Original Article

Received: 2022-04-12
Accepted: 2022-09-07

BCCR
2021, No 4, Vol 13 :272-283
www.bccrjournal.com

Evaluation of the bone marrow transplantat recipient patients regarding fever onset, fever permanence, risk factors, and underlying causes, during the pre-engraftment phase

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ABSTRACT

Background: Patients undergoing bone marrow transplantation (BMT) are at higher risk of immune system deficiency. The immunosuppression, followed by pre-transplant chemotherapy makes patients vulnerable to a variety of infections, and fever is one of the first symptoms, which could develop as a result of infectious or non-infectious diseases. In the present study, the features of the fever during the pre-engraftment stage in BMT-receiving patients have been investigated.

Materials and Methods: Sixty-four patients receiving BMT were prospectively evaluated during the pre-engraftment phase to evaluate the evidence of the febrile reaction. Data concerning the cause of fever, microbiological tests, the treatments and fever onset pattern, and treatment outcomes were recorded and analyzed.

Results: 73.4% of the patients had autologous transplants, and the others received allogeneic. After transplantation, 75% of patients encountered fever during the pre-engraftment period. Of the 48 patients, 47.9% of the patients suffered from fever of unknown origin (FUO). Age, gender, underlying malignancy, type of transplantation, and acute phase reactants levels before transplantation were not associated with fever development. Among febrile patients, patients with autologous transplantation were significantly more likely to develop FUO (p-value = 0.036)

There was also no significant difference in the onset of fever between patients with infectious fever and who suffered FUO

Conclusions: During BMT, half of the patients developed a fever of unknown origin; nevertheless, it seems that patients undergoing autologous transplantation are at higher risk of FUO compared to patients who received an allogeneic transplant.

Keywords: Bone marrow diseases, Bone Marrow Transplantation, Fever of unknown origin, Fever, Pre-engraftment

INTRODUCTION:

Patients undergoing bone marrow transplantation (BMT) are at increased risk of reduction in granulocyte counts, and immunodeficiency due to weakened cellular and humoral immunity (1). Patients receiving BMT may suffer immunosuppression in different stages of the transplantation, and on this basis, they are more susceptible to developing infections with various pathogens, yet opportunistic organisms (2, 3). Furthermore, considering the high severity of the infections through immunodeficiency in these patients, subsequent complications can result in high morbidity and mortality (2). In the standard BMT process, bone marrow stem cells are transmitted from the donor to the recipient who has priory undergone chemotherapy (with or without radiotherapy), which is the main reason for the progression of the immunosuppression in these patients (4). The chemotherapy course mentioned above leads to a pre-engraftment phase in transplant recipient patients, that involves the first 30 days after BMT, and during this stage, the patient turns out to suffer neutropenia and a significant drop in white blood cell counts that is less than 500 per dL of the blood (5-7).

As a consequence, severe and life-threatening clinical dilemmas might arise, including pulmonary infection and following pulmonary edema due to weakening of the immune system, or impaired cardiac function (6). With due attention to these facts, several studies in the literature, have suggested a more careful follow-up and strict screening program in BMT patients during the pre-engraftment stage, and even before administration of the chemotherapy (8). A recent study reported several pathogens to be the culprit of the infections in BMT patients, including cytomegalovirus (CMV), Epstein-bar virus (EBV), Herpes simplex virus type 1, shingles, hepatitis B and C, and tuberculosis (9, 10).

According to the literature, fever is a common symptom of infection and is common finding, which occurs during neutropenia, mainly as a result of pre-engraving chemotherapy in patients receiving BMT during the pre-engraftment stage, which is known as a pre-engraftment syndrome (11, 12). The syndrome usually appears as a non-infectious fever accompanied by rashes or edema, and usually occurs at least a week before engraftment (13).

The pre-engraftment and following neutropenic stage are part of the process of treatment, particularly in patients with lymphoma and leukemia, and since the prevalence of fever is high at this stage, determining the pattern and factors, which are associated with fever development is of serious importance. Besides, identifying the causes, and examining the response to different therapies might help to make the right decisions in the pre-engraftment stages. The current study aimed to evaluate BMT recipient patients concerning the development of pre-engraftment syndrome, underlying etiology, and fever characteristics.

Material and methods

Patients

The current research was performed as a cross-sectional study on patients undergoing bone marrow transplantation (BMT). Patients affected with hematologic malignancies referring to Imam Khomeini Hospital Complex (IKHC) between 2017 to 2019, were enrolled for this study. The inclusion criteria were adult patients, diagnosed with hematologic malignancies who gave informed consent for participation in the study. Patients aged 14 years old or younger were excluded. In addition, patients who underwent BMT for reasons other than hematologic malignancies and those with a prior history of BMT were excluded as well. All patients' characteristics were recorded in individual forms.

Fever workup

All included cases were evaluated for fever using mercury-based thermometers applied in the axillary region, during the study. In this regard, the patients' body temperature was evaluated at least three times a day at 8-hour intervals, during the pre-engraftment period. Fever was defined as axillary temperature over 38 Celsius degrees in three consecutive evaluations or a single axillary temperature over 38.5°c. In case of fever incidence, time and number of incidences and their dura-

tion were documented for each patient.

A patient who experienced fever underwent complete physical examination, chest radiography, and lab tests such as central and peripheral blood cultures. Furthermore, urine analysis and culture, stool culture, and PCR for Clostridium difficile in case of diarrhea, and also if applicable wound culture was performed in these cases. In addition, serum analysis for inflammatory and viral markers such as CMV was also performed in order to determine the source of fever. Additionally, considering the patients' status and the respective treatment guidelines empiric carbapenem administration was initiated in these cases. If the fever was not relieved in 24-48 hours, vancomycin administration was added to the patients' treatment protocol. Ciprofloxacin was also added if no change of status was detected after that. Additional tests for determining the source of fever were chest or sinuses computed tomography scan, sinus endoscopy, echocardiography, etc. in case of clinical suspicion.

Patients follow up based on the source of fever

After the aforementioned evaluations, patients were divided into two groups of cases with known and unknown fever sources. Each group was daily evaluated regarding the initiation, number of incidences, duration, and potential sources of fever. In this regard, all patients' data were recorded in separate forms.

Data analysis

Later, all data was entered into SPSS version 24 (Chicago, Illinois) to indicate the study population's status regarding the incidence of fever, its duration and potentially associated risk factors and causes. Data were described as frequency, percentage, mean and standard deviation. Nominal data were analyzed using chi-square or fisher's exact test. In addition, numeric parametric data were analyzed using ANOVA, Turkey's post-hoc test and student's t-test and non-parametric data were analyzed using Kruskal-Wallis and Mann-Whitney test. In this regard, the p-value < 0.05 was considered statistically significant.

Results

Patients and demographics

Several sixty-four cases were evaluated in this study. The study population included 37 (57.8%) males and 27 (42.2%) females. Patients had an average age of 46.7 ± 12.7 years old. The underlying hematologic malignancies were multiple myeloma (50%), lymphoma (29.7%), acute myeloid leukemia (9.4%), acute lymphoid leukemia (9.4%) and myelodysplastic syndrome (1.6%). Among these patients, 73.4% (n= 47) underwent autologous transplants while the others (26.6%) received allogenic transplants. A review of patients' prior history revealed that 17 cases (26.6%) had a prior fungal infection. However, our evaluations showed that none of the cases were affected by fever before BMT. Table-1 represents patients' lab results before initiation of the BMT.

Patients' status after BMT

According to the obtained results, during the first thirty days after the bone marrow transplantation, 48 cases (75%) experienced at least a single episode of fever. The primary fever incidence was between the 1st to the 11th day after BMT (Median = 6th day). Among these patients, 23 cases (47.9%) had a positive microbiologic diagnostic test for infections e.g. positive cultures and CMV or C.difficile diagnosis. Detailed evaluations indicated

Table 1. patients' lab results before BMT initiation

	Interquartile range (IQR)	Median	Mean	Standard Deviation
WBC	9200-23900	15700	16856	10076
ESR	6/5-25	11/5	17/53	21/59
CRP	2-8	3	10/29	15/89

that 18 patients (39.5%) had a positive blood culture, 2 patients had a positive urine culture, 2 cases had CMV and one case was diagnosed with C.difficile. Table 2 reveals the pathogens discovered in the laboratory tests and cultures. According to these results, the most common pathogens were Staphylococcus epidermis and Staphylococcus aureus. Moreover, two cases were diagnosed with infectious syndromes where signs of pneumonia were observed in their radiographic. These patients experienced 34 fever cycles with a mean period of 23 ± 22.7 (Median = 16) hours. Figure 1 body temperature and fever duration in the 25 patients who had underlying infectious causes for their fever.

Interestingly, while having no fever, four patients in the current study were demonstrated to have positive blood cultures for S. aureus? S. epidermis? Coagulase-Negative Staphylococci and Non-Hemolytic Streptococci. Also, follow-up showed that two patients had passed away due to CMV infection and pre-engraftment syndrome.

However, detailed evaluations in 23 cases revealed no underlying infectious cause for the fevers. In this regard, it was shown that this group of patients experienced a total of 34 cycles of fever with a mean duration of 19 ± 13.7 (Interquartile range (IQR) = 16, Median = 16) hours for each episode of fever. Figure 2 represents body temperature and fever duration in these 23 cases.

Our investigations indicated that in order of their prevalence, diarrhea, mucositis, malaise, anal pain, loss of appetite, cough, belching, abdominal pain and edema were the most frequent clinical findings in the study population.

Associated factors with fever

Comparison of age between patients affected with fever (Mean: 49.1, SD: 12.8, Rank: 36.31) and those without

Table 2. underlying infectious fever causes detected by microbiological assessments

Total positive cultures (n = 23, 35.9%)		
Blood culture		
S. epidermidis(gr+)	9.4	4
S. aureus(gr+)	9.4	4
Coagulase-Negative Staphylococci(gr+)	7.8	3
Klebisella pneumonia (gr-)	7.8	3
Citrobacter freundii(gr-)	1.6	1
Non-Hemolytic Streptococci(gr+)	1.6	1
P. aeruginosa(gr-)	1.6	1
S. maltophilia(gr-)	1.6	1
Urine Culture		
Enterococcus faecium	1.6	1
Preoteus mirabilis	1.6	1
Blood PCR or Stool toxicology		
CMV PCR	3.2	2
C.difficile	1.6	1

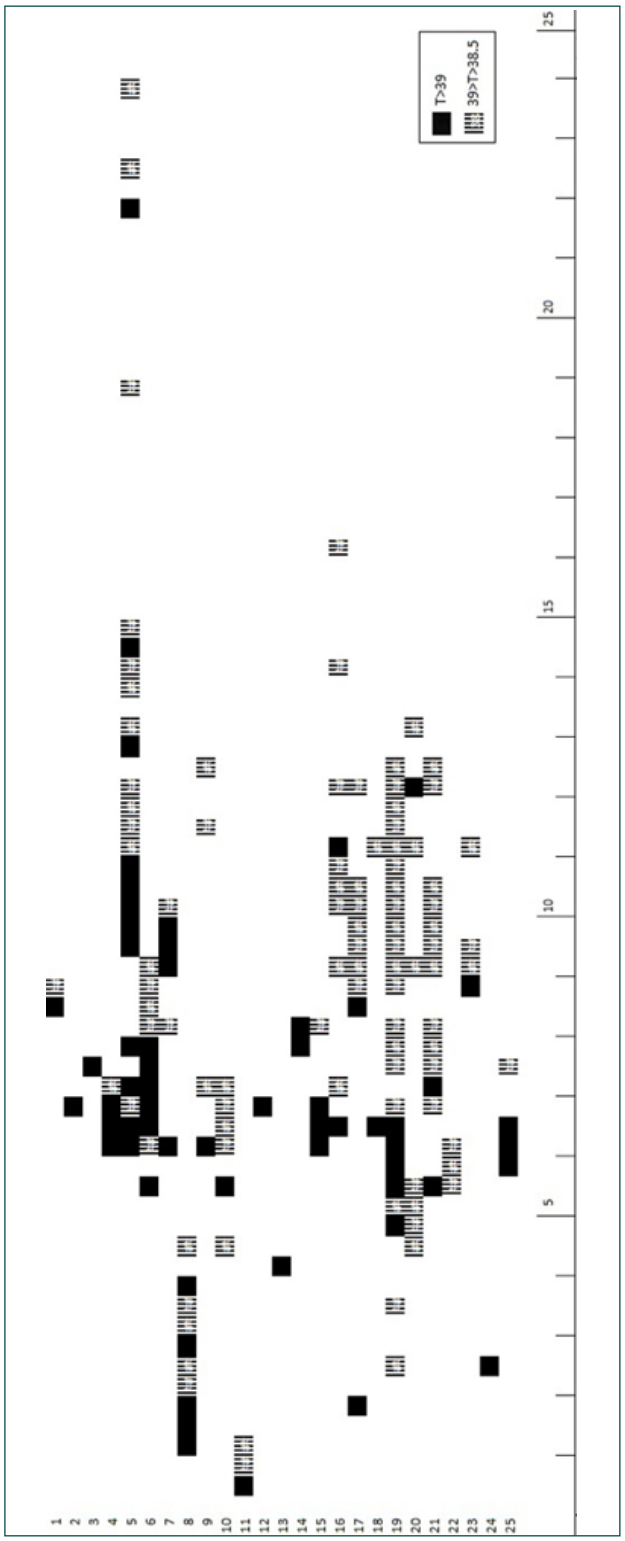

Figure.1. Represents the duration (days) and body temperature at which, each patient with underlying infection, experienced fever.

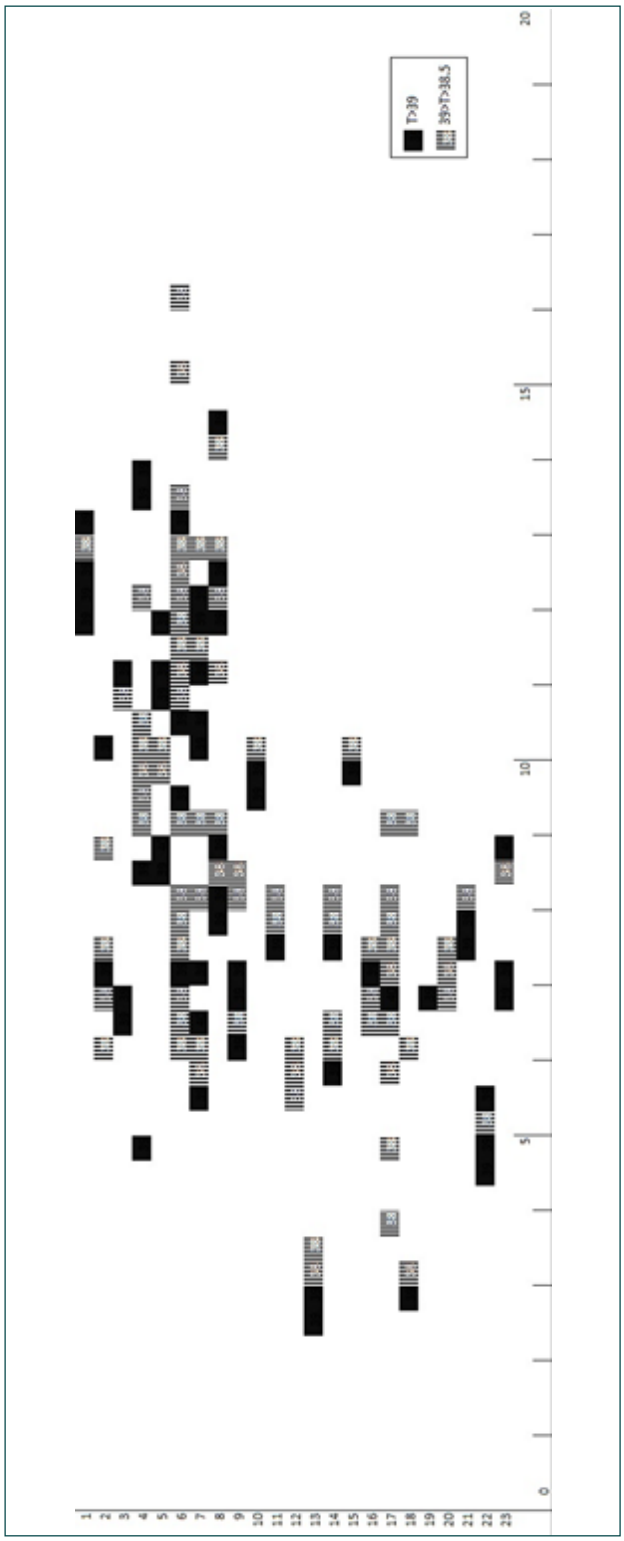

Figure.2. Represents the duration (days) and body temperature at which, each patient with no diagnosed underlying infection, experienced fever.

this complication (Mean: 45.9, SD: 12.7, Rank: 31.23) indicated that according to the Mann-Whitney U test there was no significant difference in this regard (p-value = 0.34). Furthermore, our assessments showed no correlation between patients' gender and fever incidence (p-value = 0.18). Evaluation of the potential association between the underlying malignancies and incidence of fever, using the chi-square test indicated no significant association between them (Table 3) (p-value = 0.34). Interestingly, our results indicated that those patients who received an allogeneic transplant encountered a greater number of fever incidences (82.4% to 72.3%) compared to autologous graft receiving cases. However, according to the chi-square test, the difference was not statistically significant (p-value = 0.41). In addition, it was shown that there was no significant association between prior history of fungal infection and incidence of fever in patients undergoing BMT (p-value = 0.24). Moreover, a detailed investigation of pre-BMT WBC, CRP and ESR levels studied patients revealed no statistically significant difference between those experiencing fever and those without fever incidence, in this regard p-values were as the following in order of mentioned factors (p-values = 0.80, 0.63, 0,74).

In addition, a comparison of total fever duration in patients suffering from fatigue (Mean: 35.6, SD: 37.7. Rank: 27.3) and other cases (Mean: 22.9, SD: 22.6, Rank: 21.1) revealed no significant difference (p-value = 0.11). Interestingly, our results indicated that fatigue was significantly associated with bacterial culture results (p-value = 0.011) i.e. it is more prevalent in patients with negative culture results (73.1%).

Similarly, a comparison of total fever duration in feverish patients with mucositis (Mean: 38.3, SD: 37.3, Rank: 28) and other cases suffering from fever (Mean: 25.1, SD: 28.4, Rank: 22.5) revealed no substantial difference (p-value = 0.11). However, no significant correlation was detected between bacterial culture results and mucositis incidence (p-value = 0.11).

Comparison of feverish patients with an underlying infection to those with an unknown source for fever

Comparison of age between patients known cause of fever (Mean: 47.04, SD: 11.21, Rank: 22.35) and those without an underlying infection (Mean: 47.07, SD: 14.21, Rank: 26.48) indicated that according to the Mann-Whitney U test there was no significant difference in this regard (p-value = 0.30). Also, there was no association between sex and the underlying cause of fever (p-value = 0.82). Evaluation of the potential association between the underlying malignancies and the cause of fever, using the chi-square test indicated no significant association between them (Table 4) (p-value = 0.58). Interestingly, our results showed that fever with no underlying infection was significantly more prevalent in patients undergoing allogenic BMT (38.2% compared to 74.1%, p-values = 0.03). In addition, it was shown that there was no significant association between prior history of fungal infection and source of fever in patients under-

Table 3. underlying malignancies and fever

Underlying disease	Fever		No Fever	
	n	%	n	%
Multiple myeloma	22	68/8%	10	31/3%
Lymphoma	16	84/2%	3	15/8%
Myelodysplastic syndrome	1	100%	0	0%
AML	5	83/3%	1	16/7%
ALL	4	66/7%	2	33/3%
Total	48	75%	16	25%

Table 4. underlying malignancies and fever origin

Underlying disease	Infectious Fever		Unknown origin Fever	
	n	%	n	%
Multiple myeloma	13	59.1%	9	40.9%
Lymphoma	8	50%	8	50%
Myelodysplastic syndrome	1	100%	0	0%
AML	2	40%	3	60%
ALL	1	75%	3	25%
Total	25	52.1%	23	47.9%

going BMT (p-value = 0.24). Evaluation and comparison of fever starting date revealed no statistical significance based on the origin of fever (Infection: Mean start date: 5.24, SD: 2.14, Rank: 22.4, Unknown cause: Mean start date: 6.04, SD: 2.05 Rank: 26.7, p-value = 0.27). Furthermore, the Mann-Whitney U test indicated no significant association between the underlying cause of fever and fevers duration (Infection: Mean: 23 hours, SD: 22.7, Rank: 33.9, Unknown cause: Mean: 19 hours, SD:13.7, Rank 35, p-value = 0.81). A comparison of clinical presentations revealed that patients suffering from infectious fevers experienced a lower incidence of fatigue compared to patients who had a fever of unknown source (38.4% to 61.5%), (p-value = 0.04).

WBC levels on the 1st day of the first fever cycle post-BMT were compared between the patients with an underlying infectious cause of fever and patients with fever of unknown origin. In this regard, Mann-Whitney U test revealed no statistically significant difference (Infection: Mean: 948, SD: 2051, Median: 200, Rank: 23.68 Unknown cause: Mean: 991.7, SD: 2646, Rank 25.39, p-value = 0.67). Furthermore, Table 5 indicates the differences between procalcitonin, ESR and CRP between these two groups on the 1st day of the first fever cycle post-BMT. In this regard, the Mann-Whitney U test revealed no statistically significant difference (p-value > 0.05).

Engraftment

Among the 64 evaluated patients, engraftment was achieved in 60 cases (93.75%). Interestingly, a similar number of patients from both fever and non-fever experiencing groups has successful engraftments. The mean engraftment time was 9.7 ± 1 day. The engraftment time is compared between the evaluated patient subgroups in table 6 where no significant difference has been revealed.

Antibiotics and fever

Among the 23 patients with unknown fever source, 2 cases (8.69%) were indicated for treatment with at least three different antibiotics while in the 25 patients with underlying infections 6 cases (24%) were indicated for such treatment. However, Fisher's exact test indicated no statistical significance between these findings (p-value = 0.24).

In the 21 patients who had positive bacterial cultures, fever was abolished after 2.23 ± 1.75 days of antibiotic treatment, similarly (p-value = 0.58), in the 23 cases with unknown fever origin, antibiotic therapy attenuated fever after 1.94 ± 1.71 days. Figure 10 represents the fever algorithm in the studied patients based on the causes, duration, pathogenesis and antibiotics used for fever.

Discussion

Although stem cell transplantation is a standard treatment in patients suffering hematologic malignancies, it is associated with chemotherapy-induced immunosuppression before transplantation that leads to higher susceptibility to various infections among patients, such as opportunistic pathogens, that results in a significant increase in morbidity and mortality (6, 7). It has been es-

Table 5. procalcitonin, ESR and CRP levels association with fever origin

	Fever source	Mean	SD	Median	Rank	p-value
Procalcitonin	Unknown	6/8	8/77	6/8	27/06	0/16
	Infection	1/71	3/05	0/22	22/16	
ESR	Unknown	68/63	29/29	69	26/39	0/38
	Infection	56/22	21/28	51	22/76	
CRP	Unknown	63/63	25/75	62	26/93	0/29
	Infection	48/44	26/87	51	22/28	

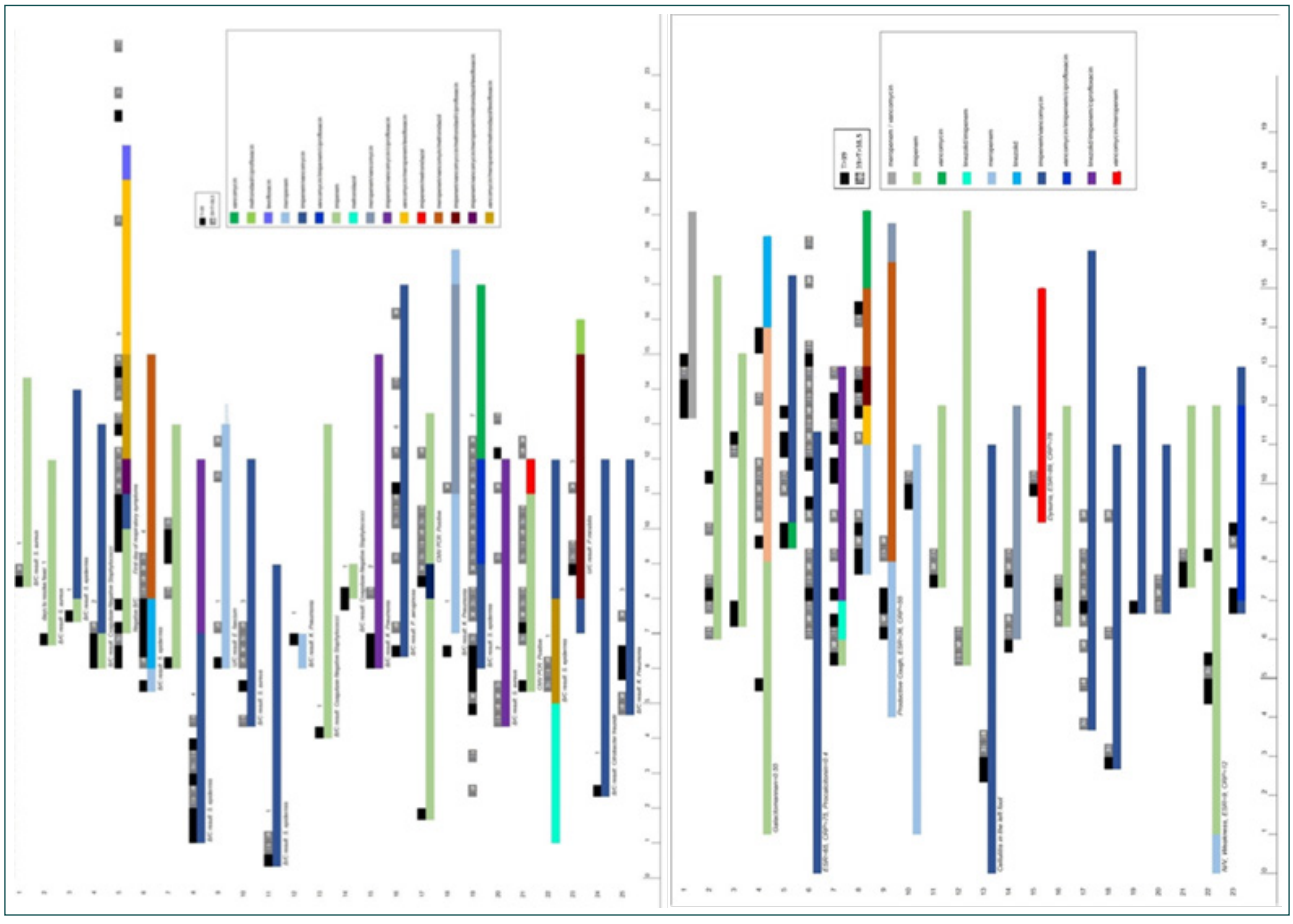

Figure.3. Represents the fever algorithm in the studied patients based on the causes, duration, pathogenesis and antibiotics used for fever.

timated that pre-engraftment syndrome may not affect transplant outcomes, but defining its diagnostic features and close monitoring of vulnerable patients is a topic of debate among experts (14). The present prospective descriptive-analytical study was conducted to determine the factors, which play a role in fever development in patients whom candidates to receive a bone marrow transplantation (BMT), during the pre-engraftment phase. For the very first time, in the current study, contrary to previous studies, patients with different bone marrow transplantation (BMT) techniques (autologous and allogeneic) were studied, which was not obtained in previous studies.

The most frequent indication for BMT was multiple myeloma, and lymphoma turned out to be the second leading underlying malignancy. Majority of the patients were a candidate to undergo autologous transplantation. After transplantation, fever developed in 75% of the patients. Fungal infection history was reported in one-fourth of the patients. Further, a patient had evidence of pneumonia during physical examination and imaging, and an increase in the thickness of the ethmoid sinus mucosa, as well, which was confirmed to be infected by fungal agents. Despite our findings, in the literature, the prevalence of previous fungal infections during the pre-engraftment stage was reported to be less than 3%, and some studies reported no infection among their patients (15-17). Fungal infections are mainly opportunistic and may not develop an infection in healthy individuals, despite contamination, in addition, its prevalence significantly varies in different regions (18, 19). Therefore, we hypothesized that the high rate of previous contamination in our patients was the culprit to a significantly high incidence of fungal infections. However, we observed no significant correlation between previous fungal infection history and the development of the fever after BMT.

Approximately half of the patients who developed febrile manifestation suffered a fever of unknown origin (FUO). Although we reported a slightly lower incidence rate for FUO, the result was similar to the data obtained from the earlier studies (15, 20). Because inflammatory responses and acute phase reactants are responsible for the development of the FUO, it seems nearly 50% of the cases are at risk of FUO (11). However, we observed no significant difference in terms of the median time of fever, while comparing with patients who had a defined pathogenic infection. Among patients who had an infection-induced fever, 47.9% had a bacterial infection. In contrast, the study by Auner et al. reported bacterial infection in 29% of patients (20). During blood culture tests among patients who had fever due to bacterial infection, we recognized gram-positive pathogens in 69.5% of the patients, which was significantly lower in comparison to the study by Auner et al. that 94% of the pathogens turned out to be gram-positive, and other studies in the literature (20-22). Besides, Fernandez-Mosteirin et al. reported gram-positive infection in 45% of patients, who had an infectious fever (23). To explain the diversity of the results presented in the literature, the authors should consider endemic pathogens of each region and the prevalence of each bacterial infection in a distinct area and declare the outcomes on an epidemiological basis.

We could not determine any correlation between fever development regardless of its origin, and different variables collected before transplantation, such as age, gender, underlying disease, type of BMT, white blood cell count, estimated sedimentation rate (ESR), and C-reactive protein (CRP). Nevertheless, in a recent study, Kollu et al. reported that high levels of CRP in multiple myeloma patients were associated with an increased risk of fever and neutropenia (24). Since we aimed to determine the factors associated with fever development during the pre-engraftment phase, we did not enroll patients concerning their underlying malignancies. Thus, we were not able to discover a relationship between laboratory test results in particular patients and febrile manifestations.

On the other hand, we focused on BMT characteristics, and we found that the prevalence of the FUO in patients who received allogeneic BMT was significantly higher. Also, patients who suffered FUO had more complaints of malaise in comparison to patients with infectious fe-

ver Reasonably, the majority of blood culture test results were negative in patients who complained of malaise; however, it was not possible to compare our findings with the literature, since it was the first study to enroll both BMT transplant types.

While comparing the incidence of infectious fever among the various group of patients with particular malignancy, no statistically significant difference was observed, which was comparable to the outcomes of the study by Auner et al. and Reich et al (16, 20).

In our study, in patients suffering from infectious fever and patients who had FUO, the fever resolved faster in patients who had an infectious fever, which was comparable to previous studies. Although some studies declared a shorter resolving time to antibiotic therapy in FUO patients (15, 25), we assume that the difference between results might be due to the various definition of response to treatment in different studies.

Our study had the following limitations. Due to the few number of patients, the sample size of the study was low. In addition, the study timeline was too short, and we were unable to follow up with patients to obtain outpatient morbidity and mortality rate.

Conclusion

Pre-engraftment syndrome is an unavoidable consequence of stem cell transplantations, particularly bone marrow transplantation, which leads to fever development in recipient patients, either due to infection or without defined origin; however, the infectious and non-infectious fever had a slightly similar incidence in our patients, in addition, fever resolving period was not significantly different in two groups. Although we reported a higher prevalence of previous fungal infection in our patients, it was not associated with an increased rate of post-transplant fever development. Gram-positive bacterias were the primary pathogen to cause infectious fever in patients. However, none of the pretransplant laboratory findings could predict the incidence of pre-engraftment syndrome.

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