



Antibiotic Prophylaxis in Neutropenic Patients

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Febrile neutropenia is one of the most serious adverse events related to chemotherapy and results in significant morbidity and mortality. All patients undergoing chemotherapy are subject to infections: 48%–60% of febrile neutropenic patients were found to have an infection, while 16–20% of profoundly neutropenic patients developed bacteremia [1-3]. In recent years, the treatment of patients with febrile neutropenia has greatly improved and the overall mortality rate has decreased from 21% to 7% [4]. However, it remains a frequent and life-threatening complication of chemotherapy. Fortunately, the management of febrile neutropenia is based on a solid body of evidence gleaned from randomized controlled trials and systematic reviews [5]. New evidence demonstrates that antibiotic prophylaxis in neutropenic patients does indeed reduce mortality.

In a previous systematic review and meta-analysis of randomized controlled trials [6] we compared prophylactic antibiotic therapy to placebo or no intervention or another antibiotic regimen in neutropenic patients receiving chemotherapy. This analysis included 95 randomized controlled trials conducted between 1973 and 2004 with 9283 patients. Death from all causes was reduced by 33% (95% confidence interval 19–45%) in neutropenic patients given any antibiotic prophylaxis, and by 48% (95% CI 23–65%) in patients given fluoroquinolones for prophylaxis. Two large contemporary randomized controlled trials published in 2005 also offer firm evidence on the benefits of prophylaxis. The GIMEMA trial [7] included 760 hospitalized adult patients in whom chemotherapy-induced neutropenia was expected to last for more than 7 days. Acute leukemia and autologous peripheral blood stem cell transplantation were the most common indications (94%). Patients were randomized to receive oral levofloxacin 500 mg once daily or placebo from the start of chemotherapy until resolution of neutropenia. Patients given levofloxacin for prophylaxis had a relative risk of 0.54 (95% CI 0.25–1.16) for

mortality compared to the placebo group, a decrease of 46%. In the SIGNIFICANT trial [8], 1565 patients with solid tumors and lymphomas were randomized to receive either levofloxacin 500 mg once daily or placebo after chemotherapy, for 7 days to cover the period of anticipated neutropenia, during up to six cycles of chemotherapy. In patients given levofloxacin the 30 day mortality was 1.5% (12 of 781 patients) and in the placebo group 2.3% (18 of 784) – a relative risk of 0.67 (95% CI 0.32–1.38) (unpublished data). A significant reduction in febrile episodes, bacterial infections and hospitalizations was shown during the first cycle of chemotherapy and for all cycles. This is by far the largest study evaluating prophylaxis in patients with solid tumors and lymphoma.

Concerns about antibiotic treatment include the cost of the drug, its toxicity, and induction of antimicrobial resistance. Since fluoroquinolones are known to be well tolerated and have an acceptable safety profile, the main consideration against the use of prophylaxis is induction of resistance. In our meta-analysis, patients given fluoroquinolones did not develop more infections with pathogens resistant to the drug than those given placebo (relative risk 1.04, 95% CI 0.73–1.5), since the overall number of infections in the treatment group was lower. A third of the microbiologically documented infections were resistant to the study drug in the treatment group and no data were available for cross-resistance to other antibiotics. However, regarding the individual, mortality was reduced and the overall impact of prophylaxis despite the potential harms of resistance induction was undoubtedly beneficial. As for the microenvironment, many reports document emergence of bacteria resistant to fluoroquinolones in hospital departments in which prophylaxis is practiced [9-12]. However, the clinical implication remains unclear. Several observational studies examined the outcomes in neutropenic patients in settings with a high resistance to fluoroquinolones when antibiotic prophylaxis is discontinued [13-17]. Three trials showed an increase in mortality, bacteremia or febrile episodes when prophylaxis was discontinued [13-15], one showed a statistically non-significant increase in bacteremia and febrile episodes [16], and in another the incidence of febrile episodes was

CI = confidence interval

not affected [17]. As for the population at large, the quantity of fluoroquinolones to be given as prophylaxis to patients with acute leukemia is probably negligible compared to the consumption of fluoroquinolones for more common infections, such as infection of the urinary tract.

Thus, existing evidence, including two very recent trials, provide strong evidence of reduced mortality due to prophylaxis, and clinicians should seriously consider antibiotic prophylaxis for neutropenic patients. We will discuss which drugs to use, which patients should be offered prophylaxis, and local factors that may affect decisions.

Choice of drug

In early trials trimethoprim-sulfamethoxazole was used, but this agent has several disadvantages, including side effects and prolongation of neutropenia. In addition, there has been an increase in resistance of Gram-negative isolates to TMP-SMZ in the last two decades. In our medical center, fewer than 50% of Gram-negative isolates in neutropenic patients are susceptible to TMP-SMZ. Fluoroquinolones were introduced in the 1980s and became popular due to their broad antimicrobial spectrum and lack of myelosuppression. In our meta-analysis, studies comparing fluoroquinolones to the control yielded a relative risk for all-cause mortality of 0.62 (95% CI 0.45–0.86), whereas in studies using TMP-SMZ the RR was 0.71 (95% CI 0.49–1.02) [6]. Therefore, fluoroquinolones are probably the better choice. Ciprofloxacin, in doses ranging between 500 mg per day and 750 mg twice daily, reduced all-cause mortality; RR 0.32 (95% CI 0.13–0.82). The two recent larger trials used levofloxacin in a single daily dose of 500 mg. Clinicians can choose to use either ciprofloxacin or levofloxacin for prophylaxis based on the advantage of ciprofloxacin against *Pseudomonas aeruginosa*, or of levofloxacin against Gram-positive bacteria, according to local distribution of pathogens among neutropenic cancer patients in each medical facility.

Which patients should be offered antibiotic prophylaxis?

- *Patients treated for acute leukemia or undergoing ablative bone marrow treatment before transplantation*

We updated our meta-analysis [6] with the two new trials [7,8] and divided trials according to the type of patient. Most studies comprised adult patients. In the studies including only patients with acute leukemia who received chemotherapy and underwent stem cell transplantation, prophylaxis with fluoroquinolones reduced the risk of death from any cause by 33% (95% CI 2–54%). Since mortality during neutropenia has declined in recent years, a death rate of 5.5% in the control group was used (derived from studies that were performed after the year 2000) to estimate that 55 high risk patients need to be given prophylaxis with a fluoroquinolone to prevent one death.

TMP-SMZ = trimethoprim-sulfamethoxazole
RR = relative risk

- *Patients treated for solid tumors or lymphoma*

In the four studies in our meta-analysis comparing fluoroquinolones to a control in patients with solid tumors or lymphoma, prophylaxis reduced the rate of death during the first month; RR 0.51 (95% CI 0.27–0.97). Using the death rate in the control groups of studies performed after 2000 (2.5%), the number needed to treat to prevent one death during the first month of treatment for solid tumors and lymphoma was 82. The SIGNIFICANT trial [8] addressed the question of prophylaxis for all cycles of treatment in these patients. At the end of follow-up the mortality rates were 4% (31 of 781) in the levofloxacin group and 4.6% (36 of 784) in the placebo group; RR 0.86 (95% CI 0.54–1.38) (unpublished data). In the same trial 47% of the deaths occurred during the first month. The second largest study of fluoroquinolone prophylaxis in neutropenic patients with solid tumors was published by Tjan-Heijnen et al. [18]. In patients given ciprofloxacin plus roxythromycin, the 30 day mortality was 1% (1 of 82 patients), and in the placebo group 5% (4 of 79) – a RR of 0.24 (95% CI 0.03–2.11) (unpublished data). Existing evidence points to an advantage to prophylaxis in patients given chemotherapy for solid tumors or lymphoma, at least for the first cycle of chemotherapy as it significantly reduces the chances of death during the first month. Evidence is less clear for the whole duration of chemotherapy.

Setting

The spectrum of pathogens observed among patients in the medical center and baseline susceptibility to fluoroquinolones should be the local determinants of prophylaxis use. In Israel, several medical facilities have documented a predominance of Gram-negative infections among cancer patients [19,20]. In our center during the last two decades, Gram-negative bacteria accounted for 55–70% of all bloodstream infections occurring among neutropenic patients. The resistance of Gram-negative blood isolates to ciprofloxacin in the first 48 hours of hospitalization was 18.3%, similar to that reported in the GIMEMA study [7]. The GIMEMA study was conducted in a population with a nearly 50% resistance to fluoroquinolones for all pathogens, and 20% resistance in Gram-negative blood isolates in the control group. It was conducted in Italy, a country with a baseline resistance of about 20% in Gram-negative isolates from the community [21] and medical departments [22]. Given that fluoroquinolone prophylaxis reduces mainly Gram-negative infections and the fact the prophylaxis was shown to be effective in settings with a similar epidemiology to Israel, prophylaxis using fluoroquinolones seems warranted in our locale. Individual hospitals should monitor pathogen prevalence and susceptibilities to guide the decision to use prophylaxis and the choice of the fluorquinolone.

Conclusions

Recent research confirms that fluoroquinolone prophylaxis reduces mortality, with a low number of patients needed to treat to prevent one death. Patients with acute leukemia treated with high dose chemotherapy and patients undergoing hematopoietic stem cell transplantation should be offered prophylaxis with cip-

rofloxacine or levofloxacin. Pending further research, prophylaxis to cover the expected period of neutropenia should be considered for the first cycle of treatment in patients with solid tumors or lymphoma.

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