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ORIGINAL ARTICLE

Engraftment Syndrome: Clinical Features and Predictive Factors in Autologous Stem Cell Transplant

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Abstract Engraftment Syndrome (ES) maybe observed in patients who undergo autologous stem cell transplant (SCT). To investigate clinical criteria for ES diagnosis and analyse the risk factors for this complication, we reviewed all auto-SCT cases (Lymphoma and Myeloma) performed during the past 9 years at two tertiary care centres. We analysed all patients with a non-infectious fever, developed within 7 days of engraftment (first day of ANC of 500 on two consecutive days) in 178 patients undergoing autologous stem cell transplant. A total of 46/178 (25.8%) patients developed non-infectious fever and one or more clinical signs of ES within 7 days of engraftment. In all, 29 (61%) fulfilled the Maiolino and 12 (26%) the Spitzer criteria. The incidence of engraftment syndrome using the Maiolino criteria in our study was 29 (15%), which compares well with Spanish study (13% using same criteria) and the original Maiolino study (20%). All patients with ES satisfactorily recovered and discharged with a median of 20 days from hospital. There was no significant difference in number of days of hospitalisation and days of antibiotics between the ES and non ES arms. All patients recovered without any morbidity and only 1 (2%) patient required readmission for fungal pneumonitis. 8 (17%) patients required ICU admission due to delay in initiation of steroids. None of the factors including number of chemotherapy cycles, conditioning regime, disease status, CD34 collection, growth factors and day of WBC engraftment except female ($p = 0.064$) were statistically significant (in univariate or multivariate analysis). Our study shows that engraftment syndrome is common in autologous transplant setting. Maiolino criteria to diagnose ES is more sensitive in our setting. If detected and treated early there is not much morbidity or mortality related to ES.

Keywords Engraftment syndrome · Autologous stem cell transplantation · Engraftment fever · Non-infectious fever

Introduction

Engraftment syndrome (ES), [1] is a well-known complication of autologous hematopoietic stem cell transplant (SCT). The pathogenesis of ES is not well defined but probably involves the release of pro-inflammatory cytokines (IL-2, TNF-a, IFN, IL-8 and IL-6), M-CSF, EPO, products of degranulation and oxidative metabolism of neutrophils and systemic endothelial damage. [2, 3].

Clinical features of ES include combinations of non-infectious fever, skin rash mimicking acute graft vs host disease (GVHD), pulmonary infiltrates, hypoxia, diarrhoea and other clinical manifestations reminiscent of capillary leak syndrome (weight gain, oedema, ascites and hypoalbuminemia) occurring during the peri-engraftment period [2].

The incidence of this syndrome varies from 7 to 59% in different reports, reflecting the different diagnostic criteria applied, [4]. Spitzer [2] proposed relatively complex clinical criteria based on the presence or absence of several major and minor symptoms and signs that developed

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within 96 h of engraftment (Table 1). In the same year, Cappizzi et al. [5] limited the diagnosis to patients with fever and pulmonary injury that occurred within 5 days of neutrophil engraftment.

Maiolino et al. [6] proposed a simpler classification that focused on non-neutropenic fever and one of the most frequent clinical signs commencing 24 h before or after the first appearance of neutrophils in the peripheral blood. Recently, Dispenzieri et al. [7] proposed maintaining the Spitzer and Maiolino clinical criteria but uncoupling the timing between clinical symptoms and neutrophil recovery.

The differential diagnosis between ES and other complications observed early after autologous-SCT, especially infections that develop at the end of the neutropenic phase, can sometimes be complex. This has a special relevance because ES responds dramatically to corticosteroids when they are administered early after the beginning of symptoms. However, when incorrectly treated or when the treatments delayed, ES can evolve to an irreversible multiple organ dysfunction syndrome [2, 6].

In this study we retrospectively analysed clinical data from 178 consecutive peripheral blood auto-SCTs performed at two tertiary care institutions between 2006 and 2014 in an attempt to better characterize the clinical criteria for the diagnosis of ES, to analyse the suspected increasing incidence and to identify risk factors favouring this complication.

Patients and Methods

Methods

To detect all cases with a possible ES, we analyzed all patients with a non-infectious fever developed within 7 days of engraftment (first day of ANC of 500 on two consecutive days) in 178 patients undergoing autologous stem cell transplant at two tertiary care centres from 2006 to 2014. We even included those patients who did not have fever but had other strong clinical features of ES like non-infectious diarrhoea, persistent vomiting or skin rash in the peri-engraftment period at least up to 7 days. In addition, we evaluated in the whole series the presence or absence of the remaining clinical manifestations and biological abnormalities reported in the Spitzer criteria (SC) and Maiolino criteria (MC) (Table 1).

Finally, we applied and compared both clinical diagnostic criteria. Non-infectious fever was defined as a new fever (38.0 °C) without clinical or microbiological documentation or response to antimicrobials. Pulmonary infiltrates were documented using X-ray or computed tomography and were considered ES if there were no signs of infection, cardiac failure or pulmonary embolism. Skin rash was defined as maculo-papular exanthema mimicking acute GVHD involving $> 25\%$ of body surface area. Weight gain was accepted when it was $> 2.5\%$ of the base. Diarrhoea was defined as at least two episodes of liquid depositions per day without microbiological documentation of infection. Hepatic dysfunction was defined as either total bilirubin 2 mg per 100 ml or transaminase levels > 2 times normal, and renal insufficiency as serum creatinine of > 2 times normal. Transient encephalopathy was accepted as part of ES if unexplained by other causes.

In addition, we analysed all patient and transplant related variables that could have an effect on ES development (sex, stage, underlying disease status prior to SCT, previous treatments, growth factor used, CD34 infused and days to engraftment).

Table 1 Spitzer and Maiolino criteria

Spitzer criteria	Maiolino criteria
Three major, or 2 major and 1 minor, within 96 h of engraftment	Non-infectious fever plus: skin rash, or
Major: non-infectious fever[a], skin rash[b], pulmonary edema[c] and hypoxemia	Pulmonary infiltrates, or diarrhoea[d], commencing 24 h before or at any time after the first appearance of neutrophils
Minor: weight gain[e], hepatic or renal[f] dysfunction, and transient encephalopathy[g]	

[a] New fever (38 °C) without clinical or microbiological documentation or response to antimicrobial treatment

[b] Maculo-papular exanthema involving 42% of body surface area

[c] Documented by X-ray or CT if there were no signs of infection, cardiac failure or pulmonary embolism

[d] At least two episodes of liquid depositions/day without microbiological documentation of infection

[e] Higher than 2.5% of basal

[f] Bilirubin × 2 mg per 100 ml or ASAT/ALAT × 2 times or creatinine × 2 times normal

[g] If unexplained by other causes

ES Treatment

All patients in whom ES was suspected (at our centre), received dexamethasone at the dose of 4 mg every 12 h. This treatment was started as soon as possible but always after administering 24–48 h of broad-spectrum antibiotics and after confirming negativity of the microbiological tests. This dose was maintained for 3 days or till the time of recovery from symptoms and then tapered over 5–6 days. However at the other centre ES was allowed to settle on its own and steroids (delayed) were used only if the symptoms did not settle from 48 to 72 h unless there were life threatening symptoms. Methylprednisolone 1 mg/kg was started for those who had severe respiratory distress.

Aims and Objectives

The primary aim of the study was to study the incidence and various clinical features associated with ES. The secondary aim was to study factors associated with incidence of ES, treatment and outcome and supportive care required with patients of ES.

Statistical Analysis

Descriptive statistical analysis was performed for various clinical parameters. To compare between two non-parametric variables Mann–Whitney test was applied. Cox regression analysis was used to find factors related to ES (univariate and multivariate analysis). Only those criteria that were significant in univariate analysis were taken into consideration for multivariate analysis (by method of backward selection). They were adjusted for various covariates.

Results

Patient Characteristics

The clinical charts of 178 consecutive patients who received a peripheral blood auto-SCT between January 2006 and December 2014 were analysed. The important clinical characteristics amongst both the groups are demonstrated in Table 2.

Clinical Characteristics

A total of 46/178 (25.8%) patients developed non-infectious fever and one or more clinical signs of ES within 7 days of engraftment. The clinical and biological data compatible with ES in these 46 patients are listed in Table 3.

In all, 29 (61%) fulfilled the MC and 12 (26%) the SC. When comparing the 17 patients with ES according to the MC that did not fulfil the SC, we observed that: 08 (50%) patients had only fever and skin rash, 5 (31%) fever and diarrhoea, 3(18%) had fever, skin rash and diarrhoea and 3 (18%) developed clinical manifestations at 5–7 days after engraftment (late signs).

Evolution

We started steroids in 25 (54%) patients, in 7 patients with fever, 9 patients with fever and rash, 4 patients with fever and diarrhoea, 7 patients with respiratory symptoms and 2 patients with hepatic dysfunction. We also used empirical steroids for 4 patients without fever but having persistent nausea for symptomatic control. We did not use steroids for 17 (38%) of patients. Methylprednisolone was started for 6 (24%) patients out of which 4 (66%) patients had fever and respiratory symptoms. The median dose of steroids was 4 mg for dexamethasone and 1 mg/kg for methylprednisolone, and the median duration was 3 days for Dexamethasone and Methylprednisolone respectively.

All patients satisfactorily recovered with the median day of discharge from hospital being 20 days. There was significant increase in number of days of hospitalisation and days of antibiotics between the ES and non ES arms as shown in Table 4.

Incidence of ES and Risk Factors

ES incidence for the whole series was 25.8%. Table 4 shows the incidence of ES among the different subgroups of patient's subgroup analyses. Incidence of ES showed correlation with female sex (37 vs. 22%, $p = 0.065$), though statistically non-significant. All other factors like number of chemotherapy cycles and regime, conditioning regime, disease status, CD34 collection, growth factors and day of WBC engraftment were not statistically significant as shown in Table 3. We could not get data on all patients, it being a retrospective study.

Discussion

Engraftment syndrome is an increasingly recognized complication in patients who receive auto-SCT. Spitzer and Maiolino laid down criteria for the correct diagnosis of this syndrome [2, 6]. Both clinical criteria are very similar and consistent for the three most relevant symptoms and signs of this syndrome: non-infectious fever, skin rash and pulmonary infiltrates with hypoxemia.

However, the SC accepts the possibility of establishing this diagnosis in a patient without fever. In our series, fever

Table 2 Demographic characters of ES patients

	Engraftment syndrome ES (n = 46) (%)
Age (median/IQR, in years)	45.5 years (22–65 years)
Sex (male)	26 (56%)
Diagnosis	
Myeloma	23 (50%)
Hodgkin's lymphoma	16 (35%)
Non-Hodgkin's lymphoma	07 (15%)
Others	00
Conditioning regime	
BEAM	6 (14%)
LACE	16 (35%)
CBV	01
Melphalan	23 (50%)
Others	00
Median CD34 counts (median, n = 120)	3.2

Table 3 Clinical features of ES population

Clinical data	Patients (n = 46)
Non-infectious fever	41 (91%)
Skin rash	18 (38%)
Pulmonary infiltrates	9 (20%)
Diarrhoea	15 (28%)
Hypoxemia	5 (11%)
Renal dysfunction	1 (2%)
Hepatic dysfunction	2 (3%)
Weight gain	0
Persistent vomiting	7 (12%)
Clinical criteria of ES	
Maiolino (+) Spitzer (+)	16 (34%)
Maiolino (+) Spitzer (−)	17 (36%)
Maiolino (−) Spitzer (+)	00 (0%)
Maiolino (−) Spitzer (−)	12 (26%)

was present in 41 (91%) as was the case in Spanish study [8]. In addition, the SC do not accept patients with only fever and skin rash (8/16, 50% of patients in our series) or with diarrhoea (5/16, 31% of our patients), consistent with other series [7, 8]. In addition, the SC limits this diagnosis to 96 h around engraftment 3 (18%), had delayed onset ES, in our group.

The incidence of engraftment syndrome using the Maiolino criteria in our study was 29 (15%) which compares well with Spanish study (13% using same criteria) and the original Maiolini study (20%).

We believe that many more cases can be diagnosed with ES if there is laxity in time criteria for SC study. This was also shown in study by Dispenzieri et al. [7]. Their incidence of ES increased from 27 to 50% after laxity in time criteria.

In our opinion, because the dynamic of the engraftment is very variable from patient to patient, the Maiolino approach is more realistic and, additionally, easy to apply.

Furthermore study from Spanish group had established that raised CRP was positively correlated with the diagnosis of engraftment syndrome [7]. All patients with ES had a sudden increase in CRP values that was not observed among those without signs of ES at engraftment (mean ± SD; 17.5 vs. 2.4; $p = 0.0001$). A cut off of 6 mg per 100 ml had the best sensitivity (90%). We did not use CRP values in our patients but it could be used as an aid to diagnosis of ES and could be included in diagnostic criteria. There will be need in future to assess more biochemical markers which would aid to diagnosis of ES.

All patients with ES satisfactorily recovered and were discharged with a median of 20 days from hospital. There was significant difference in number of days of hospitalisation and days of antibiotics between the ES and non ES arms.

No patients required rechallenging or increase in the dose of steroids. All patients recovered without any morbidity and only 1 (2%) patient required readmission for fungal pneumonitis. 8 (17%) patients required ICU admission out of which 2 (25%) required ventilatory support and 4 (50%) required inotropes. 6 out of this 8(75%) patients required life support because of delayed use of steroids (> 48 h), [2 (25%) were not even given steroids], 6 (75%) had pulmonary involvement, 2 (25%) had fever and diarrhoea. This was also because of the fact that ES was better defined only after 2009 and steroids were not used aggressively then (also due to different hospital policies).

Spanish group [7] had used a dose of Methylprednisolone 1 mg/kg for a median of 3 days and then tapered

Table 4 Univariate and multivariate analysis of various factors between ES and Non ES

	Engraftment syndrome yes/no (n = 46/132)		*P* value univariate/multivariate
Sex			
Female	20 (37%)	34 (63%)	0.065/0.073
Male	26 (22.2%)	91 (77.8%)	
Diagnosis			
Multiple myeloma	23 (26.4%)	64 (73.6%)	0.361
Non-Hodgkins lymphoma	7 (20.6%)	27 (79.4%)	
Hodgkins lymphoma	16 (33%)	32 (67%)	
Others	0	2	
Disease status			
Early	18 (27.3%)	48 (72.7%)	0.924/0.992
Advanced	25 (34%)	76 (66%)	
Number of chemotherapy regimens (median = 2)			
≤ 2	34 (26%)	94 (74%)	0.552/0.674
> 2	9 (34.6%)	17 (63.4%)	
No of chemotherapy cycles (median = 9)			
≤ 9	28 (29.2%)	68 (70.8%)	0.714
> 9	14 (25%)	42 (75%)	
Total CD34 dose (median 3.3)			
≤ 3.3	20 (32.3%)	42 (67.7%)	0.720/0.118
> 3.3	16 (26.7%)	42 (72.4%)	
CD34 > 2 on day 1			
Yes	11 (25%)	33 (75%)	0.423
No	26 (33.8%)	51 (66.2%)	
Mobilization			
Filgrastim	17 (21%)	64 (79%)	0.138/0.722
Pegfilgrastim	29 (32.2%)	61 (67.8%)	
Conditioning			
Melphalan	23 (26.4%)	64 (73.6%)	0.176
LACE	15 (36.6%)	26 (73.4%)	
BEAM	6 (20%)/24 (80%)	24 (80%)	
BeEAM	1 (50%)	1 (50%)	
CBV	1 (16.7%)	5 (83.5%)	
BACE	0	2	
Others	0	3	
Day of WBC engraftment(median = 11)			
≤ 11	22 (22.7%)	75 (77.3%)	0.211/0.446
> 11	24 (32.4%)	50 (67.6%)	
Supportive therapy and outcome of patients			
Duration (days) of antibiotic therapy, median (interquartile range-IQR)	12 (7)/10 (7)		0.011
Duration (days) of hospitalization, median (IQR)	20.5 (6)/17 (8.0)		0.028
No. of red blood cell units transfused, median (IQR)	2 (4)/2 (4)		0.917
No. of platelet units transfused, median (IQR)	4 (5)/3 (4)		0.184

it over 5–7 days. Maiolino et al. [6] had used steroids in 14/30 (48% patients). They used prednisolone from (20 mg mild ES − 120 mg/day for pulmonary symptoms, severe ES). They showed that earlier use of steroids (prior to day 13) was associated with faster recovery, lower transfusion requirements and lesser number of hospital days.

In our study, the only factor closely associated with ES was female sex, ($p = 0.065$). This correlates well with various other studies. Lee et al. [1], Moreb et al. [9], Edenfield et al. [10], Numberger et al. [11], Carreras et al. [8] and Cahill et al. [12].

In summary, ES is increasingly observed after auto-SCT. Our experience suggests that the modified Maiolino criteria (time laxity), when correctly applied, and despite being less specific than the criteria described by Spitzer, permit the detection of all cases with a possible ES. However, being lesser specific it might lead to overdiagnosis of ES.

If the fever does not respond to antibiotics and cultures are negative in the peri-engraftment period we have enough evidence to start empirical and early steroids in these patients. We would recommend a dose of dexamethasone 4 mg for 3 days tapered rapidly for less severe ES and methylprednisolone 1 mg/kg tapered after 3 days (slowly) for severe life threatening, pulmonary or hepatic ES.

There is still need for studies in future to see for utility of various biomarkers like CRP, cytokine levels and their correlation with ES. They could be included further in criteria for diagnosis of ES to improve its sensitivity.

Author's Contribution VS, RJ and AG contributed equally, wrote manuscript, analyzed data, designed study; AG, treated patients; TS, mentored paper, treated patients.

Compliance with Ethical Standards

Conflict of interest No conflict of interest or funding to be declared.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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