Management of Breast Cancer Patients with Chemotherapy-Induced Neutropenia or Febrile Neutropenia

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Keywords

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Summary

Chemotherapy-induced neutropenia (CIN) is a common toxicity caused by the administration of anticancer drugs. This side effect is associated with life-threatening infections and may alter the chemotherapy schedule, thus impacting on early and long-term outcomes. Elderly breast cancer patients with impaired health status or advanced disease as well as patients undergoing dose-dense anthracycline/taxane- or docetaxel-based regimens have the highest risk of CIN. A careful assessment of the baseline risk for CIN allows the selection of patients who need primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) and/or antimicrobial agents. Neutropenic cancer patients may develop febrile neutropenia and CIN-related severe medical complications. Specific risk assessment scores, along with comprehensive clinical evaluation, are able to define a group of febrile patients with low risk for complications who can be safely treated as outpatients. Conversely, patients with higher risk of severe complications should be hospitalized and should receive intravenous antibiotic therapy with or without G-CSF.

Introduction

The worldwide incidence of breast cancer (BC) is increasing, accounting for 29% of all new cancer diagnoses in North American women and ranking second as the leading cause of death for malignancy [1, 2]. However, over the last 6 decades,

the mortality rate of BC patients has progressively decreased [3]. Among a number of different reasons, the improvement of chemotherapy strategies and the discovery of new anticancer drugs played a crucial role in prolonging the overall survival of BC patients.

The dose intensity is the total amount of drug delivered over the time course of the treatment. The relative dose intensity is the ratio of the delivered dose intensity to the reference dose intensity for a chemotherapy regimen [4]. A strong relationship exists between the relative dose intensity and the long-term outcome of BC patients diagnosed with chemosensitive tumors (such as cancer with a high proliferative index) [4–6]. It is important to maintain the optimal dose intensity in the adjuvant setting since the survival curves of patients treated with a relative dose intensity lower than 85% resemble those of untreated patients [7].

Chemotherapy-induced neutropenia (CIN) is the most common toxicity caused by the administration of anticancer drugs. In a large prospective registry, 37% of the BC patients experienced an absolute neutrophil count (ANC) lower than 500 cells/mm³ over the first 4 cycles of treatment, and approximately 70% of the initial episodes occurred in cycle 1 [8, 9]. CIN is associated with the risk of both life-threatening infections and chemotherapy dose reductions or delays that may reduce the relative dose intensity [10]. An analysis of over 1,100 BC patients treated with adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF), or doxorubicin and cyclophosphamide (AC), or other regimens showed that CIN was the most frequent cause of dose reductions and delays [11].

According to the latest version of the Common Terminology Criteria for Adverse Events (CTCAE) [12], neutropenia is defined as ‘a finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen’. Since circulating neutrophils have a half-life of only 6–8 h after entering the peripheral blood, a rapid and efficient

Table 1. Risk assessment for the development of FN: patient-, cancer- and treatment-related factors that increase the risk of FN in BC patients receiving a new chemotherapy regimen^a

Factors increasing the risk of FN	
Patient-related	
Age	> 65 years
ECOG PS	≥ 2
Nutritional status	albumin < 35 g/dl
Number of comorbidities	1 = 27% increased odds
	2 = 67% increased odds
	3 = 125% increased odds
Cancer-related	
Cancer stage	advanced stage
Response to treatment	complete or partial response = low-risk of FN
	progressive disease = high-risk of FN
Prior episode	FN episode occurs in cycle 1 = 4-fold greater risk in cycles 2–6
Treatment-related	
Dose intensity	> 85% of the scheduled doses are administered
Adjuvant setting regimen	^b doxorubicin 60 mg/m ² + cyclophosphamide 600 mg/m ² every 14 days for 4 cycles, followed by paclitaxel 175 mg/m ² 14 days for 4 cycles
	^b docetaxel 75 mg/m ² + doxorubicin 50 mg/m ² + cyclophosphamide 500 mg/m ² every 21 days for 6 cycles
	^c cyclophosphamide 100 mg/m ² /day on days 1–14 + methotrexate 40 mg/m ² i.v. on days 1 and 8 + 5-FU 600 mg/m ² on days 1 and 8 every 28 days for 6 cycles
	^c docetaxel 75 mg/m ² + cyclophosphamide 600 mg/m ² every 21 days for 4 cycles
	^c 5-FU 500 mg/m ² + epirubicin 100 mg/m ² + cyclophosphamide 500 mg/m ² every 21 days for 3 cycles, followed by docetaxel 100 mg/m ² every 21 days for 3 cycles
Metastatic setting regimen	^c doxorubicin 60 mg/m ² + cyclophosphamide 600 mg/m ² every 21 days for 3 cycles, followed by docetaxel 100 mg/m ² every 21 days for 3 cycles
	^b trastuzumab 2 mg/kg (loading dose 4 mg/kg) + docetaxel 100 mg/m ² every 21 days
	^c docetaxel 100 mg/m ² every 21 days
Adverse events	^c paclitaxel 175 mg/m ² every 21 days
	oral mucositis with painful erythema/ulceration that requires i.v. hydration
	ANC < 500 cells/mm ³ for ≥ 7 days
	ALC < 700 cells/mm ³
	AMC < 150 cells/mm ³

^aAdapted from [16].

^bAccording to the NCCN guidelines for myeloid growth factors [27], risk of FN > 20%.

^cAccording to the NCCN guidelines for myeloid growth factors [27], risk of FN 10–20%.

ECOG = Eastern Cooperative Oncology Group, PS = performance status, i.v. = intravenous, 5-FU = 5-fluorouracil, ANC = absolute neutrophil count, ALC = absolute lymphocyte count, AMC = absolute monocyte count.

bone marrow production is essential for immune system homeostasis. In cancer patients treated with cytotoxic agents, neutropenia occurs as a result of decreased neutrophil production, accelerated utilization, or a combination of both [13]. Drug-induced neutropenia is mainly related to a direct inhibition of bone marrow precursors, although immune-mediated mechanisms have also been reported [13, 14].

Neutropenic patients may be predisposed to infections, typically arising from the endogenous skin or gut flora [13]. The link between the ANC and the risk of infection is not new. Bodey et al. [15] assessed that patients with an ANC < 1,000 cells/mm³ have a substantially increased risk of infection over time while those with an ANC < 100 cells/mm³ will likely develop severe infection within 1–4 weeks. To date, the CTCAE have graded neutropenia into 4 severity classes following the ANC:

- Grade 1: ANC from the lower normal limit to 1,500 cells/mm³
- Grade 2: ANC from 1,500 to 1,000 cells/mm³
- Grade 3: ANC from 1,000 to 500 cells/mm³
- Grade 4: ANC < 500 cells/mm³

Notably, the duration of the neutropenia significantly impacts on the risk of developing complications; in particular, patients with an ANC < 500 cells/mm³ for > 7 days will likely develop febrile neutropenia (FN) (table 1).

The American Society of Clinical Oncology (ASCO) Clinical Practice Guideline (CPG) Expert Panel has defined neutropenia as an ANC < 1,000 cells/mm³, severe neutropenia as ANC < 500 cells/mm³, and profound neutropenia as ANC < 100 cells/mm³ [16]. According to the European Society of Medical Oncology (ESMO) [17] and the European Organisation for Research and Treatment of Cancer (EORTC) [18]

Fig. 1. Management of BC patients with CIN or patients who are expected to develop CIN, and FN, in the outpatient and inpatient setting. ANC = absolute neutrophil count, G-CSF = granulocyte colony-stimulating factor, FN = febrile neutropenia, HBV = hepatitis B virus, BT = body temperature, TMP-SMZ = trimethoprim/sulfamethoxazole, MASCC = Multinational Association for Supportive Care in Cancer risk index, PCP = primary care physician, IV = intravenous.

guidelines, FN is defined as an oral temperature $> 38.5^{\circ}\text{C}$ or two consecutive readings of $> 38.0^{\circ}\text{C}$ for 2 h and an ANC $< 500\text{ cells/mm}^3$ or expected to fall below this threshold.

Risk of Developing Neutropenia

Factors impacting on the risk of CIN can be grouped into patient-, disease-, and treatment-related factors.

Age is the most important patient-related risk factor; increasing age is associated with the greatest risk of CIN because of immunosenescence phenomena [19, 20]. Elderly patients may have reduced bone marrow reserves or declines in renal and hepatic function, and are more prone to treatment-related complications [21]. Similarly, patients with abnormal baseline laboratory values have a higher risk of CIN; in particular, aspartate aminotransferase $> 35\text{ }\mu\text{l}$, alkaline phosphatase $> 120\text{ }\mu\text{l}$, or total bilirubin $> 1\text{ mg/dl}$ are associated with severe neutropenia or FN [21]. Moreover, patients with a poor performance status (PS) [21] or impaired nutritional status may have a compromised immune system due to deficiencies in proteins and micronutrients such as vitamins C and B6, zinc, iron, copper, and selenium [22]. Lastly, female patients have higher risks of CIN compared with male patients [21, 23, 24].

Disease-related factors include bone involvement, type of cancer, and previous history of myelotoxicity. Disease extension is a significant predictor for neutropenia, FN, septic shock, and death [24]. Overall, patients with hematologic cancers are at greater risk for myelosuppression than patients with solid tumors [24]. Moreover, a low baseline and first-cy-

cle nadir white blood cell count and high chemotherapy dose intensity are significant predictors of neutropenic events [24].

Treatment-related risk factors for developing CIN include radiation therapy to the bone marrow, type of prior chemotherapy, and treatment regimen. BC patients exposed to dose-dense anthracycline/taxane- and docetaxel-based regimens have a $> 20\%$ risk of developing neutropenia [25]. A recent Korean study showed that the incidence of FN in BC patients who received AC for 4 cycles followed by docetaxel (D) for 4 cycles or docetaxel, adriamycin, and cyclophosphamide (TAC) for 6 cycles without primary granulocyte colony-stimulating factor (G-CSF) prophylaxis was 29.7% and 63.4%, respectively [26]. However, the overall taxane-induced toxicity reported in the literature is higher in Asian compared with Caucasian populations [27]. Furthermore, the vast majority of the standard regimens used in clinical practice are associated with an intermediate risk of neutropenia (10–20%) [27].

Management of Neutropenia

Baseline Risk Assessment

BC patients have an average risk for FN of 4.4%, but several different factors could affect this value [16]. Thus, in patients with CIN or in those expected to become neutropenic, a comprehensive systematic risk assessment for FN is mandatory.

Patients ≥ 65 years, with advanced disease, an Eastern Cooperative Oncology Group (ECOG) PS > 1 , an albumin concentration $< 35\text{ g/l}$, or with significant comorbid conditions

have an increased risk of developing FN. Moreover, patients whose disease is progressing despite the treatments given are more likely to experience complications compared to those who achieve a complete/partial response (table 1).

In the risk assessment of neutropenic patients, characteristics related to the treatment and the reported adverse events should also be taken into account. The risk of neutropenic complications is higher if an anthracycline/taxane- or an anthracycline/gemcitabine-based regimen is administered. Moreover, severe mucositis, severe neutropenia for at least 1 week, lymphopenia of < 700 cells/mm³, and monocytopenia of < 150 cells/mm³ are all associated with a higher risk of neutropenic complications (table 1).

Prophylaxis in Non-Febrile Neutropenic Outpatients

The international guidelines recommend primary prophylaxis with G-CSF whenever the risk of FN is $> 20\%$ [19, 27, 28]. Both the National Comprehensive Cancer Network (NCCN) [27] and the ASCO guidelines [29] recommend the use of G-CSF for chemotherapy administered every 3 weeks, but not for weekly chemotherapy regimens. Antibacterial, antiviral, and antifungal prophylaxis should be considered only for patients expected to experience profound neutropenia likely to last longer than 1 week or in very select cases (fig. 1) [16]. On the other hand, patients with severe neutropenia but with a good PS and without risk factors for the development of complications could be only closely monitored until ANC recovery (table 1). An antibacterial prophylaxis with oral fluoroquinolones is recommended to prevent invasive infection by Gram-negative bacilli in outpatients with profound neutropenia and mucositis expected to last for at least 7 days. The use of an orally administered triazole antifungal is recommended in the outpatient setting as prophylaxis in patients with $> 10\%$ risk of invasive *Candida* infection. Prophylaxis with trimethoprim/sulfamethoxazole should only be used if the risk of pneumonia from *Pneumocystis jirovecii* is $> 3.5\%$. Lamivudine is recommended as prophylaxis in patients at high risk for reactivation of hepatitis B virus (HBV) infection (fig. 1) [16].

The primary prophylaxis of seasonal influenza with a trivalent inactive vaccine is suggested in all patients receiving chemotherapy [30].

Management of Febrile Neutropenia

Risk Assessment for the Development of Medical Complications

All patients who experienced CIN have a risk of developing FN potentially followed by serious medical problems. However, the risk may depend on previous neutropenic complications. Based on a review of chemotherapy-based regimens in the Breast Cancer Canadian Database Initiative, 72%

of the patients reporting a first episode of neutropenic complication experienced further medical problems during following treatment cycles [29].

FN represents a heterogeneous condition with different patient outcomes. As a result, a number of decision-making models and scoring systems have been validated as guidelines for its upfront management.

The Multinational Association for Supportive Care in Cancer (MASCC) risk index allows the prediction of complications taking into account the type and the burden of illness and related symptoms, the presence of hypotension, chronic obstructive pulmonary disease, previous fungal infection, and dehydration, the age of the patient, and the outpatient status (table 2) [31]. In solid malignancies, a MASCC score ≥ 21 identifies a subgroup of patients at low risk for complications.

Although the MASCC risk index has been validated in several publications over the last decade [32, 33], additional clinical criteria should be considered during a patient's baseline risk assessment. Patients with significant cardiovascular disease, and patients with impaired liver or renal function, should be considered at increased risk even if they have a MASCC score ≥ 21 . Accordingly, patients with active/possible sites of infection, altered mental status or any other sign or symptom of central nervous system involvement, or with gastrointestinal disturbance should be considered at higher risk and managed carefully. Finally, ascites, pleural or pericardial effusion, pancytopenia, electrolyte abnormalities or renal impairments also need to be considered.

Treatment of FN in the Out- and Inpatient Setting

Bacterial infection is the most frequent cause of fever in cancer patients [34]. For this reason, BC patients with an oral body temperature > 38.5 °C should undergo a clinical interview, an accurate physical examination, laboratory tests including complete blood count, electrolytes and creatinine, and a radiological assessment according to clinical suspicions, in order to maximize the possibility of a microbiologic diagnosis that may require specific antibacterial treatment [35].

As mentioned previously, once febrile patients have been carefully examined for infections and FN has been diagnosed, a risk assessment for complications is mandatory. Identification of patients suitable for outpatient management is crucial since this cost-effective strategy allows savings, limits the risk of hospital-acquired infections and improves the patients' quality of life [36, 37]. FN patients with a MASCC score ≥ 21 and without other clinical warning signs can be safely managed in the outpatient setting if they are able to take oral medication and have a committed caregiver [38, 39]. Successful management of CIN in BC outpatients requires the patients and their caregivers to be educated to rapidly recognize signs and symptoms of possible infection. Furthermore, it is essential to provide them with written instructions on when and how to contact health care practitioners. Ideally, FN candidates eligible for outpatient management require: (1) resi-

Factors		Score
Burden of symptoms	no or mild symptoms	5
	moderate symptoms	3
	severe symptoms	0
Blood pressure	systolic blood pressure > 90 mmHg	5
	systolic blood pressure ≤ 90 mmHg	0
Chronic obstructive pulmonary disease	no	4
	yes	0
Previous fungal infection	no	4
	yes	0
Dehydration requiring parenteral fluids	no	3
	yes	0
Onset of fever	in outpatient status	3
	in inpatient status	0
Age	< 60 years	2
	≥ 60 years	0
Total score		
Total score ≥ 21 points: patients with a low risk for serious complications of FN (including death, intensive care unit admission, confusion, cardiac complications, respiratory failure, renal failure, hypotension, bleeding, and other serious medical complications).		
Total score < 21 points: patients with a high risk for serious complications of FN.		

Table 2. Calculation of the risk of serious complications in patients with FN using the MASCC risk score

dence at < 1 h from the hospital, (2) agreement of the primary care physician to outpatient management, (3) the ability to observe logistic requirements, (4) the presence of a caregiver 24 h a day, (5) access to a telephone and transportation 24 h a day, (6) the absence of a history of non-compliance with treatment protocols (fig. 1) [16].

A meta-analysis of 22 trials showed similar mortality and treatment failure rates between oral and intravenous antibiotic treatment [38]. The analysis confirmed that oral treatment is a reasonable option in FN patients who are hemodynamically stable and have no organ failure, pneumonia, or a central line or severe soft-tissue infection. Similar safety and efficacy of oral versus intravenous therapy as initial empiric therapy have also been demonstrated in a Cochrane review [39]. According to the ASCO guidelines [16], cancer patients with FN at low risk of complications should be treated as outpatients and should receive a combination of oral fluoroquinolones (ciprofloxacin or levofloxacin) and amoxicillin/clavulanate (or clindamycin in patients allergic to penicillin) (fig. 1). According to a recent study, oral moxifloxacin administered once daily could be considered as efficacious and safe as amoxicillin/clavulanate in low-risk FN outpatients [40]. Oral medication intolerance may be circumvented in exceptional cases with home-based intravenous administrations. Notably, the first administration of therapy should be given in the hospital within 1 h from the diagnosis of FN, and patients selected for outpatient management should be monitored for at least 4 h before discharge, to verify clinical stability [16, 41].

A recent study reported that almost 40% of patients with a respiratory tract infection due to *Staphylococcus aureus* were resistant to ciprofloxacin, and similar results were observed in patients with urinary tract infections due to *Escherichia coli*

[42]. In patients who developed fever after a fluoroquinolone-based primary prophylaxis, or if a prevalence of fluoroquinolone resistance > 20% has been documented, intravenous therapy is still suitable for outpatient administration (fig. 1). However, if patients are infected by fluoroquinolone-resistant Gram-negative pathogens that are co-resistant to β -lactams, inpatient management and administration of meropenem every 8 h or piperacillin/tazobactam every 6 h are required. Similarly, patients with FN at high or intermediate risk need to be hospitalized for intravenous antimicrobial therapy (fig. 1). In these patients, local epidemiological bacterial isolate and resistance patterns are crucial in determining the first-choice empirical therapy.

G-CSF should not be routinely used in patients with FN. However, in high-risk patients, the use of G-CSF could be considered as adjunctive treatment with antibiotic therapy [29].

Conclusions

In BC patients, FN is relatively common. Up to 23% of them experience at least 1 episode of FN secondary to standard chemotherapy, and this figure skyrockets to 98% in patients exposed to high-dose chemotherapy regimens [43, 44].

A recent case-control study showed that FN is associated with higher health care resource use in BC patients compared to non-FN patients [45]. BC patients with a history of FN had an increased risk of all-cause hospitalization in the first month after the febrile event compared with patients who never experienced FN (odds ratio (OR) = 23.0, 95% confidence interval (CI) 8.3–63.7) and they also had a longer median length of

stay of all-cause hospitalizations (4 days vs. 1 day). Moreover, regardless of the type of cancer diagnosed, the length of hospital stay for FN patients is 6.5–8.8 days [46, 47], with an overall cost of USD 15,231 per FN episode or USD 1,455 per day of hospitalization [48].

An Australian cost analysis showed a 30% saving for ambulatory care strategies when compared with standard hospital care [49]. Considering the high economic cost for the health care system of hospitalized BC patients with FN, managing as many patients as possible in an outpatient setting should be a key task in modern medical oncology.

Moreover, outpatient management of low-risk FN patients is safe and cost-effective. In a sample of more than 700 patients with low-risk FN, the response rate to the empirical antibiotic regimen was 81% in outpatients and 80% in inpatients ($p = 0.94$). Moreover, the mean durations of the fever (2.0 vs. 2.4 days; $p = 0.04$) and the antibiotic therapy (8.5 vs. 9.2 days; $p = 0.08$) were significantly shorter among outpatients compared with inpatients [38]. Accordingly, a Cochrane review demonstrated that oral antibiotic treatment is an acceptable

alternative to intravenous treatment in selected FN cancer patients [38]. The mortality rate was 32 out of 1000 patients treated with an intravenous antibiotic regimen versus 30 out of 1000 patients treated with an oral regimen (risk ratio (RR) = 0.95, 95% CI 0.54–1.68).

As expected, a health-related quality-of-life study showed that 75% of patients preferred an outpatient strategy for FN. In particular, 36% preferred an outpatient management with oral antibiotics, 21% an outpatient management with intravenous antibiotics, and 18% an oral treatment at home after an initial observation in the hospital [37].

In conclusion, improving the outpatient management of low-risk FN patients will have a positive impact not only on cost saving but also on the patients' quality of life.

Disclosure Statement

The authors did not provide a disclosure statement.

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