications of self-grafting, as reported in the literature [1].

Therapeutic intensification followed by autologous transplantation in MM significantly increased progression-free survival (PFS) [4]. Despite the development of new therapies such as proteasome inhibitors and immunomodulators, it remains a standard of first-line treatment for people under 65 [5]. It practice in the elderly has remained controversial for a long time, mainly because of fears of a possible excess of toxicity [6]. In a French study, 50 patients with newly diagnosed MM over the age of 65 had autografting. They had previously received induction therapy based on 4 to 6 cycles of bortezomib associated, according to the patients, with lenalidomide, thalidomide or cyclophosphamide as well as with dexamethasone, according to standard diagrams. The therapeutic intensification was carried out according to the choice of the investigator by melphalan 140 mg / m2 or 200 mg / m2. Mortality related to the 100 day graft was 0%.

In our series, the mortality related to the transplant was zero in the so-called"elderly" subjects. These results demonstrate the interest and feasibility of an intensive approach, even for those over 65, at least in those without major co-morbidities.

The high proportion of NHL observed in our study can be explained by the fact that the consensual strategy for the first-line treatment of LBDGC in young subjects is an immuno-chemotherapy treatment followed by a therapeutic intensification with peripheral stem cell autografting. Indeed, most of these autografts were performed before the recent GAINED trial, which resulted in an adaptation of the treatment regimen to the TEP-scan response. The postponement of the autograft in the case of a complete metabolic response to PET scan performed after 2 courses resulted in a 2-year progression-free survival of 90%. These results are comparable to the regimens incorporating systematic autograft in consolidation [8]. The main complications found in our study are digestive and infectious, and the mortality associated with the 100-day graft is less than 5%. Our results join the data of the literature [1, 7].

Vomiting is usually minor. Oral mucositis appears to be a major toxicity with a high incidence of severe mucositis [9-11]. Its clinical consequences are important: intense pain, dysphagia, risk of undernutrition requiring parenteral nutrition and increased risk of infections due to the alteration of the mucosal barrier in patients who are otherwise neutropenic and immunocompromised. The mortality rate associated with superinfected mucositis ranges from 6 to 30% [12]. Despite the identification of certain risk factors such as sex, age or type of conditioning, preventive treatment options remain limited to date and only symptomatic treatment [11-13]. Prevention by oral cryotherapy seems promising and deserves to be tested on a large scale [14, 15].

5. Conclusion

The multiple myeloma of the young subject and the diffuse large B cell lymphoma constitute the essential indications of the autograft. Oral mucositis and fever are major complications. Death due to transplantation is less than 5%. Peripheral stem cell autograft is a technique that can be applied in subjects over 65 years of age without major co-morbidities.

REFERENCES

[1] Costello R, Venton G, Colle J, Labiad Y, Poullin P. Autogreffe de cellules souches hématopoïétiques. Paris, Elsevier. 2015, 13-06 0-A-10.

[2] Gorin NC. Hématologie et thérapie cellulaire. Historique de l'autogreffe de cellules souches hématopoïétiques : rôle actuel en hématologie. Nouveautés pour le traitement des leucémies aiguës myéloblastiques de l'adulte. Bulletin de l'Académie Nationale de Médecine Available online 15 June 2019. In Press, Corrected Proofhttps://doi.org/10.1016/ j.banm.2019. 03.0 25

[3] Passweg JR, Baldomero H, Bader P, Bonini C, Cesaro S, Dreger P et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40000 transplants annually. Bone Marrow Transplant.2016; 51(6):786–92.

[4] Moreau P, Attal M, Facon T. Frontline therapy of multiple myeloma. Blood 2015; 125(20):30 76-84.

[5] Passweg JR, Baldomero H, Bader P, Bonini C, Cesaro S, Dreger P et al. Impact of drug development on the use of stem cell transplantation: a report by the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2017; 52(2):191-6.

[6] Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet Lond Engl 2007;37 0:1209-18.

[7] Garderet L, Beohou E, Caillot D, Stoppa AM, Touzeau C, Chretien ML et al. Upfront autologous stem cell transplantation for newly diagnosed elderly multiple myeloma patients: a prospective multicenter study. Haematologica 2016; 101:1390-7.

[8] Rossi C, Bastie JN. Actualités thérapeutiques dans les lymphomes non hodgkiniens et le lymphome de Hodgkin. Rev Med Interne. 20 19; 40(4):246-54.

[9] Blijlevens N, Schwenkglenks M, Bacon P, D'Addio A, Einsele H, Maertens J et al. Prospective oral mucositis audit: oral mucositis in patients receiving high-dose melphalan or BEAM conditioning chemotherapy--European Blood and Marrow Transplantation Mucositis Advisory Group. J Clin Oncol. 2008; 26(9):1519-25.

[10] Colita A, Colita A, Bumbea H, Croitoru A, Orban C, Lipan LE et al. LEAM vs. BEAM vs. CLV Conditioning Regimen for Autologous Stem Cell Transplantation in Malignant Lymphomas. Retrospective Comparison of Toxicity and Efficacy on 222 Patients in the First 100 Days After Transplant, On Behalf of the Romanian Society for Bone Marrow Transplantation. Front Oncol. 2019; 9:892.

[11] Strobel ES, Bauchmüller K, Ihorst G, Engelhard. Frequency, severity and risk factors for oral mucositis after BEAM conditioning and autologous peripheral blood stem cell transplantation: a single center analysis and review of the literature. Leuk Lymphoma. 2007; 48(11):2255-60.

[12] Bourdelin M, Daguindau E, Larosa F, Legrand F, Nerich V, Deconinck E et al.

[13] La mucite post-allogreffe de cellules souches hématopoïétiques : facteurs de risque, conséquences cliniques et prévention. Pathol Biol (Paris). 2015; 63(2):106-10.

[14] Vokurka S, Bystrická E, Koza V, Scudlová J, Pavlicová V, Valentová D et al. Higher incidence of chemotherapy induced oral mucositis in females: a supplement of multivariate analysis to a randomized multicentre study. Support Care Cancer. 2006; 14(9):974-6.

[15] Batlle M, Morgades M, Vives S, Ferrà C, Oriol A, Sancho JM et al. Usefulness and safety of oral cryotherapy in the prevention of oral mucositis after conditioning regimens with high-dose melphalan for autologous stem cell transplantation for lymphoma and myeloma. Eur J Haematol. 20 14; 93(6):487-91.

[16] Chen J, Seabrook J, Fulford A, Rajakumar I. Icing oral mucositis: Oral cryotherapy in multiple myeloma patients undergoing autologous hematopoietic stem cell transplant. J Oncol Pharm Pract. 2017; 23(2): 116-120.

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