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Autologous Stem-Cell Transplantation in Patients with Multiple Myeloma

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ABSTRACT

Introduction: Multiple myeloma is a cancer of the plasma cells that attacks and destroys bone. 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, immunomodulators, 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 Australia, 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 cytopheresis, 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)
Autologous Stem-Cell Transplantation in Patients with Multiple Myeloma

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.](image)

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](image)

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

<table>
<thead>
<tr>
<th>Status</th>
<th>Patient condition</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-transplant status 1</td>
<td>Complete response (CR)</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Relapse</td>
<td>30.1</td>
</tr>
<tr>
<td></td>
<td>Deceased</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>VGPR</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Biological relapse</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Progression</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Lost sight of</td>
<td>20.6</td>
</tr>
<tr>
<td>100-day status</td>
<td>CR</td>
<td>49.5</td>
</tr>
<tr>
<td></td>
<td>VGPR</td>
<td>30.7</td>
</tr>
<tr>
<td></td>
<td>Deceased</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Progression</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Lost sight of</td>
<td>16</td>
</tr>
</tbody>
</table>

**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).

**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).
Autologous Stem-Cell Transplantation in Patients with Multiple Myeloma

41

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).

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 ($P=0.994$).
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 main 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 $3.82\pm2.02 \times 10^6$/Kg CD34+ cells, whereas the required value is $2.5-5 \times 10^6$/Kg and the target value for double autografting is $6 \times 10^6$/Kg (Allan, D. et al., 2002). Similarly, to our findings, J. Vorliecek and colleagues noted a median level of perfused CD34+ cells of $4.7 \times 10^6$/kg (Vorliecek 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

Fig. 6: Effects of patient’s age and gender on their Life span.
develop oral mucositis as a result of conditioning chemotherapy with a high dose of melphalan. 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 main choice criteria for treatment.

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

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Autologous Stem-Cell Transplantation in Patients with Multiple Myeloma


