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ORIGINAL ARTICLE Supportive Care

Epedimiologic, clinical profile and factors affecting the outcome in febrile neutropenia

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Abstract

Background: Febrile neutropenia (FN) is common in cancer patients particularly hematologic malignancies due to intensive cytotoxic chemotherapy. It is an important cause of morbidity, mortality and treatment delays. The risk is greater in patients with ANC < 500/ mm3 and increases dramatically in those with ANC < 100/ mm3 and duration of neutropenia more than 1 week. **Aims and Objectives:** The purpose of this study was to evaluate the incidence, demographic characteristics, clinical profile, mortality, outcome and factors affecting the outcome in patients with febrile neutropenia (FN) admitted at our Center between January 2011 and November 2012. **Materials and Methods:** All cases of FN admitted in our Institute between January 2011 and November 2012 were analyzed. Data was analyzed using IBM statistic SPSS version 19. **Results:** A total of 333 episodes of FN were reviewed. Hematologic malignancies accounted for 299 (89.7%) episodes and 88% of all the episodes had grade 4 neutropenia. There was a significant association noted between high serum bilirubin, creatinine and outcome. Isolation of an organism from blood culture, positive findings on chest X-ray and fungal infection was associated with higher mortality . Association between transfusion requirements and outcome was analyzed and it was observed that patients who had multiple component transfusions vs single component ones were at a significantly higher risk of death. There were only 7 deaths noted among the patient population. **Conclusion:** Leukemias are the leading cause of FN at our Institute. Higher bilirubin, creatinine, chest imaging favoring pneumonia, positive isolates and multiple transfusions had significant association with mortality. Large scale prospective studies are needed to determine the association of preemptive therapy with higher mortality. The outcome of high risk FN in this study is favorable.

Key words: Epidemiology, febrile neutropenia, outcome

Introduction

Cancer patients are at increased risk of infections as they are rendered immunocompromised by chemotherapy, receive cytotoxic treatment and need prolonged hospitalization. Use of prophylactic antibiotics, mucositis, vascular catheters and parenteral nutrition are other significant factors which add to the risk.[1]

Febrile neutropenia (FN) is a medical emergency with a high mortality rate if not treated promptly and aggressively. In surveys in Singapore the mortality rate attributed to postchemotherapy FN is between 3% and 8.8%.[2-4] This is similar to results from European and American studies.[5,6]

Treatment practices vary between Institutions due to Institution policies, hospital isolates, physician preferences etc. This study was undertaken to determine the incidence, demographic characteristics, clinical profile, antibiotic, antifungal use and outcome of FN patients at our center.

Materials and Methods

Institute Ethics Committee approval was taken for this study. All cases of FN admitted to the Medical Oncology services at the Nizam's Institute of Medical Sciences between January 2011 and November 2012 were analyzed. FN was defined as a single oral temperature of >38.3°C (101F) or a temperature of >38.0°C (100.4F) sustained over a 1-h period with neutrophil count of <500 cells/mm^3 or <1000/mm^3 with a predicted decrease to <500/mm^3 in the next 24 h.[5]

Patients were classified as high and low risk groups based on the Multinational Association for Supportive Care in Cancer risk score[7] [Table 1].

Standard procedures as outlined by Infectious disease Society of America 2010 guidelines were followed (complete blood counts, liver and renal function tests, two sets of blood cultures taken 1 h apart (one from central line/peripherally inserted central catheter [PICC] and one from peripheral line, in case central line/PICC is present), cultures as necessary from other areas and chest X-ray/high resolution computed tomography chest (if having respiratory symptoms).

Results

A total of 333 episodes were documented during the study period (January 2011–November 2012). The demographic characteristics are described in Table 2.

Hematologic malignancies accounted for 299 (89.7%) episodes. Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), acute promyelocytic leukemia, Ewing's sarcoma and Diffuse large B cell lymphoma accounted for 129 (38.3%), 117 (35.1%), 36 (10.8%), 14 (4%) and 7 (2%) patients respectively.

There was a significant association noted between mean serum bilirubin and outcome. Higher deaths were seen in patients having mean serum bilirubin more than 1.5 mg% (P = 0.000), odds ratio: 20.139). A mean serum creatinine >1.2 mg% resulted in higher deaths with statistical significance (16% vs. 1%) (P = 0.000), odds ratio: 19.365 (95% confidence interval [CI] of mean: 4.066–92.237). With regard to serum albumin there was no association with outcomes.

Isolation of an organism from blood culture and infiltrates on chest X-ray were other factors which had a significant association with outcome (P = 0.017 and 0.002) respectively. Growth of a Gram-negative organism was associated with more deaths (4 deaths).

Association between transfusion requirements and outcome was analyzed and it was observed that patients who had multiple component transfusions versus single component ones were at a significantly higher risk of death (6 deaths vs. 1) (P = 0.002).

There were 20 (6%) possible, 33 (10%) probable and 10 (3%) proven fungal infections documented in our study. There was a significant association between occurrence of fungal infections and outcome (P = 0.000). There were 5 deaths in the proven/

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Table 1: MAASC risk-index score

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms	5
No hypotension (systolic blood pressure 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral IV fluids	
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age <60 years	2

MAASC=Multinational Association for Supportive Care in Cancer, IV=Intravenous

Table 2: Baseline characteristics

Characteristic	Numbers
Mean age	26.7 years
Range	6 months-72 years
Male	200
Female	133
Male: female	1.5:1
Hematologic malignancies	299
Solid tumors	34
Auto BMT	12
<18 years	142
>18 years	191
High risk verses low risk	291 verses 42

BMT=Bone marrow transplant

possible/probable group (9.4% vs. 0.7%). The risk of death in those with fungal infection was 14.323 (95% CI of mean: 2.70–75.952).

Discussion

A total of 333 episodes were observed during the study period. A male preponderance was observed. Similar male preponderance was reported by André *et al*. in a prospective multicenter study.[8] Roy *et al*. on the other hand reported a higher incidence of FN in females (62.5%).[9]

The mean age in our study was 26.7. This was similar to other reported studies.[8,9] In our study hematologic malignancies were associated with more FN episodes in comparison to solid tumors (89.7% vs. 10.3%). Timothy and Bodkyn described a higher number of FN episodes due to acute leukemia while André *et al*. described 56% FN episodes in solid tumors.[8,10] This may be an Institution bias.

Acute leukemia accounted for 84.6% of the FN episodes. This is probably due to the reason that our center is a referral center for acute leukemias in the state and is one of the few Institutes in the state treating acute leukemias under the state sponsored health insurance scheme. AML followed by ALL were the commonest acute leukemias leading to FN. ALL accounted for 43.7% cases of FN in a study by Timothy and Bodkyn which is slightly higher than our study (35.1%).[10] Genitourinary cancers attributed to 45% of the episodes whereas soft tissue tumors accounted to only 18% in a study by Roy *et al*.[9] The difference may be due to the following factors: Absence of hematologic malignancies in their study, our study being conducted in the Department of Medical Oncology and theirs by the radiotherapy unit explaining the spectrum seen be the respective departments and also to the more numbers of soft tissue sarcomas we see compared to genitourinary cancers.

Isolation of an organism from blood culture had a significant association with outcome, that is, mortality (P = 0.017) and when adjusted for other factors there was a trend favouring worse outcome. Odds ratio - 6.429 (95% CI of mean - 1.400–29.521). The predominant organisms isolated in neutropenic patients are Gram-negative bacteria. There is an increasing incidence of multi drug resistant strains like extended-spectrum beta-lactamase producing organisms and Carbapenamase resistant *Escherichia coli* and due to rampant and indiscriminate use of antibiotics.[11,12]

Positive findings on chest X-ray resulted in higher deaths on univariate analysis which was significant (P = 0.002). Odds ratio - 14.479 (95% CI of mean - 2.731–76.777). When adjusted for other factors there was a trend towards higher deaths without significance. Pneumonia-bacterial or fungal in the presence of neutropenia and cancer is in itself an independent risk factor.[13,14] Pneumonia in the neutropenic patient carries a very high mortality if not treated promptly.

Very low neutrophil counts are harbingers for infection and the risk increases manifold when absolute neutrophil count (ANC) is <500 cells/cu mm. In our study more number of deaths were observed in patients with ANC < 200 cells/cu mm (6 deaths vs. 1) (P = 0.285). The lack of significance may be explained due to the small number of deaths relative to the total number of patients.

Association between transfusion requirements and outcome was analyzed and it was observed that patients who had multiple component transfusions versus single component ones were at a significantly higher risk of death (6 deaths vs. 1) (P = 0.002). Risk was greater in those receiving packed cells + platelet transfusions and other components (fresh-frozen plasmas, cryoprecipitates, etc.) when compared to packed cells and platelets alone (11.5% vs. 1.5%). Patients who receive multiple transfusions are more sick, have concomitant underlying problems like thrombocytopenia, coagulation abnormalities, liver disease, uremia etc., which worsens their outcome.

Higher deaths were seen in patients having longer duration of neutropenia (>8 days) (5 vs. 2) with a trend towards significance (P = 0.061). Longer duration of neutropenia is associated with longer hospital stay, greater risk of acquiring hospital infections, longer duration of IV lines, parenteral nutrition, higher chances of loss of mucosal integrity, use of multiple antibiotics and development of drug resistant clones.

On multivariate analysis there was a significant association between higher mean serum bilirubin (>1.5 mg%) and higher serum creatinine (>1.2 mg%). Odds ratio was 8.598 (95% CI of mean: 1.235–59.855) for mean serum bilirubin. Odds ratio for serum creatinine was 7.127 (95% CI of mean: 1.086–46.753. When controlling for other variables there was a 5.53 times higher risk of mortality with positive Chest X-ray findings.

Finally the outcome in our study was that 94% of the FN episodes improved with appropriate treatment, a finding noted in other studies.

Our study has a few limitations:

- Retrospective in nature
- Nonuniform antibiotic policy in all patients
- Fewer events thereby limiting the ability to get significant results.

Conclusions

Higher bilirubin, creatinine, chest imaging favoring pneumonia, positive isolates and multiple transfusions had significant association with mortality. Large scale prospective studies are needed to

determine the association of preemptive therapy with higher mortality. The outcome of high risk FN in this study is favorable. Prospective, multicenter, well randomized studies are needed to better study the association amongst various factors in FN.

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Conflicts of interest

There are no conflicts of interest.

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