CLINICAL PROFILE AND OUTCOME OF FEBRILE NEUTROPENIC CANCER PATIENTS IN A TERTIARY CARE CENTRE

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ABSTRACT

BACKGROUND

Febrile neutropenia is a common but serious complication of chemotherapy in patients with solid tumours and haematological malignancies. It represents a major cause of morbidity, mortality and treatment costs in patients who receive chemotherapy. This study was done to study the clinical spectrum of febrile neutropenic patients.

MATERIALS AND METHODS

The present study was conducted in the Department of Medicine, M.S. Ramaiah Medical College and Hospital, Bengaluru, from (October 2014 – September 2016). The inclusion criteria were the histological diagnosis of malignancy, neutropenia which was secondary to chemotherapy, an absolute neutrophil count of < 500/cumm, oral temperature of >38.3°C or >38°C for 1 hour.

RESULTS

A total of 100 cases of febrile neutropenia were documented; 85 in solid tumours and 15 in haematological malignancies. Breast cancer was the commonest underlying malignancy (27 out of 100). E. coli was the commonest organism which was identified (9 cases).

CONCLUSION

Febrile neutropenia is seen in patients with all types of underlying malignancies, however poorer response is seen in haematological malignancy.

KEYWORDS

Febrile Neutropenia, Solid Tumours, Haematological Malignancies, Acute Leukaemia, Tachypnoea, Hypotension, Temperature, Absolute Neutrophil Count.

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BACKGROUND

Febrile neutropenia is defined as a single oral temperature of greater than 38.3°C (101°F) or 38°C or greater (100°F) for over 1 hour in a patient with an absolute neutrophil count less than 500/cumm or less than 1,000/cumm, with predicted rapid decline.[1,2]

Neutropenia, resulting from cytotoxic chemotherapy is the most common risk factor for severe infections. The duration of neutropenia also contributes significantly to the risk of serious infections. The risk is significantly greater at lower neutrophil counts, such that 100% of patients with ANC <100 cells/cumm^3 lasting for 3 weeks or more develop documented infections.[3] Infection is present only in a minority of febrile neutropenic patients.

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In approximately 50%, no infection is found in 30% an infection is microbiologically documented (most commonly, bacteraemia) and in 20% an infection is clinically documented. However, infections may develop and progress rapidly during neutropenia.

Hence, fever is used as a marker of infection, even if other potential causes of fever (e.g., the malignancy itself, drugs, blood products, deep venous thrombosis) are present.[2] The purpose of this study is to categorize febrile neutropenic episodes in cancer patients into clinically documented infections, microbiologically documented infections and fever of uncertain origin.

Objectives of the present study was to study the clinical spectrum and outcome of febrile neutropenic cancer patients caused by chemotherapy.

MATERIALS AND METHODS

Source of Data- It was a prospective study of cancer patients with febrile neutropenia at M.S. Ramaiah hospitals over a period of 2 years, from October 2014 to September 2016.

Methods of Data Collection

1) Patients were identified as per inclusion and exclusion criteria. 2) History and Physical examination was documented according to a standard Proforma. 3) Laboratory investigations included- a) Complete blood count, urine routine. b) Differential Counts and calculation of absolute neutrophil count. c) Blood culture, urine culture, swabs for culture. d) Chest X-ray radiograph. e) HIV 1 and 2 testing by ELISA.

Inclusion Criteria

Histological diagnosis of malignancy, neutropenia secondary to chemotherapy with an absolute neutrophil count of <500/ cumm and oral temperature of >38.3 degree C or >38 degree C for 1 hour.

Exclusion Criteria

HIV patients with cancer. Age less than 16 years.

Statistical Analysis

All the quantitative variables such as age, ANC etc., were analysed and expressed as mean & standard deviation. All the qualitative variable such as characteristics of burden of illness, no or mild symptoms etc, were expressed in terms of percentage. Statistical Analysis was done using the following tests: *Chi square test *Correlation and coefficient *ANOVA.

RESULTS

We studied 100 patients of febrile neutropenic episodes. In our study, the mean age was 49.8 years, with 25 years as the youngest and 86 years as the oldest. 33% of population were males. Majority of the patients in our study group had underlying solid malignancy 85 out of 100 cases. Breast cancer was the commonest underlying malignancy (27 cases) in the study. Only 15% of malignancies were of haematological type, among which acute leukaemias were most common. Diabetes was the commonest associated co-morbid condition in the study. Majority of the cases had ANC between 50-250. Most of the patients in the study had no other symptom apart from fever; remaining patients mainly had gastrointestinal symptoms and respiratory symptoms. Microbiologically documented infection (MDI) were 25%, Clinically documented infection (CDI) were 36%, Fever of uncertain origin (FUO) were 39%. Among the MDI's blood culture were positive in 8 cases and urine cultures were positive in 10 cases. Gram negative organisms were most common isolates. E coli were grown in 9 cases. Gram positive organism isolated was staphylococcus aureus. Majority of the patients recovered in 1-2 weeks of treatment in this study. In this study there was statistical significant association between age and response. Females showed better response compared to males, this was statistically significant. 40% of haematological malignancies patients died as compared to 14.11% of solid malignancies patients in the study, there was a statistically significant association between underlying malignancy and response. High grade temperature in patients with neutropenia in the study group had poor response, this was statistically significant. Febrile neutropenic episodes with tachypnoea had poor response; this had very high statistical significance. Febrile neutropenic episodes with tachypnoea had poor response; this too had very high statistical significance. In this study patients with absolute neutrophil count of <50 cumm had poor response to treatment. This had very high statistical significance. In this study patients who had altered renal function tests had poor response to treatment which shows statistical significance. In patients who had blood culture positive had poor response to treatment. This had very high statistical significance. Patients with MDI origin 17 out of 25 cases had poor response as compared to CDI and FUO. This showed statistical significance. Febrile neutropenic episodes in patients who were inpatients at the onset of fever had a poor response compared to patients who were outpatients at the onset of fever. This showed statistical significance. In this study patients with longer duration of fever had poor response. When the duration of fever was more than 7 days, patients had increased risk of persistent neutropenia or death.

Similarly patients with prolonged neutropenia had poor response. Both these had high statistical significance. There is a positive correlation between duration of fever and duration of neutropenia. In patients with prolonged neutropenia, the duration of fever was also prolonged. Majority of the patients 88 % were treated with 3rd generation cephalosporin. Oral treatment was given for 11 cases with ciprofloxacin or metronidazole. 23 cases out of 100 cases were given gram positive coverage either with vancomycin or teicoplanin based on the clinical/ microbiological indications.

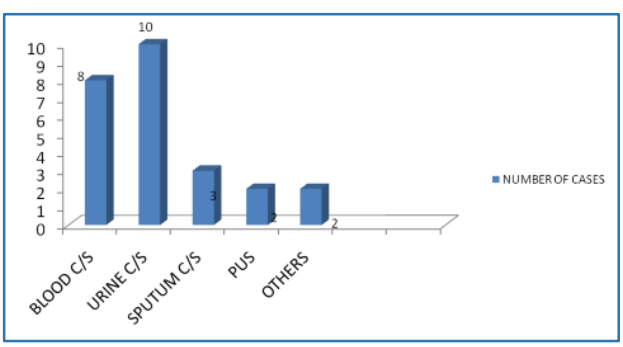

Figure 1. Culture Positive Cases

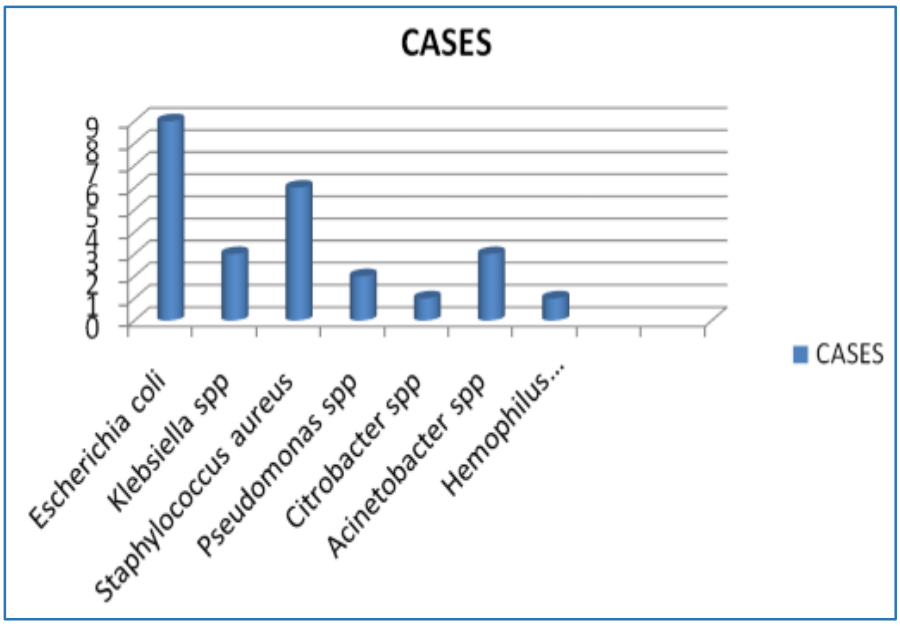

Figure 2. Organisms in Culture Positive Cases

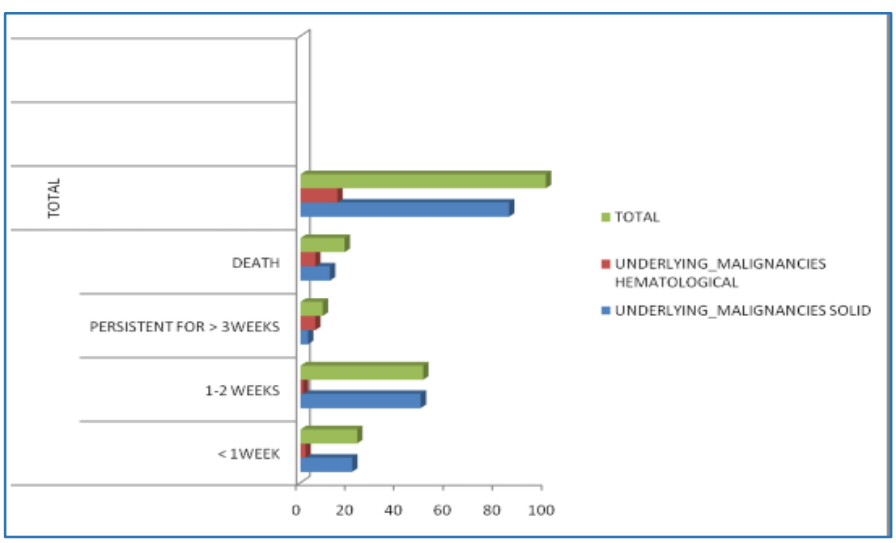

Figure 3. Association between Underlying Malignancy and Response.

Response	MDI	CDI	FUO	Total
< 1 week	2	13	8	23
1-2 weeks	6	18	26	50
Persistent for ≥ 3 weeks	0	5	4	9
Death	17	0	1	18
Total	**25**	**36**	**39**	**100**

p = < 0.001

Table 1. Association between Category of Febrile Neutropenic Episode and Response

DISCUSSION

Fever in the setting of neutropenia, or febrile neutropenia, generally prompts immediate hospitalization for evaluation and the administration of empiric broad-spectrum antibiotics. It represents a major cause of morbidity, mortality and cost in patients receiving chemotherapy. Risk stratification to identify low risk patients is essential as these patients may improve with outpatient treatment and this approach reduces the economic burden and thereby improves quality of life. Febrile neutropenia is common in haematological malignancies following chemotherapy compared to solid tumours. This association of febrile neutropenia was originally demonstrated in acute leukaemia patients by Bodey et al[4] In our study, out of 100 cases of febrile neutropenia, 15 cases had underlying haematological malignancies and 85 cases had underlying solid cancer. Acute leukaemia was the commonest underlying haematological malignancies. Breast cancer was the commonest underlying malignancy in our study and it was the commonest type of malignancy among solid tumours. Patients with haematological malignancies are immunocompromised as a result of the underlying malignancy or due to the therapeutic interventions employed to manage it[3] Febrile neutropenia can occur in both sexes, there were 33 males and 67 females in the study. Majority of the cases were in the age group of 41-50 years and >61 years, most of the patients had underlying

solid malignancies. It is known that the risk of febrile neutropenia is not uniform across treatment cycles, but is greatest during first cycle.[5] In this study majority of the episodes occurred following first and second cycle of chemotherapy. This is an expected finding as aggressive chemotherapy during induction phase of treatment puts a patient at higher risk for neutropenia and thus infection. A classic time frame for neutropenia is 7-14 days post chemotherapy.[5] In this study 31% of febrile episodes occurred in this time frame, 60% of febrile episodes occurred >14 days post chemotherapy. The depth and duration of neutropenia was prolonged in patients with haematological malignancy. Febrile neutropenic episodes were classified into clinically documented infection, microbiologically documented infection and fever of uncertain origin based on clinical and laboratory parameters. It is known that infection is documented only in a minority of febrile neutropenic patients.[2] In approximately 50% no infection is found, in 30% an infection is microbiologically documented (most commonly, bacteraemia), and in 20% an infection is clinically documented. However, infections may develop and progress rapidly during neutropenia. Hence, fever is used as a marker of infection, even if other potential causes of fever are present. In our study, 25% of the cases had microbiologically documented infection, no infection was documented in 39% and 36% had clinically documented infection. In patients with clinically documented infections, majority of the patients had gastrointestinal symptoms and respiratory symptoms such as; pain abdomen, diarrhoea, vomiting, cough with expectoration, breathlessness.

The initial evaluation of febrile neutropenic patients consists of a complete history and swift, meticulous physical examination with special attention to the mouth, skin, catheter exit site, and perianal region. It is important to carefully examine these sites to identify early signs of infection. Even subtle evidence of inflammation must be considered as sign of infection. Minimal perianal erythema and tenderness may rapidly progress to perianal cellulitis. Minimal erythema or serious discharge at the site of a CVC may herald tunnel or exit site infection. Particular attention should be paid to sites that are frequently infected or serve as foci for dissemination of infection such as oropharynx, lung, paranasal sinuses, perineum, and vascular catheter insertion sites. In patients with microbiologically documented infections, blood culture was positive in 8 out of 25 cases. Gram negative organisms were most common isolates. Escherichia Coli was grown in 9 cases. Gram positive organism isolated was staphylococcus aureus.

In the early 1950s and 1960s staphylococcus aureus was the most frequent isolate in immunosuppressed patients. With the introduction of beta-lactamase-resistant antistaphylococcal penicillins, gram-negative bacilli became the predominant bacterial organisms including Escherichia coli, Klebsiella species and Pseudomonas aeruginosa. Since the 1980s, several studies have collectively demonstrated a shift in the etiology of bacterial infections from a predominance of gram-negative pathogens to gram-positive cocci.[6] However, in this study, gram negative organisms were commonly isolated. This is consistent with other studies.[7,8,9,10,11] A number of efforts to identify risk factors for occurrence of febrile neutropenia and or its consequences in patients with established febrile neutropenia have been reported. Increasing age as a predictor of poor outcome was demonstrated in several studies.[3,12,13] In our study there was statistically significant relationship found between age and recovery.

Studies by Talcot et al identified other important risk factors of serious medical consequences of established febrile neutropenia including inpatient status at the onset of fever, hypotension, sepsis, co-morbidities including cardiovascular and pulmonary disease, leukaemia or lymphoma diagnosis, severity and duration of neutropenia, previous fungal infection, visceral organ involvement, organ dysfunction, uncontrolled malignancy.[14] Freifeld et al[15] demonstrated that the presence of hemodynamic instability, abdominal pain, nausea and/or vomiting, diarrhoea, neurological or mental changes, catheter-related infection, new pulmonary infiltrates, renal failure, and liver insufficiency are associated with poor prognosis. In this study, patients with tachypnoea, hypotension, temperature >103°F, inpatient status at the onset of fever, ANC< 50 cumm, deranged renal parameters and demonstrable bacteraemia had poor outcome.

Response of the patients was studied with respect to recovery of absolute neutrophil count. Twenty three patients had recovery of ANC within 1 week. Persistent neutropenia for 3 weeks was observed in nine patients. There were eighteen deaths in the study. Six patients who died had underlying haematological malignancy.

Several studies.[16,17,18,19] demonstrated the use of monotherapy versus combination therapy as empirical treatment in febrile neutropenia. However, the Infectious Disease society of America guidelines to manage febrile neutropenia patients by categorising into low risk and high risk group by using a validated risk assessment tool is widely employed.[15] In our study, 88 out of 100 cases were treated empirically with combination therapy with parenteral III generation cephalosporin plus aminoglycoside. If patient remained febrile after 4 days of empirical treatment without isolation of any organism, parenteral antifungals were added. Gram positive coverage was given when there was clinically apparent serious catheter related infection or in the presence of hypotension or septic shock without identified pathogen. Numerous studies have been conducted on the efficacy and safety of the CSFs in the prevention of neutropenic complications and the infection risk associated with cancer chemotherapy in a variety of malignancies using several different chemotherapy regimens.[20] The major economic impact of neutropenic complications is clearly the cost associated with hospitalization and the ensuing length of stay (LOS). Lyman et al[21] demonstrated that length of hospital stay was prolonged in patients with haematological malignancy with mean of 16 days and in patients with solid tumours, the mean length of hospitals stay was 7 days. Swati et al. and Gupta et al. reported a mortality rate of 20.3% and 17.9% respectively in FN patients with HM from

India.[9,10] Recent studies report a wide range of mortality rate (7–33%) in FN patients.[22,23,24] This was in accordance with our study.

CONCLUSION

1. Febrile neutropenia is seen in patients with all types of underlying malignancies, however poorer response is seen in haematological malignancy.
2. Majority of the patients have no other symptoms apart from fever.
3. The occult sites of infection are perianal region, oral cavity and central venous catheter site, even evidence of subtle inflammation at these sites should be considered as a sign of infection.
4. Gram negative organisms are commonly isolated in febrile neutropenic patients. Escherichia-coli being the commonest organism.
5. Patients with tachypnoea, hypotension, temperature >103^{0}F, inpatient status at the onset of fever, ANC <50 cumm, deranged renal parameters and demonstrable bacteraemia have poor outcome in terms of recovery of ANC, mortality and length of hospital stay.
6. The standard empirical broad-spectrum-intravenous-antibiotic treatment and hospitalization though safe may lead to over-treatment of substantial group of patients.
7. Validation of additional parameters to identify low-risk febrile neutropenia that can be safely treated in an outpatient setting with minimal treatment is needed.

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