Original Article

Oral Ciprofloxacin Compared with Intravenous Ceftazidim on Low Risk Febrile Neutropenia in Acute Lymphocytic Leukemia

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Abstract

Objective

Fever and neutropenia are a common complication of chemotherapy in cancer. It is usually managed by hospitalization and empiric administration of antibiotics. Use of Fluroquinolones is limited because of joint/cartilage toxicity. This study attempted to compare the efficacy of oral ciprofloxacin with intravenous ceftazidim in low risk febrile neutropenic lymphocytic leukemia.

Methods

Ninety two episodes of febrile neutropenia in 72 patients under 14 years old were studied prospectively for two years. All the patients received G-CSF plus intravenous ceftazidim 100 mg/kg/d and amikacin 15 mg/kg/d for 24 hours. These episodes randomly allocated into two groups. Group A received IV ceftazidim and amikacin for at least 3 days. After discharge they got oral cefixim 8 mg/kg daily. Group B discharged and received oral ciprofloxacin (20 mg/kg.day) for seven days. Failure was defined as temperature higher than 38 °C for more than 72 hours or major complication.

Results

Failure of intravenous ceftazidim plus amikasin for at least 4 days in hospital, in low risk febrile neutropenic children, was 6.5%, but failure of oral ciprofloxacin for 7 days after 24h intravenous ceftazidim plus amikasin was 4.3%. There was no arthrotoxicity in patients received ciprofloxacin.

Conclusion

Empirical therapy with oral ciprofloxacin is safe and effective in children with leukemia and low risk FN.

Keywords

Ciprofloxacin, Neutropenia, Acute Lymphocytic Leukemia

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Introduction

Febrile neutropenia is a common complication of cancer chemotherapy. It is easily managed by hospitalization and empiric administration of parenteral antibiotics (1). This management clearly has proved to reduce infection morbidity and mortality and has been considered as the standard of care. However, recent reports and a previous randomized trial suggested that a low risk subset of children with febrile neutropenia under chemotherapy might benefit of an oral antibiotic outpatient approach (2).

Over the past three decades, considerable changes have occurred in the types of bacteria causing infections in febrile patients with neutropenia and cancer. They include a substantially lower incidence of gram-negative infections, such as Pseudomonas aeruginosa, and an increase rate of gram-positive infections, mainly staphylococcus epidermidis and various strains of streptococci (3). Mortality of the gram-positive coccal bacteremia in neutropenic patients is relatively low. Gram-negative bacteremic episodes are associated with higher mortality rates, which still represent 30% of all bacteremias (4). In the past several years, a combination of ceftazidime plus amikacin has been established as a standard regimen in febrile neutropenia (5,6). Several studies have used different regimens, either as monotherapy or as combined therapy, which have been conducted in order to find the most effective regimen (7–10). Ceftazidim is a third-generation cephalosporin with a broad spectrum of action that is easy to use. Ciprofloxacin is a synthetic 4-quinolone bactericidal antibiotic against a broad range of gram-positive and gram-negative organisms, including P. aeruginosa, that has a low rate of nephrotoxicity (11).

The fluoroquinolones are an important group of antibiotics widely used in the treatment of various infections disease in adults as a result of an excellent spectrum of activity, good tissue penetration and convenient ways of administration. Their use in children is limited as a result of possible fluoroquinolone-induced joint cartilage toxicity observed mainly in juvenile animal researchs (12). With the exception of cystic fibrosis and life endangering infections, the use of fluoroquinolones in pedietric should be limited to gram-negative neonatal meningitis, salmonella, and shigella, infections, chronic suppurative otitis media and some cases of complicated acute otitis media. (12) Unskilled uses of flouroquinolones in children particularly in community-acquired lower respiratory infection could accelerate the emergence of pneumococal resistance (12).

Selection of patient with low risk febrile neutropenia is important for the best management. Low risk patients defined as patient with early signs of bone marrow recovery, short duration of fever, absence of comorbidity factors, and a predictive period of neutropenia of less than 10 days (2).

Several randomised controlled trials have addressed the use of haematopoietic growth factors in febrile neutropenic patients (13). These studies show that granulocyte colony stimulating factor (GCSF) used in febrile neutropenic patients, consistently shortens the duration of neutropenia, but does not consistently lead to resolution of infection or shorter time in hospital (14).

This study aimed to compare oral ciprofloxacin in early hospital discharge patients with intravenous ceftazidim and amikacin for low risk febrile neutropenia.

Materials and Methods

This prospective, randomized, controlled study was conducted from March 2008 to June 2009. The aim of this study was to evaluate the safety and efficacy of intravenous ceftazidim plus amikacin given for 24 hours followed by oral ciprofloxacin, in children with febrile neutropenia

after chemotherapy with ALL. Ninety two episodes of low risk febrile neutropenia in 72 children (mean age: 7.185 years; range: 0-14 years) were included in randomized controlled single institution trial.

The inclusion criteria was age under 14 years old, fever (equal or more than 38 °C), sever neutropenia (absolute neutrophil count less than 500/mm3), negative blood culture, good clinical condition, control of local infection, remission, and parents' cooperation. The exclusion criteria included hemodynamic instability, serious comorbidity, dehydration, sever mucositis, pneumonia, and bone marrow transplantation (2).

Peripheral blood and urine cultures and chest X-ray were performed for all patients before treatment. Blood samples from port catheters and peripheral veins for quantitative differential cultures were taken. Skin and soft tissue infections, diarrhea, pharyngitis, or any suspected infection were roll out using bacterial cultures. All of the patients received intravenous ceftazidim 100 mg/kg plus amikacin 15 mg/kg daily, for 24 hours. Then they randomly allocated to two 46 episodes. Group A received IV ceftazidim & amikacin for at least three days and discharged with oral cefixim (8 mg/kg/day) for 4 days. Patients in group B were discharged and received oral ciprofloxacin (20 mg/kg/day) for seven days. All of the patients received G-CSF.

Failure was defined, as temperature higher than 38 °C for more than 72 hours after antibiotic therapy. Successful treatment was defined no fever and no re-admission due to a new fever infection event within 7 days of discharge or a new febrile episode during the same episode of neutropenia. Outcomes were compared by the Fisher exact test or Chi square test. P value less than or equal to 0.05 was assumed as significant.

Result:

Seventy two patients presented 92 episodes of febrile neutropenia, who were entered in this study. Forty six randomly episodes allocated in two groups A and B. Demographic characteristics of patients showed in table 1. No significant difference in gender and age was observed between both groups. Three patients (6.5%) in group A and 2 patients (4.3%) in group B failed to treat. Forty eight hours after administration of the antibiotics, 24 patients (52%) in group A and 14 patient (30%) in group B had fever, which difference was significant (P = 0.034). There were no sever complications in two groups. Patients failed the treatment had fever more than 72 hours. There was no significant difference in ALT, AST, urea and creatinin levels between two groups before treatment. Liver complication was defined as ALT or AST equal or more than 40 after treatment. Liver complication was not significantly different between two groups (ALT P = 0.335, AST P = 0.632). Renal complication was defined as urea equal or more than 50 mg/dl, or creatinin equal or more than 1mg/dl after treatment. Renal complication was not significantly different between two groups (urea PV= 0.153, creatinin PV= 0.153). No arthrotoxicity was seen in patients after treatment.

Table 1. Demographic characteristics of the two groups.

Characteristic	Group A	Group B	*P* value
Episodes treated	46(50)	46(50)	
Age Range (year) Mean (year) Median (year)	 1-14 7.717 7	 2-14 6.652 6	 NS NS
Male/Female	21/25	24/22	NS

The table shows differences between two groups were not significant.

Table 2. Clinical course and outcome of the 93 episodes of fever and neutropenia

Characteristic	Group A (Ceftazidim + amikacin) (%)	Group B (Ciprofloxacin)(%)	*P* value
Temperature ≥38 °C after 48h	24(52.2)	14(30.4)	Significant 0.034
Temperature ≥38 °C after 72h	3(6.5)	2(4.3)	NS
AST ≥40 before treatment	10(21.7)	12(26.1)	NS
AST ≥40 after treatment	10(21.7)	14(30.4)	NS
AST ≥40 after treatment if AST <40 before treatment	3(8.3)	4(11.8)	NS
ALT ≥40 before treatment	10(21.7)	14(30.4)	NS
ALT ≥40 after treatment	10(21.7)	14(30.4)	NS
ALT ≥40 after treatment if ALT <40 before treatment	1(2.9)	0(0)	NS
Urea ≥50 before treatment	3(6.5)	2(4.3)	NS
Urea ≥50 after treatment	0(0)	2(4.3)	NS
Urea ≥50 after treatment if urea <50 before treatment	0(0)	0(0)	
Cr ≥1 before treatment	2(4.3)	2(4.3)	NS
Cr≥1 after treatment	0(0)	2(4.3)	NS
Cr1 after treatment if Cr <1 before treatment	0(0)	0(0)	
Neutropenia after treatment Mild Moderate sever	2(4.3) 12(26.1) 21(45.7)	4(8.7) 8(17.4) 25(54.3)	NS

Discussion:

Fever and neutropenia remains a potentially life threatening complication of anticancer chemotherapy (7). Until recently, all febrile neutropenic patients were hospitalized for the administration of empiric, broad-spectrum, intravenous antibiotic therapy (2). However, it is possible to give more convenient treatment and less-intensive care for low risk patients (15). The careful selection of the lower risk patients was a crucial factor in the success of the new

regimens. Other studies have used similar criteria, affirming their predictive value in the setting of fever and neutropenia (16,17 and 2).

This study demonstrates that febrile neutropenic children with low risk criteria might be safely and effectively managed using daily intravenous ceftazidim plus amikacin followed by oral ciprofloxacin for 7 additional days. In compliant patients, with lower risk criteria, the treatment could be changed after 1 day of intravenous therapy to an oral antibiotic, such as cefixime, ciprofloxacin, ofloxacin, clindamycin, or quinolone associated with amoxicillin/clavulanic acid. The patients could be discharged earlier from the hospital, with careful follow up (2,18)

Amikacin could cause nephrotoxicity. Thus, combination of high, once daily dose of ceftriaxon with ciprofloxacin, a synthetic 4-quinolone antibiotic, are used. This bactericidal regimen is against a broad range of gram-positive and gram-negative organisms including P. aeruginosa, which has a low rate of nephrotoxicity (11). In a study conducted by the EORTC (European Organization for Research and Treatment of Cancer), the incidence of nephrotoxicity in groups receiving a single daily dose of amikacin was between 1.2% and 3.0%, while the incidence of ototoxicity was 9% in the amikacin group receiving a single daily dose compared to 7% in the amikacin group receiving it every 8 hours (19).

The use of fluoroquinolons in children should be selective and administered more carefully. These drugs are currently used in pediatrics as second-line antibiotics, mostly in cases in which all other previous treatment have failed. With the exception of cystic fibrosis and life threatening infections, their use as first line therapy should be limited to gram-negative neonatal meningitis, salmonella, and shigella spp. infections, chronic suppurative otitis media and some cases of complicated acute otitis media non-responsive to initial treatment. Most of the published studies failed to detect an increased rate of articular adverse effects in children treated with fluoroquinolons (12). In this study sever complication was not seen but minor complication such as mild nausea and headache were observed.

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