Double -Control, Randomized Study of Antibiotic Prophylaxis during Standard Dose Chemotherapy in Cancer Patients

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Abstract: Background: Dilemma of antibacterial prophylaxis after chemotherapy still opened. Patients and methods:Double, control trial in patients who were receiving cyclic chemotherapy for solid tumors or lymphoma and who were at risk of temporary, sever neutropenia (fewer than 500 neutrophils/ml). Patients were randomly divided into two group, the first groups assigned to receive oral 500 mg of quinolone once daily for seven days during the expected neutropenic period, while the second group received no prophlaxis (control group). The primary end point was the incidence of clinically documented febrile episodes (FE) (temperature of more than 38°C) due to infection. Assessment of the risk of FE in controll group on first versus non first cycles with or without first cycle FE in the light of different pretreatment factors. Secondary end point included the incidence of all infections, severe infections, hospitalization and cost. Results: A total of 403 patients randomly divided into 201 patients received antibacterial prophylaxis quinolone (levofloxacin®) and 202 patients as control group. The tumors included breast cancer 238 (59.1 percent), lung cancer 82 (20.3%), testicular cancer 34 (8.4%) and lymphoma 49 (12.2%). During the first cycle of chemotherapy, 3.5% of patients in the quinolone group had at least one febrile episode, as compared with 8.4% in the control group (P=0.009).The per- cycle FE rate for the first cycle was 8.4% compared with 4.4% in non first cycles in control group. During the entire chemotherapy course, 9.5% of patients in the quinolone prophylactic group had at least one febrile episode; as compared with 16.3% in the control group (P ≤0.005).There was significant reduction in the rate of G3&G4 neutropenia in quinolone group (52%). The respective rates of infections were 33.8% and 42.1% (p=0.098) for quinolone versus control group. Hospitalization was required for treatment of infection in 3% of patients in the quinolone group and 7% of patients in the control group (P≤0.05). Respective rates of reduction of cost and length of stay (LOS) were 51.8% and 51.6% for infections in quinolone prophylactic group. Respective rates of sever infections were 1.0% and 2.0% (p≤0.06), for quinolone and control group, with one infection related death in each group. An organism was isolated in 194/250 cycles (77.6% of infections). Conclusions: Quinolone prophylaxis (levofloxacin is preferred) should be offered to those receiving standard dose chemotherapy for solid tumors and lymphomas to reduce incidence of fever, infection, hospitalization and cost with rational selection of patients for antibacterial prophylaxis with first cycle chemotherapy.
[Fatma Zakaria[*1] and Mohamad Zakaria. **Double -Control, Randomized Study of Antibiotic Prophylaxis during Standard Dose Chemotherapy in Cancer Patients**. Journal of American Science 2010;6(12):1124-1135]. (ISSN: 1545-1003). http://www.americanscience.org.

Keywords: Antibiotic Prophylaxis; standard Dose; Chemotherapy; Cancer; Patient

1. Introduction:

Chemotherapy induced neutropenia (table 1) is not only a major risk factor for infection related morbidity and mortality, but also a significant dose - limiting toxicity in cancer treatment. Patients developing sever (grade 3/4) febrile neutropenia (FN) during chemotherapy frequently underwent dose reduction and/or delay to their chemotherapy. This may impact on the success of treatment, particularly when treatment intent is either curative or to prolong survival[1].

Meta-analysis of nine trials (731 patients) comparing fluoroquinolone prophylaxis with no prophylaxis demonstrated significant reductions in a number of outcomes of infections[2-3-4].

Quinolone (Levofloxacin ®) is an agent with an acceptable side-effect profile that is administered orally once daily, thus optimizing compliance, a major issue in prophylaxis[5].

It is active against a wide range of gram negative pathogens, as well as some gram-positive bacteria and organisms causing atypical pneumonias[5].

We conducted randomized trial designed to determine the efficacy of quinolone prophylaxis offering seven days prophylaxis during the period of anticipated neutropenia in patients with solid tumors or lymphomas.

2. Patients and Methods:

Four hundred and three adult patients with solid tumors and lymphomas treated inclusively during the period from January 2006 to December 2008, at Clinical Oncology Department, Tanta University. All patients at risk of bacterial infection were randomly divided into two groups the first one 201patients assigned to receive qinolone for seven days to cover the period of anticipated neutropenia

and another control group 202 patients. Patients remained enrolled in the trial for up to six cycles of chemotherapy. A cycle of chemotherapy was defined as the standard, minimal duration of a particular regimen between the start of one treatment and the next that was sufficient to allow recovery from acute adverse effects, including myelosuppression. Exclusion criteria at the time of randomization were active infection, current antibacterial therapy, planned use of G-CSF, a history of adverse reactions to fluoroquinolones, epilepsy, a creatinine clearance below 40 ml per minute, pregnancy, and breast-feeding. All patients gave written informed consent.

End points measures:

The primary end point was the incidence of clinically documented febrile episodes (FE), (defined by a temperature exceeding $38^{o}C$ due to infection) with or without neutropenia with assessment of grading for neutropenia, and assessment of febrile episodes in control group on first versus non first cycles with or without first cycle febrile episode. Infections incidence were the secondary outcome measure, infections were defined by at least one of the following: a clinically documented febrile episode, other signs attributed to a systemic response to infection, such as hypothermia (temperature below $35.6^{o}C$), low grade fever (temperature, 37.5 to $37.9^{o}C$), tachycardia (more than 90 beats per minute),or tachypnea (more than 20 breaths per minute), signs of a focus of infection, or the use of antibacterial therapy, we were reported episodes that occurred during each chemotherapy cycle or within four weeks after the final cycle. The incidence of hospitalization for infection and the frequency of severe infection were further secondary outcome measures. Severe infections were defined by the presence of infection-related sepsis syndrome (i.e. infection causing hypotension with or without

evidence of impaired organ perfusion), death from infection or both.

Microbiologic outcomes included causative organisms isolated during infection, the clinical significance of isolates was assessed by a microbiologist. For episodes of infection, study medication was withdrawn for that cycle alone, but patients could remain in the trial for subsequent cycles.

Trial medication:

Trial medication consisted of 500 mg tablets of quinolone (as prophylaxis) once daily for seven consecutive days, treatment began on day 8 for 14 day and 21-day cycles, and on the day 15 for 28-day cycles.

Cost:

Costs were derived from charges reported on patients' tickets. Total costs per patient were computed by summing individual cost, where all patients were treated at our inpatient unit.

Statistical Analysis:

Statistical presentation and analysis of the present study was conducted, using mean, median, analysis of variance [ANOVA] test and the relative differences between the treatments groups were expressed as relative risks with 95 percent confidence intervals. Data on secondary outcomes relating only to cycles with infection are presented descriptively to identify patients at greater risk of infection during chemotherapy without antibacterial prophylaxis. The analysis assesses the association of baseline patients' characteristics with FE incidence using all the patients randomly assigned to the control arm and a multivariable analysis that includes all variables in the model is also used by SPSS v.12. P-value is considered significant, if ≤ 0.05, determined by chi-square test.

Table (1):Common chemotherapy regimens associated with intermediate or high risk of febrile neutropenia[1,2,3,4,5,6,7,8,9,10]

Malignancy	FN risk category (%)	Chemotherapy regimen	FN risk
Breast cancer	>20	AC→ docetaxel	5-25
		Paclitaxel→AC	40
		Doxorubicin/docetaxel	33-48
		Doxorubicin/paclitaxel	21-32
		TAC	21-24
		DD/DDG FEC	71/59
		DDG doxorubicin→paclitaxel→cyclophosphamide	2
		DDG doxorubicin/cyclophosphamide→paclitaxel	2
		DDG epirubicin/cyclophosphamide	8

Cont. Table (1)

Malignancy	FN risk category (%)	Chemotherapy regimen	FN risk
	10-20	AC	10-20
		Doxorubicin/vinorelbine	15
		Docetaxel	16-17
		Capecitabine/docetaxel	13
		Cyclophosphamide/mitoxantrone	11
		Epidoxorubicin/cyclophosphamide	13
		CEF	14
		FEC	9-14
	<10	FEC	0-2
		CMF	0-3
		CMF oral	1
		Doxorubicin/cyclophosphamide	2
		Doxorubicin→paclitaxel→cyclophosphamide	3
		Doxorubicin/cyclophosphamide→paclitaxel	5
		FAC	5
		Epirubicin/cyclophosphamide+lonidamide	7
Small cell lung cancer	>20	ACE	24-57
		Topotecan	28
		Topotecan/paclitaxel	>20
		ICE	24
		VICE	70
		DDG ACE	34-56
		DDG ICE	18
		DDG CAV→PE	4
	10-20	CAV	14
		Etoposide/carboplatin	10-20
		Topotecan/cisplatin	19
		CODE	19
	<10	CAV	3-9
		Paclitaxel/carboplatin	9
Non-small cell lung cancer	>20	Docetaxel/carboplatin	26
		Etoposide/cisplatin	54
		VIG	25
	10-20	Paclitaxel/cisplatin	16
		Docetaxel/cisplatin	5-11
		Vinorelbine/cisplatin	1-10
	<10	Paclitaxel/carboplatin	0-9
		Gemcitabine/cisplatin	1-7
		Gemcitabine/cisplatin	4
Non-Hodgkins lymphoma	>20	DHAP	48
		ESHAP	30-64
		GHOP	17-50
		DD/DDG VAPEC-B	44/23
		DD/DDG ACVBP	78/52
	10-20	ACOD	11
		R-CHOP	19
		Fludarabine/mitoxantrone	11

Cont. Table (1)

Malignancy	FN risk category (%)	Chemotherapy regimen	FN risk
Ovarian cancer	>20	Docetaxel	33
		Paclitaxel	22
	10-20	Topotecan	10-18
	< 10	Paclitaxel/carboplatin	3-8
		Gemcitabine/cisplatin.	9
Urothelial cancer	>20	Paclitaxel/carboplatin	25
		MVAC	26
		DDG MVAC	10
Germ cell tumors	>20	BOP→VIP-B	46
		VeIP	67
	10-20	cisplatin/etoposide	10
		BEP→EP	13
Colorectal cancer	10-20	5-FU/leucovorin	1-15
		FOLFIRI1	3-14
	<10	FOLFOX	0-8
		IFL	3-7
		Irinotecan	2-7
Other malignancies	>20	TIC (head and neck cancers)	30
		MAID (sarcoma)	58
		Paclitaxel/cisplatin (cervical cancer)	28
	10-20	Gemcitabine/irinotecan (pancreatic cancer)	17
		Stanford v (Hodgkin's lymphoma)	14
	< 10	ABVD (Hodgkin's lymphoma)	4
		Doxorubicin/cisplatin (endometrial cancer)	2
		TAP (endometrial cancer)	3

Please note that these results may vary for similar regimens depending on the patient population who participated in each study. 5-FU, 5-fluorouracil; ABVD, doxorubicin / bleomycin / vinblastine / dacarbazine; AC, doxorubicin / cyclophosphamide; AC→ T, doxorubicin / cyclophosphamide followed by docetaxel; AGE, doxorubicin / cyclophosphamide / etoposide; ACOD, doxorubicin / cyclophosphamide / vincristine / prednisolone; ACVBP, doxorubicin or mitoxantrone with cyclophosphamide/ vindesine/bleomycin; BEP→ EP, bleomycin / etoposide/cisplatin followed by etoposide / cisplatin; BOP→ VIP-B, bleomycin/vincristine / cisplatin followed by cisplatin / ifosfamide / etoposide/bleomycin, CAV, cyclophosphamide / doxorubicin/vincristine; CE, cyclophosphamide/ epirubicin; CEF, cyclophosphamide / epirubicin/5-FU; CHOP-21, cyclophosphamide / doxorubicin/ vincristine / prednisone; CMF, cyclophosphamide/ methotrexate / fluorouracil; CODE, cisplatin / vincristine / doxorubicin / etoposide; DD, dose dense; DDG, dose dense with G-CSF; DHAP, cisplatin / cytarabine / dexamethasone; ESHAP, etoposide / methylprednisolone / cytarabine / cisplatin; FAC, fluorouracil / doxorubicin / cyclophosphamide; FEC, cyclophosphamide / epirubicin / fluorouracil; FMD, fludarabine / mitoxantrone; FOLFIRI, 5-FU/l-folinic acid / d,1-folinic acid / irinotecan; FOLFOX, 5-FU / folinic acid / oxaliplatin; FN, febrile neutropenia; ICE, ifosfamide / carboplatin / etoposide, IFL, irinotecan / 5-FU / calcium folinate; MAID, mesna / doxorubicin / ifosfamide / dacarbazine; MVAC, methotrexate / vinblastine / doxorubicin / cisplatin; PE, cisplatin / etoposide; Q2W, once every 2 weeks; R-CHOP-21, rituximab / GHOP; Stanford V, mustard / doxorubicin / vinblastine / vincristine / bleomycin / etoposide / predniso lone; T→AC, docetaxel followed by doxorubicin / cyclophosphamide; TAC,

docetaxel / doxorubicin / cyclophosphamide; TAP, paclitaxel; oxorubicin / cisplatin; TIC, paclitaxel / ifosfamide / carboplatin; VAPEC-B, vincristine / doxorubicin / prednisolone / etoposide / cyclophosphamide / bleomycin; VICE, vincristine/ifosfamide / carboplatin / etoposide; VIG, vinorelbine / ifosfamide / gemcitabine.

FN risk < 10% G-CSF not indicated

FN risk 10-20% or ⎧ Overall FN risk ≥ 20% prophylactic G-CSF

⎩ Overall FN risk < 20% → G-CSF not indicated

FN risk ≥ 20%   prophylactic G-CSF recommended.[1]

Table (2): Grades of Neutropenia [11]

Grade	Absolute neutrophil cou $10^9/L$)
0	Within normal limits
1	≥ 1.5 to < 20
2	≥ 1.0 to < 1.5
3	≥ 0.5 to < 1.0
4	< 0.5

[a] According to the National Cancer Institute, Common Toxicity Criteria, version 2.0.

3. Results

From January 2006 to December 2008, 403 patients from Tanta University Hospital, Clinical Oncology Department, underwent randomization 202 as control group and 201 to quinolone prophlaxis. A total of 94.3 percent of patients had a WHO performance status of 0 or l, and more than half were treat in the adjuvant context. More than half of the patients had breast cancer, but substantial numbers were treated for lung and testicular cancer. The treatment groups were well balanced with respect to all baseline characteristics and risk factors (table 3). A total of 2278 cycles were analyzed and the number of cycles was studied.

Infection:

Of the 403 patients, 52 patients (13.0%) had at least one febrile episode, and there were 90 cycles with febrile episodes in total 2278 cycles (4.0% of cycles). At least one infection occurred in 153 patients (38.0%), and there were total of 250 cycles with infections in total of 2278 cycles (11.0% of cycles) (table 4). A clinically documented febrile episode occurred during the first chemotherapy cycle in 7 of 201 patients in the quinolone group (3.5 %), as compared with 17 of 202 patients in the control group (8.4 %) (Table 5).   The relative risk of a clinically documented febrile episode was (relative risk 1.6, 95%CI (0.40-0.71), p≤0.009), indicating a (59%) reduction in the risk of fever during the first

cycle with the use of quinolone therapy, as compared with control group.   There was also a significant reduction in the incidence of the more inclusive category of infections with quinolone prophylaxis, as compared with control group, resulting in 39% reduction in the risk during the first cycle of chemotherapy (relative risk 2.33,95%CI (0.79-1.22), P≤0.001).

Data obtained during the entire chemotherapy were analyzed per patient rather than per cycle, and quinolone antibacterial prophylaxis was found to confer a protective benefit similar to that identified in the analysis of the first cycle (Table 5). During the entire course of chemotherapy, 19 out of 201 patients in quinolone group had a clinically documented febrile episode (9.5 %), as compared with 33 of 202 patients in the control group (16.3%). Prophylactic quinolone with thus associated with a 42.0% relative reduction in the risk of a febrile episode (relative risk 1.31, 95%CI (0.99-1.18), p=0.051) and a 20% relative reduction in the risk of infections (relative risk 0.98, 95%CI (0.76-0.91), P=0.098). Only 14 patients (7.0%) from the quionolone had more than one febrile episode. As regared neutropenia, from G1 to G4 was present 13 cycles in quinolon group in comparison to 38 cycles in control group with reduction rate 65.8% in febrile episodes with neutropenia. Thirty four cycles with neutropenia (G1 to G4) in comparison to 73 cycles in quinolone versus control group respectively with 53.4% reduction rate of infections with neutropenia.

Hospitalization for infection:

The reduction in the incidence of febrile episodes and infection associated with quinolone prophylaxis was reflected in a significant reduction in the percentage of patients hospitalized for infection (Table 5). There was 71.6 percent reduction in the risk of hospitalization during cycle 1 with quinolone therapy, as compared with control group (relative risk 0.70, 95%CI (1.15-1.96), P=0.011) and a 45.4 percent reduction across all cycles (relative risk 0.32, 95%CI (0.13-0.82), P value= 0.04).

Severe infections:

Severe infection characterized by infection related sepsis manifestations, death, or both occurred in two patients in quinolone group as compared with four patient in the control one (relative risk 0.11,95%CI (0.24-1.12), P=0.06), one patient died in each group. Two severe infections in the quinolone group occurred outside the period in which the white cell count was expected to be lowest, in comparison to four patient severe infections in control group, causing death in one patient, which occurred during the expected nadir period (Table 5).

Microbiologic outcomes:

The organism that was the probable cause of the febrile episode or episode of infection was isolated less frequently among patients in the quinolone group than among patients in the control group (46.9% vs 75.9% and 45.5% vs 60.9% respectively) (Table 6).

Adverse events:

Adverse events were reported in 38 cycles of 2278 cycles of chemotherapy (1.7 percent) there was a slight excess of adverse events in the quinolone group, owing to a higher rate of minor gastrointestinal symptoms and rash (Table 6).

Cost and length of stay (LOS):

Median duration of LOS were 6.5 days Vs 5 days for FE in quinolone group and control group per hospitalization respectively, with total length of stay 28 days in quinolone group Vs 73 days in, control group. Hospitalization for infections showed total LOS was 105 days for quinolone group in comparison to 217 days for control group with reduction of cost (51.8%) for hospitalization of infection in quinolone group (table 6).

Identifying risk factors for Infection and
Hospitalization without antibacterial prophylaxis:

Tumor type: The different types carried different risks for FE across all cycles of chemotherapy and in cycle one (Table 7). Multivariable analysis identified lung and testicular cancers as the tumor types at significantly greatest risk for FE in all cycles and in cycle one (p=0.007&0.003).

Other pretreatment factors:

Poor performance status, advanced age 65 years or older and male sex have been linked to a higher risk of FE. The FE frequency was lower in patients undergoing adjuvant chemotherapy compared with those being treated for advanced disease, but this did not reach statistical significance (Table7).

First cycle versus later cycles:

Two hundred and two patients were randomly assigned to the control arm and received 1144 cycles of chemotherapy (mean, 5. 7 cycles per patient). Seventeen of them experienced a FE during the first cycle,(51.5%) (17|33).Thirty three controls, had at least one FE during the entire course of chemotherapy program,giving a per- patient FE rate of (16.3%) 33|202 .The FE rate for the first cycle was (8.4%) (17|202 cycles) compared with (4.4%)(41|942

cycles) in non first cycles.Approximately > 50% of episodes occurred in cycle one.

4. Discussion:

We studied the efficacy of antibacterial prophylaxis in patients treated for solid tumors and lymphomas with chemotherapy regimens associated with short periods of neutropenia and thus an increased risk of infection.

A simple, clinically relevant objective observation (fever, as defined by a temperature of more than 38°C) attributed to infection as the primary outcome in our study,12.9 percent receiving conventional chemotherapy for solid tumors and lymphomas had at least one febrile episode with an over all incidence of 4.0% per cycle.

During the entire course of chemotherapy approximately 33.3% reduction in febrile episodes for patients in the quinolone group versus those in the control group (9.9% Vs 16.3%) and 58.9% reduction in febril episodes during the first cycle of chemotherapy for quinolone group compared tothe control group (3.5% Vs 8.4%) respectively in. There was significant reduction in grade 3&4 febril neutropenia in quinolone group (52%).

More than 50% of febrile episodes occurred in first cycle in the control group (table 5), with FE and hospitalization rates were twice more frequent in first cycle than subsequent cycle which is in agreement with other several trials[12,13,14,15,16,17] ,which recorded several explanations for this first-cycle effect, neutropenia, The explanation of this phenomena may be dose reduction of chemotherapy in subsequent cycles. The cytoreductive effects of the first chemotherapy cycle may enable resolution of a cancer related focus of infection (e.g. beyond an obstructed air way in lung cancer patients) or improvement in performance status. The first cycle of chemotherapy is noteworthy not only because of the high frequency of FE compared with later cycles, but also because FE in cycle one appears to separate patients into low and high-risk groups for subsequent episodes .[18,19]

Under pressure to limit antibacterial use, these exploratory data support offering prophylactic quinolone on cycle 1 only for myelosuppressive cancer chemotherapy and on subsequent cycles after a cycle-1 fever [19].

Pre-treatment factors and FE in first & non first cycles in control group, lung and testicular cancers in the control group were the tumor types with higher risksfor FE in first and non first cycles (p=0.007&0.003), the possible explanations for this effect may be due to, the majority of patients received etoposide which cause severe and unpredictable neutropenia[20], mucositis is also a frequent

consequence of etoposide exposure that predisposes to infection in control group. Poor PS has been linked to a higher risk of FE[21]. Age 65 years or older has been shown to confer a higher risk of FE[22], with male sex predominance for FE in first and non- first cycles without statistical significant difference (p=0.074). The reduction in the incidence of hospitalization for the treatment of infection was significant (45.9 percent), (p=0.04) for quinolone group for the entire course of chemotherapy. Seventy five percent of fever occurred outside the expected period of neutropenia (i.e. the period of prophylaxis), table (6). The two cases of sever infections and death from infection in the quinolone group occurred outside the expected period of neutropenia (i.e the period of prophylaxis), our results are supported by other studies that received prophylaxis with marked reduction in infection related outcomes, including death particularly in a cohort receiving intensified chemotherapy with G.CSF [23,24,25,26, 27].

Table (3): Patients characteristics:

Characteristics	Quinolone prophylaxis (n=201)	Control (n=202)
Sex- no%		
Male	91 (45.3%)	98(48.5%)
Female	110 (54.7%)	104 (51.5%)
WHO performance status		
0	146 (72.6%)	162 (80.2%)
1	40 (19.9%)	32 (15.8%)
2	13 (6.5%)	6 (3%)
3 or 4	2 (1.0%)	2 (1%)
Age:		
16-39 ys	40 (19.9%)	39 (19.3%)
> 40-65 ys	88 (43.8%)	83 (41.1%)
$\geq$ 65 ys	73 (36.3%)	80 (39.6%)
Type of cancer and most commonly used chemotherapy regimens-no(%)		
Breast cancer	116 (57.7%)	122 (60.4%)
Fec	80	75
Sq T-fec	26	37
Lung cancer	42 (20.9%)	40 (19.8%)
PE	22	30
CAV	20	10
Testicular cancer	18 (9%)	16 (7.9%)
BEP	16	15
EP	2	1
Hodgkin's disease	8 (4%)	10
ABVD	8	10
Non-Hodgkin's disease	17 (8.5%)	14 (6.9%)
CHOP	17	14
Chemotherapy being given in adjuvant setting- no(%)	145 (72.1%)	151 (74.8%)
Indwelling venous catheter present no (%)	20 (10%)	26 (12.9%)
Previous myelosuppressive chemotherapy given No%	56 (27.9%)	51(25.2%)
Previous radiotherapy given no (%)	10 (5%)	14 (6.9%)

FEC denotes fluorouracil, epirubicin, and cyclophosphamide; T taxanes, PE cisplatin and etoposide, CAV cyclophosphamide, doxorubicin and vincristine, BEP bleormycin, etoposide and cisplatin; ABVD doxorubicin, bleomycin, vinblastine, and dacarbazine , CHOP cyclophosphamide, doxorubicin, vincristine, and prednisolone.

Table (4): Characteristics of 250 infections among 2278 cycles.

Variable	Focus of infection	No focus of infection	No / total (% of cycles)
Sign of probable infection	No. of probable infection (% of total)		
Fever	56(22.4%)	34 (13.6%)	(3.9) 90/2278
Other systemic signs	40(16.0%)	10(4.0%)	(2.2%) 50/2278
No systemic signs	98 (39.2%)	12* (4.8%)	(4.8%) 110/2278
Focus of infection			
Upper respiratory tract	65(26%)		
Lower respiratory tract	29(11.6%)		
Gastrointestinal tract & anal abscesses	8(3.2%)		
Urinary tract	24 (9.6%)		
Skin ad soft tissues	22(8.8%)		
Venous catheter	13(5.2%)		
Oral mucosa and teeth	24(9.6%)		
Multiple sites	9(3.6%)		
No focus of infection		56 (22.4%)	

* In these 12 episodes, the only evidence of infection was the reported use of antibacterial therapy in 8, no further data were available for the other 4 episodes.

Table (5): Incidence of febrile episodes, infections, and Hospitalization for infection

Event	Quinolone (n=201)	Control (n=202)	Relative risk &(95%) Cl	P value
Events occurring in first cycle				
-Febrile episode				
Yes	7 (3.5%)	17 (8.4%)		
No	194	185	1.60(0.40-0.71)	0.009*
-Infection				
Yes	25 (13.9%)	41 (20.2%)		
No	176	161	2.33(0.79-1.22)	0.001*
- Hospitalization for infection				
Yes	2 (0.99%)	7 (3.7%)		
No	199	195	0.70(1.15-1.96)	0.049*
Events occurring at least once in any cycle				
- Febrile episodes				
Yes for ≥ 1cycle	19 (9.5%)	33 (16.3%)		
No for all cycle	182	169	1.31(0.99-1.18)	0.051
- Infection				
Yes for ≥ l cycle	68 (33.8%)	85 (42.1%)		
No for all cycles	133	117	0.98(0.76-91)	0.098
- Hospitalization for infection				
Yes for ≥ l cycle	6(2.99%)	11(5.4%)		
No for all cycles	195	191	0.32(0.13-0.82)	0.04
-Sever infection and/or death from infection	2 (1.0%)	4 (2.0%)	0.11(0.24-1.12)	0.067

* A febrile episode was defined by temperature more than 38°C. Cl denotes confidence interval. The P values, determined by the chi-square test, are for "yes" answer as compared with "no" answer .

Table (6): Adverse events and characteristics of febrile episodes, infections, hospitalization for infections and grading of neutropenia.

Variable	Quinolone	Control
All cycles no (%)	1134	1144
Adverse events	23 (2.0%)	15 (1.3%)
Rash	6	2
Gastrointestinal effect	16	9
Central neurons system effects	--	--
Musculoskeletal effect	--	--
Multiple events including those listed above	--	3
* other	1	1
Antifungal prescribed prophylaxis	90(7.9%)-	86(7.5%)-
Incidence of mucosal candidiasis	88(7.8%)	76(6.6%)
Cycles with febrile episodes total no%	32(100%)	58(100%)
During expected nadir	8(25%)	32(55.2%)
Outside expected nadir	24 (75%)	26 (44.8%)
Hospitalization – No% duration – days	4(6.3%)	10 (8.6%)
Median	6.5 days	5days
Interquartile range	5-9 days	3-8days
Total (LOS)	28 days	73days
Grading of neutropenia at onset of infection		
G0	19	20
G1	2	13
G2	4	10
G3&4	7(21.9%)	15(25.9%)
Microbiologic analysis –No% probable causative organism.	15(46.9%)	44 (75.9%)
Cycles with infections total – no%	112(100%)	138(100%)
-During expected nadir	27(24.1%)	67(48.6%)
- Outside the expected nadir	85(75.9%)	71(51.4%)
Hospitalization for infection duration- days	15 (13.4%)	31 (22.5%)
Median	6 days	5 days
Interquartile range	4-9 days	3-9 days
Total (LOS)	105 days	217 days
Total Cost-	21195 LE	44011LE
Total (Cost) per hospitalization,		
Mean-	535.7LE	637.7LE
Median	529LE	631LE
Grading of neutropenia at onset of infection		
G0	78	65
G1	12	26
G2	10	22
G3&4	12(10.7%)	25(18.1%)
Microbiologic analysis-no% probable causative bacteria isolated	51(45.5%)	84 (60.9%)

* This category includes allergic reactions, a general feeling of malaise, breathless- ness, chest discomfort, and unspecified events, (LOS) length of stay in hospitalization.

Table (7): Number and Rate of FE by patient characteristics in controls.

		FE across all cycles			FE in cycle one		
Characteristic	No of patients	No	Rate%	P*	No.	Rate (%)	P*
Over all tumor type	202	33	16.3%	0.094	17	8.4%	0.072
Breast	122	13	10.6%		7	5.7%	
Lung	40	10	25%	0.007	5	12.5%	0.003
Testicular	16	5	31.2%		3	18.8%	
Hodjken's	10	2	20%		1	10%	
NHL	14	3	21.4%	0.052	1	7.1%	0.159
Age:							
16-39 ys	39	7	17.9%		5	12.8%	
> 40-65 ys	83	11	13.3%	0.435	7	8.4%	0.623
> 65 ys	80	15	18.8%		5	6.3%	
Sex							
Male	98	20	20.4%		10	10.2%	0.074
Female	104	13	12.5%	0.063	7	6.7%	
PS 0	162	23	14.2%		11	6.8%	
1	32	5	15.6%		5	15.6%	0.074
2	6	3	50%	0.150	1	16.5%	
3+	2	2	100%		--	--	
Adjuvant CT	151	12	7.9%	0.121	5	3.3%	0.349
Non adjuvant	51	21	41.2%		12	23.5%	
Catheter	26	5	19.2%	0.958	4	15.4%	0.099
Non catheter	176	28	15.9%		13	7.4%	
Previous RIT	14	4	28.6%	0.152	3	21.4%	0.072
No previous R|T	188	29	15.4%	0.321	14	7.4%	0.459

Abbreviations: FE febrile episode, NHL Non- Hodgkin's lymphoma ,PS performance status, CT chemotherapy, RT radiotherapy.

Microbiologic confirmation was reported in our study where organisms were isolated in 65.6% of febrile episodes and (54%) of infections, also, organisms were isolated more frequently from cultures in the control group than in the quinolone group table (6), in agreement with where was reported in Michael et al. (2005) study [12]. The lower frequency of isolation of aganiones in cases of infection may be explained by fungal or viral causes. The effect on the development of resistance with the repeated use of short periods of fluoroquinolone prophylaxis on an out patient basis on patients receiving cytotoxic chemotherapy is unknown.

In our study, there is a significant reduction of cost of hospitalization with patients in quinolone group versus the control group (45.4 percent), for infection as reported in other studies [28, 29]. Cost associated with hospitalization for FN closely correlated with length of stay in hospitalization. Despite improved medical management, Febrile neutropenia continues to be associated with substantial morbidity, mortality, and cost not only placing a significant burden on the individual patient but on the health care system as a whole as reported in Caggiano et al study[29].

In conclusion, the administration of quinolone for seven days to cover the expected period of neutropenia after cyclic, standard dose, myelosuppressive chemotherapy in patients with solid cancer or lymphoma significantly reduced incidence of febrile episodes especially with the first cycle chemotherapy, clinically documented infection, hospitalization for the treatment of neutropenic infection and cost (where use of prophylaxis antibiotic limit the share of growth factors), with minimal adverse effects.Cycle 1 infection appear to identify patients at high risk of later FE who paradoxically, may benefit from prophylactic quinolone on later cycles, but further work is required to confirm these observations.

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