Febrile neutropenia: highlighting the role of prophylactic antibiotics and granulocyte colony-stimulating factor during standard dose chemotherapy for solid tumors

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The prevention of chemotherapy-induced febrile neutropenia is important as it reduces hospitalization and is likely to improve quality of life. Several prophylactic strategies are available, although their use in patients with an anticipated short duration of neutropenia is controversial and not recommended. This paper presents the results of a review of the literature on the efficacy and cost-effectiveness of prophylactic antibiotics and/or granulocyte colony-stimulating factor, and also discusses the recommendations in current guidelines in view of recent publications. Both primary prophylactic granulocyte colony-stimulating factor and prophylactic antibiotics reduce the risk of febrile neutropenia considerably, and the addition of prophylactic granulocyte colony-stimulating factor to antibiotics is even more effective. As antibiotics, however, give rise to antimicrobial resistance and granulocyte colony-stimulating factor is expensive, tailoring of prophylaxis is clearly needed. This will increase the absolute clinical and economical benefits of prophylaxis. Patient-related, treatment-related and disease-related factors enhancing the risk of febrile neutropenia are discussed, including the, underrated, high risk of febrile neutropenia specifically in the first cycles of chemotherapy. Half of the patients developing febrile neutropenia during treatment do so in the first cycle of chemotherapy, which favors primary prophylaxis. The efficacy of secondary prophylaxis is not well documented. Finally, new interesting agents in the treatment and supportive care of solid tumors have become available, and these are discussed in relation to the incidence and prevention of febrile neutropenia. *Anti-Cancer Drugs* 17:881–889 © 2006 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2006, **17**:881–889

Keywords: antibiotics, chemotherapy, febrile neutropenia, granulocyte colony-stimulating factor, prophylaxis, review, solid tumors

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Received 16 March 2006 **Accepted** 19 May 2006

Introduction

Cancer patients treated with chemotherapy may experience therapy-related toxicity. Prevention of serious treatment-related toxicity is important to improve the quality of life. One of the major complications of chemotherapy is neutropenia and its febrile complications, in particular. Febrile neutropenia (FN) causes morbidity, leads to hospitalization and may compromise further treatment with chemotherapy in individual patients. Thirty years ago FN was a fatal complication in almost half of the patients affected [1]. Although substantial progress has been made due to immediate initiation of empiric antibiotic therapy in patients presenting with FN, at present mortality rates are still 10% [2].

FN can be prevented, but prophylaxis of FN is controversial, especially in patients expected to have only a short duration of neutropenia and a low risk of FN. In the 1980s, lithium carbonate and human lactoferrin (a natural milk protein) were tested in patients receiving chemotherapy, and were believed to be promising means of lowering the risk of infection [3,4]. Today, antibiotics and colony-stimulating factors are most commonly used in FN prophylaxis. The rationale of prophylactic antibiotics is based on the assumption that most infections are caused by endogenous pathogens, particularly when cytotoxic agents damage the mucosal barrier. Granulocyte colony-stimulating factors (G-CSF) stimulate myeloid progenitors by increasing cell division, shorten the bone marrow transit time, and modulate function and activity of developing and mature neutrophils [5].

Besides the prevention of neutropenic complications in standard-dose chemotherapy, the use of prophylaxis and especially of G-CSF to support chemotherapy dose intensification has been extensively investigated. In this article, however, we give an overview of the results and continuing debate of prophylaxis of neutropenia-associated infectious complications, focusing on adult patients with solid tumors receiving standard-dose chemotherapy and emphasizing antibacterial prophylaxis and the most widely used human recombinant hematopoietic growth factor, G-CSF.

A literature search was performed using 'Randomized Controlled Trial' (Publication Type) AND 'Anti-Bacterial

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Agents' (MeSH) OR 'Granulocyte Colony-Stimulating Factor' (MeSH) AND 'Neutropenia' (MeSH) limits: all adults: 19 + years, English. References of identified articles were scanned for additional articles. A few meta-analyses on both prophylactic antibiotics and G-CSF are available, and their results are summarized, if essential supplemented with results of later trials.

Primary prophylaxis

Prophylaxis can be given either as primary or as secondary prophylaxis. Primary prophylaxis refers to the situation that prophylaxis is started upfront in the first chemotherapy cycle. Administering prophylaxis in subsequent chemotherapy cycles after FN occurred in a prior cycle is referred to as secondary prophylaxis.

Primary prophylaxis with antibiotics

Quinolones

In the late 1990s, a meta-analysis was published on 18 randomized trials assessing the impact of prophylactic quinolones during chemotherapy [6]. It was demonstrated that quinolones resulted in a significant reduction in the incidence of Gram-negative bacterial infections [relative risk (RR) 0.21, 95% confidence interval (CI) 0.12–0.37], total infections (RR 0.54, 95% CI 0.31–0.95) and episodes with fever (RR 0.85, 95% CI 0.73–0.99) when compared with no prophylaxis or placebo. In a side analysis quinolones were compared with trimethoprim-sulfamethoxazole (TMS). One of the theoretical advantages of the quinolones over the older TMS is that the aerobic Gram-negative flora is eradicated (including *Pseudomonas* species and of newer agents some Gram-positive bacteria as well), while the anaerobic flora – which protects against super infections – stays intact [7]. Opposed to TMS, quinolones are ineffective against *Pneumocystis carinii*. It was shown that quinolones caused a significant reduction in Gram-negative (RR 0.3, 95% CI 0.17–0.54) and overall infections (RR 0.83, 95% CI 0.7–0.98), suggesting quinolones to be more effective than TMS.

The majority of trials included in this meta-analysis concerned hematological malignancies (11 trials with 773 patients) or included both solid and hematological cancer patients (six trials with 593 patients), with only one trial regarding solid tumors only (42 patients). Other drawbacks of this meta-analysis are that the definition of neutropenia, starting date of prophylaxis and other inclusion criteria varied widely, variations that could not be fully appreciated in the different analyses. Most important, the majority received high-dose chemotherapy and bone marrow transplant, thus prohibiting straightforward implementation of results for patients with solid tumors receiving standard-dose chemotherapy.

A recently published double-blind placebo-controlled randomized trial in 1565 patients confirms the efficacy of quinolone prophylaxis in patients with solid tumors receiving standard-dose chemotherapy [8]. Patients with solid tumors or lymphoma (12.8%) were included. Quinolone prophylaxis significantly reduced the incidence of fever (defined as a temperature exceeding 38°C, RR 0.71, 95% CI 0.55–0.92), probable infection (0.82, 95% CI 0.73–0.94) and hospitalization (RR 0.73, 95% CI 0.59–0.90). This study used levofloxacin, a well-tolerated quinolone that is administered only once a day, optimizing compliance of prophylaxis. The efficacy of levofloxacin was confirmed in another recently published placebo-controlled study regarding 760 patients expected to experience prolonged neutropenia (more than 7 days). Patients were stratified according to underlying disease, acute leukemia versus solid tumor or lymphoma and the effectiveness proved similar [9].

Combined antibiotic prophylaxis

Two decades ago, the majority (70%) of isolated pathogens in neutropenic patients were Gram-negative bacteria, but today up to 70% are Gram-positive cocci [10]. It is important to realize that these trends are often associated with local treatment practices, and therefore the epidemiological pattern of bacterial infection continues to evolve globally and locally at the institutional level.

During the last decade, fluoroquinolones have been used increasingly and this is thought to be one of the reasons for the shift towards Gram-positive infections. Whether the addition of prophylaxis directed against Gram-positive bacteria can more effectively reduce fever and infections than quinolones alone has been subject of a meta-analysis by Cruciani *et al.* [11] (nine trials including 1202 patients). Again, most of these nine trials concerned hematological cancer patients or patients with solid tumors receiving bone marrow transplant, reflected in a mean duration of neutropenia of 8–30 days. A combination of a quinolone with a Gram-positive-directed antibacterial agent compared with quinolones alone, significantly reduced bacteremia (RR 0.65, 95% CI 0.53–0.79) and streptococcal infections (RR 0.45, 95% CI 0.3–0.69), but hardly the incidence of FN (RR 0.98, 95% CI 0.86–1.0).

Not included in this meta-analysis was a trial of the European Organization for Research and Treatment of Cancer (EORTC) in 163 patients with small-cell lung cancer (SCLC) randomized for combined antibiotic prophylaxis – with ciprofloxacin and roxithromycin – as compared with two placebos [12]. Combined antibiotic prophylaxis significantly reduced the incidence of FN over all cycles from 43 to 24% of patients. This was a two-by-two factorial-designed trial in patients with an excellent performance status also comparing standard-dose chemotherapy to intensified-dose chemotherapy. The protective effect was more distinct in the intensified

chemotherapy group as prophylactic antibiotics reduced the incidence of FN from 56 to 24% of patients treated with intensified chemotherapy compared with from 29 to 24% of patients in the standard dose group.

Effect of antibiotic prophylaxis on mortality

Both prior discussed meta-analyses did not establish a positive effect of prophylaxis on infection-related mortality. Yet, a recently published meta-analysis by Gafter-Gvili *et al.* [13] showed that antibiotic prophylaxis reduces mortality. This large meta-analysis included 95 studies between 1973 and 2004. All-cause mortality (in 2910 patients in 40 trials, RR 0.67, 95% CI 0.54–0.81) as well as infection-related mortality (in 2913 patients in 37 trials, RR 0.58; 95% CI 0.45–0.74) were significantly reduced when comparing antibiotic prophylaxis to placebo or no intervention. Prophylaxis with quinolones (1244 patients in 14 trials) reduced both all-cause mortality and infection-related mortality more effectively compared with TMS (870 patients in 14 trials) or other systemic antibiotics (525 patients in six trials). A subanalysis in 1232 patients showed that the addition of Gram-positive-directed antibiotics to quinolones did not affect mortality when compared with quinolones alone (RR infection-related mortality 1.11, 95% CI 0.63–1.95).

Again, these results, do not apply straightforward to patients with solid tumors receiving standard-dose chemotherapy, as only five of the 95 trials included primarily patients with solid tumors treated with standard-dose chemotherapy. The largest of these five trials is the previously discussed EORTC trial in SCLC patients that demonstrated a significantly reduced mortality rate in patients receiving prophylaxis compared with patients receiving placebo. In this trial, the number of infectious deaths was nil in the antibiotics arm versus five (6%) in the placebo arm ($P = 0.02$). This is the only trial in patients with solid tumors comparing a combination of Gram- and Gram-negative-directed agents to two placebos, in contrast to the other trials comparing combined antibiotic prophylaxis to a single antibiotic agent or a single antibiotic prophylaxis to a single placebo.

Primary prophylaxis with granulocyte colony-stimulating factor

Daily granulocyte colony-stimulating factor

The first two randomized controlled trials evaluating the effectiveness of primary G-CSF prophylaxis on infectious complications of neutropenia were performed in SCLC patients receiving standard-dose chemotherapy [14,15]. Both trials demonstrated that G-CSF prophylaxis shortened the duration of chemotherapy-induced neutropenia, resulting in a decreased incidence of FN, hospitalization and use of intravenous therapeutic antibiotics by approximately 50%.

A meta-analysis published in 2002 identified eight randomized controlled trials comparing primary G-CSF prophylaxis to placebo or to no prophylaxis during standard-dose chemotherapy [16]. Included were trials in patients receiving chemotherapy for solid tumors (750 patients in five trials concerning SCLC, germ cell tumors, soft-tissue sarcoma or breast cancer) or non-Hodgkin's lymphoma (391 patients in three trials). The risk of FN in the control arm of these eight trials ranged from 7, 29, 34, 44, 52, 58, 71 to 77% per patient, respectively. The use of G-CSF was associated with a significant reduction in incidence of FN (odds ratio 0.38, 95% CI 0.29–0.49, $P = 0.001$) and overall risk of documented infections (odds ratio 0.51, 95% CI 0.36–0.73, $P = 0.001$). Moreover, this meta-analysis demonstrated that the reduction in the incidence of FN was relatively constant across the wide range of baseline risks. Infection-related mortality was not significantly affected (odds ratio 0.60, 95% CI 0.30–1.22, $P = 0.16$).

Once-per-cycle pegylated granulocyte colony-stimulating factor

In 2002 a pegylated G-CSF was introduced. All the randomized controlled trials comparing once-per-cycle pegylated G-CSF to daily G-CSF demonstrated at least equal efficacy [17,18]. Due to its convenience to the patient one can expect increasing use of pegylated G-CSF. Lyman and Kuderer [19] presented a forest plot of the RR of FN in the four most important trials (three trials with 513 breast cancer patients and one trial with 66 patients suffering malignant lymphoma), suggesting a further reduction in risk of FN with pegfilgrastim compared with daily G-CSF with a summary RR of 0.66 (95% CI 0.44–1.0).

Pegfilgrastim was also evaluated in a placebo-controlled randomized trial in 928 breast cancer patients receiving chemotherapy associated with a 17% baseline risk of FN. The incidence of FN, FN-related hospitalization and use of parenteral antibiotics were all significantly reduced (17 versus 1%, 14 versus 1% and 10 versus 2% of patients, respectively) [20]. This trial demonstrated that pegylated filgrastim can also effectively reduce neutropenic complications in a population with a relatively low baseline risk of FN.

Effect of granulocyte colony-stimulating factor prophylaxis on mortality

An updated meta-analysis presented at the American Society of Clinical Oncology (ASCO) 2005 Annual Meeting, including 14 randomized controlled trials (one in pegylated G-CSF, three in lenograstim and the remaining in filgrastim, with total 3091 patients), showed for the first time a significant reduction of infection-related mortality favoring G-CSF; subgroup estimates in solid tumors revealed an RR of 0.47 (95% CI 0.23–0.93) [21].

Table 1 Incidence of febrile episodes using different prophylactic strategies [relative risk (95% CI)]

Publication	*N*	Prophylaxis compared	Febrile episodes/FN
Meta analysis Engels *et al.* [6]	1408	Q to nil or PCB	0.85 (0.73–0.99)
		Q to TMS	0.89 (0.74–1.07)
Cullen *et al.* [8]	1565	Q to PCB	0.71 (0.55–0.92)
Bucaneve *et al.* [9]	760	Q to PCB	0.76 (0.69–0.83)
Meta-analysis Cruciani *et al.* [11]	1202	Q+ to Q	0.98 (0.86–1)
Meta analysis Gafter-Gvili *et al.* [13]	9283	all antibacterial agents to PCB	0.79 (0.72–0.87)
		Q to nil or PCB	0.67 (0.56–0.81)
		TMS to PCB	0.79 (0.69–0.90)
Meta analysis Lyman *et al.* [16]	1144	fil-/lenograstim to nil or PCB	0.38 (0.29–0.49)[a]
Vogel *et al.* [20]	928	pegfilgrastim to PCB	0.07 (0.03–0.15)[a]
Forrest plot Lyman and Kuderer [19]	579	pegfilgrastim to filgastrim	0.66 (0.44–1.00)
Schroder *et al.* [22]	40	lenograstim to Q	0.84 (NS)
Timmer-Bonte *et al.* [24]	175	Q+ plus filgrastim to Q+	0.57 (0.34–0.97)[a]

N, number of patients; Q, quinolones; Q+, quinolones plus Gram-positive-directed agents; PCB, placebo; TMS, trimethoprim-sulfamethoxazole; CI, confidence interval; FN, febrile neutropenia.
[a]Odds ratio.

Comparing primary prophylactic strategies

Antibiotics versus granulocyte colony-stimulating factor

Only one very small prospective randomized trial has been published comparing antibiotics to G-CSF (lenograstim) in stage IV breast cancer patients treated with intermediate-dose chemotherapy: 18 patients received prophylactic G-CSF, and 22 patients received prophylactic ciprofloxacin and amphotericin B. The vast majority of events occurred in the first cycle with no clear difference between both groups (seven patients in each arm developed FN), while the costs of G-CSF were almost 7 times higher than those of antibiotics [22].

In the mid-1990s the Cancer and Leukemia Group B withdrew its proposed Cancer and Leukemia Group B 9111 clinical trial of G-CSF versus ciprofloxacin as alternative strategies against FN among cancer patients with lung cancer because there was considerable opposition to direct evaluation of the (economic) impacts of both prophylactic strategies, which made it impossible to raise funding for this trial [23].

Antibiotics in combination with granulocyte colony-stimulating factor

Both prophylactic antibiotics as well as prophylactic G-CSF have been shown to reduce the incidence of FN significantly. Whether antibiotics in combination with G-CSF result in a further decline has not been studied extensively, but results are consistent and favor the combination.

We recently reported the results of a randomized controlled trial comparing the efficacy of antibiotics (ciprofloxacin and roxithromycin) only to antibiotics and daily G-CSF in 175 SCLC patients receiving standard-dose chemotherapy (cyclophosphamide, doxorubicin and etoposide), and considered at risk of FN because of age, poor performance status, prior chemotherapy or extensive disease [24]. Especially in the first cycle, combined prophylaxis significantly reduced the incidence of FN (from 24 to 10%, $P = 0.01$), while the incidence of FN declined in further cycles regardless of type of prophylaxis used (17% compared with 11% of patients experienced FN in cycles 2–5).

In the last couple of years, docetaxel–doxorubicin–cyclophosphamide (TAC) combination chemotherapy is being increasingly used in breast cancer patients. This regimen is associated with a high incidence of FN and accordingly primary prophylaxis has been applied frequently. Two abstracts reported the results of the addition of G-CSF to primary prophylaxis with ciprofloxacin during TAC chemotherapy. In the first, three consecutive cohorts receiving neoadjuvant TAC were reported [25]. The first cohort (390 patients) received prophylaxis with daily G-CSF, the second cohort (323 patients) with pegylated G-CSF, and the third cohort (236 patients) with a combination of pegylated G-CSF and ciprofloxacin. The incidence of FN was 4.3% in the cohort receiving the prophylactic combination compared with 17.1 and 6.4% in the cohorts receiving daily G-CSF or pegylated G-CSF ($P < 0.001$). The other abstract reported on 530 patients who received adjuvant TAC [26]. The first 114 patients received prophylactic ciprofloxacin with an incidence of FN of 24.6% (95% CI 16.7–32.5%), whereas in the second cohort of 416 patients daily G-CSF was added to ciprofloxacin and an incidence of FN of 5.8% (95% CI 3.5–8%) was found.

The main results of primary prophylaxis on the incidence of febrile episodes or FN are summarized in Table 1.

Secondary prophylaxis

A theoretical advantage of applying secondary prophylaxis is that it prevents the use of prophylaxis in patients who would not have developed FN anyhow. Thus far no prospective randomized controlled trials have been reported comparing secondary prophylaxis with antibiotics or G-CSF to placebo or to dose reduction. Only

indirect evidence is available that secondary prophylaxis with G-CSF prevents FN in patients having experienced FN in a prior cycle of chemotherapy.

Secondary prophylaxis with granulocyte colony-stimulating factor

The placebo-controlled trial by Crawford *et al.* [14] allowed patients in the placebo arm who developed FN to receive open-label G-CSF in subsequent cycles of chemotherapy. This resulted in a reduction in the rate of FN from 100% in cycle 1 to 23% in cycle 2. As many trials report a decline in the incidence of FN in later cycles without administering (additional) prophylaxis, however, no definite conclusions on the efficacy of secondary prophylaxis can be drawn from these observations.

Secondary prophylaxis with antibiotics and granulocyte colony-stimulating factor

In the early 1990s Maiche and Muhonen [27] briefly reported the results of the comparison of secondary use of G-CSF to secondary G-CSF and a quinolone in, respectively, 30 and 29 patients having experienced FN in the previous cycle of chemotherapy (without prophylaxis). Infectious complications occurred during grade IV neutropenia in seven of 10 G-CSF-supported cycles compared with two of seven cycles supported by G-CSF and quinolones ($P = 0.09$) [27]. More recently, Lalami *et al.* [28] conducted a prospective randomized trial in 48 patients having experienced FN. In subsequent cycles, secondary prophylactic G-CSF or G-CSF and amoxicillin/clavulanate and ciprofloxacin was started. No recurrence of FN was observed in the G-CSF strategy and one episode of FN in the combined strategy. With the small numbers of patients and lack of a placebo-controlled trial it remains difficult to draw conclusions with a high level of evidence.

Cost-effectiveness of febrile neutropenia prophylaxis

Economic evaluations of prophylactic antibiotics are scarce. Despite the availability of various publications, the cost-effectiveness of G-CSF is not settled. This is in part due to the fact that there is no consistency in costs to be considered (all or only FN-related), the perspective to be used (healthcare, social, etc.) and the time horizon (duration of chemotherapy or longer). Furthermore, clinical results can have different economic effects in different countries because of different healthcare systems [29].

Primary antibiotic prophylaxis

Prophylaxis with antibiotics is inexpensive and significantly reduces hospitalization. As the cost of hospitalization is the main cost driver of FN-related costs, it can be anticipated that antibiotic prophylaxis can be cost-saving in many situations. We identified only one report that prospectively analyzed the cost-effectiveness of prophylactic antibiotics [30]. This report is based on the earlier mentioned EORTC study in SCLC patients, and showed that prophylactic ciprofloxacin and roxithromycin was cost-saving for The Netherlands and cost-neutral for Germany. Sensitivity analysis demonstrated that antibiotic prophylaxis would be cost-saving for a broad range of baseline risks of FN. For example, for the Dutch situation antibiotics may already be cost-saving with a baseline risk of FN of 6% or more.

Primary granulocyte colony-stimulating factor prophylaxis

The high cost price of G-CSF generally prohibits cost-savings at standard-dose chemotherapy with intermediate risks of FN. In the US, a threshold above which the administration of prophylactic G-CSF was estimated to be cost-saving was initially established at a baseline risk of FN of 40% [31]. It is important to realize that hospitalization costs, the main cost driver in FN, differ to a great extent among countries. Therefore, the 2000 ASCO guideline observation that primary prophylactic-only G-CSF is expected to be cost-saving when the risk of FN 40% or higher, should be applied with prudence in other countries [32]. Moreover, in the US FN-related cost have risen in the last decade and cost-effectiveness analysis based on updated cost estimates indicated a new FN threshold of 20–25% [33,34]. When indirect costs were included this threshold was suggested to be even less than 20% [35]. Thresholds for most European countries are likely higher than US thresholds as FN-related hospitalization costs in Europe in general are considerably lower than in the US (e.g. €3300 in The Netherlands compared with $12 000 in the US) [33,36].

Most single studies did not find a survival gain in the patient group using G-CSF prophylaxis and concluded that prophylactic administration of G-CSF cannot be advised as a routine prescription in case there are no cost-savings [37,38]. So, the less-expensive arm was favored in settings in which survival was the same. In economic analyses, however, the preferred approach may be to use more than one form of analysis. For example, when two alternative strategies do not result in survival differences, but they are yet not identical with respect to other clinical effects. In that situation, a cost-minimization is unlikely to suffice. Some studies therefore express cost-effectiveness as cost per episode FN prevented [36,39]. The issue is whether one should only be willing to pay in case of life years saved or whether it is worthy to spend some money for supportive care without an impact on survival.

Prophylaxis in current guidelines

Several international guidelines address prophylaxis of infectious complications in neutropenic episodes. In

general, guidelines concentrate on either antibiotics (Infectious Diseases Society of America guideline) or on G-CSF [ASCO and National Comprehensive Cancer Network (NCCN) guideline] [32,40–42].

Antibiotic prophylaxis in current guidelines

Despite the fact that prophylactic antibiotics are proven effective in reducing the incidence of FN, the 2002 Infectious Diseases Society of America guideline does not recommended their routine use, but states that antibiotics should only be considered in patients at high risk of FN [40].

In the guideline, specifically mentioned conditions associated with a high risk of FN (cytarabine use, severe mucositis and profound neutropenia longer than one week) are, however, all conditions not frequently associated with the treatment of solid tumors. Cytarabine is seldom used in solid tumor treatment. Although some degree of mucositis develops in approximately 40% of patients receiving cancer therapy, severe mucositis interfering with normal food intake and/or needing parenteral support is not common at standard-dose chemotherapy. Finally, prolonged grade IV neutropenia (absolute neutrophil count less than 0.5×10^9/l) lasting 7 days or more is uncommon in solid cancer patients receiving standard dose chemotherapy. Nevertheless, specific patient, disease and chemotherapy-related factors may increase the risk as will be discussed later.

The recommended restrictive use results from the hazard of inducing antimicrobial resistance. The concern that resistant microorganisms emerge when prophylactic antibiotics are routinely administered seems justified. Fluoroquinolones give rise to cross-resistance within their own class as well as to unrelated antibiotics such as imipenem [43]. The resistance to fluoroquinolones is increasing. The European Antimicrobial Resistance Surveillance System is an international network of national surveillance systems, which performs ongoing surveillance of antimicrobial susceptibility in *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli* and *Enterococcus faecalis/faecium* causing invasive infections, and monitors variations of antimicrobial resistance over time and place. For example, in *E. coli* resistance against fluoroquinolones increased from 9 to 14% between 2001 and 2004 [44].

Of note, two reports in neutropenic patients with hematological malignancies demonstrated that despite emerging resistance, fluoroquinolone prophylaxis still effectively reduced the incidence of Gram-negative infections [45,46]. One prospective observational study in patients with hematological cancers was terminated ahead of planned time due to a dramatic rise in infection-related mortality after (scheduled) discontinuation of prophylaxis with quinolones. Mortality declined again after re-initiating prophylaxis (death due to infection 2, 9, 33 and 1%). *E. coli* isolated during the discontinuation period was susceptible to levofloxacin *in vitro*, whereas all *E. coli* isolated during both prophylaxis periods were resistant. So, quinolone resistance appears a poor indicator of the clinical efficacy of fluoroquinolone prophylaxis, whereas the rate of documented Gram-negative bacteremia may be a more reliable tool to detect loss of efficacy of fluoroquinolone prophylaxis.

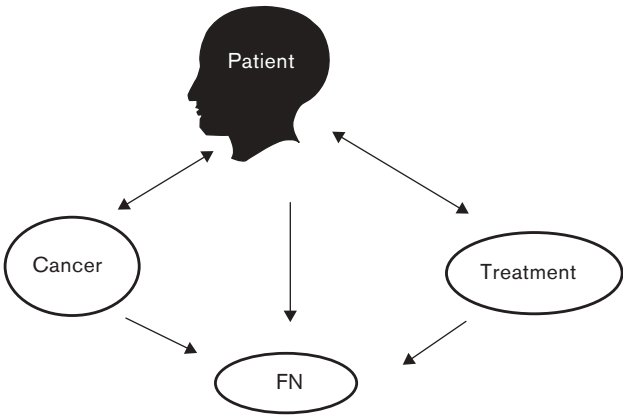
Granulocyte colony-stimulating factor in current guidelines

The 2000 ASCO guideline on CSFs did not recommend routine use of primary prophylactic G-CSF during standard-dose chemotherapy regimens unless the risk of FN is 40% or more [32]. Mainly on the basis of the trials by Vogel *et al.* and Timmer-Bonte *et al.*, the NCCN Myeloid Growth Factors Clinical Practice Guideline published in 2005 recommended the use of primary prophylactic G-CSF at a risk of FN of 20% or more. The NCCN recommends further to consider G-CSF use when the anticipated risk is 10–20%, especially when patient factors (Fig. 1) determine the anticipated risk category [42].

The 2006 update of the ASCO guideline agrees that reduction in FN was an important clinical outcome that justified the use of primary CSF when the risk of FN was approximately 20% or more, on condition that an equally effective but less myelotoxic regimen was not available [41].

Further, the ASCO 2000 and 2006 updated guideline acknowledge the lack of evidence of randomized controlled trials on secondary prophylaxis, and do not, recommend the secondary use of G-CSF, but instead to

Fig. 1



Patient, cancer and treatment-related factors. FN, Febrile neutropenia.

Table 2 Incidence of FN in cycle 1 compared to the incidence of FN in the entire treatment period (incidence per patient)[a]

Author, year	Tumor	*N*	Prophylaxis	FN per patient (%)	
				Cycle 1	All cycles
Tjan-Heijnen *et al.*, 2001 [12]	SCLC	79	placebo	20	34
		82	antibiotics	9	20
Crawford *et al.*, 1991 [14]	SCLC	102	placebo	57	77
		92	filgrastim	28	40
Trillet-Lenoir *et al.*, 1993 [15]	SCLC	64	placebo	41	53
		65	filgrastim	20	26
Vogel *et al.*, 2005 [20]	breast	465	placebo	11	17
		463	pegfilgrastim	0.7	1
Nabholtz *et al.*, 2002 [55]	breast	135	filgrastim	4	7
		139	leridistim 5 mg/kg	11	19
		139	leridistim 10 mg/kg	14	22
Green *et al.*, 2003 [17]	breast	77	pegfilgrastim	9	13
		75	filgrastim	15	20
Holmes *et al.*, 2002 [18]	breast	149	pegfilgrastim	7	9
		147	filgrastim	12	18
Schroder *et al.*, 1999 [22]	breast	18	lenograstim	28	39
		22	ciprofloxacin + amphotericin B	27	32
Timmer-Bonte *et al.*, 2005 [24]	SCLC	85	cipro + roxi	24	32
		90	cipro + roxi + filgrastim	10	18

FN, febrile neutropenia; SCLC, small-cell lung cancer.
[a]Only prospective controlled trials with neutropenic complications as primary end point are considered.

reduce chemotherapy dose in the palliative setting. The NCCN guideline recommends re-evaluation of each patient every cycle and to consider G-CSF if FN or another dose-limiting neutropenic event has occurred in the prior cycle.

Assessing risk of febrile neutropenia

Although on the basis of different arguments all guidelines advocate restrictive use of prophylaxis, in fact only in patients 'at risk' of FN. Obviously, both the absolute clinical and economical benefits will be more distinct in patients at risk of FN. The different guidelines, however, provide different information on which factors are to be considered risk factors. In effect, little high-level evidence is currently available on predisposing factors. Until now, in studies designed to evaluate neutropenic complications, only elderly age and advanced disease are consistently reported to increase the risk of FN [12,24,47,48]. Several other, but less well-documented, pretreatment factors reported to be associated with the risk of FN are: tumor type, one or more comorbidities, previous episode of FN, hemoglobin < 12 g/dl, pretreatment absolute neutrophil count $< 1.5 \times 109$/l, serum albumin < 3.5 g/dl, intended high chemotherapy dose intensity, female gender [24,49,50]. The Awareness of Neutropenia in Chemotherapy Study Group is currently prospectively registering neutropenic outcome in patients starting with chemotherapy in 125 centers in the US, and the intended result of this study is to develop a risk model for selecting patients for appropriate and timely supportive care. Preliminary results validate some of the previously cited factors [51].

The incidence of FN of several chemotherapy regimens is fairly well known, e.g. anthracycline-based regimens are frequently associated with a risk of FN of above 20% [14,51–54]. All these (interrelated) factors sum up to determine the estimated risk in an individual patient (Fig. 1). Several studies indicate that the risk of FN is highest in the first cycles of chemotherapy (see Table 2) [12,14,15,17,18,20,22,24,55]. This finding is probably not sufficiently appreciated, but at least half of patients with FN during treatment develop FN in the first cycle.

Conclusions

In conclusion, both primary prophylactic antibiotics and primary prophylactic growth factors effectively reduce the risk of FN, even more when used as a combination. The efficacy of secondary prophylaxis is not well documented and therefore dose reduction seems a reasonable alternative, especially for regimens given with a palliative treatment intent.

The prophylactic antibacterial agent of choice is a quinolone rather than TMS. The addition of a Gram-positive-directed antibacterial agent further reduces the amount of bacteremia. Prophylactic antibiotics reduce infection-related mortality, but antibiotics may also lead to microbial resistance with changing infection profiles.

G-CSF reduces FN to the same extent as prophylactic antibiotics, an approximately 50% relative decrease compared with the baseline risk. Filgrastim and pegylated filgrastim are the most widely studied growth factors, both being at least equally effective. On the other hand, G-CSF is expensive and despite the reduction in

hospitalization still too expensive for many standard chemotherapy regimens. Due to differences in healthcare organization, the economic break-even point of prophylactic G-CSF varies among countries.

Guidelines recommend prophylaxis only in patients at risk. An assessment of the risk of FN can only be made at the patient level. At present, the best-documented risk factors are elderly age and advanced disease during the first cycles of chemotherapy.

Future directions

In our view, it is important to develop new strategies to prevent FN to provide high-quality cancer care to patients receiving chemotherapy. If not for cost, at present G-CSF would likely be the prophylactic agent of choice in comparison with the use of prophylactic antibiotics. For now, further knowledge on patient, cancer and treatment-related FN-promoting factors is urgently needed, and will hopefully be provided for in the next few years. This will result in better tailored prophylaxis and may also lead to a more cost-effective use of prophylaxis.

Potential new prophylactic agents are investigated. Very recently a pilot study was published successfully exploring the use of competitive inhibition of bowel colonization by lactic acid bacteria, using a pro-biotic strain *E. faecium* M-74 [56]. A nontoxic fermented wheat germ extract (Avemar), claimed to have immunomodulatory effects, was evaluated in 22 children treated with chemotherapy for solid tumors and significantly reduced the incidence of FN [57].

Preserving the integrity of the mucosal barrier may help to reduce the incidence of systemic infections during profound myelosuppression. Palifermin, a purified recombinant truncated form of human keratinocyte growth factor, has been developed to reduce the severity and duration of oral mucositis, and was studied in patients with hematologic malignancies who received myeloablative radio- and/or chemotherapy. In the palifermin group not only the duration of grade 3 or 4 oral mucositis, but also the incidence of FN was significantly reduced compared with the placebo group [58].

Finally, new treatment strategies for solid tumors (e.g. vascular endothelial growth factor and epidermal growth factor receptor inhibitors) causing less myelotoxicity and less mucosal damage have become increasingly available, and this will reduce the incidence of FN, and thus the need of prophylaxis during antitumor therapies.

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