Interpreting febrile neutropenia rates from randomized, controlled trials for consideration of primary prophylaxis in the real world: a systematic review and meta-analysis

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Background: Guidelines recommend primary prophylaxis (PP) with granulocyte-colony-stimulating factors (G-CSF) for patients above a febrile neutropenia (FN) risk threshold of 20%. Practitioners often use FN rates of regimens based on data from randomized, controlled trials (RCTs), which are often comprised of highly selected patients. Patients in the community setting may be at higher risk of FN.

Materials and methods: A systematic literature search was conducted for full-length articles reporting FN rates for breast cancer-related chemotherapies between January 1996 and February 2014. A regimen was included if there was at least one RCT and one observational study. Meta-regression was used to model the odds of FN.

Received 14 August 2015; revised 13 December 2015; accepted 15 December 2015

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study. This meant that a 13% (95% CI 8.7% to 17.9%) FN rate in RCT would translate into 20% FN rate in observational cohorts. The univariable odds ratio (OR) for FN in the observational study compared with RCT cohorts was 1.58 [95% confidence interval (CI) 1.09–2.28; P = 0.017]. The FN rates remained significantly higher in the observational study compared with RCT cohorts (OR = 1.74; 95% CI 1.15–2.62; P = 0.012) after adjusting for age, chemotherapy intent, and regimen; this meant that a 13% (95% CI 8.7% to 17.9%) FN rate in RCT would translate into 20% FN rate in observational study.

**Conclusions:** FN rates in the observational studies are significantly higher than suggested by RCTs. Guidelines should clarify how FN rates from RCTs should be applied in clinical practice. Large population-based studies are needed to confirm FN rates in the real world.

**Key words:** febrile neutropenia, granulocyte-colony-stimulating factors, chemotherapy, cancer, risk factor

**introduction**

Neutropenic complications are a major cause of morbidity in patients treated with myelosuppressive chemotherapy regimens. Febrile neutropenia (FN) is a key driver of chemotherapy dose delays and/or reductions and predisposes patients to infections, which may increase the risk of early mortality [1]. Treatment of FN may involve hospitalization and antibiotic treatments, resulting in increased costs and deleterious effects on quality of life [2]. Granulocyte-colony-stimulating factors (G-CSFs) can be used to manage FN, and also as an adjunct to deliver dose-dense myelosuppressive regimens [3]. G-CSFs have shown effectiveness in reducing the incidence of FN by decreasing the severity and duration of neutropenia [4–8]. Current clinical guidelines recommend primary prophylaxis (PP) with G-CSF when the overall risk of developing FN is 20% or higher [9–11]. Risk factors include the type of the chemotherapy regimen and individual patient-related factors, such as age, performance status, and comorbidities [9–12].

When considering the role of PP with G-CSF, practitioners often use FN rates of regimens based on data from randomized, controlled trials (RCTs) to see if they are above the 20% threshold as recommended by most guidelines for the use of PP with G-CSF in the adjuvant or curative setting [9–11]. However, RCTs are often comprised of highly selected patients. RCTs have stringent patient eligibility criteria, resulting in a study sample that is usually younger, healthier, and of higher social status than those to which the treatment of interest is to be applied [13]. Patients in RCTs are also closely monitored and usually have access to higher quality supportive care, allowing them to receive higher doses of chemotherapy, often for longer periods of time [14, 15]. Under these conditions, any toxicities and adverse events that do arise are much more manageable.

Patients treated in the community setting have been reported to have higher FN rates than suggested by data from RCTs. For example, the pivotal PACS 01 trial comparing the survival outcomes and safety profiles of FEC-100 and FEC-Docetaxel (Doc) reported an FN rate of 11.2% in the FEC-Doc arm, which did not meet the 20% risk threshold [16]. However, a meta-analysis showed that patients treated with adjuvant FEC-Doc without PP with G-CSF outside of the clinical trial setting had a FN rate of 30.6% [17]. The higher FN rates observed in clinical practice may be due to patient-related factors [9, 10]. These factors make it challenging to apply FN rates directly from RCT to guide PP with G-CSF in the real world. The magnitude of difference between reported FN rates in RCTs and observational studies in other chemotherapy regimens or tumor sites has not yet been established. Therefore, the purpose of this systematic review and meta-analysis is to compare the rates of FN as reported in RCTs to those documented in observational cohort studies in breast cancer patients.

**methods**

**eligibility criteria and study selection**

A systematic literature search was conducted in March 2014 through Medline, EMBASE, and CENTRAL databases to identify observational studies and RCTs reporting rates of FN associated with breast chemotherapy regimens (search strategies shown in supplementary Appendix S1, available at Annals of Oncology online). To be eligible, the breast chemotherapy regimen must be specified (i.e. type and dose) and have at least one nonrandomized prospective or retrospective cohort study and one RCT reporting FN rates. Studies using concurrent radiation were excluded. RCTs comparing different types or schedules of G-CSF were also excluded. Additionally, any pilot, dose-finding, feasibility, phase I, or phase II studies were excluded. Results were also limited to full-text articles written in English, published between January 1996 and February 2014.

Two independent reviewers (JT and EL) screened the titles and abstracts identified from the electronic searches for eligibility. The full reports were obtained for studies appearing to meet the inclusion criteria and for those with insufficient data in the title and abstract. Disagreements were resolved by discussion and/or a third reviewer (KC) to reach consensus.

**data abstraction**

Data was extracted by two reviewers (JT and EL) independently from the text directly or calculated indirectly from the available information. Disagreements were resolved through discussion or consultation with a third reviewer (KC) to reach consensus. Study characteristics abstracted included year of data collection and publication, type of study (observational or RCT), design (prospective or retrospective), the number of patients involved, age, disease status (metastatic or nonmetastatic), and chemotherapy treatment intent (palliative, adjuvant, or neoadjuvant).
The chemotherapy regimen, dosage, and number of cycles were recorded. Usage of antibiotic and G-CSF prophylaxis (primary and secondary) and funding sources were also noted. The rates of FN and FN-related hospitalizations were recorded, along with the criteria used to define FN in each study.

outcomes
The primary outcome was the incidence of FN. FN was defined as per study definition. A subanalysis was conducted to determine the grade 3 and 4 FN rate on the subgroup using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 and Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [i.e. absolute neutrophil count (ANC) < 1.0 × 10^9/l and fever >38.5°C].

statistical analysis
Descriptive statistics were used to summarize study or patient characteristics and outcomes. Meta-regression using logistic regression with random effects for regimens and studies was used to model the odds ratio (OR) of FN with 95% confidence intervals (CIs) in observational studies compared with RCTs, adjusting for age, chemotherapy intent, and regimen. All statistical analyses were carried out using SAS statistical package (Version 9.4; Cary, NC). A P value <0.05 was considered statistically significant.

results
study and cohort characteristics
A total of 175 treatment arms from 130 studies were eligible for inclusion in our analysis (Figure 1). The characteristics of the included cohorts are provided in Table 1. There were 65 observational cohorts (17 prospective and 48 retrospective) and 110 RCT cohorts. In total, 50,069 patients were assessable for FN (observational cohorts n = 7812; RCT cohorts n = 42,257) and 6034 patients were assessable for FN-related hospitalizations (observational cohorts n = 3760; RCT cohorts n = 2274). The median number of patients per cohort was 62 in the observational cohorts and 222 in the RCT cohorts. The mean age of patients was 53.7 ± 6.08 (range: 43–73) years in the observational cohorts and 52.1 ± 3.78 (range: 45–69) years in the RCT cohorts. There were 54 (30.9%) metastatic cohorts, 108 (61.7%) nonmetastatic (adjuvant and/or neoadjuvant) cohorts, and 12 (6.86%) mixed cohorts. Taxane-based regimens were given in 69.2% (45/65) observational cohorts and 59.1% (65/110) of RCT cohorts. Overall, 29 chemotherapy regimens were identified (Table 2). The most common regimens studied were Doc100 (docetaxel 100 mg/m²), TAC (docetaxel, doxorubicin, and
The incidence of FN

The unadjusted overall FN rate was 11.9% (930/7812 patients) in the observational cohorts and 7.9% (3334/42 257 patients) in the RCT cohorts. (Using a random-effects model, the FN rate was 9.4% (95% CI 7.7% to 11.1%; P < 0.001) in the observational cohorts (supplementary Figure S1, available at Annals of Oncology online) and 7.2% (95% CI 6.4% to 8.0%; P < 0.001) in the RCT cohorts (supplementary Figure S2, available at Annals of Oncology online). The univariate fixed-effects OR for FN in the observational cohorts compared with RCT cohorts is 1.58 (95% CI 1.09–2.28; P = 0.017). The FN rates remained significantly higher in the observational cohorts compared with RCT cohorts (OR = 1.74; 95% CI 1.15–2.62; P = 0.012) in the multivariable meta-regression model adjusted for age, chemotherapy intent, and chemotherapy regimen, and accounted for random effects of study and chemotherapy regimen; this meant that a 13% FN (95% CI 8.7% to 17.9%) rate in RCT would translate into a 20% FN rate in an observational study. The influence of G-CSF and antibiotic usage was evaluated in sensitivity analyses (see supplementary Appendix S2, available at Annals of Oncology online). The results of the sensitivity analyses were consistent with the main findings.

The unadjusted FN rates were higher in taxane regimens than nontaxane regimens in both the observational (16.5% versus 6.4%) and RCT (10.0% versus 4.7%) cohorts (Figure 2). Using a random-effects model, the FN rate in the taxane regimens was 12.8% in the observational cohorts (supplementary Figure S3, available at Annals of Oncology online) and 9.7% in the RCT cohorts (supplementary Figure S4, available at Annals of Oncology online), whereas the rates for the nontaxane regimens were 4.6% in the observational cohorts (supplementary Figure S5, available at Annals of Oncology online) and 4.1% in the RCT cohorts (supplementary Figure S6, available at Annals of Oncology online). Figure 3 presents a summary of the forest plots showing the overall OR for FN in observational and RCT cohorts receiving taxane and nontaxane regimens. The OR for FN was 2.68 (95% CI 2.43–2.95; P < 0.001) from the univariate fixed-effects model and 1.49 (95% CI 0.86–2.78; P = 0.10) from the multivariate mixed effects model in taxane compared with nontaxane regimens and did not reach statistical significance.

The observational cohorts had FN rates that were higher in 66% (19/29) of the chemotherapy regimens (Figure 4). The sub-analysis conducted on the subgroup using the FN definition ANC < 1.0 × 10^9/l and fever >38.5°C showed that the overall grade 3 and 4 FN rate was 7.9% (164/2075) in the observational cohorts and 6.3% (300/4731) in the RCT cohorts. Finally, the FN rates were higher in the palliative intent group compared with the curative intent group in both the observational (14.5% versus 10.7%) and RCT (8.5% versus 8.0%) cohorts.

discussion

Our analyses revealed significantly higher overall FN rates in the nonrandomized cohorts compared with RCT cohorts of breast cancer patients. Observational studies may have greater generalizability to patients in the real world, since certain high-risk populations (e.g. the elderly, those with comorbidities) are often underrepresented in clinical trials, despite accounting for a large proportion of cancer patients treated in practice. Clinical guidelines recommend PP with G-CSFs for chemotherapy regimens associated with an FN risk >20% or with 10%–20% for high-risk patients [9]. Our study showed that regimens with a 13% FN rate in RCTs had a corresponding 20% FN rate in observational studies. Therefore, chemotherapy regimens that did not reach the 20% FN risk threshold based on RCT data may still benefit from PP with G-CSFs in the real world. However, further research is required to determine whether this higher risk group in the real world will receive the same benefits from G-CSF prophylaxis as study populations. In any case, extrapolating data...
from RCTs to the real world warrants careful consideration of individual patient risk factors.

Prediction models can be used as an aid in quantifying individual patient risk factors for FN, which can help mitigate the reported heterogeneity in physicians’ FN risk assessments and G-CSF utilization [147]. Several models have been developed [107, 148–153], but most have been based on retrospective data and only a few have been independently validated [154]. These prediction models may consider the impacts of age, performance status, comorbidities, disease type and stage, as well as chemotherapy regimen and baseline laboratory assessments (e.g. white blood cell counts and albumin) [3]. The validated risk model for chemotherapy-induced neutropenic complications by Lyman et al. examined predictors of developing severe neutropenia and/or FN [155]. The prediction model for FN in the first cycle of chemotherapy by Hosmer et al. was developed using SEER-Medicare data from elderly cancer patients [156]. Finally, the

**Table 2. Chemotherapy regimens of included cohorts**

<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>Observational design</th>
<th>RCT design</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohorts (n = 65)</td>
<td>Patients (n = 7812)</td>
</tr>
<tr>
<td>AC (dox 60, cyc 600 q3w) [18–29]</td>
<td>2</td>
<td>193</td>
</tr>
<tr>
<td>AC500 (dox 40, cyc 500 q3w) [30, 31]</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>AC-Doc (dox 60, cyc 600 q3w → doc 100 q3w) [32–38]</td>
<td>1</td>
<td>56</td>
</tr>
<tr>
<td>AC-Pac175 (dox 60, cyc 600 q3w → pac 175 q3w) [35, 39–44]</td>
<td>4</td>
<td>144</td>
</tr>
<tr>
<td>AC-Pac175dd (dox 60, cyc 600 q2w → pac 175 q2w) [33, 40, 45, 46]</td>
<td>3</td>
<td>211</td>
</tr>
<tr>
<td>AC-Pac80 (dox 60, cyc 600 q3w → pac 80 qw) [35, 42]</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>AT (dox 50, doc 75 q3w) [21, 24, 47–51]</td>
<td>2</td>
<td>172</td>
</tr>
<tr>
<td>BevPac (bev 10 mg/kg D1/15, pac 90 D1/8/15 q4w) [52–54]</td>
<td>1</td>
<td>62</td>
</tr>
<tr>
<td>C100MF (cyc 100 p.o. D1–14, met 40 D1–8, FU 600 D1–8 q4w) [28, 55–58]</td>
<td>1</td>
<td>406</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; bev, bevacizumab; b.i.d., bi-daily; cap, capecitabine; carb, carboplatin; cyc, cyclophosphamide; dd, dose-dense; doc, docetaxel; D#, day(s); dox, doxorubicin; epi, epirubicin; FU, 5-fluorouracil; i.v., intravenous; met, methotrexate; pac, paclitaxel; p.o., per os; q(2–4)w, every (2–4) week(s); tras, trastuzumab; vin, vinorelbine.

from RCTs to the real world warrants careful consideration of individual patient risk factors.

Prediction models can be used as an aid in quantifying individual patient risk factors for FN, which can help mitigate the reported heterogeneity in physicians’ FN risk assessments and G-CSF utilization [147]. Several models have been developed [107, 148–153], but most have been based on retrospective data and only a few have been independently validated [154]. These prediction models may consider the impacts of age, performance status, comorbidities, disease type and stage, as well as chemotherapy regimen and baseline laboratory assessments (e.g. white blood cell counts and albumin) [3]. The validated risk model for chemotherapy-induced neutropenic complications by Lyman et al. examined predictors of developing severe neutropenia and/or FN [155]. The prediction model for FN in the first cycle of chemotherapy by Hosmer et al. was developed using SEER-Medicare data from elderly cancer patients [156]. Finally, the

**Figure 2. Incidence of FN by taxane versus nontaxane regimens.** The incidence of FN (all definitions) for taxane and nontaxane chemotherapy regimens.
Multinational Association of Supportive Cancer Care (MASCC) risk index scoring system can be used to identify patients at low risk for FN complications but not for predicting patients who will develop FN [157]. In comparison, our current review of FN rates for chemotherapy regimens in RCTs and observational studies focused on translating FN risk from RCT data to the real world setting.

Our meta-analysis showed that the FN rates without PP with G-CSF in the observational cohorts was 20.2% (240/1186) and 26.7% (76/285) in the FEC-Doc and TC regimens, respectively. These results are generally congruent with the existing literature [17]. The high FN rates for these taxane-based regimens found in our analysis showed that patients who received TC and FEC-Doc regimens without primary G-CSF prophylaxis met the 20% threshold, in contrast to the lower FN rates for these regimens reported in pivotal RCTs [16, 158].

In our study, we noticed that the reported FN-related hospitalizations in RCTs were relatively infrequent compared with observational studies. A similar finding was described in a systematic review conducted by Prince et al. [159], which compared rates of hospitalizations in observational studies and RCTs among metastatic nonsmall-cell lung cancer patients (n = 11 418) receiving chemotherapy. The review found the overall hospitalization rates to be significantly higher in the observational cohorts (57.5% versus 14.8%, OR = 7.7, 95% CI 6.9–8.5, P < 0.0001), but these results are based on a small sample size (five RCTs and four observational studies) due to paucity of reported hospitalization rates. The studies included in our analysis did not report FN rates.

**Figure 3.** Summary forest plots of FN rates for observational and RCT cohorts receiving taxane and nontaxane regimens. The summary forest plots show the estimated overall ORs for FN and the 95% confidence intervals in observational (Obs.) and RCT cohorts receiving taxane and nontaxane chemotherapy regimens adjusted for random effects. Statistical heterogeneity is indicated by $I^2$ values. See supplementary Figures S1–S6, available at *Annals of Oncology* online, for details.

**Figure 4.** Incidence of FN (all definitions). The incidence of FN (all definitions) for observational and RCT cohorts for all chemotherapy regimens.
stratified according to MASCC scores. Considering the large proportion of patients hospitalized for FN and the high costs associated with inpatient management, it may be beneficial to identify low-risk patients for outpatient management using a validated risk index, such as MASCC [160]. A previous systematic review and meta-analysis of 14 studies by Teuffel et al. [161] showed that outpatient treatment of FN is safe and effective alternative for inpatient management. Further research is needed to determine when costly G-CSF prophylaxis is justified in low-risk patients and who may be treated by cheaper oral antibiotics in an outpatient setting. Future studies should consider reporting FN rates stratified by risk as well as FN-related hospitalization rates in the real world for economic analyses, since they account for a large proportion of costs [162].

Cancer patients receiving curative treatment may theoretically receive survival benefits from G-CSF prophylaxis by enabling administration of dose-dense regimens and minimizing dose intensity reductions [3, 5, 163, 164]. However, published meta-analyses [4, 5, 165, 166] have shown conflicting results on the effects of G-CSFs on survival outcomes. ASCO does not recommend G-CSF prophylaxis for patients with metastatic disease being treated with noncurative intent [10, 167]. Instead dose reductions and/or delays are recommended for palliative cancer treatments [10, 167]. This recommendation affects 30.9% of the cohorts included in our analysis. Owing to the heterogeneity and unclear reporting of G-CSF usage, we could not clearly determine the effect of G-CSF in this population. A recent retrospective review supports this recommendation as G-CSF support did not have an impact on survival compared with dose reductions and/or delays in metastatic colorectal cancer patients experiencing neutropenia [168].

There are several limitations in our study. First, we were unable to analyze the effects of G-CSF utilization due to lack of disclosure and unclear reporting of specific primary and secondary G-CSF usage. Second, we did not analyze patient-related factors, such as comorbidities, which may increase FN risk. Finally, some observational cohorts had a relatively small number of patients and only several of them were conducted prospectively. The included observational studies may also have publication bias towards higher rates of FN. Large population-based studies are needed to confirm the incidence of FN in the real world setting. Krzyzanowska et al. [169] showed that administrative data can be used with reasonable accuracy as an alternative to chart abstraction to identify acute care visits, including those related to FN, among breast cancer patients. Thus, future population-based studies can potentially use administrative data to confirm FN rates seen in the real world, but further research is needed as the study is limited to a single jurisdiction.

In conclusion, FN rates were higher in observational studies compared with RCTs in breast cancer patients. Chemotherapy regimens with <20% FN risk according to RCTs may potentially reach the threshold required for PP with G-CSF in the real world. Individual patient risk factors should be carefully assessed in the community setting to determine overall FN risk. Guidelines should clarify how FN rates from RCTs should be applied in clinical practice since there seems to be a discrepancy between RCT and real world data. Large population-based studies are needed to confirm FN rates of different regimens in the real world to ensure optimal utilization of G-CSF.

**disclosure**

The authors have declared no conflicts of interest.

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