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Quinolone prophylaxis for bacterial infections in afebrile high risk neutropenic patients ☆

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ABSTRACT

These recommendations have been developed by an expert panel following an evidence-based search of the literature assessing the role of fluoroquinolones in the prevention of bacterial infection in patients with acute leukaemia or bone marrow transplantation and neutropenia. We present results from a questionnaire on the current practice among experts in Europe, show results of the literature search, review recommendations available from other international guidelines and provide the panel's recommendations.

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1. Introduction

Several antibiotics have been used for prophylaxis of infections in neutropenic cancer patients.[1] In recent years most of the clinical studies have been conducted with fluoroquinolones. Although the results of randomised controlled trials have suggested that fluoroquinolones might be superior to either placebo, or trimethoprim-sulfamethoxazole or oral

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non-absorbable drugs for the prevention of infections in onco-haematological patients, the evidence provided by these studies was not perceived as entirely convincing.

Before 2005, few studies randomised, placebo-controlled, double-blind trials had been performed and none were large enough to provide conclusive evidence on the benefit of prophylaxis.[2–19] Most of the studies were underpowered to detect a statistically significant effect on mortality and the occurrence of fever requiring empirical antibiotic therapy was either not considered as a study endpoint or was not reduced in a statistically significant manner. Moreover, these studies did not provide clear evidence on the patients who may benefit most from antibiotic prophylaxis. Finally, the use of fluoroquinolone prophylaxis has been questioned, because of reports of increased resistance to this class of antibiotics. All these arguments explain why there was a lack of consensus on the usefulness of fluoroquinolone prophylaxis in patients with neutropenia.[1] We therefore performed a review of the literature to assess the utility of fluoroquinolone prophylaxis in neutropenic acute leukaemia patients. The following questions have been addressed: does fluoroquinolone prophylaxis reduce

(a) the rate of febrile episodes;
(b) the rate of microbiologically documented infections;
(c) the rate of Gram-negative and Gram-positive infections;
(d) all-cause and infection-related mortality.

2. Material and methods

The Cochrane Library (September 2005) and Medline (from January 1980 to September 2005) have been searched. Abstracts presented at the American Society of Haematology (ASH), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the American Society of Clinical Oncology (ASCO) and the European Bone Marrow Transplantation (EBMT) between 2002 and 2005 were also evaluated. References of all included trials and reviews were also scanned. Databases were searched using the terms neutropenia and similar, agranulocytosis and similar, anti-infective agents (including antibacterial and antibiotics), clinical trial and similar, fluoroquinolones or ciprofloxacin, enoxacin, norfloxacin, ofloxacin and pefloxacin. Selection of pertinent articles and abstracts was performed independently by two investigators of the working group, cross-checked and approved by all the members of the study group. Disagreements were resolved by consensus. All randomised, controlled trials performed in neutropenic cancer patients that compared a fluoroquinolone monotherapy versus placebo or no therapy were included in our analysis (Fig. 1). Quality of evidence and levels of recommendations were graded according to CDC methodology.

2.1. *Endpoints*

Selected endpoints were febrile episodes requiring empiric antibiotic therapy, bacterial infections and bacteraemia, Gram-negative infections, Gram-positive infections, and all-cause and infection related mortality. The emergence of resistant bacteria responsible for documented infections following the administration of fluoroquinolone-prophylaxis was also evaluated. Nineteen clinical trials[2–18,20,21] and four meta-analyses[22–25] were identified.

Two large clinical trials[20,21] published in 2005 (the number of patients enrolled in these trials far exceed the total number of patients enrolled in previous studies) and the meta-analysis by Gafter-Gvili et al.[22] were chosen as the main data

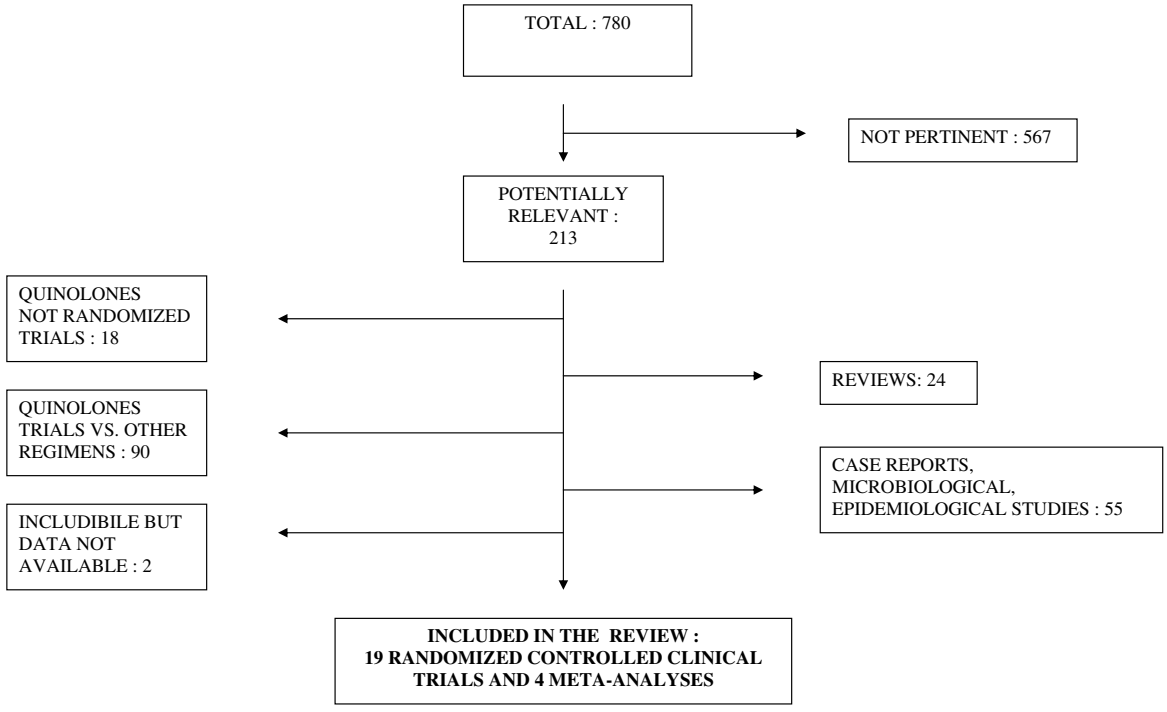

Fig. 1 – Fluoroquinolone prophylaxis: publications identified and exclusions (1980–2005).

sources. This meta-analysis is not only the most recent study on this topic, but it also used all-cause mortality as the main endpoint and included all of the 17 trials performed until 2005 that have compared fluoroquinolones to placebo or no treatment.

3. Results

The characteristics of the studies are shown in Table 1. The majority of these trials included patients with haematological malignancies, most of them with acute leukaemia as the underlying disease. Only five trials were performed in patients with solid tumours or lymphomas. Ciprofloxacin was the fluoroquinolone used in most of the studies, the other fluoroquinolones were norfloxacin, enoxacin, pefloxacin and ofloxacin. Levofloxacin was the agent used in two large, randomised, double-blind, placebo-controlled trials published in 2005. These studies were not included in any of the available meta-analyses.[20,21] The GIMEMA trial[20] was conducted in patients with acute leukaemia or with solid tumour/lymphoma undergoing haematopoietic stem cell transplantation (HSCT).

3.1. *Febrile episodes requiring empiric antibiotic therapy*

As shown in Table 2, the occurrence of febrile episodes requiring the initiation of empiric antibiotic therapy was significantly reduced in patients who had received fluoroquinolone prophylaxis. The meta-analysis of Gafter-Gvili et al.[22] based on 1409 patients (most of whom had haematological malignancies) clearly showed that fluoroquinolone prophylaxis reduced the occurrence of febrile episodes by 33%. The GIMEMA trial[20] reached the same result both in acute leukaemia and in HSCT patients. The number needed to treat to avoid one febrile episode was five in acute leukaemia patients.[21]

3.2. *Bacterial infections*

In acute leukaemia and HSCT patients, microbiologically documented bacterial infections accounted for 30–40% of all febrile episodes (Table 2).[20] Bloodstream infections, which occurred in more than 30% of the patients, were the most frequent cause of documented infections. Fluoroquinolone prophylaxis also reduced the incidence of bacterial infections.

Table 1 – Studies comparing fluoroquinolones to no prophylaxis (1980–2005)

Study (year)	Drug, dose	Total patients	Control	Type of randomised study	Underlyng disease (%)
Sleijfer et al. (1980)	Nalidixic ac. 2 gr qid; TMP-SMZ or Polymyxin	113	No intervention	Not blinded	100 (AL, AA)
Karp et al. (1987)	NOR, 400 mg bid	68	Placebo	Double blinded	100 (AL)
Hartlapp (1987)	OFLO, 200 mg bid	42	No intervention	Not blinded	100 (solid tumours: testicular germ-cell)
Lew et al. (1991)	CIPRO, 750 mg bid	26	Placebo	Double blinded	77 (AL, L, solid tumour); 100 (BMTs)
Sampi et al. (1992)	NOR, 200 mg bid	73	No intervention	Not blinded	90 (AL, solid tumour); 10 autoBMT
Schroeder et al. (1992)	OFLO, 400 mg bid	80	Placebo	Double blinded	2.5 (AL, L, solid tumour)
Maiche et al. (1993)	OFLO, 200 mg bid or CIPRO 750 mg bid	59	No intervention	Not blinded	80 (L, solid tumour: breast)
Talbot et al. (1993)	ENOX, 200 mg bid	119	Placebo	Double blinded	100 (AL)
Yamada et al., (1993)	NOR, 200 mg bid or qid	111	No intervention	Not blinded	100 (AL)
Brodsky et al. (1993)	NOR, 400 mg bid or CIPRO 500 mg bid	25	No intervention	Not blinded	100 (AL)
Carlson et al. (1997)	CIPRO, 500 mg bid	90	No intervention	Not blinded	100 (solid tumour: ovarian cancer)
Casali et al. (1997)	NOR, 400 mg tid	65	No intervention	Not blinded	17 (L, MM, AL)
Thomas et al. 2000	PEFLO, 200 mg qid	160 (3 groups)	Placebo	Double blinded	98 (AL, L, MM, solid tumour); 10 BMT
Tjan-Heijnen et al. (2001)	CIPRO, 750 mg bid and ROXIT, 150 mg bid	163	Placebo	Double blinded	100 (solid tumour: lung cancer)
Nenova et al. (2001)	CIPRO, 500 mg bid[20] PEFLO, ENOX, NOR	70	No intervention	Not blinded	100 (AL, L, MDS CL blast crisis)
Tsutani et al. (2001)	OFLOX, 300 mg bid	22	No intervention	Not blinded	100 (AL, L, MM)
Lee et al. (2002)	CIPRO, 250 mg bid and ROXYT, 150 mg bid	95	No intervention	Not blinded	100 (AL)
Bucaneve et al. (2005)	LEVO, 500 mg/day	760	Placebo	Double blinded	50 (AL), 50 (autologous HSCT)
Cullen et al. (2005)	LEVO, 500 mg/day	1565	Placebo	Double blinded	12 (L) 88 (solid tumour)

AA: aplastic anaemia; AL: acute leukaemia; BMT: bone marrow transplantation; CL: chronic leukaemia; L: lymphoma; MDS: myelodisplastic syndrome; MM: multiple myeloma.

Table 2 – Occurrence of clinically relevant endpoints in a recent randomised controlled trial and a meta-analysis on fluoroquinolone prophylaxis in neutropenic patients

	Fluoroquinolones	Placebo/no treatment	Relative risk (95% CI)	*p*
Febrile episodes				
Gafter-Gvili et al. (2005)	369/798 (46%)	505/701 (72%)	0.67 (0.56–0.81)	<0.001
Bucaneve et al. (2005)	243/375 (65%)	308/363 (85%)	0.76 (0.70–0.83)	0.001
Bacterial infections				
Gafter-Gvili et al. (2005)	171/706 (24%)	318/701 (45%)	0.50 (0.35–0.70)	<0.001
Bucaneve et al. (2005)	74/339 (22%)	131/336 (39%)	0.55 (0.43–0.71)	<0.001
Gram-negative infections				
Gafter-Gvili et al. (2005)	48/588 (8%)	192/588 (33%)	0.39 (0.32–0.46)	0.0001
Bucaneve et al. (2005)	21/339 (6%)	47/336 (14%)	0.44 (0.27–0.72)	0.001
Gram-positive infections				
Gafter-Gvili et al. (2005)	49/588 (8%)	179/588 (30%)	0.42 (0.35–0.50)	0.0001
Bucaneve et al. (2005)	42/339 (12%)	61/336 (18%)	0.68 (0.47–0.98)	0.04
All-cause mortality				
Gafter-Gvili et al. (2005)	33/652 (5.06%)	59/592 (9.9%)	0.52 (0.35–0.77)	0.001
Bucaneve et al. (2005)	10/373 (2.6%)	18/363 (4.9%)	0.54 (0.25–1.164)	N.S.
Leibovici et al. (2006)	41/798 (5%)	56/732 (8%)	0.67 (0.46–0.98)	0.05
Infectious mortality				
Gafter-Gvili et al. (2005)	14/542 (2.5%)	33/480 (6.8%)	0.38 (0.21–0.69)	0.001

All the available meta-analyses have shown a reduction of microbiologically documented infections in patients who have received antibacterial prophylaxis.[22–25] The magnitude of this reduction was about 50% in the meta-analysis by Gafter-Gvili et al. when considering only trials in which fluoroquinolones were used.[22] The results of the GIMEMA study[20] are comparable. In fact, the relative risk reduction was about 50% for patients with either acute leukaemia or HSCT; a significant reduction in the occurrence of bacteraemias was also shown in acute leukaemia and transplanted patients[20] and in the meta-analysis.[22]

3.2.1. *Gram-negative infections*

In acute leukaemia and HSCT patients Gram-negative infections account for about 10% of total febrile episodes. *Escherichia coli* and *Pseudomonas* spp. were the most frequently isolated Gram-negative bacteria (in about 6% and 2% of the total number of febrile episodes, respectively).[20] All of the available meta-analyses performed in neutropenic patients confirmed that antibacterial prophylaxis was associated with a relative risk reduction for Gram-negative infections. It was found to be about 30% in the meta-analysis of Gafter-Gvili et al. when the analysis was limited to fluoroquinolone studies.[22] In both acute leukaemia and HSCT patients,[20] the use of levofloxacin reduced the relative risk of bacteraemia by approximately 70% (Table 2). The effect of fluoroquinolones seemed mainly due to a reduction of *E. coli* infections.[20]

3.2.2. *Gram-positive infections*

In the GIMEMA trial, performed in neutropenic acute leukaemia and HSCT patients, Gram-positive infections accounted for about 15% of the total number of febrile episodes. Staphylococci (76% of coagulase-negative staphylococci) and streptococci were the most frequently isolated Gram-positive bacteria (in about 12% and 3% of total number of febrile episodes, respectively).[20] Among staphylococci, methicillin-resistant strains were predominant. In patients with acute leukaemia or autologous HSTC recipients, the use of levofloxacin was associated with a statistically significant lower rate of Gram-positive infections (relative risk reduction of about 50%) (Table 2). The same trend observed in the subgroup of bloodstream infections was analysed (RR 0.67, 0.45–1.00; $p = 0.06$)[20] (Table 2). As shown in the GIMEMA trial,[20] the effect on Gram-positive infections was mainly due to the reduction of fluoroquinolone-susceptible streptococcal and staphylococcal (primarily *Staphylococcus aureus*) infections. The meta-analysis by Gafter Gvili et al.[22] confirmed these findings (Table 2). Of note, nine of 17 trials examined in the meta-analysis included broad-spectrum fluoroquinolones, such as ciprofloxacin, ofloxacin and pefloxacin. A reduction of Gram-positive infections was also observed in clinical trials in which anti-Gram-positive agents (i.e. beta-lactams, macrolides, rifampin or glycopeptides) were added to the fluoroquinolones. In a systematic review, Cruciani and colleagues[26] found that these antibiotic regimens did not show a clear benefit in terms of morbidity and mortality and were associated with a higher incidence of adverse events. This is the reason why the authors concluded that it was not necessary to add specific anti-Gram-positive coverage to fluoroquinolones.

3.3. *Mortality in neutropenic patients*

None of the fluoroquinolone clinical trials had shown a statistically significant effect of prophylaxis on mortality. The meta-analysis by Gafter-Gvili et al.[22] based on 14 of the 17 clinical trials performed before 2005 and which included a total of 1244 neutropenic cancer patients (with acute leukaemia, solid tumours or who had undergone bone marrow transplantation) showed that fluoroquinolone prophylaxis

significantly reduced all-cause mortality (relative risk reduction of 48%) and infection-related mortality (relative risk reduction of 68%) (Table 2). The reduction of mortality associated with the use of oral antibiotic prophylaxis (i.e. fluoroquinolones and trimethoprim/sulfamethoxazole) was confirmed in the meta-analysis performed by van Wetering et al. (relative risk reduction of 49%) that included 13 trials with a total number of 966 patients.[23] In patients with acute leukaemia and bone marrow transplantation, a meta-analysis performed by Leibovici et al.[27] on 10 randomised trials conducted between 1980 and 2005 that included 1530 patients confirmed that fluoroquinolones reduced all-cause mortality in this subgroup of patients (relative risk 0.67; 95% CI 0.46–0.98). Although not designed to detect a difference in mortality, the GIMEMA trial[20] performed in acute leukaemia/HSCT patients showed that the number of deaths were lower in patients treated with levofloxacin than in those treated with placebo (relative risk 0.54; 95% CI 0.25–1.16) (Table 2).

3.4. *Emergence of resistance*

A major concern of fluoroquinolone prophylaxis is the emergence of resistant bacteria, such as resistant *E. coli*, *Pseudomonas* spp. and methicillin-resistant *S. aureus*.[28–32] The reported rate of emerging resistance differed from study to study according to the type of enrolled population. In the meta-analysis of Gafter-Gvili et al., the incidence of infections caused by fluoroquinolone-resistant bacteria was 5% in patients treated with fluoroquinolones, which was less than in patients treated with TMP-SMZ.[22] In the meta-analysis by Engels et al.,[24] the pooled incidence of quinolone-resistant Gram-negative infections was 3.0% (based on 13 trials) and that of quinolone-resistant Gram-positive infections was 9.4% (based on eight trials). This trend was confirmed in the GIMEMA study[20] with a prevalence of levofloxacin-resistant Gram-positive and Gram-negative infections of 9% and 3%, respectively. Data from several prophylactic studies suggest that the increasing resistance to fluoroquinolones among isolates from onco-haematological patients reflects the pressure exerted by these antibiotics on the endogenous flora, rather than the dissemination of fluoroquinolone-resistant strains in the general population. In fact, fluoroquinolone resistance is a multiclonal, reversible phenomenon.[33,34] Moreover, the pattern of fluoroquinolone resistance did not seem to affect clinical outcomes, such as infection-related morbidity or mortality as shown in the GIMEMA trial.[20] Although there was a high incidence of quinolone-resistant bacterial strains, no deaths occurred in patients with single Gram-negative bacteraemias.

In neutropenic cancer patients, there is no evidence that use of fluoroquinolone prophylaxis was associated with a shift in the type of infections occurring in these patients. The two meta-analyses published in 2005[22,23] do not suggest that fluoroquinolone prophylaxis is associated with a statistically significant increased risk of fungal infections. Finally, fluoroquinolones are not commonly used as empirical antibiotic regimens in high-risk neutropenic patients.[1]

Based on these data, it does not appear that the risk of resistance offsets the favourable impact of fluoroquinolone prophylaxis on mortality, microbiologically documented infections (including both Gram-negative and Gram-positive infections), number of febrile episodes and costs. However, should prophylaxis be adopted, it would seem prudent to carefully monitor the emergence of bacterial resistance (see Section 5).

3.5. *Other endpoints*

A reduction in the use of empiric antibacterial therapy and associated costs was observed in the GIMEMA study.[20]

3.6. *The results of the questionnaire on the European practices concerning antibacterial prophylaxis in neutropenic patients*

Twenty-three of the 38 (61%) clinicians who provided answers to this section of the questionnaire declared they are using antibacterial prophylaxis for the prevention of infections in neutropenic cancer patients. Ciprofloxacin and levofloxacin are the agents most often used. Trimethoprim/sulfamethoxazole is used by a minority of physicians. Among these 23 clinicians, antibacterial prophylaxis is used more often in allogeneic HSCT patients (83%) than in patients with acute leukaemia (69%) or than in recipients of autologous HSCT (61%). Most experts (about 70% in each subgroup) start antibacterial prophylaxis before the onset of neutropenia (i.e. upon hospital admission or when chemotherapy is administered) and continue prophylaxis until the resolution of neutropenia or development of fever and initiation of empirical broad-spectrum antibiotic therapy in which case prophylaxis is discontinued.

3.6.1. *Reasons for using prophylaxis*

As expected, prevention of Gram-negative infections (25%) is the main reason given for using prophylaxis, followed by the prevention of serious infectious complications and bacteraemias. Prevention of fever is in the fourth place, before mortality.

3.6.2. *Evidence from the literature and need for additional studies*

Only six of the 15 physicians not using prophylaxis provided an answer to this question. Five of the them (83%) believed that their choice was supported by data from the literature and only one thought that further studies were needed. Conversely, 15 of the 23 (65%) physicians who are using prophylaxis believed that their choice was supported by data from the literature, but considered that additional studies should be performed.

4. Summary

In high-risk patients, such as those with neutropenia expected to last for more than seven days, comprising primarily patients with acute leukaemia or autologous haematopoietic stem cell transplant (HSCT) recipients, prophylaxis with fluoroquinolones was shown to be effective in reducing (quality of evidence I) (Table 3)

Table 3 – Recommendations for fluoroquinolone prophylaxis for prevention of bacterial infections in neutropenic patients with acute leukaemia or haematopoïetic stem cell transplant

Does fluoroquinolone prophylaxis prevent bacterial infections in patients with acute leukaemia?	Yes Levofloxacin (500 mg once daily): AI Ciprofloxacin (500 mg bid): AI Ofloxacin (200–400 mg bid): BI Norfloxacin (400 mg bid): BI
When should fluoroquinolone prophylaxis be started and how long should it be continued?	Start with chemotherapy and continue until resolution of neutropenia or initiation of empirical antibacterial therapy for febrile neutropenia (AII)

- All-cause mortality and infection-related mortality.
- Febrile episodes.
- Bacterial infections (including those caused by Gram-negative and Gram-positive bacteria and bloodstream infections caused by Gram-negative bacteria).
- Use of empirical antibiotics.

5. Recommendations (Table 3)

Does fluoroquinolone prophylaxis prevent infections in patients with acute leukaemia or in recipients of haematopoietic stem cell transplantation?

Answer: Yes.

Levofloxacin (500 mg once daily): AI.
Ciprofloxacin (500 mg bid): AI.
Ofloxacin (200–300 mg bid): BI.
Norfloxacin (400 mg bid): BI.

Comments. Ciprofloxacin, norfloxacin and ofloxacin were the most frequently used fluoroquinolones for prophylaxis in randomised clinical trials. Levofloxacin has been used in the two largest randomised trials available today. Given the results obtained in these trials, ciprofloxacin or levofloxacin is the drug of first choice. One randomised trial has demonstrated that ciprofloxacin was superior to norfloxacin.[35] Ofloxacin has a lower *in vitro* activity than ciprofloxacin and levofloxacin against *Pseudomonas* spp. and was found to be less effective than ciprofloxacin in one study.[36] Ofloxacin has been used less often than ciprofloxacin in clinical trials. As shown in Table 1, the dose of levofloxacin was 500 mg given once daily in the two recent clinical trials. In contrast, different daily doses of ciprofloxacin (500–1500 mg/d), ofloxacin (400–800 mg/d) and norfloxacin (400–800 mg/d) have been used in clinical trials. The dose of ciprofloxacin recommended is the one that has been used in most studies. If fluoroquinolone prophylaxis is used for prevention of infections in neutropenic patients, it is recommended to (1) monitor the emergence of fluoroquinolone-resistant bacteria (AIII), and (2) use an empirical antibiotic therapy active against *Pseudomonas* spp. (AIII).

When should fluoroquinolone prophylaxis be started and how long should it be continued?

Answer: Start with chemotherapy and continue until resolution of neutropenia or initiation of empirical antibacterial therapy for febrile neutropenia (AII).

Comments. As a note of caution, prophylactic administration of ciprofloxacin during cyclophosphamide conditioning is a risk factor for relapse of haematological malignancy in patients undergoing allogeneic bone marrow transplantation. Ciprofloxacin administration prior to cyclophosphamide has resulted in significantly lower exposure of patients with non-Hodgkin lymphoma to 4-hydroxy-cyclophosphamide, the active metabolite of cyclophosphamide.[37–39] Thus antibacterial prophylaxis with fluoroquinolones should be started 24–48 h after the end of high dose cyclophosphamide therapy (AIII).

6. Areas for future studies

Several areas of future clinical investigation deserve consideration, such as placebo-controlled randomised trials in allogeneic HSCT patients and in paediatric cancer patients.

Conflict of interest statement

Giampaolo Bucaneve declares no conflict of interest.

Elio Castagnola has received grant support from Gilead Science and Pfizer Italy and has received fees for lectures from Gilead Science, Pfizer and Merck Sharp and Dohme.

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