Original Research Article

Clinical study of chemotherapy induced febrile neutropenia: talcott’s versus multinational association for supportive care in cancer risk assessment scoring systems

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Received: 15 November 2020
Revised: 15 December 2020
Accepted: 16 December 2020

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ABSTRACT

Background: Cancer is a leading cause of death worldwide, accounting for 8.2 million deaths in 2012. Febrile neutropenia (FN) is fever associated with abnormally low neutrophil count signifying an immunocompromised state secondary to malignancy or its treatment. The aim of this study was to evaluate clinical outcome of chemotherapy induced febrile neutropenia.

Methods: This was a hospital based prospective, descriptive observational study. Patients of either sex, age 18-90 years, with cancer on chemotherapy, single oral temperature ≥101° Fahrenheit (38.3°C) or a temperature ≥100.4° Fahrenheit (38.0°C) for ≥ one hour with absolute neutrophil count <500 cells/mm3 or <1000 cells/mm3 with a predicted decrease to less than 500 cells/mm3 in the next 24 hours, only with first febrile episode occurring during study period and prior or concurrent radiation therapy were included in this study.

Results: Among 87 patients, 70 (80.5%) were less than 60 years and 17 (19.5%) were ≥60 years. The mean age of study patients was 44.46±15 years, (range 18 to 77 years), 31(35.6%) were male and 56 (64.4%) were female. Talcott’s and MASCC risk predicting tool versus outcome, p values for Talcott’s and MASCC were significant (<0.05).

Conclusions: Neutropenic fever is a potentially life-threatening complication of cancer chemotherapy. MASCC and Talcott’s model can be used to identify low and high risk patients. MASCC risk index may have a better performance than the Talcott’s model in risk classification.

Keywords: Chemotherapy, Febrile Neutropenia (FN), MASCC, Talcott’s

INTRODUCTION

Cancer is a leading cause of death worldwide, accounting for 8.2 million deaths in 2012. More than 60% of world’s total new annual cases occur in Africa, Asia and Central and South America. These regions account for 70% of the world’s cancer deaths. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 million within the next 2 decades. Globally, during 2012 the most common cancer diagnosed were those of the lung (1.8 million), breast (1.7 million) and colorectal (1.4 million). The most common causes of cancer deaths were cancer of lung (1.6 million), liver (0.8 million) and stomach (0.7 million).¹ Healthy People 2020 goal is to reduce the number of new cases, as well as the illness, disability, and death caused by cancer in United States.²

In India as per National Cancer Registry Programme of ICMR (Indian Council of Medical Research), it is estimated that 10.15 lac new cases occurred in the
country which gives an incidence of 92.4 per lac population. Same year 6.83 lac persons died of cancer. It is reported that breast cancer is proportionately on the increase in a few metropolitan areas of India.

The Indian Society of Medical and Pediatric Oncology (ISMPO) released guidelines for fever with neutropenia in 2002. Febrile neutropenia (FN) is fever associated with abnormally low neutrophil count signifying an immunocompromised state secondary to malignancy or its treatment and is a common and often critical condition that adversely affects the prognosis of patients. It is a medical emergency.

There have been major advances in prevention and treatment of FN, this still remains one of the most feared complications of cancer chemotherapy. Prognosis is worst in patients with proven bacteraemia, with mortality rates of 18% in Gram-negative and 5% in Gram-positive bacteraemia.

Febrile neutropenia (FN) is defined as a condition in which patients have a single oral temperature ≥ 101°F (Fahrenheit) (38.3°C) or a temperature ≥100.4°F (Fahrenheit) (38.0°C) for ≥ one hour with neutrophil counts < 500 cells/mm3 or < 1000 cells/mm3 with a predicted decrease to less than 500 cells/mm3 in the next 24 hours. In some situations, where fever may not be there but obvious infection is present and absolute neutrophil count (ANC) is low, it may be treated as FN.

The single most important determinant of neutropenic fever is the ANC less than 100 and the duration of neutropenia (> 14 days). The Common Toxicity Criteria of the National Cancer Institute established a scale of four grades for neutropenia, which are, Grade 1/Mild (ANC ≥1500 to <2000 cells/mm³), Grade 2/Moderate (ANC ≥1000 to <1500 cells/mm³), Grade 3/Severe (ANC ≥500 to <1000 cells/mm³) and Grade 4/Life threatening (ANC <500 cells/mm³). The incidence of FN events following the first cycle of chemotherapy to range from 11 – 67%. In febrile neutropenic patients, the bloodstream infection (BSI) is reported to be between 11 and 38%. Some possible predictors include a 49% risk of FN if the absolute lymphocyte count is less than 700 mm³.

The aim of this study was to evaluate clinical outcome of chemotherapy induced febrile neutropenia in a tertiary care center and validation of two western risk assessment scoring systems namely; Talcott’s and Multinational Association for Supportive Care in Cancer (MASCC) for patients with febrile neutropenia in Indian scenario and correlate with treatment outcome.

**METHODS**

This was a hospital based prospective, descriptive observational study done at a tertiary eye care center in south India, over a one-year period from February 2017 to January 2018. The study was approved by the institutional review board of the parent institution and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients before undertaking treatment options.

Patients of either sex, age (18-90 years), with cancer on chemotherapy, single oral temperature ≥ 101°F (Fahrenheit) (38.3°C) or a temperature ≥100.4°F (38.0°C) for ≥ one hour with absolute neutrophil counts < 500 cells/mm³ or < 1000 cells/mm³ with a predicted decrease to less than 500 cells/mm³ in the next 24 hours, only with first febrile episode occurring during study period and prior or concurrent radiation therapy were included in this study.

Patients with FN, not on chemotherapy, age <18 years, active infection within 72 hours prior to start of chemotherapy, pregnant or lactating females and already enrolled in study presenting with repeated episode of febrile neutropenia were excluded from this study.

Data included vitals (Pulse rate, Respiratory rate, temperature, Blood pressure), type of cancer, chemotherapy setting, number of chemotherapy cycle at which patient presented with febrile neutropenia, hospital status of the patient when the patient developed FN episode, physical activity of the patient as per Eastern Cooperative Oncology Group (ECOG). Details needed to calculate Talcott’s and MASCC score were recorded. ANC was derived from TLC and DLC as TLC in litre multiply by total neutrophils (segmented neutrophil % and segmented band %) multiplied by 10.

Patients were classified into low and high risk category on the basis of Talcott’s (I to III- high risk; IV- low risk and and MASCC score (score≥21-low risk, <21-high risk). Low risk patients were expected to have neutropenia for ≤7 days (Infectious Disease Society of America guidelines) and in high risk expected duration of neutropenia was >7 days. All the patients were carefully observed for the development of complications as defined in Klastersky study.

**Sample size**

From previous study, with an expected proportion of 0.06, precision value of 5 and 95% desired confidence interval required sample size is 87.

**Statistical analysis**

Calculations were made using SPSS 16.0, EPI INFO software version 3.5.

**RESULTS**

Total 3270 patients received chemotherapy and were at risk of developing febrile neutropenia. Total 87 patients developed FN. The mean age of study patients was 44.46
± 15 years, (range 18 to 77 years), 31(35.6%) were male and 56(64.4%) were female. The highest number were in between 40-49 years (23%) and overall 80.5% were less than 60 years. Among 87 patients, 70 (80.5%) were less than 60 years and 17 (19.5%) were ≥60 years. Among 70 who were <60 age, 52 (74.3%) had good outcome, 18 (25.7%) had poor outcome.

Among 18 patients with poor outcome 15(83.3%) had fever resolution with complication and 3 (16.7%) died before fever resolution. Details of recovery with and without complications are given in, Table 1.

### Table 1: General characteristics of study patients.

| Variables | N (%) |
|-----------|-------|
| **Age (years)** |       |
| <20        | 3 (3.5%) |
| 20-29      | 14 (16.1%) |
| 30-39      | 14 (16.1%) |
| 40-49      | 20 (23%) |
| 50-59      | 19 (21.8%) |
| ≥60        | 17 (19.5%) |
| **Gender** |       |
| Male       | 31 (35.6%) |
| Female     | 56 (64.4%) |

| Age       | Good outcome | Poor outcome | Total |
|-----------|--------------|--------------|-------|
| <60 years | 52           | 15           | 3     | 70   |
| ≥60 years | 13           | 2            | 2     | 17   |
| **Total** | 65           | 17           | 5     | 87   |

RWOC- recovery without complication, RWC-recovery with complication.

Distribution as per cancer type has been shown in [Table-2]. Out of total 87 patients, 72(82.8%) were of controlled and 15(17.2%) were of uncontrolled cancer.

Thirty-five (35 /40.2%) patients had grade III and 52 (59.8%) had grade IV neutropenia. The most common treatment setting was adjuvant /neoadjuvant i.e. 43(49.4%), 1st line for advanced disease was used in 24(27.6%), 2nd line for advanced disease was used in 9(10.3%), high dose chemotherapy was given in 7(8%), concurrent chemoradiation in 3(3.4%) and bone marrow transplantation was done in 1(1.1%).

Maximum number of patients belonged to ECOG 1 (77/88.5%). Among 87 patients 56(64.4%) patients developed FN in first chemotherapy cycle, 10(11.5%) in second, 7(8%) in third and fourth, 1(1.1%) in sixth, fifth and seventh respectively Table 2. The site of infection was detected in 64 (72%) patients and not detected in 23 (28%).

Among 87 patients 68 (77%) patients had ≤7 days of fever duration, 13 (15%) had 8-14 days of fever duration, 4 (5%) had 14-21 days and 2 (2%) had >21 days of fever duration. Maximum, 65 (75%) patients had neutropenia for ≤ 7 days, 15 (17%) had for 8-14 days, 4 (5%) for 15-21 days, 3 (3%) for >21 days.

### Table 2: Clinical and Investigation findings of study patients.

| Variables                          | n (%) |
|------------------------------------|-------|
| **Grading of neutropenia**         |       |
| Grade III (≥500 -1000/mm$^3$)      | 35 (40.2%) |
| Grade IV(<500/mm$^3$)              | 52 (59.8%) |
| **Cancer type**                    |       |
| Breast cancer                      | 24/27.6% |
| Lung                               | 5/5.7%  |
| Chronic Myeloblastic Leukemia (CML)| 2/2.3%  |
| Ovary cancer                       | 5/5.7%  |
| Cervix cancer                      | 2/2.3%  |
| Stomach cancer                     | 5/5.7%  |
| Thymoma                            | 1/1.1%  |
| Cholangiocarcinoma                 | 1/1.1%  |
| Multiple Myeloma                   | 2/2.3%  |
| Colon cancer                       | 2/2.3%  |
| Hodgkin’s lymphoma                 | 2/2.3%  |
| Non-Hodgkin’s lymphoma             | 8/9.2%  |
| Acute Myeloblastic Leukemia (AML)  | 22/25.3%|
| Acute Lymphoblastic Leukemia (ALL) | 6/6.9%  |
| **Disease status**                 |       |
| Controlled                         | 72/82.8% |
| Uncontrolled                       | 15/17.2%|
| **Treatment setting**              |       |
| Adjuvant/ neoadjuvant              | 43/49.4% |
| Concurrent chemoradiation          | 3/3.4%  |
| High dose                          | 7/8.0%  |
| Bone marrow transplant (BMT)       | 1/1.1%  |
| 1st Line                           | 24/27.6%|
| 2nd Line                           | 9/10.3% |
| **ECOG (Eastern Cooperative Oncology Group)** |       |
| 1                                  | 77/88.5% |
| 2                                  | 8/9.2%  |
| 3                                  | 1/1.1%  |
| 4                                  | 1/1.1%  |
| **Chemotherapy cycle**             |       |
| I                                  | 56/64.4% |
| II                                 | 10/11.5%|
| III                                | 7/8.0%  |
| IV                                 | 7/8.0%  |
| V                                  | 2/2.3%  |
| VI                                 | 4/4.6%  |
| VII                                | 1/1.1%  |

As prophylaxis growth factor as was used in 71 (82%) and was not used in 16 (18%), Table 3.
Table 4 shows the Talcott’s and MASCC risk predicting tool versus outcome, p values for Talcott’s and MASCC were significant (<0.05).

The recovery duration of median fever and neutropenia in Talcott’s versus MASCC model have been shown in Table 5.

### Table 3: Univariate analysis of risk factors for febrile neutropenia.

| List                          | Characteristics | No. of patients (%) | Odd’s ratio | 95% Cl | P-value |
|-------------------------------|-----------------|---------------------|-------------|--------|---------|
| Age                           | ≤60             | 70 (80.5%)          | 0.111       | -0.526 | 0.461   | 0.526   |
|                               | ≥60             | 17 (19.5%)          |             |        |         |         |
| Previous FN                   | Yes             | 24 (28%)            | 2.194       | 0.357  | 13.497  | 0.396   |
|                               | No              | 63 (72%)            |             |        |         |         |
| Serious comorbidity           | Yes             | 15 (17%)            | 0.038       | -0.281 | 0.358   | 0.139   |
|                               | No              | 72 (83%)            |             |        |         |         |
| ANC                           | ≤100            | 20 (25%)            | 0.583       | 0.138  | 2.453   | 0.461   |
|                               | ≥100            | 65 (75%)            |             |        |         |         |
| Platelet                      | <5000           | 2 (2%)              | 0.126       | -0.571 | 0.823   | 0.918   |
|                               | ≥5000           | 85 (98%)            |             |        |         |         |
| Fever duration                | ≤7 day          | 68 (77%)            | 0.339       | -0.303 | 0.981   | 0.297   |
|                               | 8-14            | 13 (15%)            | 0.548       | -0.058 | 1.155   | 0.076   |
|                               | 15-21           | 4 (5%)              | 1.239       | 0.506  | 1.971   | 0.001   |
|                               | >21             | 2 (2%)              | 0.000       | -      | -       | -       |
| Neutropenia duration          | ≤7 day          | 65 (75%)            | 0.618       | 0.059  | 1.177   | 0.031   |
|                               | 8-14            | 15 (17%)            | 0.122       | -0.454 | 0.698   | 0.674   |
|                               | 15-21           | 4 (5%)              | -0.464      | -1.094 | 0.165   | 0.146   |
|                               | >21             | 3 (3%)              | -           | -      | -       | -       |
| GF use                        | Yes             | 71 (82%)            | 0.866       | 0.150  | 5.007   | 0.872   |
|                               | No              | 16 (18%)            |             |        |         |         |
| Site of infection             | Yes             | 64 (72%)            | 1.188       | 0.340  | 4.145   | 0.787   |
|                               | No              | 23 (28%)            |             |        |         |         |

### Table 4: Risk predicting tool versus outcome.

| Outcome | RWOC | RWC | Death | Total | p   |
|---------|------|-----|-------|-------|-----|
| Talcott’s model | | | | | |
| Low risk | 30 | 0 | 0 | 30 | 0.001 |
| High Risk | 37 | 15 | 5 | 57 | |
| Total | 67 | 15 | 5 | 87 | |
| MASCC model | | | | | |
| ≥ 21 low risk | 59 | 0 | 0 | 59 | 0.00001 |
| <21 high risk | 8 | 15 | 5 | 28 | |
| Total | 67 | 15 | 5 | 87 | |

### Table 5: Median fever and neutropenia recovery duration in Talcott’s versus MASCC model.

| Risk Model | Talcott’s low risk (n=30) | Talcott’s high risk (n=57) | MASCC low risk (n=59) | MASCC high risk (n=28) |
|------------|--------------------------|---------------------------|-----------------------|------------------------|
| Fever Duration | Median Range | Median Range | Median Range | Median Range |
|               | 1 (1 to 2) | 5 | 2 (1 to 3) | 5 | 1 | 17 (1 to 18) | 8 | 29 (1 to 30) |
| Neutropenia recovery | Median Range | Median Range | Median Range | Median Range |
|                   | 1 | 2 (1 to 3) | 5 | 29 (1 to 30) | 1 | 19 (1 to 20) | 9 | 29 (1 to 30) |

The comparison between Talcott’s and MASCC model for solid tumor has been shown in Table 6. P value was not significant (>0.05) as sample size became smaller.

Among 87 patients, 42 (48.3%) had hematological malignancy. The comparison between Talcott’s and MASCC model for hematological malignancy has been
shown in Table 7. P value was not significant (>0.05) as the data became smaller. Fever and neutropenia duration for solid tumor and hematological malignancy, have been shown in Table 8, 9.

Validation of MASCC and Talcott's model has been shown in Table 10.

### Table 6: Talcott’s and MASCC model for solid tumor.

| Model          | Good outcome | Poor outcome | Total | p  |
|----------------|--------------|--------------|-------|----|
|                | RWOC | RWC | Death |    |
| Talcott’s model|      |     |       |    |
| Low risk       | 27   | 0   | 0     | 27 |
| High Risk      | 16   | 0   | 2     | 18 |
| Total          | 43   | 0   | 2     | 45 |
| MASCC model    |      |     |       |    |
| Low risk       | 41   | 0   | 0     | 41 |
| High Risk      | 2    | 0   | 2     | 4 |
| Total          | 43   | 0   | 2     | 45 |

### Table 7: Talcott’s and MASCC model for hematological malignancy.

| Model          | Good outcome | Poor outcome | Total | p  |
|----------------|--------------|--------------|-------|----|
|                | RWOC | RWC | Death |    |
| Talcott’s model|      |     |       |    |
| Low risk       | 3    | 0   | 0     | 3  |
| High Risk      | 21   | 15  | 3     | 39 |
| Total          | 24   | 15  | 3     | 42 |
| MASCC model    |      |     |       |    |
| Low risk       | 18   | 0   | 0     | 18 |
| High Risk      | 6    | 15  | 3     | 24 |
| Total          | 22   | 17  | 3     | 42 |

### Table 8: Fever and neutropenia duration for solid tumor.

| Model                              | Talcott’s low risk (n=27) | Talcott’s high risk (n=18) | P   | MASCC low risk (n=41) | MASCC high risk (n=4) | P   |
|-----------------------------------|----------------------------|-----------------------------|-----|-----------------------|-----------------------|-----|
| Mean Fever Duration (in days)     | 1                          | 2                           | 0.108 | 1                      | 1                      | 0.457 |
| Mean Neutropenia duration (in days) | 1                          | 2                           | 0.567 | 2                      | 2                      | 0.380 |

### Table 9: Fever and neutropenia duration for hematological malignancy.

| Model                              | Talcott’s low risk (n=3) | Talcott’s high risk (n=39) | P   | MASCC low risk (n=18) | MASCC high risk (n=24) | P   |
|-----------------------------------|--------------------------|-----------------------------|-----|-----------------------|------------------------|-----|
| Mean Fever Duration (in days)     | 2                        | 9                           | 0.439 | 6                      | 11                     | 0.231 |
| Mean Neutropenia duration (in days) | 2                        | 10                          | 0.250 | 6                      | 12                     | 0.099 |

### Table 10: Validation of MASCC and Talcott’s model.

| Parameter                     | Estimate | Lower-Upper 95% CIs |
|-------------------------------|----------|---------------------|
|                               | MASCC    | Talcott’s            | MASCC | Talcott’s |
| Sensitivity                   | 88.06%   | 44.8%               | 77.28 - 94.33 | 32.7-57.41 |
| Specificity                   | 100%     | 100%                | 79.95 - 100  | 79.95-100  |
| Positive Predictive Value     | 100%     | 100%                | 92.38 - 100  | 85.86-100  |
| Negative Predictive Value     | 71.43%   | 35%                 | 51.13 - 86.04 | 23.24-48.94 |

Continued.
DISCUSSION

Incidence of FN in our study was 17%. In a study by Roy et al incidence was 13.3%, 15% in Bhavik Doshi et al, 19.4% in Schelenz s. et al study, 14% in Crawford J et al study.13-16

The mean age in our study population was 45±15 years, (range 18 to 77 years). Male to female ratio was 31: 56, (0.55). Overall number of females (56/64.4%) were more than males (31/35.6%). In Roy et al study mean age was 41.2 years, range 16 to 72 years and male to female ratio was 79:132.12 Overall female (62.5%) were more than males (37.5%). James Talcott et al study had 64% females, range 17 to 75 years. M Okera et al had 59% female and 49% male.18,19

Overall maximum 24 (27.6%) patients had carcinoma breast. As per WHO carcinoma Breast carcinoma is commonest in India. Talcott et al study carcinoma Breast (31%) was the most common diagnosis.14

In our study 77(88.4%) had ECOG 1 performance status. In some studies, it has been found that poor performance status (e.g., WHO Grade > 1), as a measure of frailty, is a significant risk factor.17

In our study, 64.4% developed FN during 1st chemotherapy cycle. In a study by Roy et al 67.2% developed FN in 1st chemotherapy cycle, 70% in Bhavik Doshi et al study 50% in M Okera et al study 75% in Mezha M et al study 65% in first 2 cycles.13,14,19,8,20

The maximum number of patients had fever (78.2%) and neutropenia recovery duration (74.7%) ≤ 7 days. Grade IV neutropenia was noted in 59.8% and grade III in 40.2% patients at the time of presentation. In Roy et al study the average number of FN days per patient was 3.46 ± 0.13 days.13 The number of patients with grade IV neutropenia was 12.7% and grade III was 87.3%. Bhavik D. Doshi et al noted 43% grade 3 or 4 neutropenia.14

Growth factor was used in 81.7% patients in our study. M Okera et al study used growth factor in 63% patients.19 Routine use of Growth factor can reduce FN incidence to 50%.21

Overall 63% patients had comorbidities in our study. In a study by James A Talcott et al 36% had comorbidities.19 In our study, among Talcott’s high-risk patients, 37 (64.9%) had fever resolution without complication, 15 (26.3%) with complication, 5 (8.8%) died before fever resolution. In Talcott’s et al validation study high risk, had 34% complication rate, low risk had only a 5% risk of developing a medical complication.19

In our study, among MASCC high risk patients 8 (28.6%) had fever resolution without complication, 15 (53.6%) with complication and 5 (17.8%) died before fever resolution. Uys et al study showed 98.3% fever resolution without complication, 1.7% developing a serious complication in low risk, in high risk group 50% recovered without complication, 36% died before fever resolution.22

In our study, in Talcott’s low risk group, median duration of FN recovery was approximately 1 day (range 1 to 3 days) and in high risk group, 5 days (range 1 to 30 days). In MASCC low risk group median time was 1 day (range 1 to 20) and in high risk group was 9 days (range 1 to 30 days). As per Mezha et al study duration and severity of neutropenia increases the risk of infection and febrile neutropenia.8

The p value was significant only for MASCC model for solid tumor. For solid tumor, mean fever and neutropenia recovery duration was <7 days for both Talcott’s and MASCC group. For hematological malignancy, mean fever and neutropenia duration was >7 days for Talcott’s and MASCC high risk group and ≤7 days for Talcott’s and MASCC low risk group. Pizzo et al found that patients whose neutropenia resolved within 7 days were at low risk, and Bodey et al have consistently found that improvement in neutropenia in the first week improves prognosis.18,23-25

Limitations: This study was conducted in a single centre and therefore the results are not representative of the general populations.

CONCLUSION

Neutropenic fever is a potentially life-threatening complication of cancer chemotherapy. MASCC and Talcott’s model can be used to identify low and high risk patients. MASCC risk index may have a better performance than the Talcott’s model in risk classification. However, the Talcott’s model remains a valid and useful tool because of its simplicity. High risk
patients are expected to have longer duration of fever and neutropenia recovery duration. Granulocyte colony stimulating factor can shorten the duration of neutropenia and fever and improve treatment outcomes.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Gaur R et al. Int J Res Med Sci. 2021 Jan;9(1):236-242.