Original Article-I

A Randomized, Prospective Open Labeled Study of Oral Amoxicillin-clavulanate and Levofloxacin with Intravenous Ceftriaxone and Amikacin in Chemotherapy Induced Low Risk Febrile Neutropenia

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ABSTRACT

Background : We compared the efficacy of oral antibiotics with intravenous antibiotics in low risk febrile neutropenia.

Design : A prospective, randomized study

Methods: Between April 2004 - December 2005, 55 patients with low risk febrile neutropenia (expected neutropenia duration < 7 days with no co-morbid features) between 15 and 75 years of age, were randomized to receive either oral amoxicillin-clavulanate 625mg twice daily and levofloxacin -500mg once daily OR intravenous (i.v.) ceftriaxone 2g and amikacin 15mg/kg once daily. Most patients were treated on out patient basis. The primary end point was response to therapy, defervescence of fever within 72 hours with improvement in any clinical manifestation of infection and no recurrence of fever for 48 hours without use of antipyretics. Use of growth factors was not permitted except in treatment failure.

Results: A total of 64 febrile episodes were recorded (mean 1.20); 33 in the IV group and 31 in the oral antibiotics group. Both groups were equally matched for age (median 25 years in the IV group and 19 years in the oral group), gender, type of cancer, baseline absolute neutrophil count (median 200/cmm in both arms) and duration of neutropenia (5 days and 4 days in the IV and oral groups, respectively). A focus of infection was identified clinically in 15% of episodes and microbiologically in 11% of episodes; 57% of which were Gram positive organisms and the rest Gram negative. 72% in the IV arm and 77% in the oral arm responded to therapy (p=ns). One patient in IV group had one episode of seizure. Non-responding patients received second line IV antibiotics. There was no mortality in either group. Age > 60 years, neutropenia lasting > 7 days after the onset of fever and positive blood culture were predictors for lack of response to antibiotics on multivariate analysis.

Conclusion: Oral antibiotics have comparable efficacy as IV antibiotics in the management of low risk febrile neutropenia.

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INTRODUCTION

Neutropenic fever following anticancer chemotherapy is a medical emergency and requires immediate admission and empiric broad spectrum intravenous antibiotics. In the past few years several authors have attempted to stratify these febrile neutropenic patients into low and high risk based on expected duration of neutropenia and presence of co-morbid factors. This has led to the emergence of a category called 'low risk febrile neutropenia'[1-9] - associated with a low incidence of serious complications. Oral antibiotics have been proposed as a treatment option this subgroup due to ease of administration on outpatient basis, reduced risk of complications associated with IV access and nosocomial infections could be prevented. Several studies[10-15] and a meta analysis[16] have shown that oral antibiotics are as safe and effective as IV antibiotics in low risk febrile neutropenia. However, this strategy has not been adequately tested in developing countries. On one hand in these countries there is a paucity of resources hence oral antibiotics may help avoid in-patient admissions. At the same time the issues of patient compliance to therapy, periodic monitoring and access to admission in case of clinical deterioration need to be looked at. Hence we felt the need for a randomized study to compare the efficacy of oral and IV antibiotics in our setting.

PATIENTS AND METHODS

Patient of age group 15 to 75 years, with chemotherapy induced febrile neutropenia and with low risk features were included in the study after a written informed consent.

Febrile Neutropenia was defined as a single oral temperature recording of 38.3^{o}C (101^{o}F) or temperature of 38^{o} C (100.4^{o}F) for 1 hour unrelated to administration of drug or blood products and absolute neutrophil count (ANC) < 500 cells / cmm. Patients were defined to have 'low risk features' if (i) expected duration of neutropenia was 7 days or less after the onset of fever (ii) with absence of co-morbid features e.g. (a) Hypotension : systolic B.P. less than 90 mm Hg (b) Hepatic Dysfunction: 1) amino-transferases >5 times from baseline 2) Serum bilirubin = 3mg/dl (c) Renal Dysfunction:- Creatinine clearance <30ml/min (d) Diabetes Mellitus (e) altered sensorium (f) respiratory insufficiency. Exclusion criteria included – pregnancy, lactation, known hypersensitivity to any of the study drugs, patient's inability to take oral medication due the mucositis (grade III-IV) and vomiting (grade III-IV). Patients who had received antibiotics for any reason within previous 96 hours were excluded. Patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) ,lymphoblastic lymphoma, Burkitt's lymphoma on induction and consolidation chemotherapy were considered high risk and were are not included in the study.

METHODOLOGY

All patients underwent complete evaluation at the time of enrollment. This included - a detailed physical examination (to ascertain the possible focus of infection), complete blood counts (total and differential) and chest x-ray. Blood sugar, renal and liver function test , electrolytes were done at base line. Blood culture (two sets) , throat swab , urine culture, and cultures from other sites (as clinically indicated) were done in all patients. An informed written consent was taken from the patient or guardian at the time of enrollment. The study protocol was approved by the institution ethics committee.

Patients were randomized by a computer generated randomization table into two groups

Group I patients received: Inj Ceftriaxone 2g intravenously q once daily and Inj Amikacin 15 mg/kg intravenously once daily. Group II patients received : Tab Amoxycillin 500mg + Clavulinic acid 125 mg (15mg/kg Amoxycillin) orally twice daily after food and Tab Levofloxacin 500mg orally once daily after food.

Use of antacids, iron preparations, oral calcium and magnesium supplement was not

allowed 2 hours before and after administration of the study drugs. Concomitant use of theophylline derivatives and probenecid was not permitted.

FOLLOW UP

Patients who were admitted were monitored daily. Patients who were in the oral antibiotic group were followed on outpatient basis on alternate day till absolute neutrophil count (ANC) was >500 cells/ cmm. Patients were instructed to record oral temperature at home at least 4 times daily and bring the record of the temperature chart . If fever was persistent blood and other appropriate cultures were repeated. Blood counts and serum chemistries were performed every alternate day. The dose of amikacin was modified as per creatinine clearance.

Response: Response to treatment was defined as resolution of temperature within 72 hours of starting therapy and lasting for at least 48 hours without antipyretics . Resolution / improvement in the symptoms and signs of infection at identifiable sites of infection was recorded. Treatment Failure was defined as (i) lack of defervescence of fever after 72 hours of therapy (ii) If there was clinical progression in any of the documented sites of infection (iii) if patient developed hypotension, respiratory insufficiency, altered sensorium, renal failure (due to sepsis), hepatic dysfunction at any point after entry into the study. The time to respond to therapy, salvage antibiotic regimens used and complications of therapy were analyzed as secondary endpoints.

Further Therapy: If the patient responded to therapy the same antibiotics were continued for 3-4 days of the afebrile period or till the absolute neutrophil count (ANC was ≥500) cells/cmm for two consecutive days, whichever was earlier.

STATISTICAL ANALYSIS

The study was essentially a pilot study to test the feasibility of using oral antibiotics in febrile neutropenia in our hospital setting. The Chi Square test and Fischer's exact test were used to compare differences between the groups. Nonparametric tests were used for comparison when the data was not normally distributed. Logistic regression was used for multivariate analysis of outcome. All p values were two-sided. All statistical calculations were performed using SPSS Software version 10.

RESULTS

Among 55 patients randomized in this study; 53 were evaluable, one patient withdrew the consent and another belonged to high risk febrile neutropenia. A total of 68 febrile episodes were recorded; IV arm – 35 and oral arm -33. Patients characteristics are shown in table-1.

FOCUS OF INFECTION

Clinically and radiologically - site of infection could be identified in 10/64 episodes (15%). Chest – 5, (Clinical - 3, X-ray chest abnormality - 2) all in intravenous group. GIT- 4 episodes (2 in the IV and 2 in the oral group). Skin furuncles in 1 patient (oral group). Preseptal cellulitis of the eyeball in 1 episode (oral group). Eight of 33 (24%) febrile episodes in the IV group and 7 of 31 (23%) episodes in the oral group were associated with grade 1 and 2 oral mucositis. Microbiologically culture positivity could be demonstrated in seven episodes (10%) either in blood or urine. as outlined in Table 3. Gram positive organisms accounted for 53% and the rest were gram negative. In one episode two organisms were grown from blood culture.

RESPONSE TO THERAPY

24 out of 33 episodes (72%) in the IV group and 24 out of 31 (77%) in oral group responded to therapy. Testing the two groups for equivalence (assuming a 25% difference between the two groups as unequal) the two groups were equivalent with a power of 59%. ($p = 0.03$). 19 out of 28 first episodes in the intravenous group (68%) and 21 out of 25 first episodes in the oral group responded to therapy. (84%). The time to become afebrile from the start of therapy was calculated from the temperature diary maintained by the patients or from the hospital temperature charts. Table 4 shows that it was similar in both groups.

Table -1 Patients's Characteristics

Characteristics	IV Antibiotic Group	Oral Antibiotic Group	p value
Age - Median (range) in years	25 (15-73)	19 (15-64)	0.209
Gender (M:F)	2.6:1	1.2:1	0.136
Hemoglobin (g/dl) - Median (range)	8.2 (3.5 - 13.3)	8.6 (4.5 - 12.9)	0.437
Platelet (cells/cmm) Baseline Median (range)	86000	87000	0,587
ANC (baseline) (cells/cmm) Median (range)	200 (0 - 400)	200 (0 - 400)	0.448
Duration of neutropenia (Days) Median (range)	5 (2 - 17)	4 (2 - 11)	0.223
Number of patients treated as Outpatients	21	29	
Diagnosis			
Haematological malignancies*	13	8	
Bone & Soft tissue sarcomas	14	18	
Other solid tumours	6	5	

IV group–non Hodgkin's lymphoma-6, Hodgkins lymphoma-2, CML-1, ALL-4, Oral group-NHL-6, ALL-2

Toxicity : The details of adverse effect of treatment are given in table 7. There was no mortality in any group. In the IV group one patient had one episodes of generalized tonic clonic seizures during primary therapy; CAT scan of the head was normal, and patient was found to have hypocalcemia. The patient recovered without any sequelae. 2 patients in the IV group had evidence of thrombo-phlebitis and 3 patients in the oral group had diarrhoea considered related to antibiotics. Change or modification of antibiotics was not required in any patient due to side effects or abnormal liver or renal function.

DISCUSSION

Oral antibiotics are a feasible option in low risk febrile neutropenia The commonly used combination is amoxycillin - clavulanate with a quinolone which has been adhered to in this study. Levofloxacin was preferred to ciprofloxacin due to convenience of once daily dose administration and a broader gram positive coverage.[17] The culture reports revealed a high incidence of ESBL positivity among the gram negative organisms (3 out of 4). This justifies the need for a beta lactamase inhibitor in the antibiotic combination. We used a 72 hour time period for primary end point assessment, as the median time to respond to antibiotics in low risk febrile neutropenia is 2 days. Broadly the study follows the International guidelines for the design and analysis at studies on febrile neutropenia[18] except for the method of risk stratification. The MASCC system[4] of risk stratification was avoided as we felt that stratifying patients using a visual analog scale was not always reproducible. Retrospectively scoring patients by the MASCC score revealed 94% patients had a score of > 21 (low-risk) but retrospective scoring

has its own limitations. Risk stratification in this study was based on duration of neutropenia and the presence or absence of co-morbid features. Based on these criteria for risk stratification, there was no mortality and the incidence of serious complications was about 8% which is acceptable. A major criticism of the use of expected duration of neutropenia for risk stratification is that it may not accurately predict the actual duration but in 91% of patients we did not encounter this problem. However, as we discovered during the course of this study certain clinical situations such as imatinib induced myelosupression may have prolonged neutropenia (17 days for the patient in this study) and may not be suitable for low risk therapy. The response rates to both oral and

Table - 2 : TYPE OF CHEMOTHERAPY

Type of Chemotherapy	Intravenous Antibiotic Group (# episodes)	Oral Antibiotic Group (# episodes)
CHOP	6	4
Ifosfamide + etoposide	3	7
VAC	3	5
VAC- RMS	2	2
ALL maintenance (MCP-841)	2	2
ALL C phase (MCP-841)	1	0
ICE	2	0
R CHOP	0	1
Imatinib	1	0
BEP	1	1
HDMTX	1	1
Cisplatin + adriamycin	5	5
Cisplatin + Etoposide	2	0
CAP	1	1
Carboplatin	1	0
EMACO	1	0
ABVD	1	0
+ Ifosfamide +Adria mycin	0	1
Folfox 4	0	1

CHOP- cyclophosphamide, adriamycin, vincristine and prednisolone, ABVD- adriamycin, bleomycin, vinblastine and DTIC, CAP-cisplatin, acriamycin and cyclophosphamide, EMA-CO – etoposide, methotrexate and actinomycin-D, cyclophosphamide and vincristine, BEP-bleomycin, etoposide and cisplatin, HDMTX-high dose methotrexate.

Table 3 : Microbiology Spectrum

Group	Sample	Organism	Sensitive to	Resistant to	End point
Intravenous	Urine	Escherichia Coli ESBL* Positive	Cefaperazone sulbactum	Ceftriaxone, amikacin, amoxiclav, levoflox	Failure
Intravenous	Blood	(MSSA)	Ceftriaxone, amikacin, amoxiclav, cefaperazone sulbactum	Levofloxacin	Failure
Intravenous	Blood	Coagulase negative Staphylococcus Acinetobacter	amikacin, levofloxacin, cloxacillin Amikacin, Imipenem,	Ceftriaxone, augmentin Ceftriaxone, amoxiclav, levoflox	Responded
Oral	Blood	Pseudomonas ESBL* positive	Piperacillin, Piperacillin tazobactum	Ceftriaxone, amikacin, amoxiclav, levoflox	Responded
Oral	Blood	Enterococcus faecium	Vancomycin, teicoplanin, linezolid	Ceftriaxone, amikacin, amoxiclav, levoflox	Failure
Oral	Blood	Coagulase negative Staphylococcus	Ceftriaxone, amikacin, amoxiclav, levoflox	Penicillin erythromycin	Responded
Oral	Blood	Acinetobacter ESBL* Positive	Levofloxacin, Amikacin, amoxiclav,	Ceftriaxone	Failure

ESBL-Extended spectrum beta lactamase, MSSA- Methicillin sensitive Staphylococcus aureus

intravenous antibiotics in the present study are similar to what was obtained in earlier randomized studies as illustrated in Table 9.

The study was not designed to establish the equivalence of outpatient and inpatient therapy. However since 50 out of 64 episodes in the study were treated on outpatient basis this approach can be considered a feasible option. Patients must be instructed carefully to follow up at least every third day on outpatient basis, to reside near the hospital and report to the casualty in case of any emergency. Maintaining daily telephonic contact with patients, which was part of the protocol in some Western studies [21] may not be practical for our patients.

A cost analysis was not performed as part of this study. However, the approximate daily cost of oral antibiotics used in this study was Rs. 100/- and that of intravenous antibiotics. Rs. 225/-. Further use of oral antibiotics is cost effective as

TABLE 4 : TIME TO RESPONSE TO ANTIBIOTICS

Time to respond	Intravenous Antibiotic Group	Oral Antibiotic Group
< 24 hrs	7 (29 %)	5 (21%)
24 to 48 hrs	8 (33%)	9 (38%)
48- 72 hrs	9 (38%)	10 (41%)

TABLE 5 : REASONS FOR FAILURE

Reason	*Intravenous Antibiotic Group (# of episodes)*	*Oral Antibiotic Group (# of episodes)*
No response within 72 hours of therapy	6/9	5/7
Clinical deterioration	2/9	2/7
Breakthrough fever after response	1/9	0/7

TABLE 6 : SECOND LINE TREATMENT

Intervention	Intravenous Antibiotic Group (no of episodes)	Oral Antibiotic Group (no of episodes)
Addition of antibiotic	1	0
Continuation of same antibiotic	1	0
Second line antibiotics	7, Cefaperazone + sulbactum in all patients	7 Ceftriaxone -6 Cefaperazone + sulbactum 1 Vancomycin - 1
Third line antibiotics	0	1 - Cefaperazone sulbactum
Growth factors	0	3

the transportation and hospitalization charges can be avoided. The limitations of this study area small sample size, (a power of 80% would have been ideal), lack of stratified randomization strategy, which could have permitted a subgroup analysis and the heterogeneity in admission of patients. This study could be a model for more studies on this topic with more number of patients and different antibiotic combinations.

TABLE-7 : PROGNOSTIC FACTORS

Variable	Univariate p value	Multivariate p value	Odds ratio (95% C.I.)
Age ≤ 60	.045	.046	10.846(1.040 to 113.165)
Age ≤ 50	.401		
Clinical focus of infection	.099		
Hb < 8g/dl	.769		
ANC 100 baseline	.657		
ANC 100 nadir	.451		
Duration of neutropenia > 7 days	.007	.018	10.098 (1.494 to 68.267)
Culture positivity	.059	.038	6.659 (1.112 to 39.865)
Hospitalization status	.031	.232	2.55 (0.549 to 11.846)

TABLE 8 : REVIEW OF LITERATURE

Study (ref), year	Response to IV antibiotics	Response to oral antibiotics
Malik (14) 1992	53%	53%
Rubenstein (13)1993	95%	87.5%
Velasco (19) 1995	93%	94%
Hidalgo (20) 1999	87%	79%
Freifield (10) 1999	59%	70%
Kern (11) 1999	84%	85%
Innes (21) 2003	90%	84%
Present study	72%	77%

Factors responsible for failure to respond to antibiotics in both groups were studied. Prognostic factors : Age 60 years and above, duration of neutropenia >7 days from randomization and a positive culture during the episode emerged as significant prognostic factors on multivariate analysis (Table-7)

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REFERENCES:

1. *Rubin M, Hathorn JW, Pizzo PA. Controversies in the management of febrile neutropenic cancer patients. Cancer Invest 1988;6-167.*
2. *Talcott JA, Finberg R, Mayer RJ, Goldman L. The medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. Arch Intern Med 1988;148-2561*
3. *Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. J Clin Oncol 1992;10-316.*
4. *Klasterky J, Paesman M, Rubenstein EB et al . The multinational association for supportive care in cancer risk index: a multinational scoring system for identifying low risk febrile neutropenia . J.Clin Oncology 2000;18 :3038-51.*
5. *Rolston KVI. New trends in patient management: risk-based therapy for febrile patients with neutropenia. Clin Infect Dis 1999;29:515-21.*
6. *Aquino VM, Tkaczewski I, Buchanan GR. Early discharge of low-risk febrile neutropenic children and adolescents with cancer. Clin infect Dis 1997;25:74-8.*
7. *Klaasseen RJ, Goodman R, Pham BA, Doyle JJ. Low-risk prediction rule for pediatric oncology patients presenting with fever and neutropenia. J Clin Oncol 2000;18:1012-9.*
8. *Lucas KG ,Brown AE, Armstrong D et al. The identification of febrile neutropenic children with low risk for bacteremia and complications of sepsis. Cancer 1996;77:791-798.*
9. *Kern WV, Cometta A, DeBock R, et al. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. N Engl J Med 1999;341:312-8*
10. *Freifeld A, Marchigiani D, Walsh T, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. N Engl J Med 1999;341:305-11.*
11. *Rackoff WR,Gonin R, Robinson C et al . Predicting the risk of bacteremia in children with fever and neutropenia. J Clin Oncology 1996;14:919-924.*
12. *Talcott JA, Whalen A, Clark J, Rieker PP, Finberg R. Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. J Clin Oncol 1994;12-107.*
13. *Rubenstein EB, Rolston K, Benjamin RS, et al. Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. Cancer 1993;71-3640.*
14. *Malik IA, Abbas Z, Karim M. Randomised comparison of oral ofloxacin alone with combination of parenteral antibiotics in neutropenic febrile patients [published erratum appears in Lancet 1992; 340(8811):128]. Lancet 1992;339-1092.*
15. *Malik IA, Khan WA, Karim M, Aziz Z, Khan MA. Feasibility of outpatient management of fever in cancer patients with low-risk neutropenia: results of a prospective randomized trial Am J Med 1995;98-224.*
16. *Liat Vidal, Mical Paul, Istik Ben dor,Karla Soares-Weiser,Leonard Leibovici. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients: a systematic review and meta-analysis of randomized trials. J Antimicrobial Chemotherapy 2004;54-29.*
17. *Fu KP, Lafredo SC, Foleno B, et al. In vitro and in vivo antibacterial activities of levofloxacin, an optically active ofloxacin. Antimicrob Agents Chemother 1992;36-860.*
18. *Feld R, Paesmans M, Freifeld AG, et al. Methodology for clinical trails involving patients with cancer who have febrile neutropenia: updated guidelnies of the Immuno-compromised Host Society / Multinational Association for Supportive Care in Cancer with emphasis on outpatients studies. Clin Infectious Dis 2002;35:1463-8.*
19. *Velasco E, Costa MA, Martins CA, et al. Randomized trial comparing oral ciprofloxacin plus penicillin V with amikacin plus carbenicillin or ceftazidime for empirical treatment of febrile neuropenic cancer patients. Am J Clin Oncol Cancer Clin Trials 1995;18:429-35.*
20. *Hidalgo M, Homedo J, Lumbreras C, et al. Out patient therapy with oral ofloxacin for patients with low risk Neutropenia and fever a prospective, randomized clinical trial. Cancer 1999;85:213-9.*
21. *Innes HE, Smith DB, O' Reilly SM, et al. Oral antibiotics with early hospital discharge compared with in patient intravenous antibiotics for low-risk febrile Neutropenia in patients with cancer: a prospective randomized controlled single center study. Br J Cancer 2003;89:43-9.*
22. *Elting LS Rubenstein EB Rolston K et al. Time to clinical response : an outcome of antibiotic therapy of febrile neutropenia with implications for quality and cost of care. J Clin Oncol 2000;18:3699-3706.*