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PROSPECTIVE EVALUATION OF MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER RISK INDEX SCORE FOR GYNECOLOGIC ONCOLOGY PATIENTS WITH FEBRILE NEUTROPENIA

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Abstract

Background: The Multinational Association of Supportive Care of Cancer (MASCC) risk-index score has been validated as a stratification tool for febrile neutropenia (FN) risk in a heterogeneous group of cancer patients; recently, it has been deemed a suitable tool in gynecologic oncology patients in a retrospective study. This is a prospective multi-institutional study wherein we sought to validate MASCC score for stratifying FN morbidity in gynecologic oncology patients.

Methods: IRB approval was obtained at 4 institutions for prospective data collection of gynecologic cancer patients admitted with FN from 3/1/2013–9/1/2014. Participating institutions have a policy of inpatient management of FN patients receiving chemotherapy. De-identified data was compiled and processed at the leading institution.

Results: 31 patients met inclusion criteria. Most had advanced stage disease (67%). 100% of patients were receiving chemotherapy (57% for primary, 43% for recurrent disease). 55% had a positive culture. Median MASCC score was 21 (range, 10–26); 58% of patients were considered low risk. High risk patients more often had one (11% vs 38%, p=0.09) or multiple (6% vs 23%,

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p=0.28) severe complications, ICU admission (0% vs 15%, p=0.17), and delay in next chemotherapy cycle (33% vs 54%, p=0.25). No patients died from FN during the study period.

Conclusions: This pilot data suggests that MASCC score may be a promising tool for determining suitability of outpatient management of FN in gynecologic oncology patients. Larger studies are warranted to achieve statistically significant results, which may enable us to effectively utilize this risk stratification tool for cost containment and avoidance of nosocomial infections.

Keywords

febrile neutropenia; MASCC; Multinational Association of Supportive Care in Cancer; gynecologic cancer; chemotherapy complications

Introduction

Febrile neutropenia (FN) is a frequent complication in cancer patients, which may result in treatment delays, reduced quality of life, or death [1–3]. It is defined as either a single oral temperature >38.3 °C or ≥38.0 °C sustained over a 1-hour period with an absolute neutrophil count (ANC) <1500 cells/mm^3 or an ANC expected to decrease to <500 cells/mm^3 during the subsequent 48 hours [3]. The risk of clinically significant infection rises as the ANC falls below the critical value of 500 cells/mm^3, also known as severe neutropenia [4,5]. Chemotherapy-induced FN is a common yet potentially severe complication; its influence on morbidity and mortality has been recognized since the 1960s [6]. Due to iatrogenic immunosuppression, fever may be the only manifestation of infection, which can progress to a catastrophic state; thus, empiric antimicrobial therapy is indicated for FN [7]. It has become evident that FN is a heterogeneous entity with disparate outcomes, due to varying level of ensuing complications and resultant prognosis [8].

Numerous studies have attempted to predict ensuing risk with FN based on a number of clinical parameters, with the goal of identifying subsets of patients for whom outpatient management may be safe, in contrast to the doctrine of universal inpatient management with parenteral antibiotics and close observation. Talcott et al proposed a model in 1994 which was effective at predicting low risk of complications, but it was associated with a 30% readmission rate and thus did not gain consensus [9]. In 2000, the Multinational Association for Supportive Care in Cancer (MASCC) demonstrated a reproducible risk index scoring system to estimate the risk of serious complications or death in patients with FN (Table 1), accounting for age, clinical presentation, and components of the patient's medical history [10]. The MASCC score's ability to identify low risk FN patients has been validated, and subsequently, it has become an accepted tool in the standard practice of estimating risk of complications by the Infectious Disease Society of America and the European Society of Medical Oncology [3,11–13]

In order to study the utility of this tool in discrete patient populations, the MASCC scoring system has been evaluated in specific FN populations, as the initial studies enrolled heterogeneous groups of both solid tumor and hematologic malignancy patients. It has been shown to be a reliable tool for identifying hematologic malignancy patients with a low risk for complications from FN [14,15]. Our research group previously reported on retrospective

application of the MASCC scoring system specifically to gynecologic cancer patients. We noted a 90% negative predictive value and 50% positive predictive value, with high-risk patients being significantly more likely to endure a severe complication, multiple severe complications, intensive care unit (ICU) admission, and death due to FN [16]. Given the bias introduced by retrospective assessment, herein, we sought to prospectively score gynecologic cancer patients with the MASCC system to evaluate the efficacy and predictive values in this population.

Materials and Methods

We performed a prospective, multi-institutional study (Stephenson Cancer Center at University of Oklahoma Health Sciences Center, University of Alabama at Birmingham, University of North Carolina, and Washington University in Saint Louis) involving risk stratification of gynecologic oncology patients with FN using the MASCC risk index score. Institutional Review Board approval was obtained at each site. The study period was 3/1/2013–9/1/2014. At all 4 academic centers, the policy was for inpatient management of FN in gynecologic oncology patients who were receiving chemotherapy. Use of granulocyte colony stimulating factors (G-CSF) was per institutional policy or per protocol for patients being treated on clinical trials.

Patients were identified sequentially as they were admitted by study investigators. Febrile neutropenia was defined by an absolute neutrophil count of ≤1500 cells/microliter in combination with a temperature greater than 38.0 degrees Celsius for >1 hour or a single oral temperature of 38.3 degrees Celsius. Only the first admission was counted for patients who were admitted multiple times for FN. Patients who were admitted for other indications who developed FN while hospitalized were excluded from the study.

Demographic, oncologic, and treatment characteristics were extracted from patient medical records. Dates of admission and discharge were recorded, and a risk index score was prospectively calculated based on admission characteristics using the MASCC scoring system (Table 1); there was no knowledge of hospital course at the time of risk score calculation. Low risk was considered ≥21, and high risk was defined as MASCC score <21. Characteristics of neutropenic fever episode were recorded including the number, length, and type of antibiotics used; use of granulocyte stimulating factor (G-CSF); duration of hospital stay; and frequency of severe complications. Severe complications were defined as death within 14 days of hospital discharge, hypotension, respiratory or renal failure, ICU admission, confusion or mental status changes, congestive cardiac failure, bleeding requiring transfusion, electrocardiogram (EKG) changes, arrhythmia requiring treatment, fungal infection, and allergic reaction.

De-identified data was compiled and processed at the lead institution (University of Oklahoma). Descriptive statistics were utilized to characterize the demographic and clinical attributes of the study subjects. Chi-square and Fisher’s exact tests were used as appropriate to evaluate categorical associations. To compare medians between low and high-risk groups, the Wilcoxon test was used. P values of <.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.3 (SAS Institutes, Cary, NC).

Results

Thirty-one patients were identified, enrolled, and admitted for treatment of FN at one of the 4 participating institutions. During the study period, 17,394 cycles of chemotherapy were administered to gynecologic oncology patients at the 4 sites, giving an incidence of 0.17% per cycle. Table 2 depicts the subject demographics. Median age was 63 years (range, 47–77). Most patients were Caucasian (84%), had advanced stage disease (67%), and had one or more medical comorbidities (71%). One-third of patients used tobacco. The majority of patients (61%) had ovarian cancer as their primary disease site, followed by nine patients (29%) with endometrial cancer, and 3 patients (10%) with cervical cancer. Fifty-two percent of patients were receiving chemotherapy for primary disease. The median number of prior lines of chemotherapy was 1.

All 31 patients had received chemotherapy recently, and 26% had been hospitalized within the previous 30 days. The median time from most recent chemotherapy administration was 10 days (range, 0–38 days), and the median length of hospitalization for FN was 4 days (range, 2–13).

Upon admission, median ANC was 160 cells/mm^3 (range, 0–1309), and the median nadir ANC during admission was 142 cells/mm^3 (range, 0–1065). Admission characteristics and hospital outcomes are detailed in Table 3. Thirty-nine percent of patients received a single broad-spectrum antibiotic upon admission, and the median length of antibiotic use was 4 days (range, 2–14 days). A variety of antibiotics were prescribed upon admission, and 42% received additional antibiotics during their hospital course beyond those initially prescribed. Fifty-eight percent of patients received G-CSF during hospitalization.

Seventeen patients (55%) had a documented positive culture, including three (18%) with a positive urine culture, three (18%) with a positive blood culture, two (12%) with a positive abscess culture, and nine patients (53%) with miscellaneous other positive cultures. One patient had 2 positive cultures (intra-abdominal sepsis and pneumonia). Sixty-five percent were prescribed antibiotics upon hospital discharge. Within 2 days of admission, 24 patients (77%) patients were afebrile, and only two patients (7%) remained severely neutropenic for >7 days. Twenty-three percent of patients experienced a severe complication, including 13% hypotension, 10% confusion or mental status changes, 6% ICU admission, and 3% bleeding requiring transfusion. Only four patients (13%) had multiple severe complications. No patients died due to FN or complications surrounding FN.

Fifty-eight percent of the entire group was scored as low risk. Table 4 stratifies patient outcomes by risk category. Median MASCC score of the entire group was 21 (range, 10–26); however, median MASCC score for those incurring a severe complication was 13 (range, 10–22), and median MASCC score for patients enduring multiple severe complications was 12 (range, 10–22). High-risk patients more frequently experienced ICU admission (15% vs 0%, p=0.168), a severe complication (38% vs 11%, p=0.099), and multiple severe complications (23% vs 6%, p=0.284), but these parameters did not reach statistical significance.

Discussion

This study provides prospective pilot data that suggests that MASCC score may be a promising tool for determining suitability of outpatient management of FN in gynecologic oncology patients who are actively receiving chemotherapy. We found that a greater percent of high-risk patients required ICU admission and incurred one or more severe complications. Although the sample size was small and thus the comparisons did not attain statistical significance, we feel that these measures are clinically significant and suggest that MASCC may be a useful tool for FN risk stratification in gynecologic oncology patients.

FN is one of the most dangerous consequences of immunosuppression with a mortality rate ranging from 2–20%; unfortunately, it is frequently encountered with myelosuppressive therapy. Tai et al reported that there were 91,560 hospital admissions for adults with FN in the United States in 2012 totaling $2.3 billion in hospital costs, based on nationally representative estimates [17]. As the number of patients in the United States diagnosed with cancer continues to increase annually [18], the frequency of chemotherapy administration and resultant incidence of FN should both rise, thus imposing an even greater financial burden on the healthcare system. Hospitalization for FN is resource-intensive, with the aforementioned National Inpatient Sample (NIS) study reporting a mean hospital cost of $24,770 per patient [17]. A similar cost per patient ($20,462-$37,555) was reported in a recent large Kaiser study of breast, lung, and non-Hodgkin's lymphoma patients with febrile neutropenia [19]. Median hospitalization in the NIS study was 9.6 days [17]. Length of stay in our study was shorter (median of 4 days), but duration of hospitalization varies with cancer type and characteristics of the population studied, and patients with hematopoietic malignancies (56% of NIS study) are known to receive more myeloablative therapies, often associated with higher risk FN episodes. Additionally, over half of our patients were being treated for primary disease, and thus they are generally considered lower risk FN patients than those who have received prior chemotherapy or radiation given greater bone marrow reserve. Finally, efforts to improve infection control and minimize the development of FN from nosocomial infections are key initiatives in this vulnerable population.

The American Society of Clinical Oncology published clinical practice guidelines in 2015 that outline specific scenarios in which the use of G-CSF is indicated. Primary prophylaxis for patients receiving chemotherapy is indicated if a ≥ 20% risk of FN is predicted [20]. While this pre-treatment risk is also driven by patient factors such as older age and presence of comorbidities, ≥20% risk of FN is not usually associated with chemotherapy regimens prescribed for gynecologic cancers. Although many gynecologic oncology patients are older and have comorbidities, increasing health care costs should motivate one to consider the risks and benefits of various interventions, including not only G-CSF use but also outpatient management of FN for appropriately selected candidates.

There are several notable limitations of this study. First, the sample size is relatively small, which limits statistical significance for several parameters analyzed. We captured far fewer patients than anticipated during study design, likely due to variable and more frequent use of G-CSF than projected. However, we did not record frequency of G-CSF used in all chemotherapy cycles administered (i.e. patients who did not develop FN). Second, the true

incidence of FN may be underreported if patients were admitted to outside hospitals or unknowingly received outpatient care for FN by another provider or clinic. Third, patients included had various insurance types and were treated at academic medical centers, which may not be generalizable to managed care settings or community practices, especially in more rural locations. Nonetheless, the study was a prospective observational cohort of a variety of gynecologic cancer patients with FN from four large academic centers with extensive experience in treating gynecologic malignancies.

In conclusion, MASCC risk stratification for FN appears to be a useful tool for prospective risk assessment in gynecologic oncology patients receiving chemotherapy. Further study of mechanisms for improving patient care and reducing health care costs for chemotherapy complications such as FN is warranted. Although FN is a relatively rare complication in gynecologic oncology patients who are receiving chemotherapy, prevention and appropriate outpatient management of low-risk patients may be cost saving, more convenient, and safe. Larger studies may enable further elucidation of this tool and potentially statistically significant results, which could lead to effective utilization of this risk stratification instrument for cost containment and avoidance of nosocomial infections.

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Table 1:

Multinational Association of Supportive Care in Cancer risk index scoring system

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 symptoms	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age <60	2
	TOTAL: if ≥21, LOW RISK
	if <21, HIGH RISK

Table 2:

Patient demographics

Characteristic	Number of subjects, n=31(%)
Age, median	63 (range, 47–77)
Race/Ethnicity	
White	26 (84%)
Black	5 (16%)
Interval since diagnosis (median, days)	156 (range, 22–3443)
Interval since last chemotherapy (median, days)	10 (range, 0–38)
Tobacco abuse, former/current smokers	10 (32%)
Median pack-years among smokers	10 (range, 1–30)
Medical comorbidities	
None	9 (29%)
One comorbidity	12 (39%)
Two or more comorbidities	10 (32%)
Type of medical comorbidities	
Hypertension	18 (58%)
Obesity	9 (29%)
Diabetes mellitus	5 (16%)
Autoimmune disease	1
COPD	0
Non-chemotherapy immunosuppression	2 (7%)
Primary disease site & histology	
Endometrium	9 (29%)
Endometrioid	3
Clear cell/Uterine papillary serous	1
Sarcoma/Carcinosarcoma	5
Ovary	19 (61%)
High grade serous	17
Low grade serous	1
arcinosarcoma	1
Cervix	3 (10%)
Squamous cell carcinoma	3
Stage	
I	7 (23%)
II	2 (6%)
III	18 (58%)
IV	3 (10%)
Unstaged	1 (3%)
Currently receiving chemotherapy	31(100%)

Characteristic	Number of subjects, n=31(%)
Primary disease	16 (52%)
Recurrent disease	15 (48%)
Received prior therapy	
None	16 (52%)
Chemotherapy only	11 (35%)
Radiation only	0 (0%)
Both	4 (13%)
Received prior surgery	28 (90%)
ANC on admission (median, days)	160 (range, 0–1309)
ANC nadir (median, days)	142 (range, 0–1065)

* COPD: chronic obstructive pulmonary disease; ANC: absolute neutrophil count

Table 3:

Hospital outcomes

	Number of subjects (%)
MASCC score	
Median (range)	21 (10–26)
Low (% ≥ 21)	18 (58%)
Antibiotic monotherapy at admission	12 (39%)
Antibiotics administered at admission	
Ceftazidime	3 (10%)
Piperacillin/Tazobactam	11 (35%)
Carbapenem	4 (13%)
Cefepime	14 (45%)
Vancomycin	15 (49%)
Other	4 (13%)
Positive culture	
None	14 (45%)
One	16 (52%)
Two	1 (3%)
Type of positive culture among patients with a positive culture (n=17)	
Urine	3 (18%)
Blood	3 (18%)
Sputum	0
Abscess/drain	2 (12%)
Other	9 (53%)
Severe complication	7 (23%)
Death	0
Hypotension	4 (13%)
Respiratory/renal failure	0
ICU admission	2 (6%)
Confusion or ΔMS	3 (10%)
Congestive cardiac failure	0
Bleeding requiring transfusion	1 (3%)
EKG changes	0
Arrhythmia requiring treatment	0
Fungal infection	0
Allergic reaction	0
Discharged on antibiotics	20 (65%)
Days of hospitalization (median, days)	4 (range, 2–13)

* MASCC: Multinational Association of Supportive Care in Cancer; ICU: intensive care unit; MS: mental status; EKG: electrocardiogram

Table 4:

Outcomes based on risk stratification category

	Low risk, n(%)(MASCC ≥ 21)n=18	High risk, n(%)(MASCC < 21)n=13	p-value
Days of hospitalization, median, range	4 (2–14 days)	6 (3–10 days)	0.123
Positive culture or documented infection	10 (56%)	7 (54%)	0.925
Multiple positive cultures	0 (0%)	1 (8%)	0.419
Positive blood or urine culture	3 (17%)	3 (23%)	0.676
Antibiotic monotherapy at admission	7 (39%)	5 (38%)	0.981
ICU admission	0 (0%)	2 (15%)	0.168
Severe complication	2 (11%)	5 (38%)	0.099
Multiple severe complications (≥2)	1 (6%)	3 (23%)	0.284
Overall mortality	0 (0%)	0 (0%)	-
Death due to neutropenic fever	0 (0%)	0 (0%)	-
ANC on admission, median, range	249 (20, 1309)	150 (0, 990)	0.418
ANC nadir, median, range	249 (0, 1065)	132 (0, 989)	0.464
G-CSF given during hospitalization	9 (50%)	9 (69%)	0.284
Neutropenic ≥7 days	1/17 (6%)	1/13 (8%)	1.000
Chemotherapy delay	6 (33%)	7 (54%)	0.253

++ Did not reach statistical significant given low sample size, but one may appreciate a clinically distinct difference in outcomes.

** MASCC: Multinational Association of Supportive Care in Cancer; ICU: intensive care unit; ANC: absolute neutrophil count; G-CSF: granulocyte colony stimulating factor