original article

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Pegfilgrastim ± ciprofloxacin for primary prophylaxis with TAC (docetaxel/doxorubicin/cyclophosphamide) chemotherapy for breast cancer. Results from the GEPARTRIO study

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Background: TAC (docetaxel/doxorubicin/cyclophosphamide) is associated with high incidences of grade 4 neutropenia and febrile neutropenia (FN). This analysis compared the efficacies of four regimens for primary prophylaxis of FN and related toxic effects in breast cancer patients receiving neoadjuvant TAC.

Patients and methods: Patients with stage T2–T4 primary breast cancer were scheduled to receive 6–8 cycles of TAC. Primary prophylaxis was: ciprofloxacin 500 mg orally twice daily on days 5–14 (n = 253 patients; 1478 cycles), daily granulocyte colony-stimulating factor (G-CSF) (filgrastim 5 μg/kg/day or lenograstim 150 μg/m^2/day) on days 5–10 (n = 377; 2400 cycles), pegfilgrastim 6 mg on day 2 (n = 305; 1930 cycles), or pegfilgrastim plus ciprofloxacin (n = 321; 1890 cycles).

Results: Pegfilgrastim with/without ciprofloxacin was significantly more effective than daily G-CSF or ciprofloxacin in preventing FN (5% and 7% versus 18% and 22% of patients; all $P < 0.001$), grade 4 neutropenia, and leukopenia. Pegfilgrastim plus ciprofloxacin completely prevented first cycle FN ($P < 0.01$ versus pegfilgrastim alone) and fatal neutropenic events.

Conclusion: Ciprofloxacin alone, or daily G-CSF from day 5–10 (as in common practice), provided suboptimal protection against FN and related toxic effects in patients receiving TAC. Pegfilgrastim was significantly more effective in this setting, especially if given with ciprofloxacin.

Key words: breast cancer, ciprofloxacin, docetaxel, febrile neutropenia, granulocyte colony-stimulating factor, primary prophylaxis

introduction

TAC (docetaxel/doxorubicin/cyclophosphamide) has become an established adjuvant treatment of early node-positive breast cancer [1, 2]. The GEPARTRIO study was the first investigation of TAC in the neoadjuvant phase 3 setting in patients with large (T2–T4) primary breast cancer. TAC showed high efficacy in the integrated pilot phase of the study, with a partial response in 46%, a complete response in 42% and no change in 8% [3].

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TAC is associated with marked hematologic and nonhematologic toxic effects [2, 4]. The Breast Cancer International Research Group (BCIRG) found that grade 3–4 neutropenia occurred in 66%, and febrile neutropenia (FN) in 25%, of patients receiving TAC adjuvant therapy [2]. Although prophylactic use of granulocyte colony-stimulating factor (G-CSF) reduces the severity and duration of chemotherapy-induced neutropenia, and the consequent risk of FN [5], guidelines in place at the time of starting the GEPARTRIO pilot phase recommended that routine G-CSF prophylaxis be reserved for regimens associated with a ≥40% risk of FN [5]. Thus, primary antibiotic prophylaxis alone was used in the GEPARTRIO pilot phase. The prophylactic regimen was subsequently intensified stepwise by protocol amendment

according to interim safety data, to daily G-CSF (filgrastim or lenograstim), then pegfilgrastim, and finally, to pegfilgrastim plus ciprofloxacin. The present analysis compares the efficacies of these supportive regimens in preventing FN and other TAC-related toxic effects.

patients and methods

patients

Female patients aged ≥18 years with previously untreated, histologically confirmed stage T2–T4 uni- or bilateral primary breast carcinoma (bidimensionally measurable by palpation, with one diameter ≥2 cm) and no evidence of distant metastases were eligible for enrollment in the GEPARTRIO study. Patients were requested to have normal hematopoetic, liver, renal, and cardiac function [3]. The study was conducted in accordance with the Declaration of Helsinki. Ethical review boards of all participating institutions approved the final protocol and amendments. All patients provided written informed consent.

study treatment

neoadjuvant chemotherapy. All patients were scheduled to receive two initial cycles of TAC (doxorubicin 50 mg/m^2 followed by cyclophosphamide 500 mg/m^2 and docetaxel (Taxotere) (Sanofi–Avantis, Germany) 75 mg/m^2, all on day 1, every 3 weeks). Tumor response was determined during the third week of the second cycle. Patients with responding tumors continued with four (pilot phase), or were randomly assigned to four or six (phase 3 part), more cycles of TAC. Nonresponders (tumor reduction <50%) were randomized to either four more cycles of TAC, or four cycles of vinorelbine plus capecitabine (NX, these patients are not included in the analysis). Within 21 days after completing chemotherapy, patients underwent surgery. TAC dose reductions (20%) were planned, if severe hematologic or nonhematologic toxic effects occurred.

supportive treatment. Prophylaxis of FN was consecutively intensified throughout the study by three protocol amendments. In the pilot phase, patients received primary prophylaxis with ciprofloxacin 500 mg orally twice daily on days 5–14; daily G-CSF (filgrastim 5 μg/kg/day or lenograstim 150 μg/m^2/day) was reserved for treatment and secondary prophylaxis of FN and delayed recovery of neutrophil count. As more toxicity data for TAC became available, daily G-CSF (on days 5–10, without ciprofloxacin) was introduced as primary prophylaxis in July 2002 with the start of the phase 3 part of the study. From January 2003, pegfilgrastim primary prophylaxis was given as a single 6 mg fixed dose on day 2 of each cycle. A further protocol amendment in October 2002 stipulated combined primary prophylaxis with pegfilgrastim and ciprofloxacin.

In case of delayed neutrophil recovery [absolute neutrophil count [(ANC) <1.5 × 10^9/l on day 21], daily G-CSF (filgrastim or lenograstim) was given. If recovery to >1.5 × 10^9/l was not observed by day 35, chemotherapy was stopped. In the case of a second episode of prolonged recovery, overall chemotherapy dose was reduced by 20% for subsequent cycles.

Other supportive treatments included dexamethasone and standard antiemetics (mainly serotonin-H_3 antagonists). In the phase 3 part, epoetin beta was given in subsequent cycles if hemoglobin decreased to <10 g/dl.

objectives and end points

Analysis of safety data was prospectively defined in the GEPARTRIO study protocol and it was subsequently decided to conduct a comparison of the respective primary prophylactic regimens when pegfilgrastim was first introduced into the study protocol, for the time point when data from cohorts of similar size would be available. The primary objective of this analysis was to compare the incidence of FN (three oral temperature determinations >38°C during a 24-h period/single elevation >38.5°C and ANC <1.0 × 10^9/l) during TAC treatment of each of the four primary prophylactic regimens. Secondary objectives were to compare the incidence of neutropenia and other hematologic toxic effects, infection, nonhematologic toxic effects, and hospitalization. All toxic effects were graded by severity according to National Cancer Institute Common Toxicity Criteria (version 2) [6].

statistical analysis

The analysis included all patients who had been completely documented in the trial database by November 2005 and received at least one cycle of TAC but were not randomized to NX. *P* values were calculated using the chi-square test. The software used was SPSS version 12 for Windows. A test over all four cohorts was carried out for the incidence per cohort of all end points: FN and grade 4 neutropenia, first cycle FN, other hematologic toxic effects, nonhematologic toxic effects, and hospitalizations. *P* values were considered statistically significant at the 0.05 level. Pairwise comparisons were made between the cohorts and were considered significant at the 0.01 level, to allow for multiple testing.

results

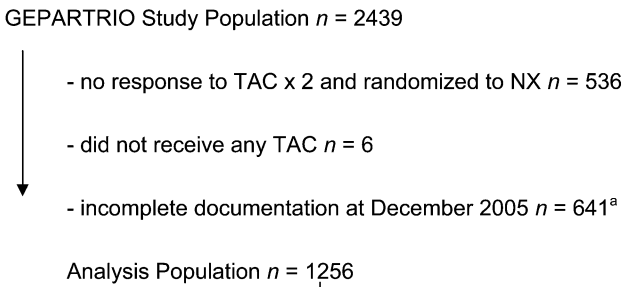
patients

The analysis included 1256 assessable, documented patients enrolled in 89 German sites from 15 April 2001 to 14 June 2005: 253 received ciprofloxacin alone (1478 cycles), 377 received daily G-CSF (2400 cycles from 1 July 2002), 305 received pegfilgrastim (1930 cycles from 24 January 2003), and 321 received pegfilgrastim plus ciprofloxacin (1890 cycles from 27 October 2003) (Figure 1). Exploratory analysis did not reveal any differences between the cohorts with respect to patient characteristics (Table 1).

A total of 1057 patients received all planned six (n = 793) or eight (n = 264) cycles of chemotherapy (Figure 1). TAC dose reductions occurred in 2%–3% of cycles in all four cohorts. Fifteen patients in the first cohort (6%) received G-CSF as primary prophylaxis in their first TAC cycle, and in 2%–10% of patients in the other three cohorts primary growth factor support was omitted during the first cycle (Figure 1). Additionally, some patients (3%) assigned to daily G-CSF did not receive growth factor support in any cycles.

efficacy

FN and severe neutropenia. Both pegfilgrastim plus ciprofloxacin and pegfilgrastim alone were significantly (P < 0.001) more effective than either ciprofloxacin or daily G-CSF in preventing FN (5% and 7% versus 22% and 18% of patients, and 1% and 2% versus 5% and 5% of cycles, respectively) (Table 2; Figure 2). Indeed, primary prophylaxis with daily G-CSF did not significantly reduce FN compared with primary antibiotic prophylaxis. With ciprofloxacin or daily G-CSF alone, FN tended to occur most frequently during the first TAC cycle (~9% of patients in both cohorts), whereas first cycle FN was seen in only 2% of patients receiving pegfilgrastim alone and did not occur in the pegfilgrastim plus ciprofloxacin cohort (Table 2). Indeed, both pegfilgrastim regimens were superior to ciprofloxacin and daily G-CSF



Primary prophylaxis	Ciprofloxacin	Daily G-CSF	Pegfilgrastim	Pegfilgrastim + ciprofloxacin
Patients (*n*)	253	377	305	321
- received all planned cycles	233 (92%)	311 (82%)	252 (83%)	261 (81%)
- stopped early due to:				
- patient's request	8	36	33	30
- adverse event	6	14	10	15
- progression	2	4	6	6
- death	1	2	1	1
- other/unknown	3	10	3	8
Total no. of TAC cycles	1478	2400	1930	1890
Cycles without G-CSF	1028 (70%)[b]	163 (7%)	28 (2%)	25 (1%)
Pts without primary G-CSF in 1st cycle[c]	238 (94%)[b]	36 (10%)	10 (3%)	6 (2%)
Pts without any G-CSF[c]	120 (47%)[b]	12 (3%)	1 (<1%)	0 (0%)

Figure 1. Patient disposition. Superscript 'a' indicates: this analysis was started during the course of the study and full data were not available for the last cohort at the cut-off date. Superscript 'b' indcates: 15 patients received primary prophylaxis with daily granulocyte colony-stimulating factor (G-CSF) in their first cycle (due to protocol violations) and 133 patients received secondary prophylaxis with daily G-CSF in 435 cycles. Superscript 'c' indicates: These categories do not overlap.

($P < 0.001$), and the combination was significantly more effective than pegfilgrastim alone ($P < 0.01$), for preventing first cycle FN.

Pegfilgrastim plus ciprofloxacin and pegfilgrastim were also associated with significantly lower incidences of grade 4 neutropenia than ciprofloxacin or daily G-CSF, both per patient (34% and 37% versus 62% and 58%, respectively; $P < 0.001$ and $P < 0.01$) and per cycle (16% and 15% versus 33% and 27%, respectively; $P < 0.001$). Daily G-CSF was superior to ciprofloxacin with regard to the incidence of grade 4 neutropenia per cycle but not by patient (Table 2; Figure 2).

other hematologic toxic effects. Both pegfilgrastim plus ciprofloxacin and pegfilgrastim alone were significantly superior to ciprofloxacin ($P < 0.001$ and $P < 0.01$) and daily G-CSF ($P < 0.01$) with regard to the incidence of leukopenia. Anemia (hemoglobin <10 g/dl) was less common with pegfilgrastim plus ciprofloxacin than with ciprofloxacin or

Table 1. Patient baseline demographic and medical characteristics

	Ciprofloxacin ($n = 253$)	Daily G-CSF ($n = 377$)	Pegfilgrastim ($n = 305$)	Pegfilgrastim + ciprofloxacin ($n = 321$)
Age (years)				
<40	35 (14%)	65 (17%)	49 (16%)	45 (14%)
40–60	151 (60%)	226 (60%)	201 (66%)	201 (63%)
>60	67 (27%)	82 (22%)	51 (17%)	64 (20%)
>70	4 (2%)	4 (1%)	4 (1%)	11 (3%)
ECOG status				
0	195 (77%)	319 (86%)	264 (87%)	272(86%)
1	58 (23%)	52 (14%)	39 (13%)	46 (14%)
Unknown	0	6	2	3
Clinical T-staging				
1	5 (2%)	3 (1%)	2 (1%)	6 (2%)
2	186 (74%)	279 (74%)	237 (78%)	211 (66%)
3	34 (13%)	74 (20%)	55 (18%)	82 (26%)
4	28 (11%)	21 (6%)	11 (4%)	20 (6%)
Unknown	0	0	0	2
Clinical N-staging				
0	134 (54%)	198 (56%)	160 (56%)	115 (38%)
1	105 (42%)	139 (40%)	112 (39%)	164 (54%)
2	3 (1%)	15 (4%)	10 (4%)	15 (5%)
3	7 (3%)	3 (1%)	2 (1%)	11 (4%)
Unknown	4	22	21	16
Tumor grade				
1	11 (5%)	11 (3%)	13 (5%)	7 (2%)
2	122 (56%)	193 (60%)	143 (56%)	161 (56%)
3	84 (39%)	116 (36%)	98 (39%)	118 (41%)
Unknown	36	57	51	35

G-CSF, granulocyte colony-stimulating factor; ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

Table 2. Incidence of FN and grade 4 neutropenia in patients receiving TAC[a]

	Ciprofloxacin	Daily G-CSF	Pegfilgrastim	Pegfilgrastim + ciprofloxacin	*P* value across cohorts
FN					
Number of patients	55/253 (22%)	67/374 (18%)	22/303 (7%)**††	17/314 (5%)**††	<0.0001
Number of cycles	74/1478 (5%)	111/2303 (5%)	28/1855 (2%)**††	17/1736 (1%)**††	<0.001
First occurrence of FN, number of patients					
Cycle 1	24/248 (10%)	34/360 (9%)	7/293 (2%)**††	0/299 (0%)**††§	<0.001
Cycle 2	6	9	1	5	
Cycle 3	7	7	2	5	
Cycle 4	9	4	3	3	
Cycle 5	5	8	4	4	
Cycle 6	4	2	3	0	
Cycle 7	NA	2	2	0	
Cycle 8	NA	1	0	0	
Grade 4 neutropenia					
Number of patients	154/248 (62%)	214/366 (58%)	108/290 (37%)**†	104/308 (34%)**††	$P < 0.001$
Number of cycles	414/1237 (33%)	565/2093 (27%)*	236/1620 (15%)**††	255/1583 (16%)**††	$P < 0.001$

[a]Denominators differ because of missing data for some patients.

*$P < 0.01$, **$P < 0.001$ versus ciprofloxacin.

†$P < 0.01$, ††$P < 0.001$ versus daily G-CSF.

§$P < 0.01$ versus pegfilgrastim alone.

TAC, docetaxel/doxorubicin/cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; FN, febrile neutropenia; NA, not applicable.

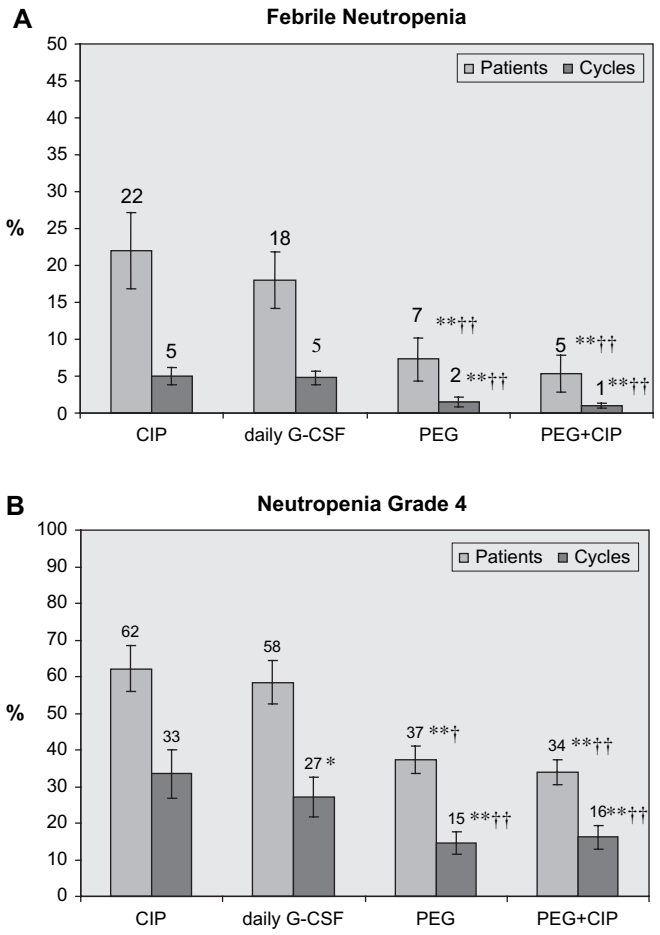


Figure 2. Incidence of (A) febrile neutropenia and (B) grade 4 neutropenia per patient and per cycle. Consecutive cohorts received ciprofloxacin (CIP; $n = 253$), daily granulocyte colony-stimulating factor (G-CSF) (filgrastim or lenograstim; $n = 374$), pegfilgrastim (PEG; $n = 303$) and pegfilgrastim + ciprofloxacin (PEG + CIP; $n = 314$) as primary prophylaxis. Bars show the 95% confidence intervals. *$P < 0.01$, **$P < 0.001$ versus ciprofloxacin. †$P < 0.01$, ††$P < 0.001$ versus daily G-CSF.

daily G-CSF ($P < 0.01$ and $P < 0.001$). Compared with pegfilgrastim plus ciprofloxacin, thrombocytopenia was significantly less common with ciprofloxacin ($P < 0.001$), but there were no statistically significant differences between the growth factor regimens (Table 3). This difference was not considered clinically relevant, as bleeding complications were not reported.

related nonhematologic toxic effects. Infection without neutropenia was comparable between treatment groups (~9%–14% of patients). Other nonhematologic toxic effects that might relate to neutropenia and/or infections included stomatitis/mucositis, dysphagia/esophagitis, and diarrhea, which were least common in the pegfilgrastim plus ciprofloxacin group. This combination was superior to ciprofloxacin for stomatitis/mucositis ($P < 0.001$), and to daily G-CSF for diarrhea ($P < 0.01$). Daily G-CSF was superior to ciprofloxacin in terms of stomatitis/mucositis ($P < 0.01$) (Table 3).

hospitalization. The daily G-CSF group had a lower rate of hospitalization for neutropenia and overall hospitalization (both $P < 0.001$) than the ciprofloxacin group. Both pegfilgrastim groups showed lower rates of hospitalization for FN and neutropenia, and for total hospitalizations, than ciprofloxacin alone ($P < 0.001$). Furthermore, compared with daily G-CSF, there were lower rates of hospitalization for neutropenia, and total hospitalization in the pegfilgrastim plus ciprofloxacin and pegfilgrastim groups, respectively (both $P < 0.01$) (Table 4).

fatal complications. Neutropenia-associated death occurred in three patients: two in the daily G-CSF group and one in the pegfilgrastim alone group. All three developed abdominal pain, diarrhea, and neutropenia on day 6–7 after the first TAC cycle. Sepsis was diagnosed the next day and in one case bowel perforation was suspected. All three patients died of neutropenic enterocolitis the following day. No neutropenia-associated deaths occurred in either of the two cohorts that included ciprofloxacin as primary prophylaxis. Two further deaths that occurred during the study were not neutropenia related (cardiac or embolic events).

Table 3. Incidence of other hematologic and nonhematologic (grade 2–4) toxic effects in patients receiving TAC

	Ciprofloxacin	Daily G-CSF	Pegfilgrastim	Pegfilgrastim + ciprofloxacin	*P* value across cohorts
Leukopenia	213/253 (84%)	296/373 (79%)	168/303 (56%)*†	170/314 (54%)**†	<0.001
Anemia	91/253 (36%)	142/373 (38%)	86/303 (28%)	66/314 (21%)*††	<0.01
Thrombocytopenia	12/253 (5%)§	32/330 (10%)	30/268 (11%)	41/281 (15%)	<0.01
Infection without neutropenia	24/253 (9%)	54/373 (14%)	28/303 (9%)	33/314 (11%)	<0.2 NS
Stomatitis	96/253 (38%)	90/374 (24%)*	86/303 (28%)	58/313 (19%)**	<0.001
Dysphagia/esophagitis	36/253 (14%)	47/373 (13%)	47/303 (16%)	28/313 (9%)	<0.2 NS
Diarrhea	43/253 (17%)	95/374 (25%)	53/303 (17%)	47/314 (15%)†	<0.025

*$P < 0.01$; **$P < 0.001$ versus ciprofloxacin.
†$P < 0.01$; ††$P < 0.001$ versus daily G-CSF.
§$P < 0.001$ versus pegfilgrastim + ciprofloxacin.
TAC, docetaxel/doxorubicin/cyclophosphamide; G-CSF, granulocyte colony-stimulating factor.

Table 4. Incidence of hospitalization (episodes/cycle) in patients receiving TAC

	Ciprofloxacin (n = 1478)	Daily G-CSF (n = 2400)	Pegfilgrastim (n = 1930)	Pegfilgrastim + ciprofloxacin (n = 1890)	P value across cohorts
Total incidents	92 (6%)	76 (3%)**	36 (2%)**†	39 (2%)**	<0.001
For FN	21 (1%)	19 (1%)	6 (<1%)**	7 (<1%)**	<0.001
For neutropenia	44 (3%)	30 (1%)**	11 (1%)**	9 (<1%)**†	<0.001
For infection without neutropenia	12 (1%)	15 (1%)	10 (1%)	10 (1%)	NS
Other reason	15 (1%)	12 (1%)	9 (<1%)	13 (1%)	NS

*P < 0.01; **P < 0.001 versus ciprofloxacin.

†P < 0.01; ††P < 0.001 versus daily G-CSF.

TAC, docetaxel/doxorubicin/cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; FN, febrile neutropenia; NS, not significant.

discussion

Primary antibiotic prophylaxis is not generally supported by official guidelines [7], but in a recent meta-analysis (n = 95 trials) it was found to significantly reduce mortality in patients receiving myelosuppressive chemotherapy, with fluoroquinolone prophylaxis almost halving the risk of death (Response rate: 0.52; 95% confidence interval: 0.35–0.77) [8]. However, consistent with the phase 3 Spanish Breast Cancer Group (GEICAM) 9805 and BCIRG 001 studies [2, 4], we found that primary antibiotic prophylaxis alone (ciprofloxacin on days 5–14) provided insufficient protection against neutropenic events in patients receiving TAC, with FN occurring in >20% of patients.

Recent evidence has shown that primary growth factor support significantly reduces the risk of FN when the risk level is well below the previously defined 40% threshold [9, 10]. Accordingly, updated guidelines from the American Society of Clinical Oncology, the European Organization for Research and Treatment of Cancer, and the National Comprehensive Cancer Network, now advocate routine primary growth factor prophylaxis for regimens with a ≥20% risk of FN [11–13]. We amended the GEPARTRIO study protocol to include primary daily G-CSF prophylaxis, but this did not significantly reduce the risk of FN compared with ciprofloxacin (18% versus 22% of patients). As with ciprofloxacin alone, most episodes of FN occurred during the first cycle of TAC, when two fatal cases of neutropenic enterocolitis occurred.

It should be noted that we did not use daily G-CSF according to manufacturers' recommendations, which are to start 24 h after the last dose of chemotherapy and continue until ANC has recovered to within the normal range (or for 14 days) [14]. It has been common clinical practice, for economic and practical reasons, to initiate treatment at a later point and/or administer a shorter course of treatment [15–18]. Indeed, the GEICAM group [4] used a 7-day course of filgrastim from day 4 of TAC, together with ciprofloxacin. Data from several clinical studies have confirmed that 10–11 days' filgrastim treatment is required for optimal protection against FN [19, 20] and emerging data from various cancer settings indicate that suboptimal use can potentially compromise clinical outcomes [15, 16, 21].

We subsequently substituted filgrastim or lenograstim with the second generation agent, pegfilgrastim, which is cleared primarily by neutrophil-dependent mechanisms and therefore has 'self-regulating' pharmacokinetics [22]. A single injection of pegfilgrastim on day 2 appears to be equivalent to 10–11 days of filgrastim in providing neutrophil support, and possibly more effective for preventing FN [19, 20, 23].

In our study, pegfilgrastim was significantly more effective than a 6-day course of daily G-CSF as primary prophylaxis, reducing the incidence of FN to 7% of patients (2% of cycles) (P < 0.001) and grade 4 neutropenia to <40% of patients (15% of cycles) (P < 0.01 and P < 0.001, respectively). Leukopenia was also significantly reduced, and anemia and nonhematologic events tended to be less common versus daily G-CSF. However, a third case of neutropenic enterocolitis during a first TAC cycle in a cohort not receiving antibiotics, although possibly a chance occurrence, prompted addition of ciprofloxacin to pegfilgrastim for primary prophylaxis in the final cohort.

The combination of pegfilgrastim plus ciprofloxacin gave the best results. Significant differences versus pegfilgrastim alone were not seen with regard to the primary end point, but the combination was more effective in reducing first cycle FN and also significantly reduced anemia and diarrhea versus daily G-CSF. The incidence of FN was reduced to 5% of patients (1% in 1736 cycles), with no first cycle FN or fatal neutropenic sepsis. Although addition of fluoroquinolones may increase adverse events, recent data showing a survival benefit for these agents in this setting [8] lend support to use of this combination.

Reduction of anemia and nonhematologic toxic effects tended to follow a similar pattern to reduction of neutropenia with the different prophylactic regimens, consistent with observations from other studies [4]. The GEICAM 9805 investigators found that growth factor support reduced other TAC-related toxic effects, including anemia, asthenia, anorexia, myalgia, nail disorders, and mucositis, possibly as a result of reduced infection/fever and cytokine release. Our study was not specifically designed to compare the four prophylactic regimens and P values should be interpreted in this context. Nevertheless, the regimens were utilized within a prospective study in sequential cohorts of patients treated at the same centers with the same chemotherapy regimen. Furthermore, the large number of patients analyzed strengthens the data. Comparisons between the ciprofloxacin and growth factor cohorts with regard to events per cycle should be made with caution, because of the confounding effects of secondary daily G-CSF prophylaxis in the first cohort (133 patients; 435 cycles). Although some protocol violations occurred with regard to

primary prophylaxis, a sensitivity analysis, excluding patients who received primary growth factor prophylaxis in error, and those allocated to this treatment who did not receive it, showed that these did not impact on the results (data not shown). Had we used the more stringent definition of FN (fever as previously defined with grade 4 neutropenia) used in the GEICAM study [4] for example, the incidences per patient would be 17%, 10%, 4%, and 4% for ciprofloxacin, daily G-CSF, pegfilgrastim, and pegfilgrastim plus ciprofloxacin, respectively. The pattern of statistical significance for comparisons between the regimens did not change, except that daily G-CSF became superior to ciprofloxacin alone ($P = 0.01$).

In conclusion, our findings indicate that an abbreviated 6-day course of daily G-CSF started on day 5, as commonly administered in clinical practice, or ciprofloxacin from days 5 to 14, provides suboptimal primary prophylaxis against FN and other toxic effects, especially during the first cycle, in patients receiving TAC. A single dose of pegfilgrastim on day 2, alone or with ciprofloxacin, was significantly more effective in this setting. A combination of pegfilgrastim and ciprofloxacin tended to give the best results and was more effective than pegfilgrastim alone for preventing first cycle FN. This combination warrants further evaluation in prospective studies. Our data confirm the benefit of effective neutrophil support, from the first cycle of treatment, for TAC and regimens with similar hematologic toxicity, as now recommended in official guidelines [11–13].

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