1st European Conference on Infection in Leukemia

Fluoroquinolone Prophylaxis In neutropenic patients

For the working group Giampaolo Bucaneve

Sept. 30th / Oct. 1st 2005 Juan-les-Pins - France

ELN European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

ICHS International Society for Compromised Host

Questionnaire on European practices: Antibacterial Prophylaxis

38 respondants : 23 (61%) use antibacterial prophylaxis

Setting in which prophylaxis is used	
Allo HSCT	83%
AutoHSCT	61%
AL induction	69%

Time of Initiation	alloHSCT	autoHSCT	induct.
Before the onset of Neutropenia	78%	78%	87%

Duration of proph.	alloHSCT	autoHSCT	induct.
Until the end of of Neutropenia	79%	86%	87%

STOP at onset of fever ? YES	
Allo HSCT	68%
AutoHSCT	64%
AL induction	69%

Type of Regimen	alloHSCT	autoHSCT	induct.
QUINOLONES	**16/23 (70%)**	**12/16 (75%)**	**13/18 (72%)**
Ciprofloxacin	11/19 (58%)	8/14 (57%)	10/16 (62%)
Levofloxacin	3/19 (16%)	3/14 (21%)	2/16 (25%)
TMP/SFM	**1/23 (4%)**	**1/16 (6%)**	-

Questionnaire on European practicies: Antibacterial Prophylaxis

REASONS FOR USING PROPHYLAXIS

To prevent gram-negative infections	14	(25%)
To prevent serious infection complications	11	(20%)
To prevent bacteremia	9	(16%)
To prevent fever during neutropenia	8	(14%)
To prevent mortality due to infection	7	(13%)
To prevent another event	4	(7%)
To prevent gram-positive infections	3	(5%)

Is there evidence from the literature ?

15 do not use prophylaxis, only 6 respondants

5/6 (83%) belive that their choice is supported by literature

23 use prophylaxis

15/23 (65%) believe that their choice is supported by literature

Need for additional studies ?

15 do not use prophylaxis, only 5 respondants

1/5 (20%) considers that additional studies are needed.

23 use prophylaxis

15/23 (65%) consider that additional studies should be done

Prophylaxis with quinolones : Problems (1)

- Only few placebo-controlled, double-blind, randomized clinical trials.
- None of the studies were sufficiently large to provide conclusive evidence.
- Most of the studies were unpowered to detect a statistically significant effect on mortality.

Prophylaxis with quinolones : Problems (2)

- In most studies the occurrence of fever requiring empirical antibiotic therapy was not considered or was not significantly reduced.

- No clear indications were provided on the neutropenic population who may benefit most from prophylaxis.

- The routine use of fluoroquinolones prophylaxis has been questioned, because it can increase bacterial resistance.

Scope of the Review

- To assess the clinical evidence supporting the efficacy of antibiotic prophylaxis with fluoroquinolones in neutropenic cancer patients.

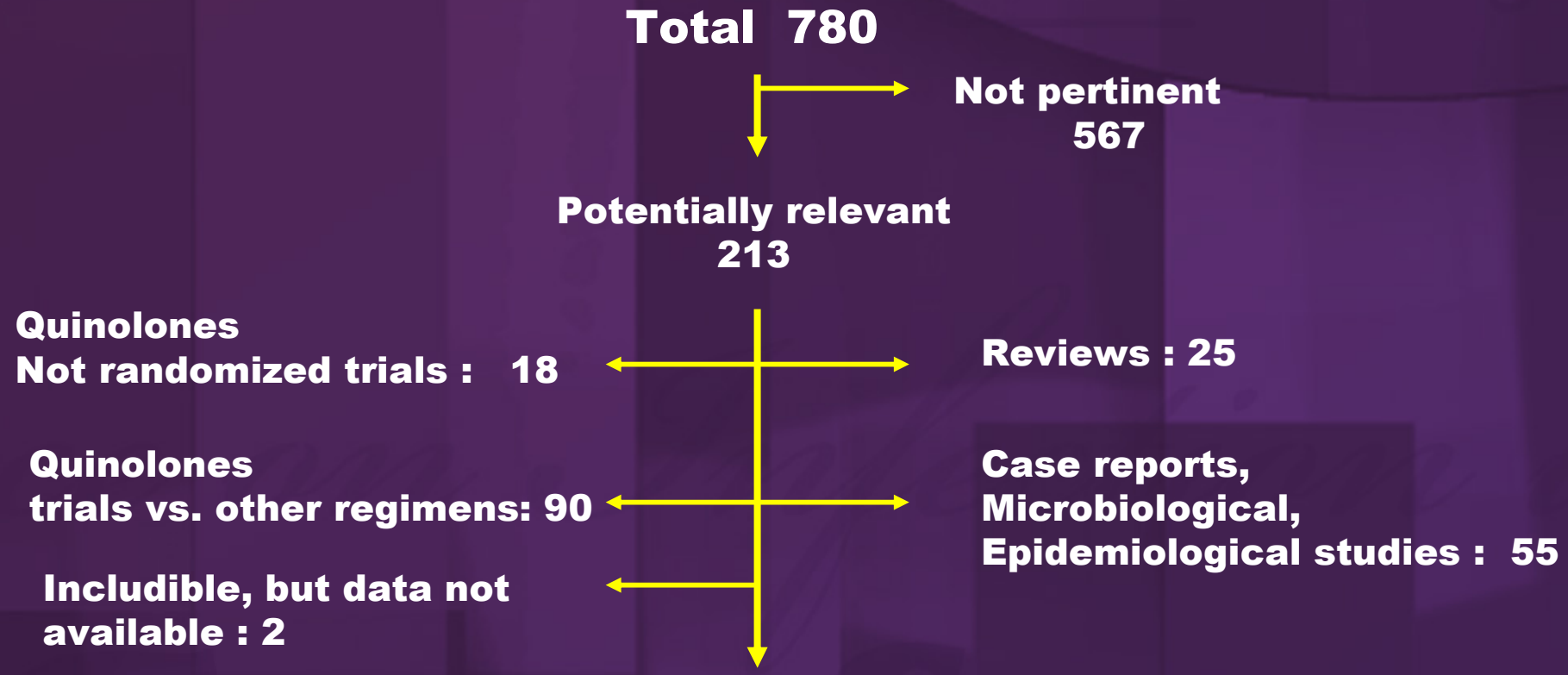
ADOPTED STRATEGY

- Review of the literature according to previous mentioned methodology.

- Inclusion criteria:
  - Randomized, controlled trials performed in neutropenic cancer patients comparing fluoroquinolones with placebo or no intervention.

Fluoroquinolone prophylaxis : Publications identified and exclusions

(1980-2005)



TRIALS COMPARING FLUOROQUINOLONES WITH PLACEBO OR NO INTERVENTION

- **TESTED QUINOLONES** :
  - Norfloxacin, Ciprofloxacin, Ofloxacin, Pefloxacin, Enoxacin, Levofloxacin, Nalidixic Ac.

- ***TREATED POPULATIONS***
  - Haematologic Malignancies : 10 trials (6 Acute Leukemia)
  - Solid Tumors/Lymphomas : 5 trials
  - Mixed : 4 Trials

Quinolone prophylaxis : Publications identified

META-ANALYSES

Anat Gafter-Gvili et al.
Annals of Internal Medicine, 2005: 17 trials (1409 patients)

Van de Wetering et al.
European Journal of Cancer, 2005: : 8 trials (746 patients)

Engels et al.
Journal of Clinical Oncology, 1998 : 9 trials (731 patients))

CLINICAL TRIALS

Bucaneve and GIMEMA
New England Journal of Medicine, 2005 (760 patients)

Cullen et al.
New England Journal of Medicine, 2005 (1565 patients)

Febrile Episodes

META-ANALYSIS 1409 patients	Fluoroquinolone	Placebo/No Treatment	RR	P
Overall	369/798 (46%)	505/701 (72%)	0.67 (0.56-0.81)	<0.001

Anat Gafter Gvili et al. Annals of Internal Medicine, 2005

RCT: AL, HSCT 760 patients	Levofloxacin	Placebo	RR	P
Overall	243/375 (65%)	308/363 (85%)	0.76 (0.70, 0.83)	0.001
AL	123/183 (67%)	154/179 (86%)	0.78 (0.69, 0.97)	<0.001
HSCT	129/192 (62%)	154/184 (84%)	0.80 (0.71, 0.90)	<0.001

Bucaneve and GIMEMA New England Journal of Medicine, 2005

Acute Leukemia and HSCT patients

NNT to avoid 1 Febrile Episode = 5

Bucaneve and GIMEMA . New England Journal of Medicine, 2005

Microbiologically Documented Infections :

META-ANALYSIS 1409 patients	Fluoroquinolone	Placebo/No Treatment	RR	P
Overall	171/706 (24%)	318/701 (45%)	0.50 (0.35-0.70)	<0.001

Anat Gafter Gvili et al. Annals of Internal Medicine, 2005

RCT: AL, autoHSCT 760 patients	Levofloxacin	Placebo	RR (95%CI)	P
Overall	74/339 (22%)	131/336 (39%)	0.55 (0.43,0.71)	<0.001
AL	39/165 (24%)	74/165 (45%)	0.52 (0.38,0.72)	<0.001
HSCT	35/174 (20%)	57/171 (33%)	0.60 (0.41, 0.86)	0.007

Bucaneve and GIMEMA New England Journal of Medicine, 2005

Gram-negative Infections (1)

RCT: AL, autoHSCT 760 patients	Levofloxacin	Placebo	RR (95%CI)	P
Total infections	21/339 (6%)	47/336 (14%)	0.44 (0.27, 0.72)	0.001
Bacteremias	15/339 (4%)	38/336 (11%)	0.39 (0.21, 0.69)	0.001

Bucaneve and GIMEMA New England Journal of Medicine, 2005

Gram-negative Infections (2)

Leibovici , data not published, 2005

Gram-negative Infections

META-ANALYSIS* 3416 patients	Fluoroquinolone	Placebo/No Treatment	RR (95%CI)	P
Overall	79/1708 (4.6%)	279/1708 (16%)	0.29 (0.23-0.37)	<0.001
AL, BMT (HSCT)	64/673 (9.5%)	194/668 (29%)	0.33 (0.25-0.43)	<0.001

* Including GIMEMA and Cullen' Trials , 2005

Gram-negative Bacteremias

META-ANALYSIS* 2949 patients	Fluoroquinolone	Placebo/No Treatment	RR (95%CI)	P
Overall	40/1476 (2.7%)	18/1473 (8%)	0.35 (0.25-0.49)	0.005
AL, BMT (HSCT)	38/598 (6.3%)	106/592 (17.9%)	0.36 (0.25-0.50)	<0.001

* Including GIMEMA ans Cullen' Trials , 2005

Gram-positive Infections (1)

Acute Leukemia and auto-HSCT

	Levofloxacin	Placebo	RR (95%CI)	P
Total infections	42/339 (12%)	61/336 (18%)	0.68 (0.47, 0.98)	0.04
Bacteremias	37/339 (11%)	54/336 (16%)	0.67 (0.45, 1.00)	0.06

Bucaneve and GIMEMA New England Journal of Medicine, 2005

Gram-positive Infections (2)

Leibovici , data not published, 2005

Gram-positive Infections

META-ANALYSIS* 3413 patients	Fluoroquinolone	Placebo/No Treatment	RR (95%CI)	P
Overall	109/1708 (6.3%)	295/1705 (17%)	0.38 (0.31-0.46)	<0.001
AL, BMT (HSCT)	91/680 (13.3%)	204/679 (30%)	0.45 (0.36-0.56)	<0.001

* Including GIMEMA and Cullen' Trials , 2005

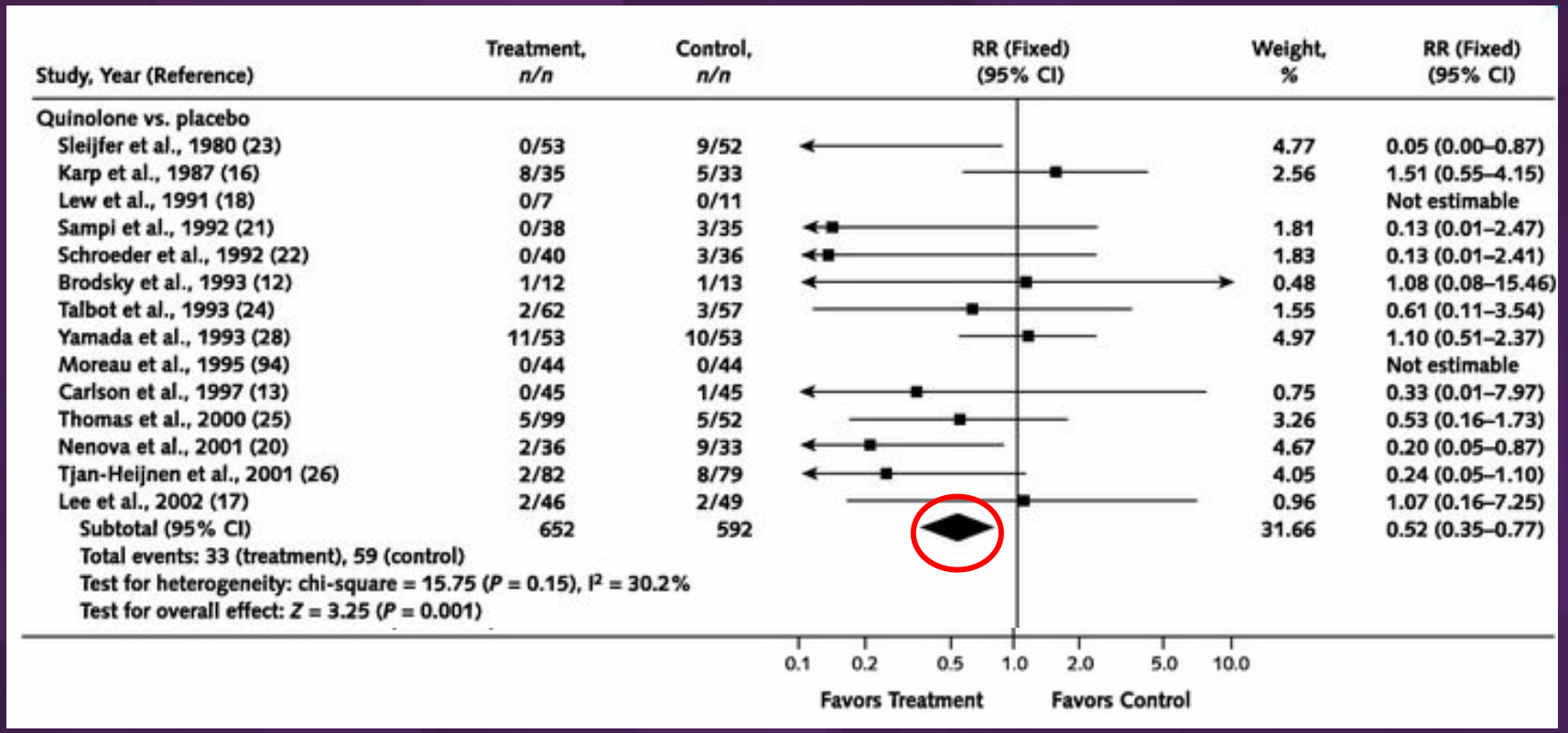
Gram-positive Bacteremias

META-ANALYSIS* 2949 patients	Fluoroquinolone	Placebo/No Treatment	RR (95%CI)	P
Overall	114/1476 (7.7%)	147/1473 (9.9%)	0.77 (0.63-0.96)	0.03
AL, BMT (HSCT)	108/605 (17.8%)	133/603 (22%)	0.81 (0.65-1.01)	0.07

* Including GIMEMA ans Cullen' Trials , 2005

All Cause Mortality :
Quinolone prophylaxis vs. Placebo or no treatment

Anat Gafter Gvili et al. Annals of Internal Medicine, 2005



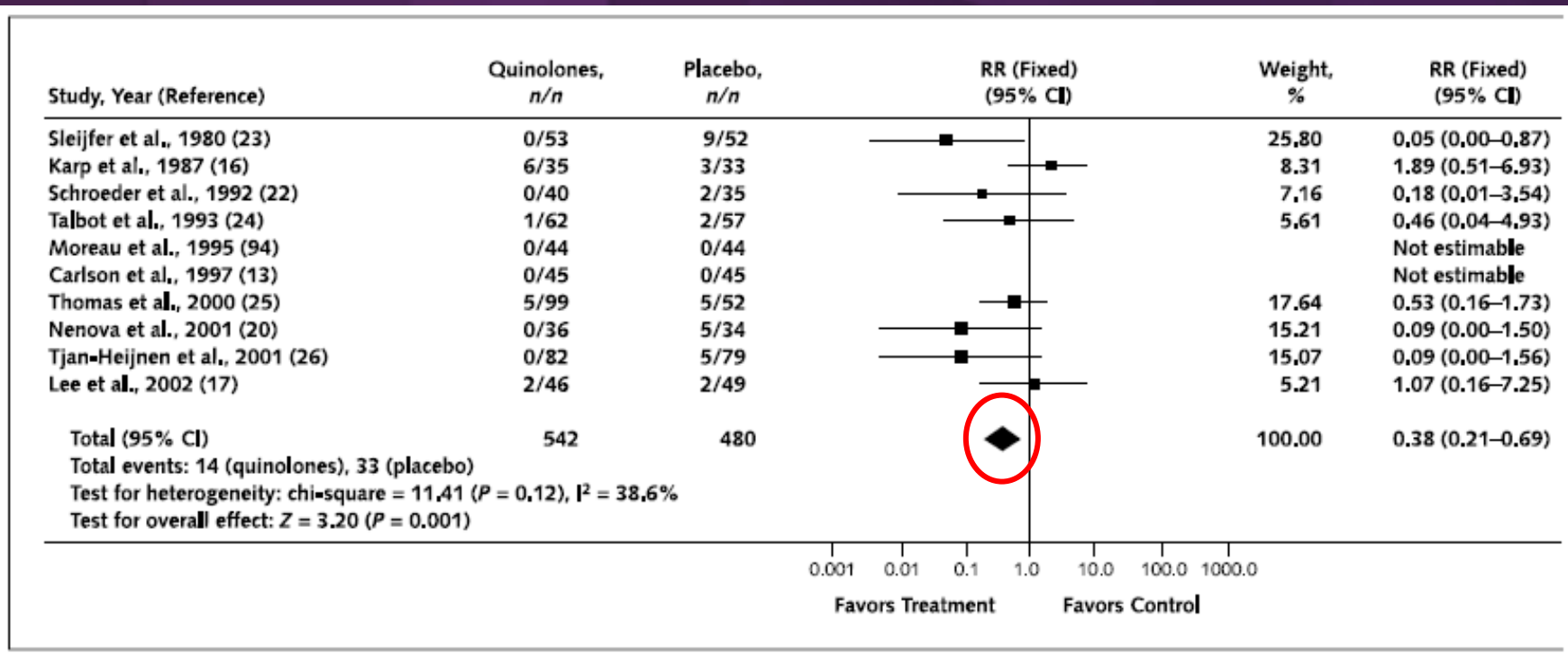
Study, Year (Reference)	Treatment, *n/n*	Control, *n/n*	RR (Fixed) (95% CI)	Weight, %	RR (Fixed) (95% CI)
Quinolone vs. placebo					
Sleijfer et al., 1980 (23)	0/53	9/52		4.77	0.05 (0.00–0.87)
Karp et al., 1987 (16)	8/35	5/33		2.56	1.51 (0.55–4.15)
Lew et al., 1991 (18)	0/7	0/11			Not estimable
Sampi et al., 1992 (21)	0/38	3/35		1.81	0.13 (0.01–2.47)
Schroeder et al., 1992 (22)	0/40	3/36		1.83	0.13 (0.01–2.41)
Brodsky et al., 1993 (12)	1/12	1/13		0.48	1.08 (0.08–15.46)
Talbot et al., 1993 (24)	2/62	3/57		1.55	0.61 (0.11–3.54)
Yamada et al., 1993 (28)	11/53	10/53		4.97	1.10 (0.51–2.37)
Moreau et al., 1995 (94)	0/44	0/44			Not estimable
Carlson et al., 1997 (13)	0/45	1/45		0.75	0.33 (0.01–7.97)
Thomas et al., 2000 (25)	5/99	5/52		3.26	0.53 (0.16–1.73)
Nenova et al., 2001 (20)	2/36	9/33		4.67	0.20 (0.05–0.87)
Tjan-Heijnen et al., 2001 (26)	2/82	8/79		4.05	0.24 (0.05–1.10)
Lee et al., 2002 (17)	2/46	2/49		0.96	1.07 (0.16–7.25)
Subtotal (95% CI)	652	592		31.66	0.52 (0.35–0.77)
Total events: 33 (treatment), 59 (control)					
Test for heterogeneity: chi-square = 15.75 (P = 0.15), I^2 = 30.2%					
Test for overall effect: Z = 3.25 (P = 0.001)					

1244 patients

RR = 0.52 (95% CI 0.35-0.77)

Infection related Mortality :
Quinolone prophylaxis vs. Placebo or no treatment

Anat Gafter Gvili et al. Annals of Internal Medicine, 2005



RR = relative risk.

1st European Conference on Infection in Leukemia

1022 patients

RR = 0.38 (95% CI 0.21-0.69)

All-cause Mortality :

Quinolone prophylaxis vs. Placebo or no treatment *

META-ANALYSIS* 3440 patients	Fluoroquinolone	Placebo/No Treatment	RR (95%CI)	P
Overall	54/1753 (3%)	82/1687 (5%)	0.62 (0.37-0.74)	<0.01
AL, BMT (HSCT)	41/798 (5.1%)	56/732 (7.6%)	0.67 (0.45-0.86)	0.05

* Including GIMEMA Trial , 2005

Leibovici , Cancer, 2006; Oct 15;107(8):1743-51.

Fluoroquinolone prophylaxis and costs

(Acute Leukemia and autoHSCT patients)

	Levofloxacin	Placebo	P
Mean Cost per patients of antibiotics (Euro)	1.953,00	2.841,00	<0.0001

Bucaneve - GIMEMA. New England Journal of Medicine, 2005

Prophylaxis with fluoroquinolones in neutropenic patients. Relative risk and numbers needed to treat in order to prevent one death, a febrile episode and a bacterial infection according to meta-analysis (Gafter-Gvili, 2005 *) and the recent, largest randomized controlled trial (Bucaneve, 2005 **)

Patients (study)/event	Relative risk [95% CI)	Absolute risk in the control group%	Numbers needed to treat to prevent one event
All patients * :			
Death from any cause	0.52 [0.35-0.77]	8.7	24
Febrile episode	0.67 [0.56–0.81]	72	4
Bacterial infection	0.50 [0.35–0.70]	45	5
Patients with expected prolonged neutropenia**			
Death from any cause	0.54 [0.25–1.16]	5	43
Febrile episode	0.76 [0.69–0.83]	85	5
Bacterial infection	0.56 [0.44–0.71]	39	6

Leibovici , Cancer, 2006; Oct 15;107(8):1743-51.

Fluoroquinolone resistance in neutropenic patients receiving prophylaxis

- The occurrence of resistant Gram negative (E.coli, Pseudomonas spp) from surveillance cultures and bacteremias has been reported. (Kern 1994, Cometta 1994, Carratala 1995)

- E.coli and Pseudomonas quinolone resistant strains and cross-resistant to other antibiotics (cotrimoxazole, doxyciclin,CAF, beta-lactams) have been reported. (Sanders 1984, Piddock 1987, Lagakis 1989, Banerfeind 1994)

- Emergence of methicillin resistant staphylococci during prophylaxis with quinolones. (Oppenheim 1989, Cometta 1994)

Fluoroquinolone resistance in neutropenic patients receiving prophylaxis

- The fluoroquinolone resistance is a multiclonal phenomenon with a limited sharing of clones among hematology-oncology patient population

  (Tascini,Clin Microbiol Infect, 1999; Kern, J Clin Microbiol Infect Dis, 2005)

- The fluoroquinolones resistance is a reversible phenomenon (Martino, Acta Haematol, 1998; Kern, J Clin Microbiol Infect Dis, 2005)

- The fluoroquinolones resistance did not seem to affect clinical outcomes, such as infection-related morbidity or mortality (Bucaneve, New England Journal of Medicine, 2005).

Fluoroquinolone resistance and infection related mortality

Levofloxacin resistance in single-agent bacteremias — no. resistant/total no. available for analysis	41/47	32/68
Gram-positive isolate	31/34	28/44
S. aureus	0	1/7
Coagulase-negative staphylococcus	27/30	26/31
Streptococcus species	4/4	1/3
Other gram-positive organisms	0	0/3
Gram-negative isolate	10/13	4/24
Pseudomonas species	4/6	1/4
E. coli	5/5	2/16
Other gram-negative organisms	1/2	1/4

77%

Table 3. Mortality Rates in the Treated Population.

Variable	Levofloxacin (N=373)*	Placebo (N=363)	P Value
	no. of patients		
Death	10	18	0.15
Death due to infection	9	14	0.36
Microbiologically documented infection	4	7	0.25
Microbiologically documented infection with bacteremia	3	5	0.34
Single gram-positive isolate	2	2	
Single gram-negative isolate	0	2	
Polymicrobial (gram-positive and gram-negative) isolate	1	1	
Microbiologically documented infection without bacteremia	1	2	0.48
Single gram-positive isolate	0	1	
Single gram-negative isolate	1	1	
Clinically documented infection	2	4	0.33
Lung	1	2	
Other site	1	2	
Fever of unexplained origin	3	3	0.64
Death from noninfectious causes	1	4	0.17

* Two patients were lost to follow-up.

Bucaneve and GIMEMA. New England Journal of Medicine, 2005

Recommendations

QUALITY OF EVIDENCE

High risk patients
(expected duration of neutropenia > 7 days)

Acute Leukemia and Auto-HSCT

Antibacterial prophylaxis with fluoroquinolones showed to be effective in reducing (quality of evidence I) :

- Mortality
- Febrile episodes
- Bacterial infections and bacteremias
- Gram-negative infections and bacteremias
- Gram-positive infections but not bacteremias
- The use of empirical antibiotics

Allo-HSCT

Because the expected duration of neutropenia is more than seven days also in allo HSCT patients, this group is considered at high risk.

Data on efficacy of quinolone prophylaxis are available only for bone marrow transplanted but not for allo HSCT patients.

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

YES

Drug of Choice	Strength of Recommendation and level of evidence
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)

As a note of caution, antibacterial prophylaxis with fluoroquinolones should be started 24-48 hours after the end of high dose cyclophosphamide therapy (AIII).

The prophylactic administration of ciprofloxacin during cyclophosphamide conditioning was a risk factor for relapse of haematological malignancy in patients undergoing allogeneic bone marrow transplantation (Carlens S, *Clin Transplant* 1998) and the same quinolone 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 (Afsharian P *Eur J Haematol* 2005).

"Caveat"

- Periodic monitoring for any marked increase in (AIII):
  - Use of empirical antibacterial therapy
  - Fluoroquinolone resistance among gram-negative
  - Mortality

Fluoroquinolone Prophylaxis In neutropenic patients

WORKING GROUP

Giampaolo Bucaneve
Elio Castagnola
Leonard Leibovici
Francesco Menichetti
Claudio Viscoli

LEADERS

Francesco Menichetti
Claudio Viscoli

1st European Conference on Infection in Leukemia