Febrile Neutropenia (FN) Risk Assessment And Granulocyte Colony-stimulating Factor (G-CSF) Guideline Adherence in Patients with Breast Cancer – Results from a German Prospective Multicentre Observational Study (PROTECT)

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INTRODUCTION

- Febrile neutropenia (FN) is one of the most common dose-limiting side effects of chemotherapy.[1,2]
- The occurrence of FN after chemotherapy may result not only in the development of infection and life-threatening sepsis, but may also result in chemotherapy dose reductions and delays.[3,4]
- Chemotherapy dose reductions and delays can lead to reductions in the planned chemotherapy dose intensity and reduced patient survival.[3,4]
- International guidelines recommend the use of granulocyte-colony stimulating factor (G-CSF) as primary prophylaxis in patients at high (≥ 20%) overall risk for FN.
  - Overall FN risk is assessed from the combination of chemotherapy risk and patient-related risk factors.
  - G-CSF primary prophylaxis is recommended in all patients receiving a chemotherapy regimen associated with a high risk of FN.
  - G-CSF primary prophylaxis may also be recommended in patients receiving a chemotherapy regimen associated with a moderate (10-20%) risk of FN and who have one or more patient-related risk factors.[1,2]
- Pegfilgrastim is indicated to reduce the duration of neutropenia and the incidence of FN in cancer patients treated with cytotoxic chemotherapy.[5]

OBJECTIVES

- Primary objective
  - To describe the proportion of patients with an investigator-assessed overall risk of FN > 20% or 10-20% (with risk factors) receiving pegfilgrastim primary prophylaxis (PP) or pegfilgrastim secondary prophylaxis (SP).
- Secondary objectives
  - To assess the proportion on patients developing FN and to assess the proportion of patients experiencing chemotherapy dose delays/reductions.
  - To describe the occurrence of patient risk factors in patients in whom FN occurred.
- Data from the breast cancer patients only are reported in this analysis.

METHODS

Study Design

- PROTECT is a multicenter, prospective, non-interventional observational study conducted in Germany.
- Patients were enrolled consecutively at centres that had been selected based on their experience and geographical spread. This is an interim analysis of patients who were enrolled from November 2007 to September 2010; the planned total number of patients is 2167 across all tumour types.
- Planned prophylaxis with pegfilgrastim (PP or SP) was recorded by the investigator. Actual prophylaxis was determined programmatically: PP was defined as pegfilgrastim within 24 hours of completing chemotherapy in the first cycle; SP was defined as pegfilgrastim within 24 hours of completing chemotherapy in the second or later cycle; all other use was defined as therapeutic use. Continuous prophylaxis (ie, in each cycle after the first use) was not required to meet the definition of PP or SP.

Key Eligibility Criteria

- Diagnosis of solid tumour or lymphoma.
- Physician-assessed overall FN risk ≥ 10% (chemotherapy risk plus individual risk factors per EORTC guidelines).
- Planned PP or SP with pegfilgrastim. Planned pegfilgrastim was to be administered according to the SPC; administration > 3 days after chemotherapy completion was classified as therapeutic use.

RESULTS

- In total 1448 eligible patients were enrolled in the study (including patients with breast, ovarian, lung, prostate, gastric cancer or malignant lymphoma), of whom 69% were breast cancer patients and are the focus of this analysis.

Table 1. Demographics and Characteristics of Breast Cancer Patients in the PROTECT Study

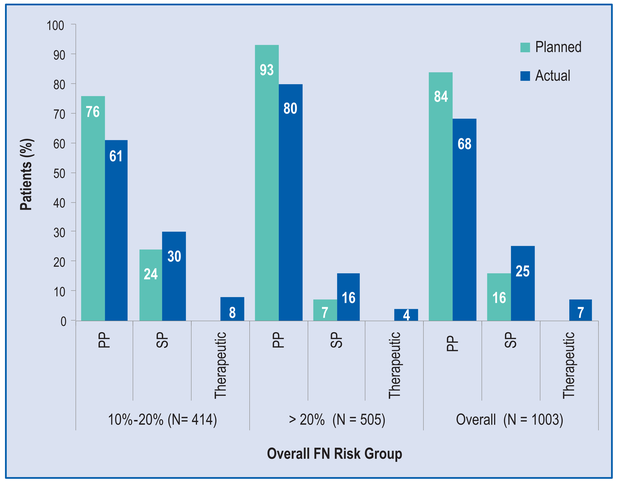
	All Patients N = 1003	Patients who received PP N = 680
Age, median (range)	55 years (22 – 86 years)	54 years (22 – 80)
Female, n (%)	996 (99%)	676 (99%)
Karnofsky index, n (%)		
100% (not restricted)	570 (57%)	417 (61%)
90%-80% (slightly limited)	402 (40%)	243 (36%)
80%-30% (significantly reduced)	31 (3%)	20 (3%)
Comorbidities – any, n (%)	590 (59%)	408 (60%)
Heart disease	127 (13%)	73 (11%)
Allergy	50 (5%)	33 (5%)
Pulmonary disease	22 (2%)	12 (2%)
Kidney disease	11 (1%)	7 (1%)
Neurological disease	23 (2%)	12 (2%)
Liver disease	15 (1%)	8 (1%)
Other	274 (27%)	182 (27%)
Prior treatment, n (%)		
Surgery	701 (70%)	479 (70%)
Radiotherapy	58 (6%)	30 (4%)
Chemotherapy	92 (9%)	45 (7%)
Treatment intent, n (%)		
Curative	808 (81%)	560 (82%)
Palliative	82 (8%)	49 (7%)
Missing	113 (11%)	71 (10%)
Metastatic stage, n (%)		
M0	796 (79%)	554 (81%)
M1	70 (7%)	40 (6%)
MX	137 (14%)	86 (13%)

Table 2. Investigator-assessed Overall FN Risk

	N = 1003
< 10%	84 (8%)
10%-20%	414 (41%)
> 20%	505 (50%)

- Despite eligibility criteria, 84 (8%) patients were assessed by investigators as < 10% risk; reasons for inclusion of low-risk patients were not documented.
- All patients in the study had at least 1 patient-related risk factor for FN.
- Measured baseline patient risk factors were similar between the total population and those who received PP with pegfilgrastim. (Table 1). Compared with PP patients, those who received SP with pegfilgrastim tended to be older (median age 56 years [range 26-86 years]), have a worse performance status (Karnofsky index 100% in 48% of patients), and less likely to receive chemotherapy with curative intent (76% of patients), but comorbidities and prior treatment were similar.

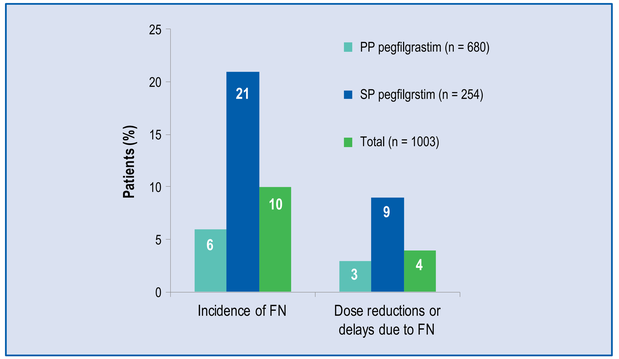
Figure 1. Planned and Actual Administration of Pegfilgrastim



Note: Data from 84 patients assessed at < 10% FN risk not presented.

- Differences between planned and actual prophylaxis use were observed (Fig 1).
- Not all patients at high overall risk of FN were supported with G-CSF PP per guideline recommendations.

Figure 2: Incidence of FN, and Dose Reductions or Dose Delays Due to FN



- 100/1003 (10%) patients overall experienced FN (Fig. 2) and 133 FN events occurred in total
  - 43/680 (6%) patients in the PP group experienced FN
  - 53/254 (21%) patients in the SP group experienced FN
    - FN occurred during the first cycle in 36/53 (68%) patients who received SP and experienced FN
- In total 6081 cycles of chemotherapy were administered (median 6 cycles per patient, range: 1-24 cycles).
- Chemotherapy delays or dose reductions due to FN occurred in 45 (4%) of patients overall; 22/680 (3%) in the PP group and 22/254 (9%) in the SP group (Fig. 2).

Administration of anti-infectives

- Oral anti-infectives were used in 198 patients (20%) and intravenous anti-infectives were used in 42 patients (4%).

Hospitalizations and deaths

- 71 patients (7%) were hospitalized due to FN or infection, for a median duration of 7 days (range: 2-37 days).
- 16 patients died (2%), predominantly due to the tumour or underlying disease.
- There were no deaths due to FN.

CONCLUSIONS

- Pegfilgrastim was used in patients at high risk of FN and in patients with baseline risk factors for FN; however, not all patients at high risk received primary prophylaxis as recommended by G-CSF guidelines.
- Reasons for differences between planned and actual prophylaxis warrants further assessment. The programmatic definitions of actual prophylaxis may account for some, but not all, of the differences between planned and actual prophylaxis.
- Most FN events occurred in cycle 1 in the SP group suggesting that better targeting of PP is required.
- Comparisons of outcomes between the prophylaxis groups should be interpreted with caution due to the potential for confounding differences in baseline characteristics between these groups.
- FN incidence remained low with pegfilgrastim PP among breast cancer patients in German clinical practice.

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DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

- The study was sponsored by Amgen GmbH, Munich. The authors acknowledge medical writing support by James O'Kelly, an employee of Amgen Ltd.