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# BIOLOGICAL SCIENCES

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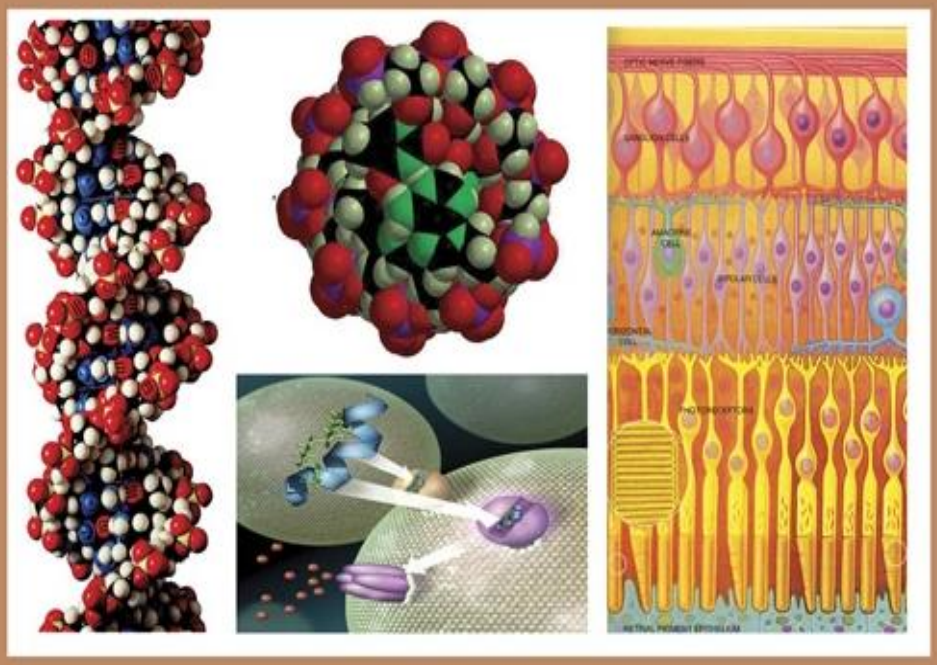

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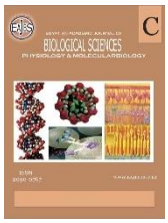

# Autologous Stem-Cell Transplantation in Patients with Multiple Myeloma

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Multiple Myeloma, survival rate, hematopoietic stem cells transplantation, cryotherapy.

**ABSTRACT**

**Introduction:** Multiple myeloma is a cancer of the plasma cells that attacks and destroys bones. Myeloma is the second most common cancer of the blood and accounts for about 12% of diagnosed hematologic cancers. Depending on the patient's condition and age, the treatment of multiple myeloma aims to eliminate the manifestations of the disease, to contain its progression and/or to treat the complications to ensure a better patient's quality of life. The survival rate in multiple myeloma patients is significantly improved through new therapeutic agents such as monoclonal antibodies, immunomodellers, proteasome inhibitors and hematopoietic stem cells transplantation, which is considered as the standard protocol in patients under 65 years old. The objective of this study is to determine the importance of autologous hematopoietic stem cell transplantation in improving the survival rate and quality of life of patients with multiple myeloma.

**Materials and methods:** 319 multiple myeloma patients who underwent hematopoietic autologous stem-cell transplantation, were included in this retrospective descriptive and analytical study.

**Results:** multiple myeloma can affect both sexes, the results of our study revealed a male predominance with a percentage of 61%.

Data analysis shows a significant correlation between the patient's age and the CD 34+ count and a highly significant correlation between cryotherapy and overall survival rate that was about 5 years.

**Conclusion**: through our study, we have confirmed that autologous transplantation strongly contributes to improving the survival rate of myeloma patients. Hematopoietic stem-cell transplantation remains the first-line treatment for patients under 65 years of age.

## INTRODUCTION

Multiple myeloma (MM), also known as Kahler's disease, is a malignant hemopathy characterized by the multiplication of tumor plasma cells in the bone marrow, often with the secretion of monoclonal immunoglobulin (free light oak) (Anne Cairoli, Michel André Duchosal, 2013).

The annual incidence of multiple myeloma is approximately 86,000 cases which represent about 0.8% of all cancers (Nikolaus Becker, 2011). The highest incidence is recorded in the industrialized regions of Asutralia, New Zealand, Europe and North America (Nikolaus Becker, 2011).

The annual incidence in Algeria is about 0.9 to 1.1/100,000 inhabitants/year (Bekadja MA, 2009; Saidi M, 2013). The etiology of MM is still unknown and no predisposing factors have been clearly identified yet (Charlot-Lambreacht I. *et al.*, 2011). Indeed, the only known apparent risk factor is exposure to ionizing radiation (Manier S, Leleu X, 2011; Kayel RA, Rajkumar SV, 2007; I. Charlot-Lambrecht *et al.*, 2008; Rajkumar SV *et al.*, 2007).

A case-control study conducted by Dalus Baris and al in 2004 indicates that occupational exposure to pesticides does not present an increased risk of multiple myeloma, while some animal viruses may be implicated in MM development in farmworkers and residents (Dalsu Baris *et al.*, 2004). Multiple myeloma manifests as pain caused by bone damage (58%), anemia (73%), hypercalcemia (13%) and kidney failure (20-40%) (Laubach *et al.*, 2016), (Kyle R.A. *et al.*, 2003). However, these criteria are based on monoclonal plasmocyte medullary infiltration followed by a determination of whether or not symptomatic multiple myeloma (Anne Cairoli, Michel André Duchosal, 2013).

Despite the development of new therapeutic approaches, multiple myeloma is still an incurable disease and is gradually becoming resistant to all treatments (Fouquet G. *et al.*, 2017). Multiple myeloma treatment is based on several protocols. The choice of treatment depends on the age, the patient's general condition and prognostic criteria for multiple myeloma (Fouquet G. *et al.*, 2017), the symptomatic or non-symptomatic criteria and the detected genetic abnormalities (Riccardi O. *et al.*, 2000).

The treatment of MM is based on the use of several substances. However, alkaylating agents and corticosteroids, proteasome inhibitors, bisphosphonate and immunomodellants are the most used anticancer substances (Anne Cairoli, Michel André Duchosal, 2013).On the other hand, autotransplantation remains the first-line treatment in patients under 65 years old (Alexis Genthon, 2016).

At present, the haematopoietic stem cells (HSCs) used for autologous transplantation come from peripheral blood. These cells are recovered by cytapheresis, obtained from patients who have received recombinant haematopoietic growth factors such as GM-CSF and G-CSF. Moreover, the use of HSCs from bone marrow has become exceptional (Jean-Luc Harousseau, 2013). The rate of progression and relapse remains high in multiple myeloma patients even though the overall survival rate is improved. Long-term data indicate a risk of recurrence of the disease after first-line treatment.

Autotransplantation is one of the mean therapeutic protocols used in the treatment of MM that gives maximum survival. The aim of this study is to analyze the general state and life span of patients who have undergone autologous haematopoietic stem-cell transplantation in the western Algeria region.

## PATIENTS AND METHODS

This is a retrospective, descriptive and analytical study of records of multiple myeloma patients who have undergone autologous transplantation. This survey took place in the western Algeria region over a period of 10 years, from 2010 to 2020. Hence, 319 patients were included in our study. Therapeutic response, progression and relapse were defined according to EBMT (Bladé J. *et al.*, 1998)

and international myeloma working group criteria (S. Manier, X. Leleu, 2011).

Complete remission was defined by the disappearance of the serum and urinary monoclonal component and the disappearance of extramedullary plasmacytomas. The state of progression was also defined by the increase of the serum monoclonal component > 25 % and the increase > 25 % of the medullary plasmacytosis **(**Bladé J. *et al.*, 1998). Overall survival is calculated from the first day of the autograft.

All data were analyzed using the IBM SPSS version 25 software, through the Chi-square and the Anova tests.

## RESULTS

### Distribution by Gender:

Figure 1 shows the distribution by gender of our study population. Among the 319 patients of our series, 195 men with a percentage of 61% and 124 women with a percentage of 39% were recorded.

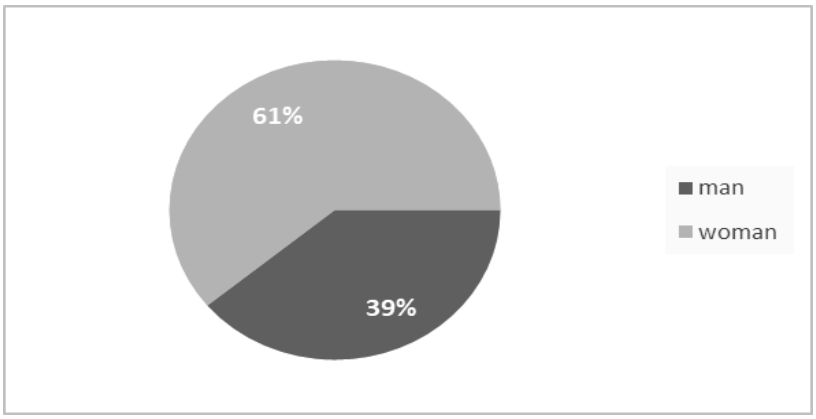


**Fig.1:** Distribution of patients by gender.

### Age Distribution :

The distribution by age of patients with multiple myeloma who underwent autologous transplantation is shown in Figure 2. The most represented age category was [46-60] The average age was 53 years with extremes ranging from 27 to 72 years.

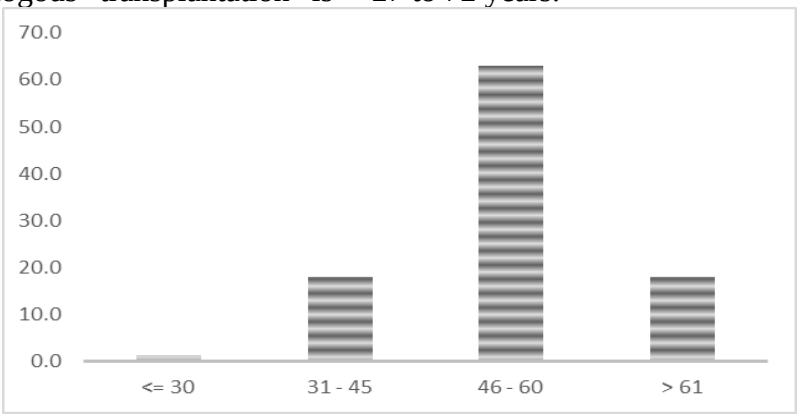


**Fig.2 :** Patients age distribution

### Distribution by Post-Transplant Status (1 and 100-day duration):

The following Table (1) shows the distribution of patients according to the 1 to 100 days post-transplant status. In our study, the majority of patients were in a state of complete responsibility for both durations (1 and 100), and 30.1% were in relapse for post-transplant status 1.

**Table 1:** Distribution according to post-transplant 1 status and 100-day status

| Status | Patient condition | Percentage % |
|---|---|---|
| Post-transplant status 1 | Complete response (CR) | 32 |
| | Relapse | 30.1 |
| | Deceased | 3.1 |
| | VGPR | 11 |
| | Biological relapse | 1.3 |
| | Progression | 1.9 |
| | Lost sight of | 20.6 |
| 100-day status | CR | 49.5 |
| | VGPR | 30.7 |
| | Deceased | 2.5 |
| | Progression | 1.3 |
| | Lost sight of | 16 |

**Influence of Gender on 100-Day Status:** The following figure (3) represents the relation between sex and status at 100 days using the chi-square test. The obtained results show a highly significant correlation between the studied parameters ($p < 0.01$).

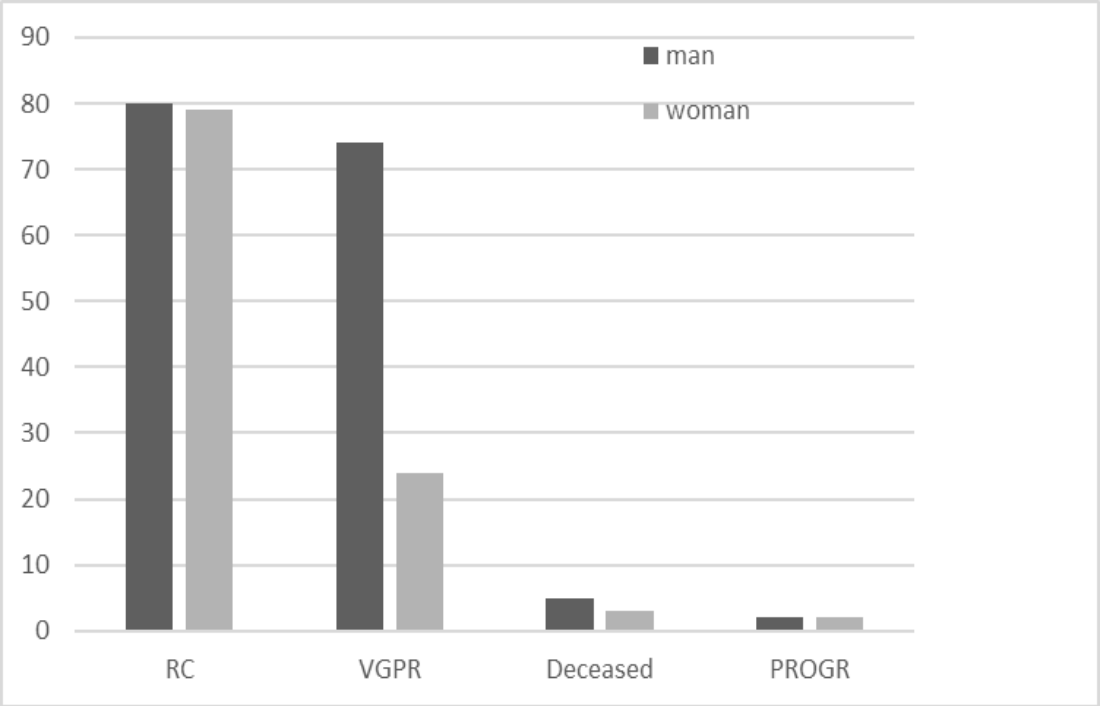


**Fig.3:** Correlation between gender and 100-day status.
RC: Complete response, VGPR: Reduction of the monoclonal component less than 90%, PROG: Progression.

**Influence of Age on CD34+ Count**: An autograft, the CD34+ stem cells number is very important because they will be collected, frozen and then re-injected to the patients when their number is very high. The results show (Fig.4) an inversely proportional relation between The CD34+ cells number and the age of patients ($p<0.01$).

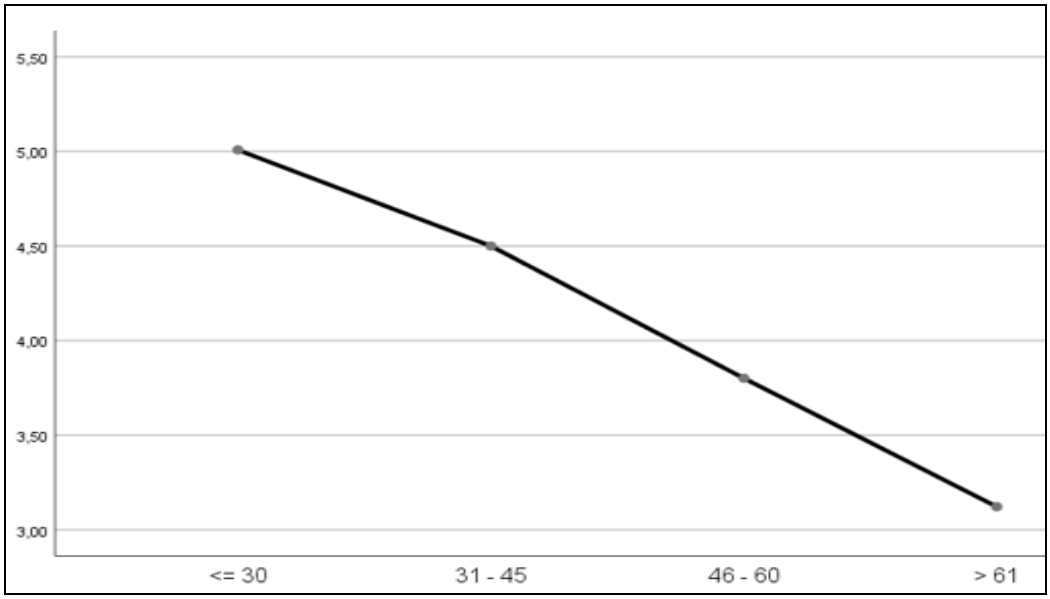


**Fig.4:** Correlation between age and the number of CD34+ cells**.**

**Influence Of Cryotherapy on Overall Survival**:

Concerning the lifespan of patients after transplant while using cryotherapy, a log-rank test was used to determine if there were differences in the survival distribution associated with either the presence or absence of this intervention: The survival distributions for the two interventions were statistically significant, $\chi 2(2) = 211{,}63$, $p < .0001$ (Fig.5).

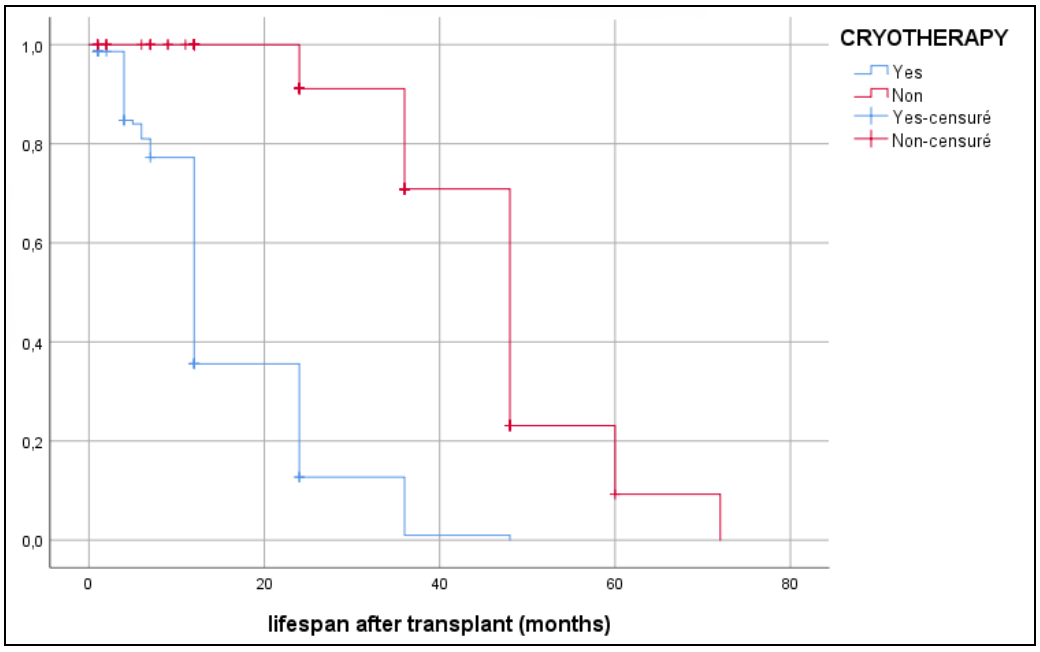


**Fig.5:** Correlation between lifespan and cryotherapy.

**Influence of Age and Gender on Lifespan:**

The two ways Anova test results show (Fig.6) no significant influence of patient's age and sex, and their lifespan after transplant (P=0.994).

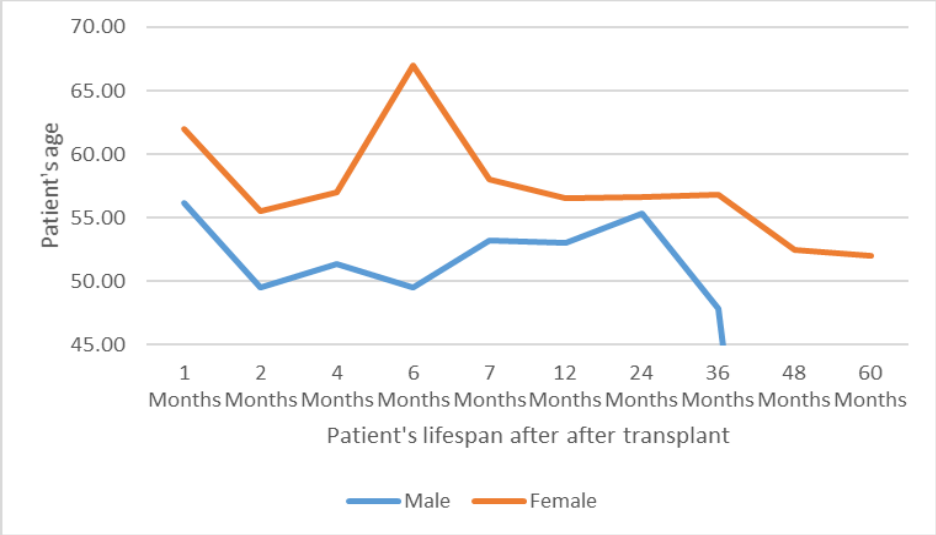


**Fig. 6:** Effects of patient's age and gender on their Life span.

## DISCUSSION

Multiple myeloma represents about 1% of all cancers and about 2% of cancer-related deaths worldwide (Manier S., Leleu X., 2011). In our study series, a male predominance was found with a sex ratio of 1.55. These results are similar to those of another study published in the Algerian journal of hematology in 2009 which indicates a sex ratio of 1.4 (Bekadja M.A., 2009).

Auto-transplantation of haematopoietic stem cells is the first-line treatment, but it is only affordable for patients under 65 years of age (Harousseau J.L., Moreau P., 2009). Indeed, the average age of patients who had undergone an autograft of CSH was 53 years in our study. These results are consistent with the literature.

Furthermore, the monitoring of patients after autograft reveals a continuous risk of relapse for several years following autograft. However, in this series, the majority of patients were in a state of complete response followed by a state of relapse. In addition, a study realized by M Krejci showed that 35% of the patients were incomplete, and 60% were in partial remission (Krejci M. *et al.*, 2005). Also, other research showed that patients treated with an autologous haematopoietic stem cell transplant had a 24% risk of disease progression (Blade´ J. *et al.*, 2003).

Gender is one of the mains choice criteria for the treatment of Multiple myeloma. Data analysis shows a very significant correlation ($p<0.01$) between the patient gender and the therapeutic response after 100 days following the autograft. The CD34+ cell count is essential to determine the richness of the sample in haematopoietic progenitors (Sparrow R.L. *et al.*, 2006). In our study, there was a very significant correlation between the number of CD34+ cells and the age of the patient. The products collected by cytapheresis contain an average of 3.82±2.02 × 106/Kg CD34+ cells, whereas the required value is 2.5-5 × 106/Kg and the target value for double autografting is 6 × 106/Kg (Allan, D. *et al.*, 2002). Similarly, to our findings, J. Vorlicek and colleagues noted a median level of perfused CD34+ cells of 4.7 × 106/kg (Vorlicek J., 2005).

Our results show also that the cryotherapy protocol has a significant influence on the median survival rate after an autologous haematopoietic stem cell transplant. Studies show that oral cryotherapy is used for the prevention of oral mucositis (Chen J. *et al.*, 2017). 70% of patients receiving an autologous haematopoietic stem cell transplant

develop oral mucositis as a result of conditioning chemotherapy with a high dose of melphalant. The results obtained by Joey et. al show that cryotherapy is potentially effective in reducing oral mucositis (Chen J. *et al.,* 2017). The multiple myeloma patient's overall survival has improved very significantly in recent years. Analysis of the results shows an overall survival rate of 5 years.Vorlicek *et al.* noted that median survival was ranged between 29.5 and 68.8 months, with a significant correlation between age and therapeutic response after autograft (Chen J. *et al.,* 2017).

In addition, other studies showed a median survival of 31.7 months (Shah N. *et al.,* 2012), 24 months (Blimark C. *et al.,* 2001) and an 18-month overall survival rate (Tricot G *et al.,* 1995). In addition, other results found by Fonseca and his team showed a more important overall survival rate of 7 to 10 years (Fonseca R.*et al.,* 2017).

The HOVON study demonstrates that autologous hematopoietic stem cell transplantation is more efficient than newer agents for the treatment of multiple myeloma (Kumar S.K. *et al.,* 2011).

**CONCLUSION**

Although haematopoietic stem cell transplantation is currently the standard therapy for the treatment of multiple myeloma in patients under 65 years of age, this study confirms that the complete response rate is very high compared to the mortality rate with a percentage of 32% for post-transplant status 1 and 49.5% for status at 100 days.The correlation between cryotherapy and overall survival after autograft is highly significant with overall survival of 5 years. Analysis of the obtained data shows that the age and the sex of the patient represent the mains choice criteria for treatment.

This study confirms the fundamental interest of autologous haematopoietic stem cell transplantation in the management of patients with multiple myeloma.

**REFERENCES**

Allan, D, Keeney, M., Howson-Jan, K. *et al.* (2002). Number of viable $CD34^+$ cells reinfused predicts engraftment in autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant* 29, 967–972 https://doi.org/10.1038/sj.bmt.1703575

Anne Cairoli, Michel André Duchosal. (2013). Myélome multiple : diagnostic et perspective thérapeutiques. *Forum Med Suisse* ; 13(38) :746-751

Bekadja MA. (2009). (Reporteur du groupe Algérien du Myélome). Approche épidémiologique nationale. Revue Algérienne d'hématologie.

Bladé J, Samson D, Reece D, Apperley J, Björkstrand B, Gahrton G, Gertz M, Giralt S, Jagannath S, Vesole D. (1998). Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *British Journal of Haematology,* 102(5):1115-23. doi: 10.1046/j. 1365-2141.1998.00930. x. PMID: 9753033.

Blade´ J, Sureda A, Ribers J, (2003). Thérapie à haute dose Auto transplantation/intensification par rapport à la poursuite de la chimiothérapie conventionnelle chez les patients atteints de myélome multiple répandant à la chimiothérapie initiale. Résultats définitifs de PETHMA après un suivi médian 66 mois. Acte de 45$^e$ réunion annuelle de l'American Society of Hematology. Blood 2003 ; 102 : 42a, résumé numéro 135.

Blimark C, Veskovski L, Westin J, Rödjer S, Brune M, Hjorth M, et al. (2001). Melphalan 100 mg/m2 with stem cell support as first relapse treatment is safe and effective for myeloma patients with long remission after autologous stem cell transplantation. *European Journal of Haematology,* 87(2): 117–22.

Charlot-Lambreacht I; Salmon J.H; Ganieux-Lemoussu L; Brochot P; Eschard J.P. (2011). Myélome multiple. *Elsevier Masson SAS, Paris, Appareil locomoteur*, 14-027-B-10, P : 1-12

Chen J, Seabrook J, Fulford A, Rajakumar I. (2017). Icing oral mucositis: Oral cryotherapy in multiple myeloma patients undergoing autologous hematopoietic stem cell transplant. *Journal of Oncology Pharmacy Practice.;* 23(2):116-120. doi:10.1177/ 1078155215620920.

Dalsu Baris , Debra T Silverman, Linda Morris Brown, G Marie Swanson, Richard B Hayes, Ann G Schwartz, Jonathan M Liff, Janet B Schoenberg, Linda M Pottern, Raymond S Greenberg, Patricia A Stewart. (2004). Occupation, pesticide exposure and risk of multiple myeloma. *Scandinavian Journal of Work, Environment & Health;*30(3):215-22. doi: 10. 5271/sjweh.782.

Fonseca R, Abouzaid S, Bonafede M, Cai Q, Parikh K, Cosler L, Richardson P. . (2017). Trends in overall survival and costs of multiple myeloma2000-2014. *Leukemia,* 31(9):1915-1921. doi: 10.1038/leu.2016.380. Epub 2016 Dec 23. PMID: 28008176; PMCID: PMC5596206.

Fouquet G, Snell KI, Guidez S, Schraen S, Boyle E, Renaud L, Desmier D, Machet A, Moya N, Systchenko T, Gruchet C, Decaux O, Arnulf B, Fohrer C, Richez V, Kolb B, Macro M, Karlin L, Royer B, Pegourie B, Hebraud B, Caillot D, Perrot A, Moreau P, Facon T, Avet-Loiseau H, Dejoie T, Hulin C, Harding S, Leleu X. (2017). Heavy + light chain analysis to assign myeloma response is analogous to the IMWG response criteria. *Leukemia & lymphoma;*59(3):583-589. doi: 10.1080/10428194.2017.1339876 . PMID : 28697637.

Charlot-Lambrecht I, J.-H. Salmon: Interne, L. Gagneux-Lemoussu : Praticien hospitalier, P. Brochot : Praticien hospitalier, J.-P. Eschard . (2011). Myélome multiple. *La revue de medecine interne,* [14-027-B- 10] - Doi : 10.1016/S0246-0521(11)57251-1

Laubach J , L Garderet , A Mahindra , G Gahrton , J Caers , O Sezer , P Voorhees , X Leleu , H E Johnsen , M Streetly , A Jurczyszyn , H Ludwig , U-H Mellqvist , W-J Chng , L Pilarski , H Einsele , J Hou , I Turesson , E Zamagni , C S Chim , A Mazumder , J Westin , J Lu , T Reiman , S Kristinsson , D Joshua , M Roussel , P O'Gorman , E Terpos , P McCarthy , M Dimopoulo s , P Moreau , R Z Orlowski , J S Miguel , K C Anderson , A Palumbo , S Kumar , V Rajkumar , B Durie , P G Richardson· (2016). Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. *Leukemia,* 1005-17. doi: 10.1038/leu.2015.356. Epub 2015 Dec 29. PMID: 26710887.

Alexis Genthon. (2016). Myélome multiple : l'autogreffe après 65 ans ?. *Hématologie,* ;22(6) :386-

387. doi :10.1684/hma.2016.1197

Vorlicek J. (2005). Prognostic factors for survival after autologous transplantation: a single centre experience in 133 multiple myeloma patients. *Bone Marrow Transplantation*, 35, pp159–164

Harousseau JL, P. Moreau. (2009). « Autologushematopoietic stem-celltransplotation for multiple myeloma ». *The New England Journal of Medicine*; vol. 360, no 25, p. 2645-2654.

Jean-Luc Harousseau. (2013). Autograft of hematopoietic stem cells in multiple myeloma. Vol 32, N°24-juillet 2013 p.1107

Kayel RA, Rajkumar SV. (2007). Epidemiology of the plasma-celldisorders. Best Practice & research. *Clinical Haematology;* (20) 4: 637-64

Kumar SK, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J, Haessler J, Feather J, Hoering A, Moreau P, LeLeu X, Hulin C, Klein SK, Sonneveld P, Siegel D, Bladé J, Goldschmidt H, Jagannath S, Miguel JS, Orlowski R, Palumbo A, Sezer O, Rajkumar SV, Durie BG. (2012). International Myeloma Working Group. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia,* 26(1):149-57. doi: 10. 1038/leu.2011.196.

Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar V, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR (2003) Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proceedings,* 78:21-33.

M Krejci, T Buchler, R Hajek, A Svobodnik, A Krivanova, L Pour, Z Adam, J Mayer, J Vorlicek. (2005). Prognostic factors for survival after autologous transplantation : a single centre experience in 133 multiple myeloma patients. *Bone Marrow Transplantation*, 35, pp159–164.

Saidi.M. (2013). Groupe d'étude et de traitement du Myélome en Algérie Xème Congrès Maghrébin d'hématologie Oran.

Nikolaus Becker. (2011). Epidemiology of Multiple Myeloma. Recent results in cancer research. Fortschritte der Krebsforschung. *Progrès dans les recherches sur le cancer*, 183 :25-35 DOI : 10.1007/978-3-540-85772-3_2

Sparrow R.L, Komodoromou H, Tippett E, Georgakopoulos T, Xu W. (2006). Apoptotic lymphocytes and CD34+ cells in cryopreserveed with loss of L-selectin (CD62L) expression. *Bone Marrow Transplant,* 61-7. Doi : 10.1038/ sj.bmt.1705405. PMID: 16788684.

Rajkumar SV, Lacy MQ, Kyle RA. (2007). Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. 255-65. doi: 10.1016/j.blre. 2007.01.002. PMID: 17367905

Riccardi O, Mora C, Tinelli P et al. (2000). « Long-term survival of stage I multiple myeloma given chemotherapy just after diagnosis or at progression of the disease: a multicentre randomized study ». *British Journal of Cancer,* 82(7): 1254-1260.

Manier S, Leleu X. (2011). Myélome multiple : diagnostic clinique et perspective de traitement. Recommandations de l'international MyelomaWorking Group (IMWG). *Immuno-Analyse et biologie spécialisée,* Bo 26, 125-136

Shah N, Ahmed F, Bashir Q, Qureshi S, Dinh Y, Rondon G, Wen S, Thall P, Khan H, Giralt S, Champlin R, Qazilbash MH. (2012). Durable remission with salvage second autotransplants in patients with multiple myeloma. Cancer. *Journal of the American Society for Blood and Marrow Transplantation,* 15;118(14): 3549-55. doi: 10.1002/cncr. 26662. Epub 2011 Nov 15. PMID: 22086552; PMCID: PMC4038445.

Tricot G, Jagannath S, Vesole D, Nelson J, Tindle S, Miller L, Cheson B, Crowley J, Barlogie B. (1995). Peripheral blood stem cell transplants for multiple myeloma: identification of favorable variables for rapid engraftment in 225 patients. *Blood, the flagship journal of the American Society of Hematology,* 15;85(2):588-96. PMID: 752906.