Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2023.251688.3027 Volume 30, Issue 6, Sept. 2024
Manuscript ID ZUMJ-2311-3027 (R1)
DOI 10.21608/zumj.2023.251688.3027

ORIGINAL ARTICLE

# Prognostic Value of Time Interval between Induction Chemotherapy and Autologous Stem Cell Transplantation among Multiple Myeloma Patients

**Heba F. Taha[1], Salah Eldin Hussein Ali Elghandour [1*], Raafat Mohamed Abdelfattah[2], Ahmed Abdelrahim Elnagar[1]**

[1]Medical Oncology Department, Faculty of Medicine, Zagazig University, Egypt

[2]Hematology and Stem Cell Transplantation Department, National Cancer Institute, Cairo University, Egypt

***Corresponding author:**
Salah Eldin Hussein Ali Elghandour

**Email:**
salahelghandour94@gmail.com

Submit Date 30-11-2024
Revise Date 28-11-2024
Accept Date 30-12-2024

**Abstract**

**Background:** Autologous hematopoietic cell transplantation (HCT) among Multiple myeloma (MM) cases has resulted in greater response rates, higher overall survival (OS) and event-free survival (EFS) over the last two decades compared with the outcome of comparable individuals given conventional treatment. We aimed at this study to determine the prognostic value of the time interval between end of induction chemotherapy and autologous stem cell transplantation among multiple myeloma patients.

**Methods:** This observational retrospective cohort study was held at Nasser Institute, Dar El-Salam Hospital and El-Sheikh Zayed Hospital on 211 cases with an initial diagnosis of MM during the study period (2017-2022). We evaluated the influence of the time interval between the end of induction of chemotherapy and Autologous Stem Cell Transplantation on free survival, relapse-free survival and overall survival.

**Results:** There was a statistically significant relation between relapse-free survival and interval from last chemotherapy date to stem cell infusion among studied patients (significantly lower 26.0 ± 1.67 months in patients with interval>60 days vs. 56.32 ± 2.22 months in patients with interval≤60 days and with increasing interval quartile (with p<0.001 for each). Similarly, there was a statistically significant relation between overall survival and interval from last chemotherapy date to stem cell infusion among studied patients (significantly lower 58.28 ± 3.97 months in patients with interval>60 days vs. 67.48 ± 1.45 months in patients with interval≤60 days with P value =0.004).

**Conclusions:** The present study demonstrated the prognostic value of the time interval between the end of induction of the chemotherapy and autologous stem cell transplantation in multiple myeloma cases, as the overall survival rate was substantially lower in patients whose intervals were greater than 60 days and with increasing interval quartiles.

**Keywords:** Time Interval, Induction Chemotherapy, Autologous Stem Cell Transplantation, Multiple Myeloma

## INTRODUCTION

The accumulation of plasma cells in the bone marrow causes multiple myeloma (MM), a cancerous tumor, which in turn causes bone damage and marrow failure. As the second most common type of blood cancer, MM is responsible for approximately 1.8% of all cancers and 18% of all hematologic malignancies globally. People between the ages of 65 and 74 have the highest prevalence of MM diagnoses, with a median age of 69. An estimated 12,830 people will lose their lives to MM in 2020, out of an anticipated 32,270 new cases,

according to the American Cancer Society [1]. With an incidence of almost 176,404 cases in year of 2020, MM constitutes around 0.9 percent of all cancers globally, making it the third most prevalent hematologic malignancy after lymphoma and leukemia [2].

The 2014 revised IMWG (International Myeloma Working Group) criteria for multiple myeloma diagnosis marked a sea change in the field, paving the way for earlier diagnoses and treatment commencement prior to end-organ destruction through the addition of three distinct biomarkers. One or more myeloma-defining events (MDE) and either a plasmacytoma confirmed by biopsy or 10% or more clonal plasma cells on bone marrow testing are the criteria for this condition. The three specific indicators that make MDE include hypercalcemia, renal failure, anemia, or lytic bone lesions; clonal bone marrow plasma cells >60 percent; serum free light chain (FLC) ratio > 100; and the presence of more than one focal lesion on magnetic resonance imaging (MRI) [3]. Risk stratification of MM is done through the Revised International Staging System (R-ISS), which combines elements of tumor burden (Serum beta-2 microglobulin and albumin levels) and disease biology (presence of high-risk cytogenetic abnormalities or elevated lactate dehydrogenase level) [4].

Individuals who are determined to have MM according to the IMWG criteria should begin treatment once the risk assessment and diagnostic evaluation are finished. The primary goal of the initial evaluation is to determine, mainly by taking age and preexisting conditions into account, if the patient is suitable for autologous stem cell transplantation (SCT) and high-dose chemotherapy [3]. In comparison to comparable patients treated with conventional therapy, who had a median OS of over 8 years, autologous HCT has produced far better response rates, increased overall survival (OS), and event-free survival (EFS) within the past 20 years [5] and 4-year survival rate more than 80% compared to median OS of 6 years for those not eligible for ASCT particularly following the advent of new antimyeloma medications such as monoclonal antibodies, immunomodulatory drugs (IMiDs), and proteasome inhibitors (PIs), there was a change in focus from a curative to an active approach to disease management with the goal of extending EFS and OS [6].

As a result, the present gold standard for MM treatment includes upfront chemotherapy, consolidative high-dose melphalan [7], and autologous stem cell transplant [8]. Maintenance therapy for transplant-eligible patients consists of either bortezomib or lenalidomide [9].

So, we aimed at this study to determine the prognostic value of the time interval between the end of induction chemotherapy and autologous stem cell transplantation among the multiple myeloma cases.

## METHODS

This observational retrospective cohort study was held at Nasser Institute, Dar El-Salam Hospital and El-Sheikh Zayed Hospital on 211patients with an initial diagnosis of MM fulfilling the 2014 updated IMWG criteria Rajkumar et al. [3] who had received frontline induction chemotherapy followed by consolidative ASCT. Medical records were collected retrospectively from the files of 211 patients who were seen at Nasser Institute, Dar El-salam Hospital and El-sheikh Zayed Hospital from 2017 to 2022.

Inclusion criteria: Patients aged 18 to 70 years from both sexes who had laboratory, radiologic and immunophenotypic evidence of MM according to the updated IMWG criteria [3] to diagnose MM, patients who have received prior induction chemotherapy, also who had Eastern Cooperative Oncology Group (ECOG) performance status score equal or less than 2 [10].

Exclusion criteria: We excluded all who had any of the following conditions: Patients with significant cardiac, pulmonary, or hepatic dysfunction or active infection; those who progressed on induction chemotherapy; incomplete files; or medical contraindications for ASCT.

This study followed the guidelines [the World Medical Association's Code of Ethics (Declaration of Helsinki) for human studies]. All participants provided informed and written consent for review of their medical records. The Institutional Review Board has approved this research (#10763).

All patients have been managed using induction chemotherapy by the combined regimens of immunomodulatory drugs (IMiDs) in addition to the proteasome inhibitors (PIs) involving VCD (Bortezomib, Cyclophosphamide and dexamethasone); or VRD (Bortezomib, Lenalidomide and dexamethasone) or VAD (Vincristine, Adriamycin and dexamethasone). Response criteria for multiple myeloma were assessed according to the Standard IMWG response criteria [11].

All patients have undergone stem cell transplantation; High-dose melphalan (HDM, 100

mg/m2 for 2 days) was used for all cases. A 25% dose reduction was made for patients who had creatinine clearance less than 60 ml/min, and a dose of 10 ugm/kg/d SC of granulocyte colony-stimulating factor (G- CSF) was used for all patients. The patient was given this dosage for four days prior to apheresis and for the duration of the procedure itself. A continuous flow cell separator was used to harvest peripheral blood stem cells (PBSCs) from all patients four days after mobilization. A sample of recently harvested PBSC was immune-stained and examined for CD34+ cells using a Coulter XL flow cytometer. To continue infusion after a maximum of three leukapheresis, 2 x 10° CD34+ cells per kg were needed.

Disease-free survival (DFS) was calculated from the date of stem cell infusion to the treatment intensification or the biochemical relapse. Overall survival (OS) was calculated from the date of stem cell infusion to the date of last follow-up or death from any cause [10].

***Statistical Analysis:***

The whole group had their baseline clinical features recorded, and we compared the categorical data using the Chi-squared test. Based on the median time to transplant (TTT), which is measured from the date of the last chemotherapy treatment to the date of the stem cell infusion, we divided the patients into two groups. Both disease-free survival (DFS) and overall survival (OS) were defined as the time from stem cell infusion to biochemical recurrence or therapy intensification or death, respectively, as endpoints in the study. A Kaplan-Meier model was utilized for the purpose of producing images and estimating the median DFS and OS. The 2-sided log-rank test was used to establish statistical significance in OS and DFS for all tests that were conducted. Multivariate analyses were conducted using the Cox proportional hazards model. We used R version 4.1.1 for all of our statistical analysis. (R Statistics Package, available at https://www.R-project.org/).

## RESULTS

This study included 211 patients, 73% of them aged less than 60 years and 61.1% of them were Males. The current study showed positive HbsAg, HCV antibodies, CMV IgG, toxoplasma IgG, and IgM prevailed in 2.8%, 2.4%, 41.7%, 14.2% and 0.9% of studied patients, respectively. About 91% of patients had hemoglobin >10 g/dl, 75% had TLC >4000 cell/ m3, 99% had ANC >1500 and platelet count >50 (109), and 97% of patients had ALT and AST <3 ULN. Concerning LDH, 77.7% had values more than the upper limit of normal. Regarding β2 microglobulin, 55%, 25.4% and 16.6% had values <3.5, 3.5 to 5.5 and >5.5 g/L, respectively. A larger percentage had IgG (78.2%), and 75.4% had kappa as a type of light chain (Table 1).

About 70% of patients received VCD as induction chemotherapy, and 21.8% received VRD. Melphalan was given to 97.6% of patients as a conditioning regimen, and 79% of patients received Lenalidomide as maintenance treatment, while 14.2% didn't receive maintenance. Also, we found that the time interval from the last chemotherapy date till the stem cell infusion ranged from 14 to 150 days with a median of 60 days.

Relapse was reported in 33 out of 211 patients (15.6%), whereas disease-free survival ranged from 1 to 64 months with a median of 17 months. There was a statistically significant relation between relapse-free survival and maintenance treatment (significantly higher in patients who received Lenalidomide with P=0.01) (Table 2).

There was a statistically significant relation between relapse-free survival and interval from last chemotherapy date to stem cell infusion among studied patients (significantly lower 26.0 ± 1.67 months in patients with interval>60 days vs. 56.32 ± 2.22 months in patients with interval≤60 days with P value <0.001) (Table 3, and Figure 1A).

Time interval>60 days, ISS stage 3, and calcium level>11 g/dl significantly increase hazard by 22.474, 6.778 and 2.659 folds, respectively. While ISS stage 2, receiving Bortezomib, Thalidomide, no maintenance, AST (>3 ULN) non-significantly increase hazard by 1.275, 1.256, 3.171, 1.301 and 1.625 folds respectively. Also, regarding Cox regression with backward Wald model, Time interval>60 days, ISS stage 3, and calcium level>11 g/dl significantly increase hazard by 22.336, 6.778 and 2.306 folds, respectively. ISS stage 2 non-significantly increase hazard by 1.275-fold (Table 4).

Table (5) showed that there was a statistically significant relation between relapse-free survival and interval from last chemotherapy to stem cell infusion among good responders (significantly lower in patients with interval>60 days with P value<0.001) (Figure 1B). Also, there was a statistically significant relation between relapse-free survival and interval from the last chemotherapy date to stem cell infusion among studied patients (significantly lower in patients with increasing interval quartile with P Value<0.001) (Figure 1C).

Table (6) showed that there was a statistically significant relation between overall survival and interval from the last chemotherapy date to the stem cell infusion among studied patients (significantly lower 58.28 ± 3.97 months in patients with interval>60 days vs. 67.48 ± 1.45 months in patients with interval≤60 days with P value =0.004) (Figure 1D). There was a statistically significant relation between overall survival and interval from the last chemotherapy date to the stem cell infusion among studied patients with P=0.002 (Figure 1E).

**Table 1:** Baseline and laboratory data of studied patients

| | N=211 | % |
|---|---|---|
| **Age** | | |
| **>60 years** | 57 | 27% |
| **<60 years** | 154 | 73% |
| **Sex:** | | |
| **Male** | 129 | 61.1% |
| **Female** | 82 | 38.9% |
| **ECOG (0-2)** | 211 | 100% |
| **BMI:** | | |
| **Average** | 134 | 63.5% |
| **Overweight** | 76 | 36% |
| **Grade I obesity** | 1 | 0.5% |
| | **N=211** | **%** |
| **Viral markers:** | | |
| Positive HbsAg | 6 | 2.8% |
| HCV antibodies | 5 | 2.4% |
| CMV IgG | 88 | 41.7% |
| CMV IgM | 0 | 0% |
| Toxoplasma IgG | 30 | 14.2% |
| Toxoplasma IgM | 2 | 0.9% |
| **Hemoglobin** | | |
| >10 g/dl | 191 | 90.5% |
| <10 g/dl | 20 | 9.5% |
| **TLC** | | |
| >4000 cell/mm$^3$ | 158 | 74.9% |
| <4000 cell/mm$^3$ | 53 | 25.1% |
| **Absolute neutrophil count** | | |
| >1500 cell/mm$^3$ | 209 | 99.1% |
| <1500 cell/mm$^3$ | 2 | 0.9% |
| **Platelet count** | | |
| >50 ($10^9$) | 208 | 98.6% |
| <50 ($10^9$) | 3 | 1.4% |
| **Serum creatinine** | | |
| >2 mg/dl | 18 | 8.6% |
| <2 mg/dl | 193 | 91.4% |
| **Creatinine clearance** | | |
| >40 ml/min | 191 | 90.5% |
| <40 ml/min | 20 | 9.5% |
| **Calcium** | | |
| >11 mg/dl | 41 | 19.4% |
| <11 mg/dl | 170 | 80.6% |
| **Albumin** | | |
| >3.5 g/dl | 112 | 53.1% |
| **<3.5 g/dl** | 99 | 46.9% |

| | | |
|---|---|---|
| **ALT** | | |
| >3*ULN | 6 | 2.8% |
| <3*ULN | 205 | 97.2% |
| **AST** | | |
| >3*ULN | 7 | 3.3% |
| <3*ULN | 204 | 96.7% |
| **ESR** | | |
| >100 mm/hr | 115 | 54.5% |
| <100 mm/hr | 96 | 45.5% |
| **LDH** | | |
| >upper limit of normal | 164 | 77.7% |
| <upper limit of normal | 47 | 22.3% |
| **β2 microglobulin** | | |
| <3.5 mg/L | 116 | 55% |
| 3.5 – 5.5 mg/L | 60 | 25.4% |
| >5.5 mg/L | 35 | 16.6% |
| **Type of M protein** | | |
| IgG | 165 | 78.2% |
| IgM | 45 | 21.3% |
| IgA | 1 | 0.5% |
| **Type of light chain** | | |
| Kappa | 159 | 75.4% |
| Lambda | 52 | 24.6% |

HbsAg: hepatitis B surface antigen, HCV: Hepatitis C virus, CMV: Cytomegalovirus, IgG: Immunoglobulin G, IgM: Immunoglobulin M, TLC: Total leucocyte count, ALT: alanine transaminase, AST: aspartate aminotransferase, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, ULN: upper limits of normal

**Table 2:** Outcome of the studied patients and relation between relapse free survival and therapeutic data among studied patients

| | | | | | |
|---|---|---|---|---|---|
| | | | **N=211** | | **%** |
| **Relapse:** | | | | | |
| **No relapse** | | | 178 | | 84.4% |
| **Relapse** | | | 33 | | 15.6% |
| | | | **Median (Inter-quartile range)** | | **Range** |
| **Disease free survival (months)** | | | 17 (8 – 28) | | 1 – 64 |
| | **Total** | **Event(%)** | **Mean ± std error** | **95% CI** | **p** |
| **Chemotherapy used in induction** | | | | | |
| VRD | 46 | 4(8.7%) | 48.17 ± 4.21 | 39.93 – 56.42 | 0.175 |
| VCD | 147 | 20(13.6%) | 48.64 ± 2.81 | 43.13 – 54.14 | |
| VAD | 18 | 9(50%) | 37.46 ± 4.7 | 28.25 – 46.67 | |
| **Type of conditioning regimen** | | | | | |
| Melphalan | 206 | 33(16%) | | | |
| Melphalan with 25% reduction | 5 | 0(0%) | | | 0.599 |
| **Maintenance treatment** | | | | | |
| Lenalidomide | 166 | 16(9.6%) | 51.61 ± 2.2 | 47.3 – 55.93 | |
| Bortezomib | 9 | 2(22.2%) | 36.5 ± 1.5 | 33.56 – 39.44 | |
| Thalidomide | 6 | 3(50%) | 40.2 ± 8.77 | 23.02 – 57.38 | 0.01* |
| No maintenance | 30 | 12(40%) | 34.87 ± 3.61 | 27.81 – 41.94 | |

p for Mantel cox test CI confidence interval of mean *p<0.05 is statistically significant

**Table 3:** Relation between relapse free survival and interval from last chemotherapy date to stem cell infusion among studied patients

| | Total | Event(%) | Mean ± std error | 95% CI | p |
|---|---|---|---|---|---|
| **Time** | | | | | |
| **≤60 days** | 111 | 9(8.1%) | 56.32 ± 2.22 | 51.96 – 60.68 | |
| **>60 days** | 100 | 24(24%) | 26.0 ± 1.67 | 22.72 – 29.28 | <0.001** |

p for Mantel cox test CI confidence interval of mean *p<0.05 is statistically significant **p0.001 is statistically highly significant

**Table 4:** Cox regression analysis of factors associated with relapse free survival among studied patients

| | β | p | AHR | 95.0% CI | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| **Time between last chemotherapy date to date of stem cell infusion (>60 days)** | 3.112 | <0.001** | 22.474 | 7.964 | 63.418 |
| **ISS stage** | | 0.006* | | | |
| **ISS stage 2** | 0.243 | 0.657 | 1.275 | 0.436 | 3.728 |
| **ISS stage 3** | 1.914 | 0.002* | 6.778 | 1.962 | 23.409 |
| **Maintenance treatment (Lenalidomide)** | | 0.447 | | | |
| **Maintenance treatment (Bortezomib)** | .228 | 0.776 | 1.256 | 0.261 | 6.033 |
| **Maintenance treatment (Thalidomide)** | 1.154 | 0.106 | 3.171 | 0.783 | 12.846 |
| **No maintenance treatment** | .263 | 0.624 | 1.301 | 0.455 | 3.716 |
| **Beta-2 microglobulin (<3.5 mg/L)** | | 0.661 | | | |
| **Beta-2 microglobulin (3.5 – 5.5 mg/L)** | -.226 | 0.661 | 0.798 | 0.291 | 2.190 |
| **AST (> 3 ULN)** | .486 | 0.452 | 1.625 | 0.458 | 5.771 |
| **Calcium (>11 mg/dl)** | .978 | 0.031* | 2.659 | 1.093 | 6.471 |

AHR adjusted hazard ratio CI Confidence interval *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

**Table 5:** Relation between relapse free survival and interval from last chemotherapy date to stem cell infusion among good responders and among the whole studied patients

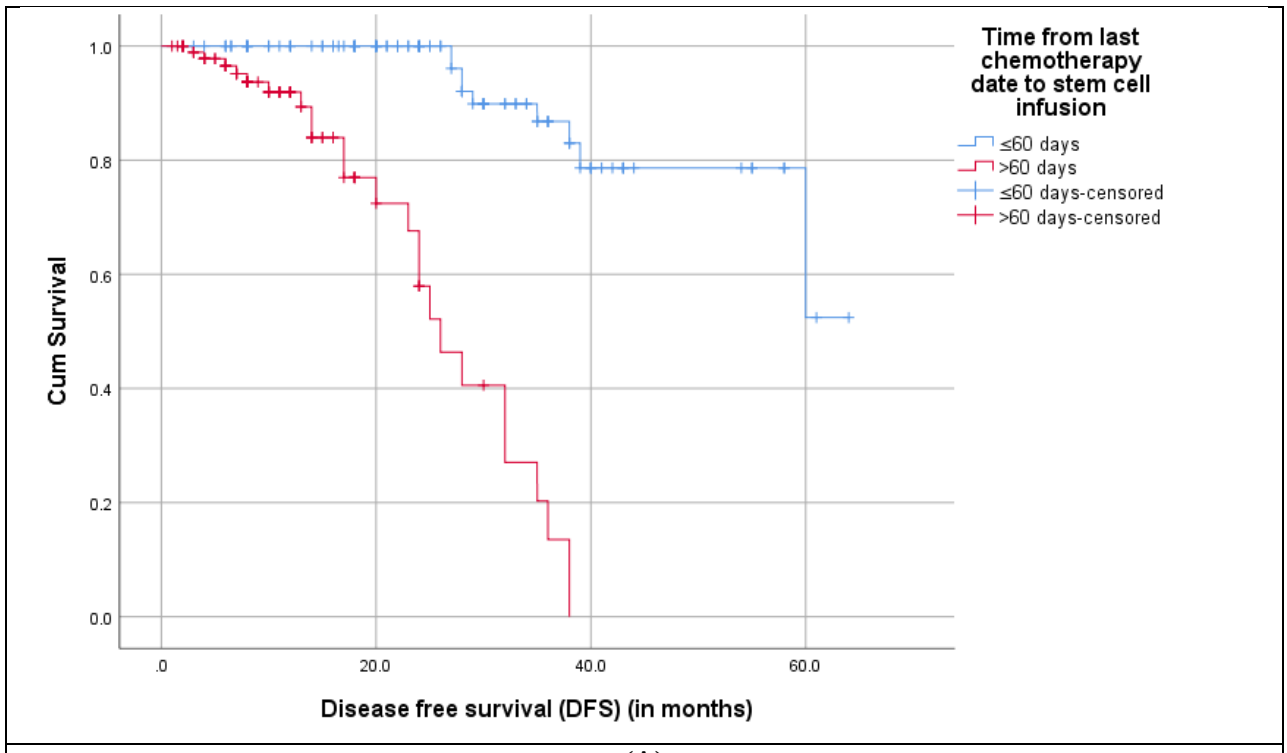
| **Relation between relapse free survival and interval from last chemotherapy date to stem cell infusion among good responders** | | | | | |
|---|---|---|---|---|---|
| | **Total** | **Event(%)** | **Mean ± std error** | **95% CI** | **p** |
| **Time** | | | | | |
| **≤60 days** | 108 | 9(8.3%) | 56.13 ± 2.28 | 51.67 – 60.59 | |
| **>60 days** | 94 | 22(23.4%) | 25.78 ± 1.72 | 22.41 – 29.14 | <0.001** |
| **Overall** | 202 | 31(15.3%) | 47.59 ± 2.35 | 42.99 – 52.9 | |
| **Relation between relapse free survival and interval from last chemotherapy to stem cell infusion among studied patients** | | | | | |
| | **Total** | **Event(%)** | **Mean ± std error** | **95% CI** | **p** |
| **Time** | | | | | |
| First quartile | 22 | 1(4.5%) | 59.86 ± 3.39 | 52.34 – 67.38 | |
| Second quartile | 89 | 8(9%) | 54.02 ± 2.25 | 49.61 – 58.42 | <0.001** |
| Third quartile | 50 | 5(10%) | 31.7 ± 2.59 | 26.63 – 36.78 | |
| Fourth quartile | 50 | 19(38%) | 21.51 ± 2.19 | 17.21 – 51.77 | |
| **Overall** | 211 | 33(15.6%) | 47.27 ± 2.3 | 42.77 – 51.77 | |

p for Mantel cox test CI confidence interval of mean *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

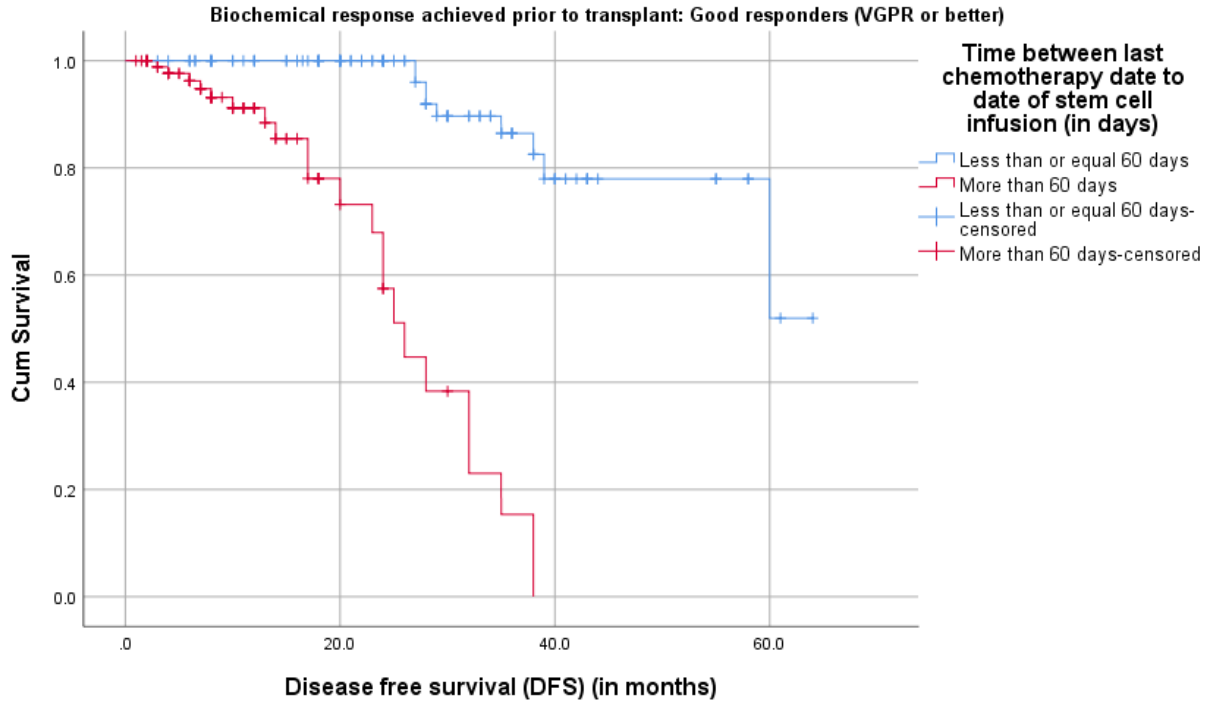
**Table 6:** Relation between overall survival and interval from last chemotherapy date to stem cell infusion

| | Total | Event(%) | Mean ± std error | 95% CI | p |
|---|---|---|---|---|---|
| **Time** | | | | | |
| **≤60 days** | 111 | 3(2.7%) | 67.48 ± 1.45 | 64.64 – 70.32 | |
| **>60 days** | 100 | 9(9%) | 58.28 ± 3.97 | 50.5 – 60.06 | 0.004* |
| **Overall** | 211 | 12(5.7%) | 63.92 ± 1.89 | 60.21 – 67.63 | |
| | **Total** | **Event(%)** | **Mean ± std error** | **95% CI** | **p** |
| **Time** | | | | | |
| First quartile | 22 | 1(4.5%) | 60.64 ± 3.24 | 54.3 – 66.98 | |
| Second quartile | 89 | 2(2.2%) | 64.31 ± 1.67 | 64.31 – 70.86 | 0.002* |
| Third quartile | 50 | 4(8%) | 32.15 ± 4.27 | 32.15 – 50.29 | |
| Fourth quartile | 50 | 5(10%) | 49.88 ± 5.08 | 49.88 – 69.79 | |
| **Overall** | 211 | 12(5.7%) | 63.92 ± 1.89 | 60.21 – 67.63 | |

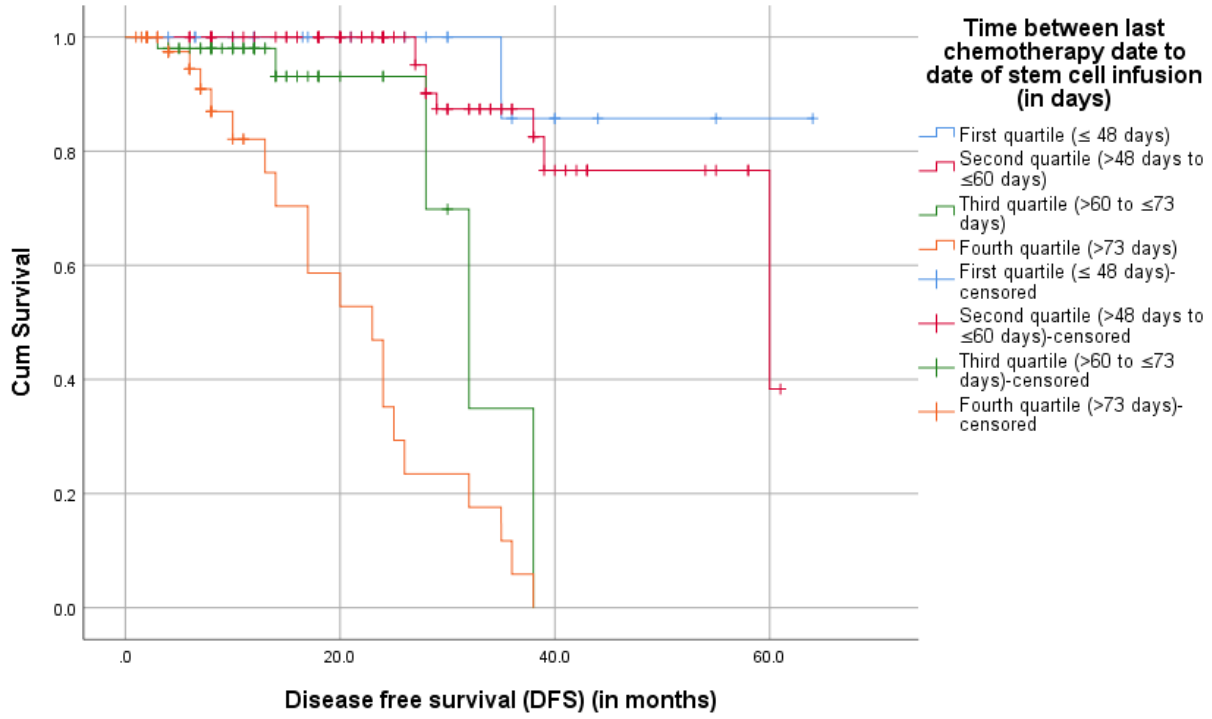
p for Mantel cox test CI confidence interval of mean *p<0.05 is statistically significant **p≤0.001 is statistically highly significant



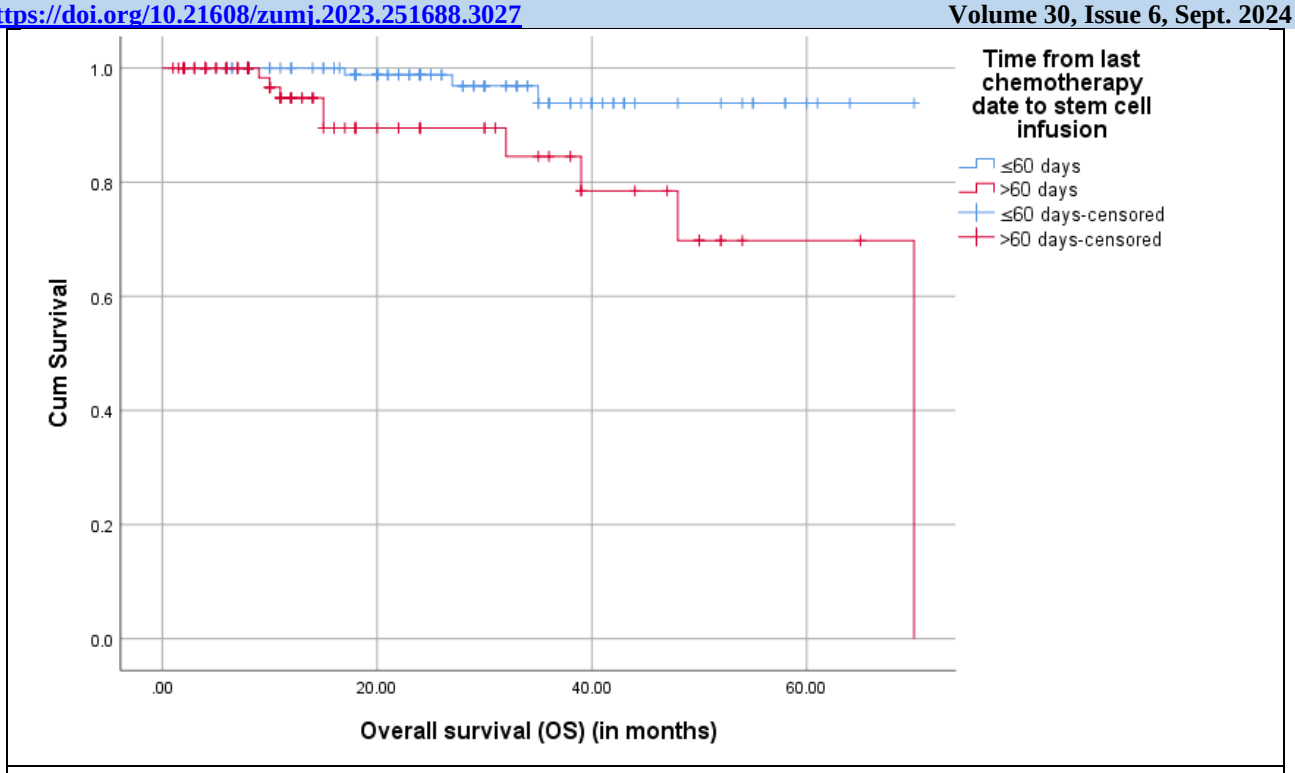

(A)


Biochemical response achieved prior to transplant: Good responders (VGPR or better)
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.0
20.0
40.0
60.0
Disease free survival (DFS) (in months)
Time between last chemotherapy date to date of stem cell infusion (in days)
Less than or equal 60 days
More than 60 days
Less than or equal 60 days-censored
More than 60 days-censored

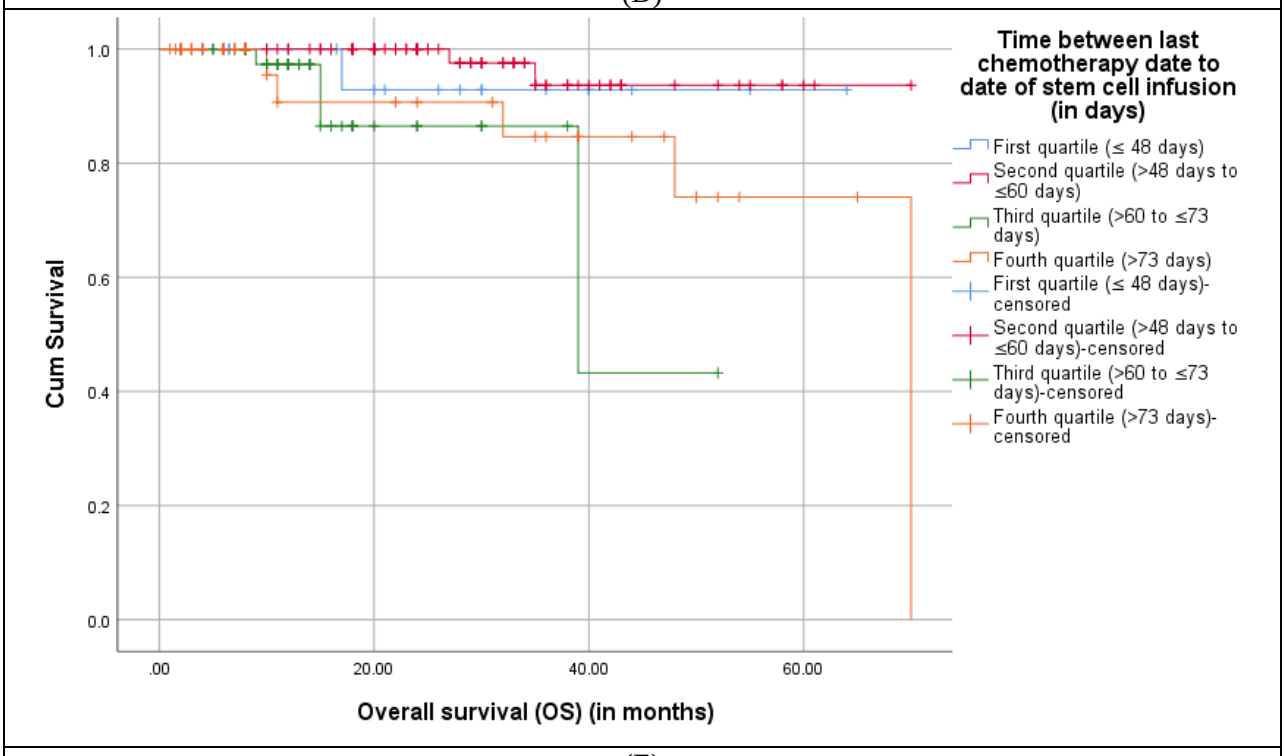
(B)


Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.0
20.0
40.0
60.0
Disease free survival (DFS) (in months)
Time between last chemotherapy date to date of stem cell infusion (in days)
First quartile (≤ 48 days)
Second quartile (>48 days to ≤60 days)
Third quartile (>60 to ≤73 days)
Fourth quartile (>73 days)
First quartile (≤ 48 days)-censored
Second quartile (>48 days to ≤60 days)-censored
Third quartile (>60 to ≤73 days)-censored
Fourth quartile (>73 days)-censored

(C)




(D)




(E)

**Figure 1:** Kaplan Meier plots showing (A): significant relation between disease free survival and interval between last chemotherapy date and stem cell infusion, (B): significant relation between disease free survival and interval between last chemotherapy date and stem cell infusion among good responders, (C): significant relation between disease free survival and interval between chemotherapy and stem cell infusion, (D): significant relation between overall survival and interval between last chemotherapy date and stem cell infusion, (E): significant relation between overall survival and interval between last chemotherapy date and stem cell infusion

## DISCUSSION

There is a lack of information about IP-related post-HDT/ASCT survival outcomes from the time induction ends until transplant day at the moment. Even if CR is not attained before the transplant, patients still benefit from HDT/ASCT, according to research. So, regardless of the response after induction, many institutions move forward with HDT/ASCT after 4–6 cycles of treatment [12-14].

The current study results were in agreement with Kim et al. [15], who investigated the impact of pretransplantation features and disease state on disease survival in patients with first chemosensitive myeloma (≥ PR) who underwent a single ASCT upfront and were registered in the Korean Multiple Myeloma Working Party (KMMWP) online registry. The majority of the 197 patients (77%) were under the age of 60, and 52.7% were men.

Also, the present study results were in agreement with Huang et al. [16], who demonstrated that IgG-type myeloma was the most common diagnosis at 52.4%, with IgA-type coming in second at 23.2% and light-chain type coming in third (21.4 percent).

As well, Sucak et al. [17] revealed that Eighteen patients (62.1%) had immunoglobulin G (IgG) as their immunological subtype. In contrast, six patients (20.7%) had IgA, one patient (3.4%) had IgD, and four patients had light chains (13.7 percent). Generally, according to the immunological subtype, their study revealed that a larger percentage of their studied cases had IgG which was consistent with our results.

Our results revealed that 70% of patients received VCD as induction chemotherapy, and 21.8% received VRD. Melphalan was given to 97.6% of patients as a conditioning regimen, and 79% of patients received Lenalidomide as maintenance treatment, while 14.2% didn't receive maintenance. Also, we found that the time interval from the last chemotherapy date till the stem cell infusion ranged from 14 to 150 days with a median of 60 days.

Also**,** Malhotra et al. [18] revealed that 37.4% of their studied cases received VCD as induction chemotherapy, 25.4% received VTD, 17.5% received VRD, and 19.7% received miscellaneous regimens such as TD or combination of regimens. They also reported that all patients were conditioned with melphalan. Additionally, their study demonstrated that VCD was the most commonly received regimen as induction chemotherapy among their studied cases, which was in line with our findings.

Similarly, the current study agreed with Chakraborty et al. [19], who explored the effect of induction therapy duration on PFS post-transplant in the modern period. Induction chemotherapy with VCD was administered to 29% of patients, whereas VRD was administered to 18%. On the other hand, they found that lenalidomide-dexamethasone RD was the most often utilized induction regimen (35 percent).

The current study showed that relapse was reported in 33 out of 211 patients (15.6%), whereas disease-free survival ranged from 1 to 64 months with a median of 17 months; the current study in agreement with Aggarwal et al. [20] who revealed that progression-free survival (PFS) ranged from 57.7 to 89.9 months with mean 73.8 months. In addition, Charalampous et al. [21] found that three and a half years was the median progression-free survival and overall survival after the stem cell infusion date.

Our findings showed a statistically significant relation between relapse-free survival and maintenance treatment. Also, we found that relapse-free survival was significantly higher in patients who received Lenalidomide. According to Aggarwal et al. [20], patients who had VCD, LD, or VTD induction in addition to maintenance therapy did not vary in progression-free survival ($p = 0.547$).

Also, our results are consistent with Charalampous et al. [21], who revealed that 33 days was the median time to treatment (with an interquartile range of 27–42 days) from the last chemotherapy date. A substantially longer progression-free survival (35.6 vs. 32.1 months, $p < 0.03$) was seen in patients whose (TTT) was less than 33 days.

According to the Cox proportional hazards model, Patients with multiple myeloma who undergo an autologous hematopoietic peripheral stem cell transplant are at increased risk of experiencing an early relapse, according to the criteria described by Pourmoussa et al. [22]. (HSCT). Their findings showed that maintenance therapy ($p < 0.0001$), the complete response at HSCT ($p = 0.004$), lower ISS ($p = 0.005$), and lower FCI ($p = 0.024$) were significantly linked to enhanced relapse-free survival.

Regarding Cox regression analysis, According to Aggarwal et al. [20], improving overall survival can be achieved through lenalidomide maintenance therapy and CR/VGPR responses obtained after

ASCT. On the other hand, improving PFS can be achieved through CR/VGPR responses obtained before ASCT and while in first remission, as can be achieved through transplant. In regards to the univariate analysis, it was discovered that the kind of maintenance therapy (lenalidomide vs. thalidomide) substantially predicted the overall survival (OS), and patients who obtained CR/VGPR response post-ASCT had a p-value less than 0. 001. In addition, the disease status at transplant (p=0.021), transplant in first remission (p=0.034), and response attained post-ASCT (p=0.001) were all determined to be significant predictors of PFS.

Our study reported a statistically significant relation between relapse-free survival and interval from last chemotherapy to stem cell infusion among good responders (significantly lower in patients with interval>60 days). The present study is in agreement with Charalampous et al. [21], who reported that Regarding the group of good responders, they discovered no statistically significant differences in progression-free survival, overall survival, or quartile comparisons; however, they did find that patients in the first quartile had a noticeably longer PFS than those in the fourth quartile, which aligns with our findings.

The current study revealed a statistically significant relation between relapse-free survival and interval from the last chemotherapy date to the stem cell infusion among studied patients (significantly lower in patients with increasing interval quartile). According to patients grouping based on inter-quartile TTT, the study of Charalampous et al. [21] revealed that The PFS was considerably longer in patients with a TTT below 27 days (1st quartile) (36.7 vs. 30.9 months, $p < 0.01$).

Among the patients we analyzed, we found a statistically significant correlation between the time it took from the end of chemotherapy to the infusion of stem cells and overall survival. In contrast, our results disagreed with Charalampous et al. [21], who showed that when comparing patients with a TTT greater than 33 days to those with a shorter TTT, there was no statistically significant difference in overall survival (128 vs. 122.2 months, $p = 0.68$).

The study has some limitations, chief among them a lower-than-average sample size. Additionally, The study's inherent biases and weaknesses are made more apparent by its retrospective approach. Lastly, we couldn't tell if the discrepancy in free survival was due to disease development during the chemotherapy-free time as most patients didn't have myeloma lab tests done at the end of induction and right before transplant. Patients exhibiting relapse symptoms during this brief drug-free period may constitute a distinct cohort with more aggressive disease biology and subpar prognosis; hence, this issue warrants further investigation in future research.

## Conclusions:

The current study demonstrated the prognostic value of the time interval between the end of induction chemotherapy and autologous stem cell transplantation among multiple myeloma cases. We revealed a statistically significant relation between relapse-free survival and interval from the last chemotherapy date to the stem cell infusion among studied patients, significantly lower in patients with interval>60 days and with increasing interval quartile. Similarly, there was a statistically significant relation between overall survival and interval from the last chemotherapy date to stem cell infusion among studied patients. We conclude that the overall survival rate was substantially lower in patients whose intervals were greater than 60 days and with increasing interval quartiles.

## REFERENCES


1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-49.
3. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated the criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12): 538-48.
4. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863-9.
5. Goldschmidt H, Lokhorst HM, Mai EK, van der Holt B, Blau IW, Zweegman S, et al. Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial. *Leukemia*. 2018;32(2):383-90.
6. Bergin K, McQuilten Z, Moore E, Wood E, Spencer A. Myeloma in the Real World: What Is Really Happening?. *Clin Lymphoma Myeloma Leuk*. 2017;17(3):133-44.

7. Moreau P, Facon T, Attal M, Hulin C, Michallet M, Maloisel F, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. *Blood*. 2002;99(3):731-5.
8. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19):1782-91.
9. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial [published correction appears in J Clin Oncol. *J Clin Oncol*. 2012;30(24):2946-55.
10. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-55.
11. Durie BGM, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068):519-27.
12. Bao A, Zhao Q, Kudalkar R, Rodriguez J, Sharma N, Bumma N,et al. Impact of interval progression before autologous stem cell transplant in patients with multiple myeloma. *Front Oncol*. 2023; 13:1216461.
13. Al Hamed R, Bazarbachi AH, Malard F, Harousseau JL, Mohty M. Current status of autologous stem cell transplantation for multiple myeloma. *Blood Cancer J*. 2019;9(4):44.
14. Dhakal B, Szabo A, Chhabra S, Hamadani M, D'Souza A, Usmani SZ, et al. Autologous Transplantation for Newly Diagnosed Multiple Myeloma in the Era of Novel Agent Induction: A Systematic Review and Meta-analysis. *JAMA Oncol*. 2018;4(3):343-50.
15. Kim JS, Kim K, Cheong JW, Min YH, Suh C, Kim H,et al. Complete remission status before autologous stem cell transplantation is an important prognostic factor in patients with multiple myeloma undergoing upfront single autologous transplantation. *Biol Blood Marrow Transplant*. 2009;15(4):463-70.
16. Huang TC, Huang SY, Yao M, Lin CY, Hwang WL, Gau JP, et al. Autologous stem cell transplantation in multiple myeloma: Post-transplant outcomes of Taiwan Blood and Marrow Transplantation Registry. *J Formos Med Assoc*. 2019;118(1 Pt 3):471-80.
17. Sucak GT, Aki SZ, Yüzbaşioğlu B, Akyürek N, Yağci M, Bağriaçik U, et al. Prognostic value of bone marrow microvessel density and angiogenic cytokines in patients with multiple myeloma undergoing autologous stem cell transplant. *Leuk Lymphoma*. 2011;52(7):1281-9.
18. Malhotra P, Yanamandra U, Khadwal A, Prakash G, Lad D, Law AD, et al. Autologous Stem Cell Transplantation for Multiple Myeloma: Single Centre Experience from North India. *Indian J Hematol Blood Transfus*. 2018;34(2):261-7.
19. Chakraborty R, Muchtar E, Kumar SK, Buadi FK, Dingli D, Dispenzieri A,et al. Impact of duration of induction therapy on survival in newly diagnosed multiple myeloma patients undergoing upfront autologous stem cell transplantation. *Br J Haematol*. 2018;182(1):71-7.
20. Aggarwal M, Agrawal N, Yadav N, Verma P, Ahmed R, Mehta P, et al. Autologous stem cell transplantation in first remission is associated with better progression-free survival in multiple myeloma. *Ann Hematol*. 2018;97(10):1869-77.
21. Charalampous C, Goel U, Kapoor P, Binder M, Buadi FK, Cook J, et al. Outcomes of patients with primary refractory multiple myeloma in the era of triplet and quadruplet induction therapy. *Blood Adv*. 2023;7(16):4371-80.
22. Pourmoussa AM, Spielberger R, Cai J, Khoshbin O, Farol L, Cao T, et al. Predictive Factors for Early Relapse in Multiple Myeloma after Autologous Hematopoietic Stem Cell Transplant. *Perm J*. 2019;23:19.012.

## Citation

**Taha, H., Elghandour, S., Abdelfattah, R., Elnagar, A. Prognostic Value of Time Interval Between Induction Chemotherapy and Autologous Stem Cell Transplantation among Multiple Myeloma Patients. *Zagazig University Medical Journal*, 2024; (2638-2649): -. doi: 10.21608/zumj.2023.251688.3027**