

Treatment of febrile neutropenia in patients with neoplasia

George Samonis MD, PhD
Medical Oncologist – Infectious Diseases Specialist
Professor of Medicine
The University of Crete, Heraklion, Crete, Greece

Definition of febrile neutropenia

- Definition of fever: A single oral $T \geq 38.3^{\circ}\text{C}$ or $T \geq 38^{\circ}\text{C}$ for at least 1 hour
- Definition of neutropenia: $\text{ANC} < 500/\mu\text{l}$ or $\text{ANC} < 1,000$ with predicted decline to $< 500/\mu\text{l}$ within the next 24 to 48 hours
- Both needs to be present for an episode to be characterized as febrile neutropenia (F+N)

Introductory comments on F+N

- WHO grades neutropenia based only on the ANC
- However, the risk of infection also correlates with the duration of neutropenia
- $ANC < 100/\mu l$ for 3 weeks is associated with 100% risk of infection
- Additional risk factors should be considered (mucositis, poor oral hygiene, surgical wounds, use of corticosteroids, immunosuppressants, etc)

Common sites of infection in patients with cancer and F+N

- Bloodstream infections (BSIs), catheter insertion site infections
- Pneumonia, upper respiratory tract infections
- Skin and soft tissue infections
- Gut infections (enterocolitis, perirectal abscesses)
- Urinary tract infections (UTIs)
- Surgical wound infections

Microbiology of F+N in cancer patients-I

- Most bloodstream infections are due to Gram positive organisms from the patient's skin flora
- Most gut infections are due to Gram negative, anaerobic and mixed pathogens
- Lung infections are usually hospital-acquired or health-care associated and due to Gram negative pathogens
- Fungal infections common in patients with hematological malignancies and prolonged F+N

Microbiology of F+N in cancer patients-II

- In >50% of cancer patients with F+N, no source of infection can be identified
- Most of these patients respond to empirical antibiotic therapy and likely have an infection that can not be identified with the usual microbiological and imaging studies
- Significant institutional differences in patterns of infection, microbiology and resistance
- Resistance is on the rise for both Gram positive and Gram negative pathogens

Treatment of febrile neutropenia

- For many years combinations of β -lactam antibiotics and aminoglycosides are considered standard therapy for febrile neutropenia
- Among β -lactam antibiotics, ceftazidime has been extensively used, because of its efficacy and favorable toxicity profile, which allows administration in the presence of mild or moderate renal dysfunction and in patients who receive nephrotoxic drugs
- Fluoroquinolones have been successfully evaluated as monotherapy or combination therapy in febrile neutropenic patients, but experience is much less compared to the "gold standard" combination of ceftazidime plus amikacin

Prospective matched case control study of patients with cancer and F+N

- Comparison of the "gold standard" antibiotic combination ceftazidime (2 g IV every 8 hours) plus amikacin (15 mg/kg IV once daily) (arm A-controls) with the combination ceftazidime plus levofloxacin (500mg IV every 12 hours) (arm B-study group) in adults with solid tumors or hematological malignancies including MDS and febrile neutropenia
- Patients on both arms enrolled over 36 months (arm A was not a historical control)
- Filgrastim use (5µg/kg SC) allowed at investigator's discretion

Ceftazidime antimicrobial spectrum

- *E. coli*, *Proteus* spp., *Klebsiella* spp., *Enterobacter* spp., *Serratia*, *Citrobacter*, *Neisseria*, *H. influenzae*, *P. aeruginosa*
- Less active against most Gram positive organisms compared to first-generation cephalosporins
- Inactive against enterococci, *Listeria*, MRSA

Amikacin antimicrobial spectrum

- Gram-negative bacteria (*E. coli*, *Proteus*, *Klebsiella*, *Pseudomonas*) etc.
- Active against some staphylococcus strains (*S. epidermidis* and *S. aureus*)

Levofloxacin antimicrobial spectrum

- Gram negative organisms, but less active compared to ciprofloxacin against some strains of *P. aeruginosa*
- *H. influenzae* and *M. catarrhalis*, increased potency against *S. pneumoniae*
- MSSA, usually not MRSA and enterococci
- *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila*
- *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*
- *M. tuberculosis*, *M. fortuitum*, *M. kansasii*, and some strains of *M. chelonae*

Study population

A matched case control study

- Age \geq 18 years
- Presence of malignant disease and of febrile neutropenia
- Exclusion criteria: Known allergy to cephalosporins, aminoglycosides or quinolones, multi-organ failure due to sepsis, CNS infection and prior antibiotic treatment with any of the study drugs within 72 hours preceding the febrile episode

Study population

- 285 patients [168 M (58.9%) and 117 F (41.1%)]
- 95% had grade 3 (ANC <1,000/ μ l) or grade 4 (ANC<500/ μ l) neutropenia at study entry
- 159 (55.8%) suffered from solid tumors and 126 (44.2%) from hematological malignancies
- 148 patients enrolled on arm A and 137 on arm B
- Age: Median 67 years on both arms (range 21-89 and 20-85 years, respectively)

Statistics

- Categorical variables of interest were compared between treatment arms by χ^2 or Fisher's exact test, as appropriate

Underlying cancers of patients enrolled

■ SOLID TUMORS

Breast cancer 52 (32.7%), lung cancer 49 (30.8%), colon cancer 15 (9.4%), ovarian cancer 9 (5.7%), gastric cancer 6 (3.8%), sarcomas 6 (3.8%), head and neck cancer 4 (2.5%), testicular cancer 3, pancreatic cancer 2 (1.3%), prostate cancer 2 (1.3%), others 8 (5%)

■ HEMATOLOGICAL MALIGNANCIES

AML 65 (51.6%), lymphomas 27 (21.4%), MDS 17 (13.5%), ALL 11 (8.7%), CLL 4 (3.2%), MM 1 (0.8%) and WM 1 (0.8%)

Arm assignment by underlying malignancy			Solid tumors ↓	Regimen A n=69	Regimen B n=90
			Breast n=52	26	26
Blood cancers ↓	Regimen A n=79	Regimen B n=47	Lung n=49	26	23
			Colon n=15	1	14
AML n=65	46	19	Ovaries n=9	2	7
Lymphomas n=27	17	10	Stomach n=6	2	4
MDS n=17	7	10	Sarcomas n=6	4	2
ALL n=11	7	4	H&N n=4	2	2
CLL n=4	1	3	Testicles n=3	0	3
Others (MM+WM) n=2	1	1	Bladder, n=3	3	0
			Prostate, n=2	0	2
			Pancreas, n=2	0	2
			Others, n=8	3	5

Patient characteristics

- 18/285 patients (6.3%) carried a CVC (Arm A-9, Arm B-9)
- Filgrastim administered in 244/285 patients (85.6%) (arm A-126, arm B-118) (p NS)
- Duration of filgrastim use: Arm A-median 4 days (range 0 to 32 days), arm B-median 4 days (range 0-30 days) (p NS)
- Duration of fever: Arm A-median 3 days (range 1-16 days), arm B-median 3 days (range 1-33 days) (p NS)
- Duration of neutropenia: Arm A-median 4 days (range 2-45 days), arm B-median 4 days (range 2-34 days) (p NS)

Microbiology of F+N

- In 72 patients (25%), the etiology of fever was identified by appropriate microbiological, serological and/or imaging studies
- BSIs (46): Gram negative (21), Gram positive (20), mixed (4), fungus (1)
- UTIs (9): Gram negative (4), Gram positive (3), mixed (1), fungus (1)
- *Pneumocystis jirovecii* pneumonia (4)
- *C. difficile* colitis (4)
- *Rickettsia* spp. (2)
- Others (7)

Infection ↓	Regimen A n=40	Regimen B n=32
BSIs	26	20
UTIs	5	4
<i>Pneumocystis jirovecii</i>	2	2
<i>C. difficile</i>	3	1
<i>Rickettsia</i> spp.	0	2
Others	4	3
		p=0.67

Results-I

- In 79 patients (27.7%) [Arm A-45, arm B-34, $p=0.35$ by Fisher's exact test] no change of the initial antibiotic regimen was required because the patients defervesced quickly
- In 48 patients (16.8%) [Arm A-27, arm B-21, $p=0.53$], a change of the initial antibiotic regimen, i.e., discontinuation of one or both drugs of that arm and substitution with other antibiotics was necessary based on poor clinical and/or microbiological response
- In 158 patients (55.5%) [Arm A-76, arm B-82, $p=0.15$] some antibiotic addition, usually for additional Gram positive anti-bacterial coverage was required, but without stopping the study drugs

Results-II

- Among the 126 patient-episodes of F+N in those with hematological malignancies, the cause of fever was identified in 46 (36.5%)
- Among the 159 patient-episodes of F+N in those with solid tumors, the cause of fever was identified in 26 (16.4%)
- The difference was highly significant ($p=0.0001$)

Results-III

Most common Gram negatives isolated from blood in patients with BSIs: *K. pneumoniae* (9), *E. coli* (5), *Ps. aeruginosa* (4)

Most common Gram positives isolated from blood in patients with BSIs: *S. epidermidis* (8), *E. faecium* (4), *S. mitis* (2), *Corynebacterium* spp. (2)

13/148 (8.8%) patients in Arm A versus 9/137 (6.6%) in Arm B died of complications related to the infectious episode ($p=0.51$)

Treatment was well-tolerated on both arms

Conclusions

- Empirical treatment of febrile neutropenic episodes in cancer patients with ceftazidime plus levofloxacin appears to be at least as effective as the “gold standard” ceftazidime/ amikacin combination

