Chemotherapy-induced neutropenia among pediatric cancer patients in Egypt: Risks and consequences

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Abstract. Chemotherapy-induced neutropenia (CIN) is the major dose-limiting toxicity of systemic chemotherapy and it is associated with significant morbidity, mortality and treatment cost. The aim of the present study was to identify the risk factors that may predispose pediatric cancer patients who receive myelosuppressive chemotherapy to CIN and associated sequelae. A total of 113 neutropenia episodes were analyzed and the risk factors for CIN were classified as patient-specific, disease-specific and regimen-specific, while the consequences of CIN were divided into infectious and dose-modifying sequelae. The risks and consequences were analyzed to target high-risk patients with appropriate preventive strategies. Among our patients, 28% presented with a single neutropenia attack, while 72% experienced recurrent attacks during their treatment cycles. The mean absolute neutrophil count was 225.5±128.5 x10^9/l (range, 10-497 x10^9/l), starting 14.2±16.3 days (range, 2-100 days) after the onset of chemotherapy and resolving within 11.2±7.3 days, either with (45.1%) or without (54.9%) granulocyte colony-stimulating factor (G-CSF). No significant association was observed between any patient characteristics or disease stage and the risk for CIN. However, certain malignancies, such as acute lymphocytic leukemia (ALL), neuroblastoma and Burkitt's lymphoma, and certain regimens, such as induction block for ALL and acute myelocytic leukemia, exerted the most potent myelotoxic effect, with severe and prolonged episodes of neutropenia. G-CSF significantly shortened the duration of the episodes and enhanced bone marrow recovery. Febrile neutropenia was the leading complication among our cases (73.5%) and was associated with several documented infections, particularly mucositis (54.9%), respiratory (45.1%), gastrointestinal tract (38.9%) and skin (23.9%) infections. A total of 6% of our patients succumbed to infection-related complications. Neutropenia was responsible for treatment discontinuation (13.3%), dose delay (13.3%) and dose reduction (5.3%) in our patients. The mean cost for each episode in our institution was 9,386.5±6,688.9 Egyptian pounds, which represented a significant burden on health care providers.

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Introduction

Neutrophils belong to the phagocyte system and represent the first cellular components of the inflammatory response and key components of innate immunity (1). Chemotherapy-induced neutropenia (CIN) is the most serious hematological toxicity of cancer chemotherapy (2). CIN is associated with the risk of life-threatening infections, as neutropenia blunts the inflammatory response, allowing bacterial multiplication and invasion (3). In neutropenic patients, infection may occur with minimal signs and symptoms and may rapidly progress to sepsis with multi-organ failure (4). As fever may constitute the only sign in these patients, febrile neutropenia (FN) should be considered a true emergency (5).

FN is the most frequent complication and the leading cause of morbidity and mortality in oncology patients undergoing intensive chemotherapy; it is also associated with a significant economic and social burden on the health system (6). Early recognition of FN and initiation of broad spectrum empirical systemic antibacterial therapy is crucial for avoiding progression to sepsis and possible death (7). CIN may also necessitate chemotherapy dose reductions, delays or even discontinuation, which may compromise treatment outcome (8).

Recently, high-dose chemotherapy has been performed more often for malignant diseases, such as leukemia (9); this is partly due to improved patient care, and partly due to the advances in the methods for preventing and handling adverse effects (2,10). Granulocyte colony-stimulating factor (G-CSF) is a cytokine that mobilizes CD34 stem cells, increases neutrophil production and stimulates neutrophil function. Following myelotoxic chemotherapy, recombinant human G-CSF mobilizes progenitor cells from the bone marrow into the peripheral circulation and, thus, is used to prevent neutropenia (11). European recommendations stipulate that prophylactic G-CSF use may reduce treatment-related morbidity and the duration of the treatment protocol, by reducing the proportion of patients with FN (12). A meta-analysis concluded that primary prophylaxis reduced the incidence of FN in patients receiving chemotherapy for solid tumors and lymphoma (10). Despite these benefits, however, G-CSF is not administered to all patients receiving systemic

chemotherapy due to the unaffordable cost associated with its routine use. The selective use of G-CSF in patients at high risk for CIN and its complications may be more cost-effective (13).

Several studies in adults have sought to identify risk factors that may predispose patients to CIN and its consequences (3,14,15) in an attempt to develop a predictive model capable of identifying patients at greater risk and provide clear guidelines to use expensive preventive strategies more cost-effectively (11); however, similar trials in pediatrics are sparse. The aim of the present study was to determine the risk factors associated with CIN and its consequences in pediatric patients undergoing systemic chemotherapy in order to apply appropriate preventive strategies.

Patients and methods

Patients. Data for this prospective cohort study were collected from 50 pediatric cancer patients who presented with 113 episodes of neutropenia as a consequence of systemic myelosuppressive therapy. The patients were admitted to the Pediatric Oncology Unit of the Zagazig University Children's Hospital (Zagazig, Egypt) in the period from the 1st of June, 2013 to the 1st of June, 2014. All the patients were subjected to full medical history taking, thorough clinical examination, routine investigations and management according to our standard institutional guidelines (16).

Methods. Risk factors associated with CIN were classified as patient-specific (age, gender and anthropometric measurements), disease-specific (tumor type and stage) and regimen-specific (phase/cycle, drug used and dosage).

The consequences of CIN, namely FN, systemic and/or local infections, dose modifications (reduction, delay or discontinuation of chemotherapy, in-hospital stay and total medical costs for the treatment of neutropenic episodes were evaluated and analyzed.

CIN was defined as an absolute neutrophil count (ANC; polymorphonuclear and band forms) $<0.5x10^9$/l, or $1.0x10^9$/l and expected to decrease, or a leukocyte count $<1.0x10^9$/l (1).

FN was defined as single oral temperature measurement of ≥38.5, or 3 measurements of ≥38 within a 24-h period, taken at least 4 h apart (17).

Ethics. This study was conducted in accordance with the ethical standards and approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University. Written informed consent was obtained from each patient or guardian prior to enrollment in the study.

Statistical analysis. Data were prospectively tabulated and analyzed using the SPSS software, version 16 (SPSS Inc., Chicago, IL, USA). Unpaired t-test, analysis of variance (ANOVA), Chi-square and Pearson's correlation coefficient were used as appropriate. P-value <0.05 was considered to indicate statistically significant differences.

Results

Patient characteristics. A total of 50 patients, who presented with 113 episodes of CIN during the study period, were enrolled in this study. Their mean age was 5.6±2.8 years (range, 10 months-13 years) and 58/113 (51.3%) of the patients were male. Acute lymphoblastic leukemia (ALL) of different subtypes was the leading primary diagnosis among our cases, whereas other hematological malignancies and solid tumors exhibited significantly lower prevalence rates (Fig. 1).

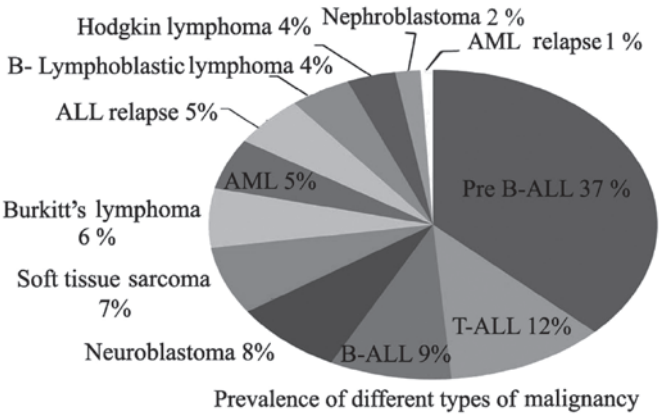

Figure 1. Prevalence of different types of malignancy. ALL of different subtypes was the leading primary diagnosis among our cases, whereas other hematological malignancies and solid tumors exhibited significantly lower prevalence rates. ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia.

Neutropenic episodes. A description of the neutropenic episodes is presented in Table I. Among our patients, 28% presented with significant neutropenia for the first time, while 72% had recurrent episodes throughout the treatment course. The mean ANC was 225.5±128.5 $x10^9$/l (range, 10-497 $x10^9$/l) starting at 14.2±16.3 days (range, 2-100 days) after the onset of chemotherapy and resolved within 11.2±7.3 days, either with (45.1%) or without (54.9%) G-CSF.

ANC correlation with patient-, disease- and regimen-specific characteristics. Analysis of our data revealed no significant correlation between ANC and any of the patient-specific characteristics, such as age (r=0.16), or anthropometric measurements (weight, r=0.14; height, r=0.15; body mass index, r=0.02; P>0.05). Moreover, no statistically significant difference in ANC was detected between different genders (male vs. female, 216.3±140.3 vs. 234.5±114.8, respectively; P=0.47). One-way ANOVA for comparing ANC in different underlying diseases revealed a significantly lower ANC in B-ALL, neuroblastoma, Burkitt's lymphoma and lymphoblastic lymphoma, B-immunophenotype (Fig. 2). However, no significant correlation was found between ANC and different disease stage (r=-0.15) or patient risk (r=-0.03). A significant inverse correlation between neutropenia duration and G-CSF was obvious in our study, with faster bone marrow recovery with G-CSF implementation (Fig. 3). Different chemotherapy regimens were associated with a variable suppressive effect on the bone marrow. The effect of different protocols on neutrophil dynamics is presented in Table II.

CIN sequelae. Children diagnosed with CIN may experience infectious and dose-modifying consequences. FN was the leading complication in 73.5% of our cases, persisting for a

Table I. Description of neutropenia episodes (n=113).

Variables	Values
Age, years	
Mean ± SD	5.61±2.82
Gender	
Male, n (%)	58 (51.3)
Female, n (%)	55 (48.7)
Pre-treatment TLC, x10^9/l	
Mean ± SD	14.300±3.810
Range	1.300±23.000
Previous neutropenias, n (%)	
No	32 (28.3)
Yes	81 (71.1)
Number of previous attacks	
Mean ± SD	3.3±1.95
Range	1-9
TLC during neutropenia, x10^9/l	
Mean ± SD	1.450±5.480
Range	1.000-10.000
ANC during neutropenia, x10^9/l	
Mean ± SD	225.0±128.3
Range	10-497
Onset after chemotherapy, days	
Mean ± SD	14.2±16.3
Range	2-100
Duration of neutropenia, days	
Mean ± SD	11.2±7.3
Range	2-42
Recovery, n (%)	
With G-CSF	51 (45.1)
Without G-CSF	62 (54.9)
Duration of G-CSF, days	
Mean ± SD	4.98±3.1
Range	1-18

SD, standard deviation; TLC, total leukocyte count; ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor.

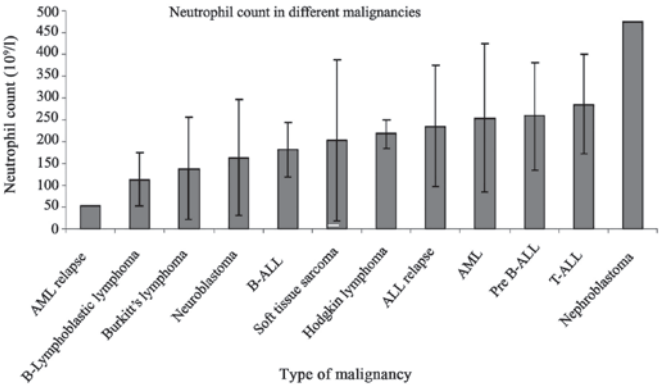

Figure 2. Absolute neutrophil count (ANC) in different malignancies. The ANC was significantly lower in B-ALL, neuroblastoma, Burkitt's lymphoma and lymphoblastic lymphoma (B-immunophenotype). ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia.

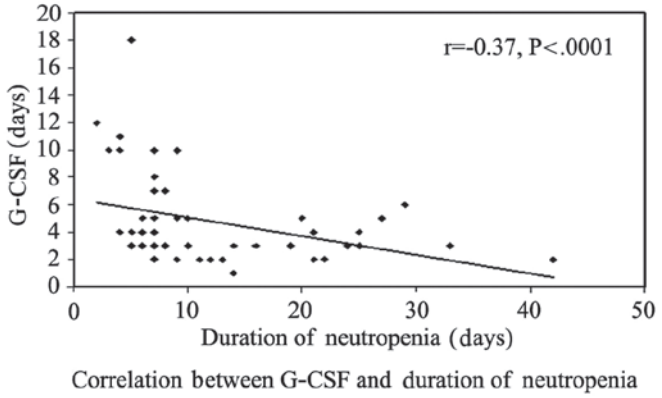

Figure 3. Correlation between granulocyte colony-stimulating factor (G-CSF) and duration of neutropenia. There was a significant inverse correlation between the duration of neutropenia and G-CSF, with faster bone marrow recovery with G-CSF implementation.

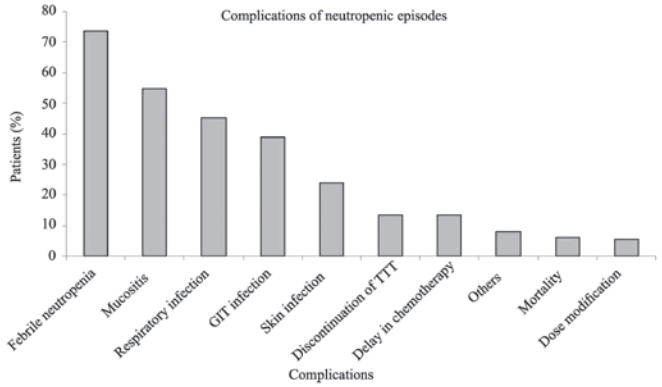

Figure 4. Complications of neutropenic episodes. Febrile neutropenia was the leading complication, followed by mucositis, respiratory, GIT and skin infections. Prolonged neutropenia necessitating chemotherapy dose reduction, delay or even discontinuation was also reported. GIT, gastrointestinal tract; TTT, treatment.

mean of 5.7±3.7 days (range, 1-18 days); mucositis, respiratory, gastrointestinal and skin infections were also documented. The incidence of infection-related mortality [severe septicemia, disseminated intravascular coagulation (DIC)] was 6% (3/50) in our study. Prolonged neutropenia, necessitating chemotherapy dose reduction, delay or even discontinuation, was also reported. The complications of CIN are summarized in Fig. 4.

Association of CIN complications with neutrophil count and duration of neutropenia. An analysis of the association of ANC and duration of neutropenia with different complications emphasized the following: First, neutropenic cases complicated with infections, particularly mucositis and gastrointestinal tract infections, exhibited a significantly lower ANC and a longer duration of neutropenia compared with non-infectious cases; and second, patients who received dose modification exhibited significantly more prolonged

Table II. Effect of treatment protocols on neutrophil dynamics.

Protocols	Onset of neutropenia (mean ± SD)	ANC (mean ± SD)	Duration of neutropenia (mean ± SD)
Chemotherapy blocks for neuroblastoma			
HDP/VP	8.8±2.9[b]	120.3±138.7[a]	6.5±2.58[d]
CAV	5.3±4.0[b]	226.0±73.0	12.3±5.0
IF/VP	11±0.0	234.0±0.0	7.0±0.0[d]
Chemotherapy blocks for rhabdomyosarcoma			
I^2Vad^2	8.8±1.708[b]	90.0±.14.1[a]	6.5±0.7[d]
I^2Va	7.5±0.7[b]	139.5±142.1[a]	7.5±0.7[d]
VAC	9.0±0.7	474.0±0.0	13.0±0.0
ICE	9.0±0.0	474.0±0.0	9.0±0.0
Chemotherapy blocks for Burkitt's lymphoma			
COPADM (methotrexate: 8 gm/m^2)	8.9±2.1	183.3±69.5	8.1±1.8
CYVE	11.7±2.1	154.3±106.8[a]	5.8±1.3[d]
COPADM (methotrexate: 3 gm/m^2)	7.0±2.1[b]	72.2±19.6[a]	5.5±2.4[d]
CYM	5.5±007[b]	175±35.355	5.0±0.0[d]
CCG protocol for ALL			
Induction (standard risk)	3.7±1.505[b]	301.167±107.949	15.0±5.831
Induction (high risk)	7.6±2.97[b]	268.1±117.9	15.8±9.1
Consolidation (standard risk)	9.5±3.5	147.0±60.8[a]	13.5±16.2
Consolidation (high risk-standard arm)	13.3±6.5	418.0 ±0.0	13.7 ±11.9
Consolidation (high risk-augmented arm)	13.2±7.7	221.6±96.8	14.2±8.6
Delayed intensification-2 (standard risk)	8.0±0.0[b]	127.5±135.0[a]	10.5±2.1
Delayed intensification-1 (standard risk)	11.4±2.9	196.0±72.6	13.2±6.1
Delayed intensification-2 (high risk)	18.5±0.7	234.0±0.0	9.5±2.1
Delayed intensification-1 (high risk)	12.3±8.7	313.7±113.7	6.3±3.2[d]
Maintenance phase	46.7±26.6[c]	310.9±139.3	8.6±3.8
Interim maintenance (standard risk)	14.7±9.2	275.3±153	12.8±6.6
Interim maintenance (high risk)	19.5±24.7	250.5±120	10.5±4.9
BFM 2004 protocol for AML			
AIE induction blocks	5.4±2.1[b]	284.6±170	23.0±13.6[e]
HAE block	8.0±0.0[b]	100.0±0.0[a]	11.0±0.0
BFM 2002 protocol for ALL relapse			
F1 block	7.5±0.7[b]	183.5±17.7[a]	24.5±6.4[e]
R1 block	9.0±0.0	468.0±0.0	8.5±2.1
R2 block	13.0±0.0	160.0.±0.0[a]	5.0±0.0[e]
FLAG conditioning protocol for BMT	12.0±0.0	54.0±0.0[a]	8.0±0.0
ABVD protocol for Hodgkin lymphoma	7.75±3.6[b]	217.5±33.0	18.5±7.7

[a]P<0.05; these protocols had the lowest ANC. [b]P<0.05; these protocols had the earliest onset of neutropenia. [c]P<0.05; these protocols had the latest onset of neutropenia. [d]P<0.05; these protocols had the shortest duration of neutropenia. [e]P<0.05; these protocols had the longest duration of neutropenia. SD, standard deviation; ANC, absolute neutrophil count; HDP/VP, high-dose cisplatin/etoposide; CAV, cyclophosphamide, adriamycin, vincristine; IF/VP, ifosfamide/etoposide; I^2Vad^2, ifosfamide (2 doses), vincristine, adriamycin (2 doses); I^2Va, ifosfamide (2 doses), vincristine, actinomycin; VAC, vincristine, actinomycin, cyclophosphamide; ICE, ifosfamide, cyclophosphamide, etoposide; COPADM, cyclophosphamide, oncovin, prednisone, adriamycin, methotrexate; CYVE, cytarabine (high-dose), etoposide; CYM, cytarabine, methotrexate (high-dose); CCG, Children's Cancer Study Group; BFM, Berlin-Frankfurt-Münster; AIE, Ara-C, idarubicin, etoposide; HAE, high-dose Ara-C, etoposide; FLAG, fludarabine, Ara-C, granulocyte colony-stimulating factor; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia.

neutropenia compared with those who received full-dose treatment. However, lower ANC and longer duration of neutropenia were observed among patients requiring treatment delay or discontinuation when compared with those who received treatment on time, but the difference did not reach statistical significance (Table III).

Table III. Association between complications of CIN and neutrophil count.

	Neutrophil count		Duration	
Complications	Mean (SD)	t (P-value)	Mean (SD)	t (P-value)
Mucositis		2.46 (0.01)		1.79 (0.07)
Absent	262.3 (123)		9.8 (4.6)	
Present	201.2 (131)		12.3 (8.8)	
Respiratory infection		1.72 (0.06)		0.00 (0.99)
Absent	249.9 (119)		11.2 (7.6)	
Present	205.3 (142)		11.1 (6.9)	
GIT infection		2.26 (0.02)		1.13 (0.26)
Absent	251.5 (127)		10.6 (5.9)	
Present	193.3 (130)		12.2 (9)	
Skin infection		0.32 (0.74)		2.16 (0.03)
Absent	232 (123)		10.4 (5.8)	
Present	222.1 (155)		13.8 (10.4)	
Others[a]		1.17 (0.24)		0.78 (0.43)
Absent	225.8 (129)		11 (7.2)	
Present	286 (145)		13.1 (8.7)	
TTT discontinuation		1.34 (0.18)		1.05 (0.29)
No	223.4 (129)		11.4 (7.5)	
Yes	275.5 (136)		9.3 (4.9)	
TTT delay		0.82 (0.4)		1.70 (0.09)
No	225.9 (133)		10.7 (7)	
Yes	258.1 (111)		14.1 (8.4)	
Dose reduction		1.24 (0.21)		2.35 (0.02)
No	225.9 (127)		10.8 (6.4)	
Yes	294.3 (179)		17.8 (15.8)	

[a]Sepsis or disseminated intravascular coagulation. CIN, chemotherapy-induced neutropenia; SD, standard deviation; t, Student's t-test; GIT, gastrointestinal tract; TTT, treatment.

Effect of CIN on total treatment cost. In our study, the mean medical cost of each neutropenic episode was 9,386.5±6,688.9 Egyptian pounds, divided as 1,574.4±783 for hospital stay, 2,381.7±2,535 for antimicrobials, 3,536±2,123 for supportive treatment, 1,417.3±1,131 for investigations and 475.8±115.5 for surgical measures. There was a significant positive correlation between the total cost and the duration of neutropenia ($r=0.66$, $P<0.001$) but not between the cost and ANC ($r=0.1$, $P>0.05$).

Discussion

Therapeutic strategies for cancer continue to evolve, and chemotherapy regimens continue to play important roles in cancer treatment (18). Despite the importance of CIN as a primary dose-limiting toxicity of chemotherapy, its risks and consequences, particularly among pediatric patients, have not been fully elucidated. In the present study, we classified the risk parameters for CIN as patient-, disease- and regimen-specific. No significant association between any of the patient characteristics (age, gender and anthropometric measurements) and the risk of CIN was identified. These findings are opposite to those reported by several investigators in adult populations, who documented advanced age and female gender as significant risk factors (3,14). The hormonal effect of gender on immunity may be more apparent in older age, as the aging process, either *per se* (physiological aging) (19), or due to the associated comorbidities, such as diabetes, renal disease and hypertension, may exert a negative effect on neutrophil dynamics (20), thus increasing the risk, incidence, severity and duration of neutropenia in advanced age (18). A total of 62.8% of neutropenic episodes in the present study occurred in ALL, 6.2% in acute myeloid leukemia (AML), 14.1% in lymphomas, and the remaining 16.8% were associated with solid tumors; these percentages are either consistent with the previous conclusion that hematological malignancies are associated with a higher incidence of CIN compared with solid tumors, due to the underlying disease as well as the intensity of the required treatment (3,21), or they merely represent the fact that CIN is a common complication of the most prevalent childhood malignancy (ALL) (22). However, ANC was not found to be associated with cancer stage or patient risk grade.

Different chemotherapy protocols were associated with a variable suppressive effect on the bone marrow; a

similar observation was documented by Lyman *et al,* who described certain regimens as 'more myelotoxic' compared with others (23). Induction blocks for the treatment of ALL and AML were associated with early-onset neutropenia (3.66±1.5 vs. 5.4±2.1 days, respectively) compared with the late neutropenia onset in patients who received maintenance therapy for ALL. In addition, the longest neutropenia episode occurred in patients treated with induction block for relapsed ALL and AML. These findings were in concordance with previous studies reporting that the greatest risk for severe and prolonged neutropenia was observed during the early treatment cycles (23-26). These results allowed some clinicians to consider early cycle hematological response to chemotherapy as a functional assessment of the effect of treatment on bone marrow and, subsequently, predict which patients are candidates for further dose modification or conditioned G-CSF prophylaxis (27). The high incidence of neutropenia with early cycles may be explained by the heavier doses of chemotherapy during induction, while the lower incidence with subsequent cycles is likely due to dose modifications and hematopoietic cell adaptation that may occur later on.

Therapy with G-CSF was associated with faster bone marrow recovery, with a significant negative correlation between G-CSF and duration of neutropenia (r-0.37, P≤0.001). Likewise, Ghalaut *et al* reported a significant shortening of CIN and FN, as well as of the mean duration of hospitalization (28). These advantages have been documented by other researchers (3,29,30). In agreement with our results, a recent study on urological cancer patients reported a good outcome when G-CSF was administered (18).

The majority of our patients (73.5%) developed FN, with a significant positive correlation between the duration of neutropenia and that of fever (r=0.37, P<0.001). Similarly, FN was the most commonly recorded complication (61.4%) of systemic chemotherapy for hematological oncology adult patients in a recent study conducted in Uruguay (8). By contrast, Mahmud *et al* reported a significantly lower incidence (25-40%) of FN in their series (31). Our high incidence of FN may be explained by the higher prevalence of underlying hematological malignancies that increase the risk for FN, as 10-50% of patients with solid tumors may develop FN, compared with 80% of those with hematological malignancies (6).

The most common infections encountered in our neutropenia episodes were mucositis (54.9%), respiratory (45.1%), gastrointestinal tract (38.9%) and skin (23.9%) infections. Respiratory tract and skin infections were the most common according to Boada Burutaran *et al* (8), while Anunnatsiri *et al* reported urinary tract infection, soft tissue infection and bacteremia as the most common occurrences (32). Variable sites of infections may be associated with different invasive procedures that provide a portal of entry for pathogens (18). Keefe *et al* reported a significantly lower incidence of mucositis (10%) among their cases (33), with a higher incidence of mucositis in neutropenic children, possibly due to their higher mitotic index in the oral mucosa compared with adults, with a higher risk of mucositis with chemotherapeutics.

Neutropenia cases complicated with mucositis and gastrointestinal tract infections exhibited lower ANC compared with non-complicated cases, while cases presenting with skin infections had a significantly longer duration of neutropenia. These findings had been described in a historical review (34), and were confirmed in a recent study (8), where the extent and duration of neutropenia were significantly associated with the risk of infection.

Neutropenia was responsible for treatment discontinuation (13.3%), dose delay (13.3%) and dose reduction (5.3%) in our patients. The incidence of treatment modification in our study was significantly lower compared with that reported by Repetto (35) and Ozer (36). We consider delivered dose intensity to be a major determinant of the outcome (37); thus, every effort was made, including supportive measures and adjunctive G-CSF, prior to dose modification or delay.

A total of 6% of our patients succumbed to severe septicemia and DIC, with similar or even higher rates reported by previous studies (21,38). This finding highlights the true risk of devastating infections in these populations, if not aggressively and promptly managed (4,5).

CIN and related complications have an economic impact on health care providers (8). The mean cost for each neutropenia episode in our service was 9,386.5±6,688.9 Egyptian pounds, which was significantly lower compared with those reported in different economic analyses (39-41). Government financial support of chemotherapy and exclusion of indirect non-medical costs from our calculation, such as lost working hours, may be the causes of our lower estimated costs.

Although this study is a preliminary survey with a relatively limited patient sample, our findings are relevant to the clinical care of pediatric cancer patients in our region. Special attention to CIN prevention should be directed to hematological malignancy cases, particularly during the early cycles of treatment. Severe and prolonged neutropenia is life-threatening and requires aggressive management.

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