Evaluation of the Multinational Association for Supportive Care in Cancer (MASCC) Score for Identifying Low Risk Febrile Neutropaenic Patients at a South Indian Tertiary Care Centre

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ABSTRACT

Background: Febrile neutropaenia prompts immediate hospitalization for its evaluation and the administration of empiric broad-spectrum antibiotics. It represents a major cause of morbidity, mortality and treatment costs in patients who receive chemotherapy. Risk stratification to identify the low risk patients is essential, as these patients may improve with outpatient treatment. This approach reduces the economic burden and thereby improves the quality of life.

Objective: Evaluation of the Multinational Association for Supportive Care in Cancer (MASCC) score and also other factors for identifying the low risk febrile neutropaenic patients at a south Indian tertiary care centre.

Materials and Methods: This is a prospective study which was done at a tertiary care hospital in Mangalore, from December 2009 to July 2011. The inclusion criteria were the histological diagnosis of malignancy, neutropaenia which was secondary to chemotherapy, an absolute neutrophil count of $< 500/cumm^3$, oral temperature of $>38.3^0C$ or $>38\ ^0C$ for 1 hour and age > 13 years. The patients were stratified, based on the MASCC score. Other clinical laboratory parameters were explored for identifying the low risk patients.

Results: A total of 50 cases of febrile neutropaenia were documented; 13 in solid cancers and 37 in haematological cancers. Acute leukaemia was the commonest underlying malignancy (26 out of 50). Seventeen cases were clinically documented, 16 cases were microbiologically documented and in 17 cases, no cause was found. Bacteraemia was the commonest (8 out of 16) among the MDI and *E coli* was the commonest organism which was identified (5 cases). All the patients were classified, based on the MASCC score. The association of the MASCC score and its outcome in terms of the recovery of the counts were found to be statistically significant ($p < 0.001$). Other factors which were found to be statistically significant in identifying the risk of complications were; tachypnea rate$> 24/minutes$ ($p < 0.001$), Temperature$>1020F$ ($p= 0.049$), hypotension (BP) value of $<90/60$ ($p<0.001$), ANC$< 50/Cumm3$ ($p < 0.001$), deranged renal parameters ($p=0.05$), bacteraemia ($p=0.001$) and the inpatient status ($p=0.006$).

Conclusions: The MASCC score correctly identifies patients with low risk febrile neutropaenia.

INTRODUCTION

Febrile neutropaenia is defined as a single oral temperature of greater than 38.3^0C (101^0F) or 38^0C or greater (100^0F) for over 1 hour in a patient with an absolute neutrophil count of less than $500/cumm^3$ or less than $1,000/cumm^3$, with a predicted rapid decline [1]. The pattern of the fever in neutropaenia is non-specific and it is not pathognomonic of any type of infections or non-infectious processes. Neutropaenia which results from cytotoxic chemotherapy is the most common risk factor for severe infections. The duration of the neutropaenia also contributes significantly to the risk of serious infections. This risk is significantly greater at lower neutrophil counts; such that 100% patients with an ANC of <100 cells/$Cumm^3$ which lasts for 3 weeks or more develop documented infections [2].

The risk for developing complications in patients with febrile neutropaenia is variable. Differentiating between the high and low risk patients with fever and neutropaenia has a significant impact on the decisions that affect the patients' quality of life and the overall medical costs. In 2000, an internationally validated scoring system to identify the low risk febrile neutropaenia cancer patients was developed by the Multinational Association of Supportive Care in Cancer (MASCC). This study included 1351 patients from 20 institutions in 15 countries. A numeric risk index score was constructed, which could weigh the different features which were associated with a high probability of a favourable outcome. A higher global score indicated a greater likelihood of fever resolution without any serious complications. A MASCC risk index score of 21 or more points identified the low risk patients [3]. Considering the heterogenicity of the populations with febrile neutropaenia, efforts continue to be made to separate the patients who are at a low and high risk of serious complications and to characterize each population. These efforts will have important implications in terms of the management of these patients.

The purpose of this study was to categorize the febrile neutropenic episodes in cancer patients into clinically documented infections, microbiologically documented infections and fever of unknown origin. It also aimed to evaluate the usefulness of the MASCC scoring index and to identify other risk factors.

OBJECTIVES

The objectives of the present study were, to investigate the clinical spectrum of febrile neutropaenia and to evaluate the Multinational Association of Supportive Care in Cancer (MASCC) score for identifying the low risk febrile neutropaenia patients.

MATERIALS AND METHODS

The present, cross sectional, prospective study was carried out in our tertiary care hospital during December 2009 to July 2011. The study population consisted of all the cancer patients who were hospitalized with febrile neutropaenia. The study had the approval of the institutional ethics committee.

Inclusion Criteria

Fever: A single oral temperature of greater than 38.3 ^{0}C (101 ^{0}F) or 38 ^{0}C or greater (100 ^{0}F) for over 1 hour.

Neutropaenia: an absolute neutrophil count of less than 500/cumm^3.

The suspicion that the patient could have any underlying malignancy which could be treated by chemotherapy.

Exclusion Criteria

Patients under 13 years of age.

The selected patients were studied in detail. The evaluation consisted of taking a complete history and a swift, meticulous, physical examination with special attention being given to the mouth, skin, catheter exit site, and the perianal region. The laboratory investigations included a complete blood count, a differential count and the calculation of the absolute neutrophil count. A conventional broth culture (by using Tryptic soy broth) was used for the blood culture. Other clinical specimens were inoculated on blood agar, chocolate agar and Mac Conkey's agar and they were incubated at 37^{0}C for 24-48 hours. The bacterial isolates were identified by using standard methods [4]. A chest X-ray was done when respiratory symptoms were present. The absolute neutrophil count was determined by: WBC count × (% mature neutrophils + % bands). Each patient was given a MASCC score based on the following scoring system and the response was studied.

Scoring system for risk of complications among febrile neutropenic patients, based on the Multinational Association for Supportive Care in Cancer predictive model MASCC score: [3]

Maximum score: 26

The statistical analysis of the results was done by using the Chi square test, ANOVA and the Unpaired T test.

RESULTS

A total of 50 cases of febrile neutropaenia were studied; out of them 27 were males and 23 were females. A bimodal peak in the age group was seen, with 13 cases in the age group of 20-30 yrs and 11 cases in the 40-50 yrs age group. A majority of the patients in the study group had an underlying haematological malignancy (37 out of 50 cases) [Table/Fig-1]. Acute leukaemia

was the commonest underlying malignancy which was observed in the study (26 cases). Among the solid cancers, breast cancer was the commonest one which was observed in the study. A majority of the cases, ie. 68 percent had fever between 7 to 14 days following the chemotherapy cycle. Each episode was categorised. 17 cases had clinically documented infection (CDI), 16 cases had microbiologically documented infection (MDI) and 17 cases had fever of uncertain origin (FUO). Special attention was given to the occult sites of the infection like the oral cavity, the catheter sites and the perianal region. Out of 50 cases, 25 patients had infection at the occult sites. The commonest site which was infected was the perianal region, which was seen in 13 cases. Among the MDIs, eight cases showed a positive blood culture. Gram negative organisms were the most common isolates which were found. *E coli* grew five cases, out of which two cases grew ESBL producers. The gram positive organism which was isolated was *Staphylococcus aureus,* which was MRSA [Table/Fig-2]. The response to the treatment was studied in terms of the recovery of the absolute neutrophil count. Out of the 50 cases, thirty patients had the recovery of counts within 1 week, nine patients had it within 1-2 weeks and two patients had persistent neutropaenia beyond 3 weeks. There were nine deaths. The mean length of the hospital stay (16 days) was more in the patients with underlying haematological malignancies. Each patient was given a MASCC score based on the scoring system[3]. The association of the MASCC score and the outcome in terms of the recovery of the counts was found to be statistically significant (p <0.001) [Table/Fig-3]. Other factors which were found to be statistically significant in identifying the risk of the complications were; a tachypnoea rate of > 24/min (p <0.001), a temperature of >102^{0}F (p= 0.049), a hypotension (BP) value of <90/60 (p<0.001), an ANC of < 50Cumm^3 (p <0.001), deranged renal parameters (p=0.05), bacteraemia (p=0.001) [Table/Fig-4] and the inpatient status (p=0.006).

There was a negative correlation between the MASCC score, the duration of the neutropaenia and fever. The longer the duration of the fever and the neutropaenia was, the lower was the MASCC score. There was a positive correlation between the duration of the fever and the duration of the neutropeania. In patients with prolonged neutropaenia, the duration of the fever was also prolonged.

DISCUSSION

Over the past several decades, there has been a substantial progress in the treatment of neoplastic diseases; however infections

Characteristic	Point score
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection in hematologic tumor	4
Outpatient status at the onset of fever	3
No dehydration	3
Age <60 years	2

[Table/Fig-1]: The statistical analysis of the results was done by using the Chi square test, ANOVA and the Unpaired T test.
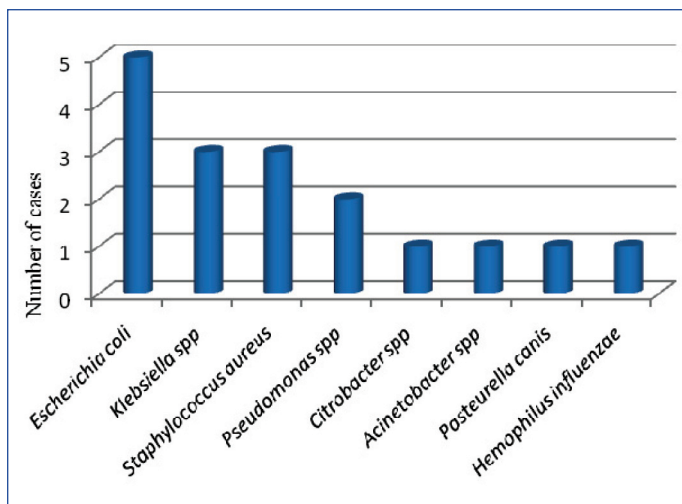
[Table/Fig-2]: Organisms in culture positive cases

Response	MASCC Score		Total
	<21	≥21	
<1 week	8	22	30
1-2 weeks	5	4	9
Persistent for 3 weeks or more	1	1	2
Death	9	0	9
Total	23	27	50

[Table/Fig-3]: Association of MASCC score and response
p< 0.001.

Response	Blood culture results		Total
	Negative	Positive	
<1 week	28	2	30
1-2 weeks	9	0	9
Persistent for 3 weeks or more	1	1	2
Death	4	5	9
Total	42	8	50

[Table/Fig-4]: Association between bacteraemia and response
p= .001.

remain a common complication of cancer chemotherapy. The perspectives for the management of febrile neutropaenia in 21st century has changed [5].

Febrile neutropaenia is common in haematological malignancies following chemotherapy as compared to the solid cancers. In our study, out of 50 cases of febrile neutropaenia, 37 cases had underlying haematological malignancies. Acute leukaemia was the commonest underlying malignancy which was observed in this study (26 out of 50 cases). The patients with haematological malignancies were immunocompromised as a result of the underlying malignancy or due to the therapeutic interventions which were employed to manage it [2].

Febrile neutropaenia can occur in both the sexes; there were 27 males and 23 female patients in the present study. The cases were almost equally distributed among all the age groups. A bimodal peak was observed, with 13 cases in the 20-30 years age group and 11 cases in the 40-50 years age group, which was in agreement with the bimodal peak which was observed in the haematological malignancies, as 74% of the cases in the study had an underlying haematological malignancy.

It is known that the risk of febrile neutropaenia is not uniform across the treatment cycles, but that it is greatest during the first cycle [6]. In this study, a majority of the episodes occurred following the first and second cycles of chemotherapy. In acute leukaemia, a majority of the episodes occurred after the induction therapy. This was an expected finding as aggressive chemotherapy during the induction phase of the treatment and the uncontrolled leukaemia puts a patient at a higher risk for neutropaenia and thus, for infection. The classic time frame for neutropaenia is 7-14 days post chemotherapy [6]. In this study, 68% of the febrile episodes occurred in this time frame. The depth and the duration of the neutropaenia were prolonged in patients with haematological malignancies.

The febrile neutropaenic episodes were classified into clinically documented infection, microbiologically documented infection and fever of uncertain origin, based on the clinical and laboratory parameters. It is known that infection is documented only in a minority of the febrile neutropaenic patients [1]. In approximately 50% of the patients, no infection was found, in 30%, an infection was microbiologically documented (most commonly, bacteraemia), and in 20%, an infection was clinically documented. However, infections may develop and progress rapidly during a neutropaenic episode. Hence, fever is used as a marker of infection, even if other potential causes of fever are present. In our study, 32% of the cases had a microbiologically documented infection, no infection was documented in 34 % and 34 % had a clinically documented infection. In patients with clinically documented infections, a majority of the patients had gastrointestinal symptoms and respiratory symptoms such as; pain in the abdomen, diarrhoea, vomiting, cough with expectoration and breathlessness.

The initial evaluation of the febrile neutropaenic patients consisted of taking a complete history and a swift, meticulous, physical examination with special attention being given to the mouth, skin, catheter exit site, and the perianal region. In our study, twenty five cases had abnormalities at the occult sites of the infection i.e. the oral cavity, the catheter exit site and the perianal region. A majority of the patients (as high as 13 cases) had a perianal pathology. It is thus important to carefully examine these sites to identify the early signs of the infection. Even a subtle evidence of inflammation must be considered as a sign of an infection. The minimal perianal erythema and tenderness may rapidly progress to perianal cellulitis. Minimal erythema or serous discharge at the site of insertion of a central venous catheter may herald a tunnel or exit site infection. Particular attention should be paid to the sites that are frequently infected or those which serve as foci for the dissemination of the infections, such as the oropharynx, the lung, the paranasal sinuses, the perineum, and the vascular catheter insertion sites.

Among 16 patients with bacterial infections, the blood culture was positive in eight patients. Gram negative bacilli were the most common isolates. *E coli* was isolated from five cases, out of which two cases grew Extended spectrum β lactamase producers which were resistant to the cephalosporins and aztreonam. The gram positive bacteria which was isolated was *Staphylococcus aureus,* which was methicillin resistant. In the early 1950s and 1960s, Staphylococcus aureus was the most frequent isolate in the immunosuppressed patients. With the introduction of beta-lactamase-resistant antistaphylococcal pencillins, gram-negative bacilli became the predominant bacterial organisms, which included *E coli, Klebsiella spp* and *Pseudomonas aeroginosa* . Since the 1980s, several studies have collectively demonstrated a shift in the aetiology of the bacterial infections from a predominance of gram-negative pathogens to that of gram-positive cocci [7]. However,

in this study, gram negative organisms were predominant. In our study, a patient with Non Hodgkin's lymphoma developed right arm cellulitis on day 7 following chemotherapy and the pus culture grew *Pasteurella canis*. Although there have been reports on the presence of *Pasteurella multocida* in cancer patients; to the best of our knowledge, there have been no reports on the presence of *Pasteurella canis* in febrile neutropaenic patients worldwide.

A number of efforts which have been made to identify the risk factors which were responsible for the occurrence of febrile neutropaenia and or their consequences in patients with established febrile neutropaenia have been reported. Increasing age, as a predictor of a poor outcome, was demonstrated in several studies [3,5,8]. However, in our study, no statistically significant relationship was found between age and the recovery. This observation was probably because of the small sample size. Studies with a larger sample size may provide better results. Previous studies have identified other important risk factors for the serious medical consequences of established febrile neutropaenia which included, inpatient status at the onset of the fever, hypotension, sepsis, comorbities which included cardiovascular and pulmonary diseases, leukaemia or lymphoma diagnosis, the severity and the duration of the neutropaenia, previous fungal infections, visceral organ involvement, organ dysfunction and uncontrolled malignancy [9]. In this study, the patients with tachypnoea, hypotension, a temperature of $>102^0$ F, an inpatient status at the onset of the fever, an ANC of < 50 cumm^3, deranged renal parameters and demonstrable bacteraemia had a poor outcome.

Klastersky et al., [3] postulated a scoring system which was based on the logistic equation of the Multinational Association for Supportive Care in Cancer (MASCC) predictive model. The maximum value in this system was 26. A score of ≥ 21 was classified as low risk and a score of < 21 as high risk, which predicted a < 5 % risk of severe complications. This scoring system was applied to all the patients in our study and nearly fifty percent of the patients had an MASCC score of ≥ 21. All these patients had a better outcome in terms of the recovery of the ANC and the length of hospital stay. This was statistically significant. Twenty seven patients had a score of ≥ 21. Twenty two patients showed the recovery of the absolute neutrophil count within 1 week. There were no deaths in this group. The MASCC score is thus useful in identifying patients with a low risk. These patients who are at low risk may be given oral medications in an outpatient setting. However, the issue of outpatient management is more controversial and perhaps it needs to be contemplated on an individual basis [10,11].

The response of the patients was studied with respect to the recovery of the absolute neutrophil count. Thirty patients had the recovery of the ANC within 1 week. Persistent neutropaenia for 3 weeks was observed in two patients with acute myeloid leukaemia. There were nine deaths in the study. Seven patients who died had an underlying haematological malignancy. Bronchopneumonia with multiorgan dysfunction was the commonest cause of death (5 cases). The remaining four cases had severe gastrointestinal sepsis with an evidence of severe oral mucositis which was secondary to the cancer chemotherapy.

Several studies [12-15] have demonstrated the use of monotherapy versus combination therapy as the empirical treatment for febrile neutropaenia. However, the Infectious Disease Society of America guidelines for managing the febrile neutropaenia patients

by categorising them into low risk and high risk groups by using a validated risk assessment tool are being widely employed [16]. In our study, 45 out of 50 cases were treated empirically with combination therapy, with parenteral III generation cephalosporin plus aminoglycoside. If the patient remained febrile after 4 days of empirical treatment without the isolation of any organism, parenteral antifungals were added to the treatment. A gram positive coverage was given when there were clinically apparent serious catheter related infections or in the presence of hypotension or septic shock without the presence of an identified pathogen.

Numerous studies have been conducted on the efficacy and safety of the CSFs in the prevention of the neutropaenic complications and on the infection risk which is associated with cancer chemotherapy in a variety of malignancies, by using several different chemotherapy regimens [17]. In our study, growth factors were given to all the patients who had an underlying haematological malignancy and also in patients with solid tumours who were undergoing aggressive/salvage chemotherapy. Thirty one patients who were given growth factors had a better outcome. This had high statistical significance.

The major economic impact of the neutropaenic complications is clearly the cost which is associated with the hospitalization and the ensuing length of stay (LOS). Previous studies have demonstrated that the length of the hospital stay was prolonged in patients with haematological malignancies, with a mean of 16 days and in patients with solid cancers, the mean length of the hospital stay was 7 days [18]. In our study, the mean length of the hospital stay was 8.13 days for patients with solid tumours and it was 19.7 days for the leukaemia patients.

CONCLUSIONS

Febrile neutropaenia is more common in patients with underlying haematological malignancies as compared to those with solid cancers. A majority of the patients have no other symptom, apart from fever. The occult sites of the infection are the perianal region, the oral cavity and the central venous catheter site. Even an evidence of a subtle inflammation at these sites should be considered as a sign of the presence of an infection. Gram negative organisms are commonly isolated in febrile neutropaenic patients, Escherichia-coli being the commonest organism which is isolated. Patients with tachypnoea, hypotension, a temperature of $>102^0$F, an inpatient status at the onset of the fever, an ANC of < 50 cumm^3, deranged renal parameters and demonstrable bacteraemia have a poor outcome in terms of the recovery of the ANC, mortality and the length of the hospital stay. The first step should be the risk categorisation of the patients by using a validated risk assessment tool like the MASCC scoring system. A MASCC score of ≥ 21 suggests that the patient is at a low risk of severe complications. This scoring system was able to correctly identify the low risk patients in our study.

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