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Study of the Effect of Prophylactic Corticosteroids on the Incidence of Engraftment Syndrome in Multiple Myeloma Patients Undergoing Autologous Bone Marrow Transplant

Nada F. El-Sheltawy *, Maha Elzaafarany, Kamel Farag, Doaa H. Sakr
Medical Oncology Unit, Internal Medicine Department, Faculty of Medicine, Mansoura University, Egypt
*** Corresponding author:** Nada F. El-Sheltawy, **Email**: Nadaelsheltawy@gmail.com, **Mobile:** (+20) 01224797005

ABSTRACT

Background: Engraftment syndrome (ES) is a recognized complication following autologous bone marrow transplantation (ABMT) in multiple myeloma (MM) patients, characterized by fever, rash, diarrhea, pulmonary infiltrates, and organ dysfunction. ES incidence varies according to patient-, disease-, and treatment-related factors. Previous studies have suggested that prophylactic corticosteroids may reduce the risk of its occurrence.

Objective: This study aimed to evaluate the effect of prophylactic corticosteroids use on the incidence of ES in MM patients undergoing ABMT, and its relationship with clinical characteristics, serum C-reactive protein (CRP) levels, hospitalization duration, and post-transplant outcomes.

Patients and Methods: This retrospective-prospective cohort study included 33 MM patients (mean age 52 ± 9 years; 66.7% female) who underwent ABMT at the Oncology Center, Mansoura University (November 2019 to May 2023) and received dexamethasone (4 mg IV or oral, twice daily) before or at engraftment. ES diagnosis was based on Maiolino and Spitzer criteria. Patients were followed until day +100 to assess disease status and overall survival (OS).

Results: Fever occurred in 54.5% of patients, diarrhea in 93.9%, and rash in 6.1%. According to Maiolino's criteria, ES developed in 2 patients (6.1%), while only 1 patient (3.0%) met Spitzer's criteria. The median $CD34^+$ cell dose infused was 4.6×10^6 cells/kg. At day +100, 93.9% of patients remained complete remission. Three-year OS was 75%. Hospitalization duration was shorter compared with historical non-prophylaxis cohorts.

Conclusion: Prophylactic corticosteroid use is associated with a markedly low incidence of ES in MM patients undergoing ABMT, without apparent increase in infection risk, and may contribute to shorter hospital stays and improved post-transplant recovery.

Keywords: Multiple myeloma, Engraftment syndrome, Autologous bone marrow transplantation, Corticosteroid prophylaxis, Dexamethasone.

INTRODUCTION

MM accounts for 1% of all cancers and 10-15% of all hematologic malignant malignancies. It is characterized by bone marrow (BM) infiltration with clonal plasma cells, production of monoclonal Ig, and associated end-organ damage [1]. Transplant related mortality in autologous peripheral stem cell transplantation (PSCT) for MM has significantly diminished since the 2000s, in particular for additionally improving care support measures. On the other hand ES, a complication accompanied by hematopoietic stem cell transplant (HSCT), is boosting regarding autologous PBSCT for MM [2]. ES is a well-known adverse event of HSCT presented by hyperthermia and further clinical manifestations such as rashes, diarrhea, pulmonary infiltration, weight gain, and neurologic manifestations [3].

Spitzer and Maiolino criteria for diagnosis of engraftment syndrome [4] include **major criteria:** (Non-infectious fever (100.4∘F) without a clear infectious or microbiological cause, or response to antimicrobial treatment. Skin rash (maculopapular exanthema) covering more than 25% of the body surface area. Pulmonary edema and hypoxemia that is not due to infection, cardiac failure, or pulmonary embolism), **Minor Criteria: (**Weight gain of more than 2.5% of the patient's baseline body weight, renal or hepatic dysfunction (e.g., bilirubin ≥2mg/dL or creatinine ≥2 times normal) and transient encephalopathy that cannot be explained by other causes) and **Maiolino Criteria** (the Maiolino criteria are simpler and often considered more sensitive. They require the presence of a non-infectious fever plus at least one of the following clinical signs, commencing 24 hours before or at any time after the first appearance of neutrophils: skin rash, pulmonary infiltrates (pulmonary edema), and diarrhea)

In **Betticher *et al.*** [5] corticosteroids (CSs) prophylaxis significantly diminished the risk of ES ($p < 0.001$). Hospitalization duration was longer in cases with ES than in cases with no ES within the two cohorts ($P<0.05$ for both), but didn't vary in a significant manner between cohorts A and B.

On the adjusted analysis of **Dhakal *et al.*** [6] budesonide prophylaxis was accompanied by a significantly lower risk of developing ES [$P< .0001$]. There was no change in the 30-day readmission rates [$P = .81$], but a trend for shorter LOS in the prophylaxis group [7.3 per cent reduction in LOS (95 per cent CI, −14.4 per cent to zero per cent); $P = .06$].

Mossad ***et al***. [7] demonstrated that steroid prophylaxis reduces the possibility of ES following AHSCT by almost 10-fold, with no increase in the incidence of infection. In addition, decreasing the risk of ES is accompanied by a shorter mean Length of Stay (LOS). It has no effects on OS or PFS.

This study aimed to evaluate the effect of prophylactic corticosteroid use on the incidence of ES in MM patients undergoing ABMT, as well as its

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relationship with clinical characteristics, serum C-reactive protein (CRP) levels, hospitalization duration, and post-transplant outcomes, including disease status at day +100 and overall survival (OS).

Patients and Methods

This retrospective and prospective cohort study included 33 MM cases underwent ABMT and received prophylactic Dexamethasone before or at the time of engraftment at BMT Unit, Oncology Center, Mansoura University (OCMU) from November 2019 to May 2023.

Inclusion criteria: Patients with MM who achieved at least a very good partial response (VGPR) following induction therapy prior to undergoing transplantation. Both male and female patients were considered, provided they were between 18 and 70 years of age and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to II.

Exclusion criteria: Patients who were younger than 18 years, older than 70 years, proved to have double malignant tumors, or had any missing key data

Pretreatment assessment:

Detailed medical history, thorough physical examination , Laboratory investigations including CBC, renal function tests , liver function tests, lactate dehydrogenase, BM aspirate and biopsy, Serum protein electrophoresis with immune fixation, Bence-Jones protein, Beta-2 microglobulin, immunoglobulin assay and serum free light chains to confirm pre-transplant disease status either CR or VGPR, CRP ,ESR., HBsAg, HCV Ab, HIV and High Resolution CT chest to exclude any chest infection were done before admission to BMT unit.

Treatment schedule

Stem cell mobilization was performed by weight-adapted G-CSF (filgrastim at 10 μg/kg body weight) divided into 2 doses. CD34+ mobilization was consistently performed following mobilization with G-CSF. High-dose chemotherapy was melphalan-based in the MM cases (100 mg/m2/day on days -2 and -1; cumulative dose/m2 in case of cryopreservation of stem cells or 200 mg/m2/day on day –1 in case of non-cryopreservation of stem cells), autologous stem cell transplantation (ASCT) was performed on day 0 with at least 2.0 × 106 CD34+ cells/kg body weight. Corticosteroid prophylaxis was performed with 4 mg Dexamethasone i.v or po bid. Cases were followed up till day +100 post-transplant to determine disease status.

Assessment of ES:

Owing to multiple definitions of ES, we used Maiolino's criteria and Spitzer's criteria for Diagnosis of ES. ES was defined by the presence of non-infectious fever, characterized by a body temperature ≥38°C without clinical or microbiological evidence of infection and unresponsive to antimicrobial therapy. Diarrhea was considered significant if at least two episodes occurred daily without microbiological confirmation of infection. Skin rash was defined as an erythematous rash involving at least 25% of the body surface area, not attributable to other causes such as infection or hypersensitivity. Weight gain of ≥2.5% from baseline was also included. Hepatic dysfunction was defined as a bilirubin level ≥2 mg/dL or a rise in transaminases to at least twice the baseline level. Renal dysfunction was identified by a doubling of the baseline serum creatinine level. Any unexplained neurological signs or symptoms were considered indicative of encephalopathy. Lastly, non-cardiogenic pulmonary edema was diagnosed either radiologically (via chest X-ray or CT scan) or clinically, based on the presence of cough, dyspnea, basal crepitations on auscultation, or hypoxemia (SpO_2 <90%), in the absence of infection, heart failure, or pulmonary embolism.

***Ethical Consideration*:**

This study was ethically approved by Mansoura University's Research Ethics Committee (MS- IRB #22.10. 2177.R1.R2.R3.R4). Written informed consent was obtained from all participants. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human subjects.

Sample size Calculation:

Taking into consideration the low rate of MM cases (1-2 cases /month) undergoing ABMT in BMT unit, OCMU, this study involved thirty-three MM patients.

Statistical analysis

Data analyzed on a personal computer running SPSS for windows (Statistical Package for Social Scientists) Release 16. P value of < 0.05 considered statistically significant. For descriptive statistics of qualitative variables, the frequency distribution procedure ran with calculation of the number of cases and percentages. For descriptive statistics of quantitative variables, the mean, and standard deviation or the median and range used as appropriate.

RESULTS

The patients in this study were 33 patients, 22 of them were females (66.7 %) while the other 11 were males (33.3%) **(Table 1)**. Mean age was 52 years (±9) ranging from 33 to 68 years. BMI mean of all patients was 31 kg/m^2. The mean plasma cell % at diagnosis was 45 % (±29**) (Table 2)**. Out of the studied patients, 9 patients (27.3 %) had significant comorbidities, while the other 24 patients (72.7 %) had no comorbidities. Among the 9 patients with significant comorbidities, 5 patients were known to be hypertensive (15.2%), 1

patient had cardiac disease (3%), 2 patients were diabetic (6%),1 patient had facial palsy (3%),1 patient had history of poliomyelitis (3%), and 1 patient had history of HCV **(Table 3)**.

Out of the studied 33 patients, 28 of them (84.8%) underwent autologous BMT after induction while in CR and 5 patients (5%) were at VGPR at time of transplantation.

During mobilization, 8 patients (24.2 %) needed the use of plerixafor prior to HSC apheresis due to low expected CD 34+ cell dose, while in the mobilization of the other 25 patients (75.8%) plerixafor was not used. Mean dose of CD34+ cell received was 4.6 $\times 10^6$/kg (±2) ranging from 2-10.7 $\times 10^6$/kg **(Table 4).**

As regard clinical manifestations that can be attributed to ES,18 patients (54.5%) developed fever, 2 patients (6.1%) developed skin rash, 31 patients (93.9%) developed diarrhea, 2 patients (6.1 %) developed liver insufficiency, 2 patients (6.1%) had gain of weight, while none of the 33 patients developed any signs or symptoms of non-cardiogenic pulmonary edema **(Table 5).**

Out of the 18 patients who developed fever only 5 patients (27.8 %) had positive blood cultures while the blood cultures of the other 13 patients (72.2%) were negative for any infection **(Table 6).**

According to Maiolino's criteria 2 patients (6.1 %) developed clinical manifestations that can be explained by ES, while according to Spitzer's criteria only 1 patient (3%) did **(Table 7).**

Following up all the 33 patients up to D+100, 31 patients (93.9%) maintained their CR status **(Table 8)**. The 3-year OS of studied cases was 75%, the median was not reached **(Figure 1).**

Table (1) Gender of all patients

Gender	N	%
Female	22	66.7%
Male	11	33.3%
Total	33	100%

N: number, %: percentage.

Table (2) Age, BMI, and plasma cells % at diagnosis.

	Mean (SD)	Median	Range
Age (years)	52 (9)	53	33 - 68
BMI kg/m^2)	31.0 (6.4)	30.6	17.3 - 41.9
Plasma cells % at diagnosis	45 (29)	35	0 - 99

BMI: Body mass index, SD: Standard deviation, %: percentage.

Table (3) Types of Comorbidities among all patients.

Comorbidities	N	%
None	24	72.7
Cardiac	1	3
DM	2	6
Facial palsy	1	3
History of HCV	1	3
HTN	5	15.2
Poliomyelitis	1	3
Total Number of Patients	33	100

N: number, %: percentage, DM: Diabetes mellitus, HCV: Hepatitis C virus, HTN: Hypertension, CAD: Coronary artery disease, AF: Atrial fibrillation.

Note: One Patient had DM & HTN, while another patient had HTN and cardiac condition (CAD & AF).

Table (4) CD34+ cell dose received

Mean (SD)	4.6 (2)
Median	4.3
Range	2.0 - 10.7

$CD34^+$: Cluster of differentiation 34 positive, SD: Standard deviation.

Table (5) Clinical manifestations that can be attributed to ES among all patients

		N	%
Fever	Absent	15	45.5%
	Present	18	54.5%
Rash	Absent	31	93.9%
	Present	2	6.1%
Non-Cardiogenic Pulmonary edema	Absent	33	100%
	Present	0	0
Diarrhea	Absent	2	6.1%
	Present	31	93.9%
Liver insufficiency	Absent	31	93.9 %
	Present	2	6.1 %
Gain of weight	Absent	31	93.9%
	Present	2	6.1%

ES: Engraftment syndrome, N: number, %: percentage.

Table (6) Cultures in febrile patients.

	N	%
Positive Cultures	5	27.8 %
Negative Cultures	13	72.2%
Total	18	100%

N: number, %: percentage.

Table (7) Incidence of ES according to Maiolino *et al* and Spitzer *et al.*

		N	%
ES acc to Maiolino *et al*	Absent	31	93.9%
	Present	2	6.1%
ES acc to Spitzer *et .al*	Absent	32	97.0%
	Present	1	3.0%

ES: Engraftment syndrome, N: number, %: percentage.

Table (8) Disease status at D +100

	N	%
CR	31	93.9 %
VGPR	2	6.1 %

N: number, %: percentage, CR: Complete remission, VGPR: Very good partial response.

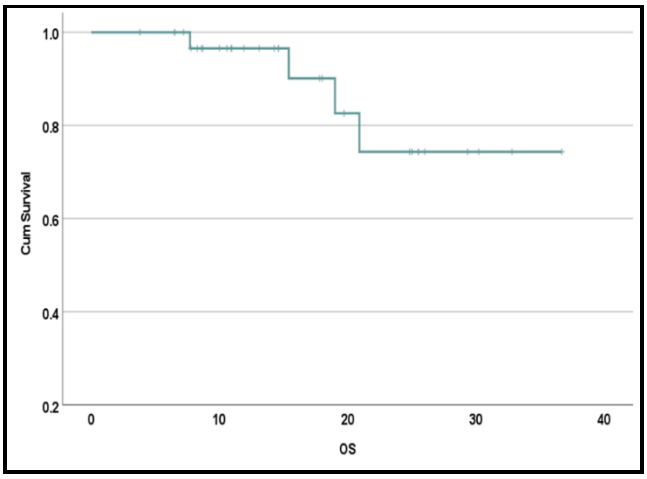

Figure (1) Overall Survival of all patients.

DISCUSSION

Post-induction high dose chemotherapy followed by ABMT is still considered the Standard of Care (SOC) in cases of Transplant-eligible MM cases followed by maintenance therapy with Lenalidomide and the addition of Bortuzumab or Daratumumab in High-risk cases [8].

ES is one of the described early complications of BMT. Criteria for diagnosis of ES has evolved throughout the years with the Spitzer's and Maiolino's criteria as the most used criteria. It is accompanied by longer duration of hospitalization and sometimes can be fatal. Incidence of ES in MM cases has been described in many studies ranging from 10 percent according to Katzel ***et al.,*** [9] ***to 29 percent in the*** *myeloma cohort of* ***Maiolino et al.,*** [10].

The BMT unit in OCMU started performing ASCT in November 2019. Our team noticed the high incidence of ES in the first few cases, as regard MM cases one of the 1st 5 cases developed ES according to Maiolino criteria. Throughout our quest to find innovative ways to provide the best medical care for our cases, the BM transplant team implemented the use of prophylactic Dexamethasone strategy to guard our cases against the development of ES.

In our study mean age was 52 years, which differed from that in the arm who received steroid prophylaxis in **Rodríguez-Lobato *et al.,*** [11] in which the mean age was 58 years. This difference could be explained by our wider range that started 33-68 years, compared with 39-70 years in the latter study. Meanwhile, the mean age in the steroid prophylaxis arm of **Mossad *et al.*** [7] was 49 years, as their participants age ranged between 20 –70 years.

Our cases were 33.3% males and 66.7% females which was not the same as the steroid prophylaxis arm in **Rodríguez-Lobato *et al***. [11] (69.6 per cent vs 30.4 per cent), **Gutiérrez-García *et al***. [2] (56 per cent vs 44 per cent) or **Mossad *et al***., [7] (51.8 per cent vs 48.2 per cent). The mortality rate was higher in male MM cases in Egypt according to GLOBOCAN 2022, in spite of no exact statistics were published nationally about the precise causes of mortality, this might explain the lower incidence of ASCT in males [12].

As regard the response before transplant, our study included more cases in CR as compared to the steroid prophylaxis arm of **Rodríguez-Lobato *et al***., [11] (84.8% vs 37%). This is owing to our long waiting list , limited number of transplant isolation rooms and in addition the COVID-19 pandemic, which obligated us to admit cases in CR in order to maintain their response and minimize the side effects of the therapy they were receiving, while cases in VGPR could continue their line of therapy or even be shifted to another line to achieve better response or at least keep that response while they are on the waiting list.

In this study our mobilization strategy was GCSF only based in 75.8% of cases while we had to use plerixafor in only 24.2% of our cases who were expected not to achieve the minimal target CD 34+ cell dose, and we did not use any chemotherapy-based mobilization. On the contrary, In the steroid prophylaxis arm in **Gutiérrez-García *et al***., [2], GCSF with cyclophosphamide was allowed to be used in 2% of cases and plerixafor was used in 24 percent of the cases. In the steroid prophylaxis arm of **Rodríguez-Lobato *et al***., [11] plerixafor was used in 23.9% of cases which is close to our study, on the other hand the strategy and the indications of its use in the previously mentioned were not explained in the previously mentioned studies.

Median CD 34^+ cell dose received in our study was 4.6 ×106/kg , 3.6 ×106/kg in the steroid prophylaxis arm of **Rodríguez-Lobato *et al***. [11] and 3.1 ×106/kg in the steroid prophylaxis arm of **Gutiérrez-García *et al***. [2]. This could be explained by the different number of participants (33 vs 46 vs 50).

In this study, the incidence of ES according to Maiolino's criteria was about 6.1% of cases which was very much lower than its incidence in the steroid

prophylaxis arm of **Rodríguez-Lobato *et al*.** [11] and **Gutiérrez-García *et al*.** [2] (22% of the participants in both studies).

Our study highlighted the effectiveness and importance of the administration of prophylactic corticosteroids (CSs) in the prevention of ES in MM cases undergoing ASCT in the BMT unit, OCMU. We managed to spare most our cases the complications of ES which can lead to death with the financial benefits of shorter hospitalization durations.

This study has several limitations. The relatively small sample size from a single-center experience might have limited the generalizability of the findings. The retrospective-prospective design introduced the potential for selection and information bias. The absence of a contemporaneous control group without corticosteroid prophylaxis prevented definitive causal inference regarding the reduction in ES incidence. Additionally, the short follow-up period restricted the evaluation of long-term outcomes and delayed adverse effects. Finally, variations in supportive care practices and the lack of standardized protocols for ES diagnosis across different studies have affected the comparability of results.

CONCLUSION

ES is a common early complication of ASCT in MM patients. Prophylactic corticosteroid use is associated with a markedly low incidence of ES in MM patients undergoing ABMT, without apparent increase in infection risk, and may contribute to shorter hospital stays and improved post-transplant recovery.

Our findings revealed that the prophylactic use of corticosteroids lead to ES incidence among our patients 6.1% according to Maoilino's criteria and 3% according to Spitzer's criteria.

We suggest that the use of prophylactic corticosteroids to prevent post-transplant ES while under the umbrella of prophylactic antibiotics might be an accepted approach in MM patients without increasing the risk of infection. The type of steroid prophylaxis used might differ according to each center policy.

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