



Chemotherapy-induced (febrile) neutropenia prophylaxis with biosimilar filgrastim in elderly versus non-elderly cancer patients: Patterns, outcomes, and determinants (MONITOR-GCSF study)



Matti Aapro^{a,*}, Carsten Bokemeyer^b, Heinz Ludwig^c, Pere Gascón^d, Mario Boccadoro^e, Kris Denhaerynck^{f,g}, Michael Gorray^h, Andriy Krendyukov^h, Karen MacDonald^f, Ivo Abraham^{f,i}

^a Institut Multidisciplinaire d'Oncologie, Clinique de Genolier, Genolier, Switzerland

^b Universitätsklinikum Hamburg Eppendorf, Hamburg, Germany

^c Wilhelminen Cancer Research Institute, Wilhelminenspital, Wien, Austria

^d Department of Hematology-Oncology, Hospital Clínic de Barcelona, University of Barcelona, Barcelona, Spain

^e Dipartimento di Oncologia e Ematologia, Azienda Ospedaliero Universitaria S. Giovanni Battista di Torino, Torino, Italy

^f Matrix45, Tucson, AZ, USA

^g Universitaet Basel, Basel, Switzerland

^h Hexal AG, Holzkirchen, Germany

ⁱ Center for Health Outcomes and Pharmacoeconomic Research, University of Arizona, Tucson, AZ, USA

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ABSTRACT

Background: Myelotoxic chemotherapy is associated with chemotherapy-induced (febrile) neutropenia (CIN/FN). The MONITOR-GCSF study evaluated biosimilar filgrastim (Zarzio®) prophylaxis patterns, associated outcomes, and determinants. We performed stratified analyses comparing elderly and non-elderly patients.

Methods: Comparative (elderly/non-elderly) analysis of demographics and clinical status, prophylaxis, associated CIN/FN outcomes (CIN grade 4 [CIN4], FN, CIN/FN-related hospitalizations and chemodisturbances, composite), and, per hierarchical modeling, determinants thereof evaluated at the patient- and cycle-level.

Results: There were no significant differences between both cohorts in prophylaxis initiation/duration and associated outcomes, but proportionately more elderly patients were correctly-prophylaxed and fewer over-prophylaxed. Common determinants of poor CIN/FN outcomes included concomitant antibiotic prophylaxis, impaired performance status, and any grade CIN in a previous cycle, whereas common determinants of good outcomes included over-prophylaxis and prophylaxis initiation within 24–72 h. In the elderly, female gender, liver/renal/cardiovascular disease, secondary prophylaxis, and under-prophylaxis were associated with poorer outcomes. In the non-elderly, CIN4 at baseline or in a prior cycle was associated with poorer CIN/FN outcomes, and higher biosimilar filgrastim dose and, perhaps counter-intuitively, under-prophylaxis with better outcomes. **Conclusion:** Adequate GCSF support is essential for all patients, but especially for elderly patients with serious chronic disease, certainly, if concomitant antibiotic prophylaxis is indicated and if a CIN4 episode occurred in a prior cycle. The potential impact of impaired performance status, especially ECOG ≥ 2 at chemotherapy start or a worsening to such during chemotherapy; under-prophylaxis, including inadequate secondary prophylaxis, should be considered in elderly patients. Timely GCSF initiation and over-prophylaxis is associated with lower rates of adverse CIN/FN events in elderly and non-elderly patients, and should be further evaluated in prospective randomized trials.

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1. Introduction

Guidelines [1–5] and reviews [e.g. [6–10]], emphasize that elderly patients with cancer are at markedly higher risk of chemotherapy-induced (febrile) neutropenia (CIN; FN) than non-elderly patients.

This has significant implications for clinical decision-making regarding prophylaxis with granulocyte colony-stimulating factors (GCSF), certainly for patients treated with myelotoxic chemotherapy regimens with an FN risk between 10% and 20%. Whereas GCSF support is not generally indicated for regimens in this myelotoxicity range, it is strongly recommended if patients are elderly.

There is limited real-world evidence about prophylaxis patterns, outcomes, and determinants of these outcomes in elderly patients

* Corresponding author.

E-mail address: maapro@genolier.net (M. Aapro).

with cancer – and whether and how these may differ from younger patients with cancer. In the European MONITOR-GCSF study of 1447 patients with cancer receiving CIN/FN prophylaxis with biosimilar filgrastim (EP2006, Zarzio®/Zarxio®, Hexal AG/ Sandoz International GmbH) [11,12], we found that 17.4% of patients were under- and 26.0% were over-prophylacted relative to amended EORTC guidelines [13]. We modeled the determinants of observed CIN/FN episodes and CIN/FN-related hospitalizations and chemotherapy disturbances, both at the patient-level ('ever' experienced during the period of chemotherapy) and the cycle-level (during a given chemotherapy cycle). We noticed an interaction between risk factors, including age ≥ 65 , and prophylaxis-intensity [14]. These analyses were not stratified by age, only by the presence of risk factors.

The MONITOR-GCSF study included 598 patients (41.3%) age ≥ 65 . We report here on analyses comparing elderly versus non-elderly patients in terms of prophylaxis patterns and five outcomes: CIN grade 4 and FN episodes, CIN/FN-related hospitalizations and chemotherapy disturbances, and a composite reflecting the occurrence of any of these outcomes. We also report on predictive modeling for elderly and non-elderly patients of determinants of these outcomes. In line with our recent full-sample modeling [14], this included both static models using patients and dynamic models using cycles as the unit of analysis. The patient-level models focus on outcomes 'ever' experienced by a patient during the chemotherapy period and identify determinants of CIN/FN risk to be assessed at the start of chemotherapy. The cycle-level models center on outcomes during a particular chemotherapy cycle and from one cycle to the next, evaluate determinants as patients progress through their chemotherapy, and enable assessment of CIN/FN risk at each cycle.

2. Methods

The methodology of MONITOR-GCSF [11–14]. Methodology elements relevant to this present analysis are summarized below.

2.1. Design

MONITOR-GCSF was a prospective real-world observational study of patients with cancer receiving myelosuppressive chemotherapy whose treating physicians prescribed CIN/FN prophylaxis with biosimilar filgrastim, conducted in 140 centers in 12 European countries. Eligible were adults (age ≥ 18) with stage 3 or 4 breast, ovarian, bladder, or lung cancer; metastatic prostate cancer; stage 3 or 4 diffuse large B-cell lymphoma or multiple myeloma. Patients were observed for up to six cycles of chemotherapy.

We adopted the classical age 65 as cut-off as the MONITOR-GCSF study was framed within the EORTC GCSF guidelines [4].

2.2. Chemotherapy Regimens

Site investigators were asked to record the chemotherapy regimen for each patient including agents, frequency, duration, and whether the standard dose for the specified regimen was used. If the standard dose was not used, investigators were requested to indicate the dosing. These data were used to determine baseline FN risk.

2.3. Outcomes

These included at both the patient- and cycle level: occurrence of a CIN grade 4 (CIN4) or FN episode; CIN/FN-related hospitalization or chemotherapy disturbance; and a composite index of any of these outcomes occurring.

2.4. Special Indices and Variables

Prophylaxis intensity classified patients as *under-prophylacted*, *correctly-prophylacted*, or *over-prophylacted* relative to the amended EORTC guidelines, as shown in Figs. 1 and 2.

The GCSF *initiation score* (GIS) (range 0–1) concerns the day of biosimilar filgrastim initiation relative to the last day of chemotherapy and the recommended time window of 24–72 h. A GIS of 1 was assigned in each cycle in which biosimilar filgrastim was started in this time window, except that multiple myeloma patients could be started after 72 h. A score of 0 was given if initiated within 24 h after chemotherapy (<24 h) or on day 10 or later. Partial credit of 0.75 and 0.50 was given if initiated on days 4–6 or on days 7–9, respectively.

Knowledge about risk factors was a 10-item questionnaire measuring physicians' knowledge about FN risk factors (range 0–10).

Advanced disease was defined as Stage 4 (Stage 3 if multiple myeloma) disease and prior chemotherapy in the metastatic setting.

2.5. Variables Included in Modeling

Patient data at enrollment: age; gender; tumor type; history of CIN grade 4 (CIN4), FN, repeated infections, and anemia; performance status (ECOG); advanced disease; antibiotic prophylaxis; hemoglobin; liver, cardiovascular, or renal disease; number of prior lines of chemotherapy; radiotherapy; prophylaxis type, intensity, biosimilar filgrastim dose, duration; GIS; and PRS. Since prophylaxis intensity was derived from the guideline algorithm and based on chemotherapy-associated FN risk categories (<10%, 10–20%, $\geq 20\%$), FN risk group was not included as a predictor in the modeling.

Patient data at each cycle: hemoglobin; prophylactic antibiotic therapy; ECOG; weight loss >5% in one month; CIN any grade (CIN1/4) in previous cycle; infection in previous cycle; biosimilar filgrastim dose; biosimilar filgrastim duration; PRS; and GIS.

Aggregate and 'ever during study' patient data: mean GIS; mean biosimilar filgrastim duration; 'ever' ECOG ≥ 2 ; 'ever' CIN4; 'ever' FN; 'ever' CIN/FN-related hospitalization; 'ever' CIN/FN-related chemotherapy disturbance; 'ever' positive CIN/FN composite score.

Center data: type (academic, academic-affiliated, non-academic); case mix (cancer patients; newly diagnosed cancer patients; chemotherapy-treated patients; chemotherapy-treated patients with FN); FN prevention policy and/or protocol (sum with range 0–2); number of guidelines used (EORTC, ESMO, ASCO, NCCN, and/or local; sum, range 0–5).

Physician data: age; gender; attendance at educational event on FN prevention in past year; knowledge about FN risk factors (range 0–10).

2.6. Specialized Statistical Issues

As cycle data were 'nested' under patients and patients under centers, we used generalized estimating equations (GEE) to adjust for this statistical dependence [15]. Chemotherapy disturbances were estimated for the cycle after (lag = 1) the CIN/FN event occurred. Logistic regression modeling was used to identify patient, center, and physician variables predictive of the outcomes in both the patient-level and cycle-level analyses. The direction and strength of associations between predictors and outcomes was measured by adjusted odds ratios (OR). The predictive performance of models was tested by means of the c-statistic of concordance with bootstrapped 95% CIs.

3. Results

3.1. Patient Groups

There were 598 (41.3%) elderly and 849 (58.7%) non-elderly evaluable patients. The non-elderly cohort had a significantly higher

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