

Out-patient Management of Febrile Neutropenia in Indigent Paediatric Patients

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Abstract

Affordability of costly in-patient medical care and accessibility to the few cancer centres are serious problems faced by cancer patients in developing countries. Febrile neutropenia in particular is a major problem because delay in institution of antibiotic therapy can be rapidly fatal. We conducted a prospective non-randomised trial to evaluate the efficacy of administration of oral ofloxacin by caregivers to paediatric cancer patients with fever and neutropenia. Patients receiving chemotherapy who resided far away and were unable to reach the oncology ward within 12 hours of onset of fever or were unable to afford the expensive in-patient care were eligible for inclusion in the study. Requirements for enrollment included an absolute neutrophil count of $\leq 0.5 \times 10^9/L$, a temperature of $\geq 38^\circ C$, and ability to take oral medications. Caregivers were instructed to immediately administer oral ofloxacin on recognition of fever and to maintain constant contact with the oncology staff. Eighty-five of the 91 episodes were evaluable. These were mostly patients with solid tumours or non-Hodgkin's lymphoma (79%). Duration of neutropenia and fever was short and majority had pyrexia of undetermined origin (84%). Seventy-seven (91%) of the febrile episodes responded to ofloxacin with resolution of fever and neutropenia and hospitalisation was never required. Eight (9%) patients required hospitalisation. Most of them had prolonged neutropenia. They all responded to parenteral antibiotic therapy. No toxicity was observed and the cost of therapy was negligible. Out-patient therapy with oral ofloxacin may be an alternative to hospitalisation for those paediatric patients who are unable to afford or do not have access to in-patient care.

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Introduction

In 1966, Bodey et al¹ demonstrated the quantitative relationship between neutrophil count and susceptibility to infection. Since classical signs and symptoms of infection are not completely evident in neutropenic patients, it results in difficulty diagnosing underlying infection. This has resulted in the empirical use of antibiotic therapy in cancer patients who develop fever while neutropenic. This approach has been clearly demonstrated to reduce morbidity and mortality due to febrile neutropenia.²⁻⁵ Standard management of these patients involves hospitalisation, extensive diagnostic work-ups to elucidate the cause of fever, reverse isolation of patients, provision of specialised nursing care, and immediate institution of empirical parenteral combination antibiotic therapy. More recently, monotherapy with one of the broad-spectrum antibiotics has become acceptable in hospitalised patients.⁶⁻⁹

Unfortunately, in many developing countries, such a course of action is not always feasible. The importance of socio-economic factors in the provision of adequate health care cannot be ignored. In-patient management

of a neutropenic febrile episode is associated with a substantial cost that a significant number of patients in economically disadvantaged countries cannot afford. Management of such indigent patients is a major problem faced by practising oncologists in developing countries. Furthermore, availability of adequate medical services is another serious problem in many countries where a small number of trained oncologists provide care to a very large number of cancer patients. Often these patients have to travel long distances to reach the cancer centres. Adequate follow-up of these patients is exceedingly difficult. Provision of medical care in-between the planned visits to the oncology centres presents a substantial problem. During this time, these patients are seen by local general practitioners who often are unfamiliar with the basic principles of oncology and are not always available or willing to care for these very sick individuals. In many small towns and villages, facilities for doing blood tests and radiologic procedures are not available. Hence, management of indigent patients or those who live far away from the cancer centres is extremely difficult. Although accurate statistics are not

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available, morbidity and mortality are expected to be high.

When we discharge our indigent patients or those who have to travel long distances, we routinely prescribe several drugs to cover most anticipated problems such as nausea and vomiting, mucositis and diarrhoea. Patients and caregivers are instructed to use these drugs when they develop a particular side effect. The most serious side effect faced by cancer patients on chemotherapy is the development of febrile neutropenia. Management of this problem is very difficult and a challenging task. In Pakistan, we have used quinolones as monotherapy of patients with febrile neutropenia. Our initial trial compared ofloxacin with combination parenteral antibiotics in hospitalised patients.¹⁰ Later, a randomised trial was conducted to evaluate the efficacy of oral quinolones in out-patient versus in-patient management of febrile neutropenia in adult patients.¹¹ Quinolones are extremely cost-effective, lack any significant toxicity and do not require close monitoring. We successfully used ofloxacin in the out-patient management of indigent and long-distance adult patients who were instructed to self-administer ofloxacin on the development of fever that was expected to be neutropenic.¹² This approach was highly effective and resulted in a significant cost-benefit. Now we have expanded our experience with out-patient management of febrile neutropenia to indigent paediatric patients.¹³

Patients and Methods

This study was conducted by the medical oncology service between July 1993 and December 1996 on paediatric patients (age ≤ 14) with cancer. An essential prerequisite for this study was inaccessibility or non-affordability of adequate in-patient oncologic care, as judged by the oncologist in collaboration with the patient's guardian. This judgement was made at the time of initial delivery of chemotherapy. Patients received full doses of combination chemotherapy protocols. For example, a regimen of ifosfamide, mitoxantrone alternating with cytosine arabinoside and etoposide along with bleomycin, methotrexate and prednisolone was given to patients with non-Hodgkin's lymphoma. Those with Hodgkin's disease received adriamycin, vinblastine, bleomycin and dacarbazine (ABVD) or nitrogen mustard, vincristine, procarbazine, prednisolone, doxorubicin, bleomycin and vinblastine (MOPP-ABV hybrid). Patients with Wilm's tumour and rhabdomyosarcoma were treated according to National Wilm's Tumor Study Group and Intergroup Rhabdomyosarcoma Study Group protocol, respectively. Similarly, patients with acute leukaemia in remission who were receiving consolidation or maintenance therapy were also included. Inaccessibility was defined as inability to receive adequate in-patient care within 12 hours of onset

of fever. The protocol for out-patient management of neutropenic febrile patients with oral ofloxacin was approved by the Institutional Human Subjects Committee.

Eligibility Criteria

Patients with persistent fever (temperature $\geq 38^{\circ}\text{C}$) or a single spike of $\geq 38.5^{\circ}\text{C}$ unrelated to the administration of pyrogenic products were eligible for accrual. Eligible patients were required to have received chemotherapy within the previous two weeks and to have an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9/\text{L}$ (or an ANC of $< 1.0 \times 10^9/\text{L}$ that fell to $< 0.5 \times 10^9/\text{L}$ within 24 hours of entry into the study). Caregivers were taught how to determine the temperature and ANC. Their ability to determine these parameters were repeatedly assessed by the oncology staff during the patients' stay at the hospital.

Reasons for exclusion from the trial were:

1. known hypersensitivity to ofloxacin or other quinolones,
2. use of other antibiotics within two days prior to the development of fever,
3. age > 14 years,
4. hepatic insufficiency (alanine aminotransferase level > 4 times normal),
5. inability to take oral medications because of painful mouth ulcers, intestinal malabsorption, or severe nausea and vomiting,
6. recurrent pyrexia of undetermined origin, and
7. any other co-morbid condition requiring hospitalisation.

Patients who were expected to have prolonged neutropenia (≥ 7 days duration), such as those with aplastic anaemia, untreated leukaemia, and severe bone marrow infiltration were excluded from the study. Some of the parameters for eligibility were assessed at the time of initial chemotherapy. Assessment of several other parameters, such as fever, blood counts, ability to take oral medications, and need for hospitalisation due to other reasons, was left to the discretion of the patients' caregivers.

Treatment Protocol

At the time of post-chemotherapy discharge, caregivers were instructed to administer oral ofloxacin 200 mg immediately and twice daily on development of fever in the next 14 days. They were instructed not to administer ofloxacin during the first week unless neutropenia could be confirmed by a haemogram. During the second week however, antibiotic therapy with ofloxacin was administered immediately and a haemogram was obtained as soon as possible thereafter. Work-ups such as blood cultures, urine cultures, and radiological examinations to elucidate the cause of fever were not mandatory. Caregivers were instructed to inform the study investi-

gators as soon as possible after the onset of fever. They were registered on the study at that time. Subsequently, telephone contact (at least once daily) was maintained between the oncology staff and the patients' caregivers. Those patients who could come for follow-up visits but could not afford in-patient care were assessed daily, free of charge, in the day-care unit. If the general condition remained stable and fever subsided over the next 4 days, antibiotics were continued for a minimum of 7 days. At that time, another haemogram was obtained and antibiotic therapy was continued as long as neutropenia persisted.

Caregivers were instructed to bring the patient to the hospital if clinical signs and symptoms worsened, e.g. the temperature increased or the fever pattern remained unchanged for >4 days, if dyspnoea or mental changes developed, or if an obvious source of infection was recognised or worsened. Those who required hospitalisation were immediately administered either a broad-spectrum parenteral antibiotic such as ceftazidime or parenteral combination antibiotics. Other instructions related to febrile neutropenia and given at the time of discharge were based on general guidelines for the management of febrile neutropenia and concerned the necessity of eating cooked food, proper washing of hands and general maintenance of cleanliness, and avoiding individuals with fever or suspected infections.

Evaluation Of Treatment Outcome

Treatment outcome was defined according to the following four categories:

1. *Success without modifications* characterised the treatment of patients who recovered from fever and neutropenia without any modification of the initial regimen and who never required hospitalisation.
2. *Success with modifications* characterised episodes in which patients ultimately recovered from fever and neutropenia but required hospitalisation, therapy with additional antibiotics, empirical or therapeutic antifungal drugs, or anti-viral therapy with acyclovir.
3. *Initial failures* were episodes in which the patients did not respond to ofloxacin, required hospitalisation but died before admission.
4. *Late failures* were episodes in which patients died in the hospital while receiving broad-spectrum antibiotics with persistent neutropenia.

Statistical Analysis

In this study, each patient corresponds with one episode of fever and neutropenia, which is the unit of analysis. Although several patients had more than one episode of fever and neutropenia, each episode was analysed separately and each patient was evaluated per episode; thus the number of evaluated episodes and the number of evaluated patients were equivalent.

Results

Ninety-one episodes involving 75 patients with cancer were included in the study. Six episodes were not evaluable primarily because of in-accurate calculation of the ANC (Table I). Clinical characteristics of all study patients (intent to treat) are shown in Table I. Most of the patients had solid tumours or non-Hodgkin's lymphoma. Nineteen episodes were observed in patients with acute leukaemia who were either on consolidation or maintenance therapy. Since determination of blood counts was not frequently repeated, information about the mean duration of neutropenia was not available. However, 25% of the patients had neutropenia of 1 week duration or longer. Since routine blood cultures were not done, incidence of microbiologically-documented infections was low. Majority (84%) of the patients had pyrexia of undetermined origin (IWO).

Seventy-seven (91%) of the febrile episodes responded to oral ofloxacin and hospitalisation was never required (Table II). Eight patients required hospitalisation, of whom none expired. Five of the 8 patients who required

TABLE I: CLINICAL CHARACTERISTICS OF THE STUDY PATIENTS

Total number of episodes (%)	91 (100)
Number of evaluable episodes (%)	85 (93)
Reason for exclusion	
Never had an ANC $10.5 \times 10^9/L$ (%)	5 (6)
Received an additional antibiotic (%)	1 (1)
Sex (M : F)	49 : 42
Mean ($\pm$ SD) age in years	9.2 (f4.3)
Underlying neoplasm (%)	
Acute leukaemia	19 (21)
Non-Hodgkin's lymphoma	25 (27)
Other solid tumours	47 (52)
Average number of days since chemotherapy ($\pm$ SD)	9.8 ($\pm$ 3.1)
Mean ANC $\times 10^9/L$ on entry (range)	0.24 (< 0.1 - 0.56)
Number (%) with ANC $< 0.1 \times 10^9/L$	25 (27)
Neutropenia for ≥ 1 week	23 (25)
Mean days of fever	3.2
Underlying cause of fever (%)	
Pyrexia of undetermined origin	76 (84)
Clinical or microbiologic infection	15 (16)

ANC: absolute neutrophil count

TABLE II: RESPONSE RATES AND SURVIVAL DATA

Outcome of therapy	No of episodes (%) (n = 85)
Success without modification (hospitalisation never required)	77 (91)
Success with modification (hospitalisation required)	8 (9)
Initial failures (early death)	0 (0)
Late failures (early death)	0 (0)

Those requiring hospitalisation received parenteral antibiotics.

TABLE III: CLINICAL CONDITIONS AND OUTCOME OF PATIENTS REQUIRING HOSPITALISATION FOR FEBRILE WORK-UP

Condition and final outcome	No of patients (%) (n = 8)
Documented infection	5 (62)
Clinical (cellulitis 2, gingivitis 1, pneumonia 1)	3 (37)
Microbiologic	2 (25)
PUO	3 (37)
Neutropenia ≥ 1 week	7 (87)
Successful outcome	8 (100)

* Microbiologic infection was with gram-positive organisms most likely from the infected IV sites.

PUO: pyrexia of undetermined origin

hospitalisation had documented infections (Table III). These included pharyngitis, cellulitis, pneumonitis, *S. typhi* gastroenteritis and *H. influenzae* otitis externa. Most of them had prolonged neutropenia. They were all successfully treated with no mortality.

Discussion

Although management of febrile neutropenia has become fairly standard, its applicability to all patients with febrile neutropenia in developing countries is at times difficult. Substantial costs and non-availability of adequate medical services are two major problems faced by socio-economically disadvantaged patients and their families. This makes provision of proper health care exceedingly difficult. An unfortunate repercussion of this problem is delivery of inadequately low doses of chemotherapeutic agents to prevent the possibility of significant myelosuppression by many practising oncologists in developing countries. Such a policy in potentially curable paediatric patients is totally unacceptable. This study offers an innovative way to manage these patients. Although unorthodox, it may be the only viable option for patients who cannot afford the expensive in-patient therapy or live far away and have no access to specialised cancer centres. Such a policy would allow optimal doses of chemotherapy to be delivered with acceptable morbidity and mortality.

This study can be criticised for the softness of criteria to initiate antibiotic therapy and for leaving several important decisions to the discretion of caregivers. Whenever possible, caregivers were instructed to contact a local physician at the onset of fever. Most of the decisions however, were made with the assistance of oncology staff who were contactable by telephone regularly. Overall successful outcome of this study is mostly attributable to close interaction between physicians and caregivers.

Caregivers were instructed not to administer ofloxacin during the first week of chemotherapy unless neutropenia was confirmed by a haemogram. This was done to

minimise indiscriminate use of ofloxacin. An onset of fever in the second week mandated immediate institution of antibiotic therapy. Most of the usual work-ups to elucidate the cause of fever were not carried out. This was done to minimise the financial burden placed on the family. In any case, our patients were expected to have low-risk febrile neutropenia. Only a minority can be expected to have microbiologically-documented infection. The absolute need for repetitive, expensive work-ups of all patients to discover the underlying cause of fever in a few, can be seriously questioned. Nevertheless, most of our patients could not afford such expensive work-ups. The caregivers were instructed to administer ofloxacin for a minimum of 7 days. This was done to cover most of the common microbiologic flora. Successful outcome of this study justifies this approach.

Another important criticism of this trial may relate to administration of ofloxacin to paediatric patients. Quinolones are generally not recommended for paediatric use. Ofloxacin has been observed to cause arthropathy and osteochondrosis in juvenile animals of several species. However, this association has not been observed in humans. Although caution is warranted, one can argue about applicability of these animal data to humans. This is particularly relevant since the drug is expected to be given for only a short duration. Furthermore, ofloxacin has been used in children with ampicillin-resistant salmonella in some developing countries.¹⁴⁻¹⁷ Since choice amongst low-cost, broad-spectrum oral antibiotics is limited and mortality from untreated febrile neutropenia is high, these incriminating circumstances justified such an approach.

There are several reasons behind the successful outcome of this study. Firstly, monotherapy with one of the several broad-spectrum antibiotics has proven to be efficacious in most of the patients with febrile neutropenia. Quinolones have also been used for monotherapy. They provide a broad spectrum of bactericidal activity. They are particularly effective in treating gram-negative bacillary infections but are also active against gram-positive organisms. They are well tolerated, have few adverse effects, and excellent oral bio-availability. Several studies have confirmed the efficacy of quinolones in the management of febrile neutropenia.¹⁰⁻¹⁸ Secondly, almost all patients in our study belonged to the low-risk category.^{19,20} They had stable disease, absence of bone marrow dysfunction, and were not previously hospitalised. They were expected to have a short-duration neutropenia. Such low-risk patients have been successfully treated on out-patient basis by several investigators.^{10,21-26}

We have previously used a similar approach of out-patient, self-administration of antibiotics in adults with febrile neutropenia.¹² In that study, 83% of patients never required hospitalisation. In the present study

involving paediatric patients, success without modification was achieved in 91% of the episodes. This may be reflective of the restricted use of quinolones in paediatric population primarily due to fear of arthropathy and osteochondrosis.

In summary, we successfully employed the policy of administration of antibiotics by the caregivers to a select group of paediatric patients with febrile neutropenia on an out-patient basis. Although dictated by prevailing circumstances in our society, this approach may be applicable to other developing countries and may suggest new avenues of research relevant to the developed world.

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