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CHEMOTHERAPY INDUCED MYELOSUPPRESSION
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CHEMOTHERAPY INDUCED MYELOSUPPRESSION

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ABSTRACT

Objective: **To evaluate chemotherapy induced myelosuppression, its management and outcome.**
Design: **Retrospective analysis of patients aged 13 years and above.**
Setting: **Hurlingham Oncology Clinic and the Nairobi Hospital during the period of June 1998 to June 2003.**
Subjects: **Two hundred and two solid tumour and lymphoma patients treated with pulsed chemotherapy at Hurlingham Oncology Clinic and those treated by the same service at the Nairobi Hospital.**
Results: **Two hundred patients were evaluable for nadir blood counts. World Health Organisation (WHO) grade 3 neutropaenia complicated 57 (26.1%), and grade 4 complicated 56 (25.7%) treatments. Grade 0 neutropaenia was seen in 40 (18.4%) treatments, 33 having included prophylactic Granulocyte-Colony Stimulating Factors (G-CSF). Neutropaenia was worst following the first and sixth courses, and repeated second line courses but the difference was not statistically significant (p=0.1 54). Fever complicated 6 grade 3 and 21 grade 4 neutropenic episodes (23.1% of 117 evaluable). Twenty eight patients were hospitalised because of severe neutropaenia (23 febrile, and five afebrile initially but with absolute neutrophil counts <0.01 x 10^9/1itre). Eight of them died, six attributable to infections (21.4% mortality) and two attributed to other causes. Median time to neutrophil recovery to ≥1.5 x 10^9/litre was three days with a mean of 4.6 days. Anaemia and thrombocytopaenia were not commonly experienced.**
Conclusion: **Prophylactic use of G-CSF may have prevented severe neutropaenia and its use in severe neutropaenia may have reduced the duration and severity of neutropaenia but the mortality rate for febrile neutropaenia remained high.**

INTRODUCTION

All cellular components of blood are derived from pluripotent stem cells in the bone marrow and other haematopoietic tissues in the body. Under the influence of haematopoietic growth factors (HGFs), the stem cell divides and differentiates via progenitor cells into various mature cell types (1). This process of formation and production of peripheral blood cells is known as haematopoiesis. Under physiological conditions, it is a tightly regulated, highly efficient system exquisitely responsive to functional demands. Maintenance of normal number of blood cells requires continuous production to replace the aging or damaged cells in circulation (2).

Chemotherapy for chemocurable cancers fails either because chemosensitive tumour cells are

spared by inadequate treatment, or resistant tumour clones persist despite chemotherapy. Adequacy of treatment is limited by drug related toxicity, especially to the rapidly proliferating normal tissue cells such as the haematopoietic cells and the gastrointestinal epithelium. The bone marrow's storage compartment can supply mature cells to the peripheral blood for 8-10 days, after which the pool of primitive haematopoietic progenitor cells ceases and the supply of these cells slows down. It ceases after depletion of the more differentiated committed progenitors (3). Following injury to the bone marrow either by chemicals, radiation or infection, the kinetics of cytopaenia induction reflects the life span of the cells in pheripheral blood. On average, neutrophils have a life of 6-10 hours, platelets 7-10 days and erythrocytes 120 days in circulation. Suppression of the peripheral blood cells is therefore generally noted approximately a week following a toxic insult to the bone marrow. In previously untreated patients, several of the most commonly used cytotoxic agents when administered cause leukopaenia and thrombocytopaenia by day 9 or 10 after treatment. Nadir counts are reached in 10-14 or even up to 18 days and recovery is evident by day 21 and complete by day 28 (3).

The consequences of reduced or absent neutrophils are dramatic in grade 3 neutropaenia, with increased susceptibility to infection. In grade 4 neutropaenia control of endogenous microbial flora is impaired and opportunistic infections set in. Below 0.2×10^9/litre the inflammatory response of the body breaks down (4). Severe degrees of thrombocytopaenia do not frequently complicate management of patients with solid tumours receiving cytotoxic chemotherapy unless the bone marrow is infiltrated (5). It occurs commonly in treatment of haematologic neoplasms. When it occurs, thrombocytopaenia increases the risk of haemorrhage, necessitates platelet transfusions and limits the dose of myelotoxic agents (6).

Severe anaemia rarely complicates cancer chemotherapy in the majority of cases and when it occurs it is easily managed with red blood transfusions or administration of recombinant erythropoietin.

We retrospectively studied files of cancer patients who had undergone pulsed chemotherapy at Hurlingham Oncology Clinic or those who had been treated at the Nairobi Hospital under the services of the clinic. The aim was to assess the impact of chemotherapy and see the effectiveness of interventions instituted in case of severe reduction in one or more of the haematopoietic cell lines. Patients with acute leukaemias including blastic phase of chronic myeloid leukaemia were excluded. Permission was obtained from the Nairobi Hospital Standards and Ethics Committee before the study was commenced. All files of patients that met the inclusion criteria were studied.

MATERIALS AND METHODS

The following information was obtained from the patient's files; age, sex, weight, height, diagnosis (histology), date of diagnosis, baseline blood counts (haemoglobin, platelets, total white cell counts and absolute neutrophil count, liver function tests, serum proteins), disease stage and staging classification, goal of treatment (neoadjuvant, adjuvant, metastatic curative, palliative), chemotherapy protocol, treatment course, nadir blood counts. Also checked were whether prophylactic G-CSF neupogen in this case was used, dose and duration of neupogen administration, grade 3-4 neutropaenia, febrile neutropaenia, septic deaths, grade 3-4 thrombocytopaenia, platelet transfusion before the next course of chemotherapy, was next course of chemotherapy delivered in time, was G-CSF used for febrile neutropaenia, the absolute neutrophil count at the time of commencing neupogen and what the duration to attainment of absolute neutrophil counts of $\geq 1.0 \times 10^9$/litre and $\geq 1.5 \times 10^9$/litre was whether treatment was completed, what the relative dose-density of the cytotoxic agents delivered was, what the outcome of treatment was, the last date of follow-up and the disease status at the last date of follow-up, if death occurred, what the cause of death was and date of death.

This information was entered in a structured proforma. The degree of reduction of haematological parameters was classified according to the WHO criteria (7). For metastatic disease, treatment outcome was classified as complete remission, partial remission stable disease or progressive disease. Data analysis was done by computer package, Statistical Package for Social Sciences (SPSS) and presented in tables. Students T-test was used for variable data and Chi-square test for continuous variables.

RESULTS

Results were evaluable for a total of 202 patients with solid tissue tumours and malignant lymphomas treated with pulsed intensive chemotherapy. Fifty (24.8%) had breast carcinoma and 47 (23.3%) had non-Hodgkin's lymphomas (NHL) of aggressive phenotype. Fourteen of the NHLs (29.8%) were AIDS-related. Twenty two patients (10.9%) had AIDS-related Kaposi's sarcoma (Table 1).

A total of 218 treatments were evaluable for nadir blood counts. The most commonly used treatment regimens were doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 at 3 week intervals (AC 60/600) for breast carcinoma. It was used in 61 treatments (27%). Doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 given at 3 week intervals (AC 50/500) was used in 20 treatments, also for breast carcinoma (8.8% of all treatments). Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was used in 31 treatments (13.7%) for aggressive phenotype non-Hodgkin's lymphoma (Table 2).

World Health Organisation (WHO) grade 3 neutropaenia complicated 57 treatments out of 218 evaluable (26.1%) and grade 4 neutropaenia complicated 56 treatments (25.7%). The CHOP protocol was complicated by grade 4 neutropaenia in seven out of 31 treatments (22.6%) and AC 60/600 was complicated by grade 4 neutropaenia in 13 out of 61 treatments (21.3%). AC 50/500 was complicated by grade IV neutropaenia in five out of 20 treatments (25%) (Table 2). Grade 0 neutropaenia was registered in 40 treatments (18.4%) of which 33 (82.5%) had been covered by prophylactic neupogen. Neutropaenia was severest after the first and sixth treatment courses, and also following repeated second line treatments, but the differences were not statistically significant (P = 0.154) (Table 3).

Fever complicated six out of 52 treatments with grade 3 neutropaenia (11.5%) and 21 out of 38 treatments with grade 4 neutropaenia (55.3%). The correlation between occurrence of fever and severity of neutropaenia was highly significant (P< 0.0005) (Table 4).

Twenty eight patients were hospitalised because of severe neutropaenia. Twenty three (82.1%) had fever on admission while five (17.9%) were admitted because of absolute neutrophil counts <0.01 x 10^9/litre but later four developed fever while in the ward. Reverse barrier nursing was instituted on all the patients admitted and G-CSF plus broad spectrum antibiotics administered. Standard septic screens were also carried out. Viral screens were not routinely carried out unless the fever persisted for over a week.

Eight of the admitted patients (28.6%) died, six of the deaths (21.4%) were attributed to sepsis and two (7 1%) were attributed to causes other than sepsis. Whereas severe thrombocytopaenia was not commonly encountered and only four treatments were complicated with life threatening thrombocytopaenia and the patients had to be given platelet transfusions, grades 3 and 4 thrombocytopaenia tended to occur in presence of grade 4 neutropaenia. This was mainly apparent for patients with grade 4 febrile neutropaenia (Table 5).

Of the 27 patients who had symptomatic neutropaenia, 11 (40.7%) had platelet counts within the normal range, 26 (96.3%) had grade 4 neutropaenia and four (14.8%) had grade 4 thrombocytopaenia. One patient with grade 3 neutropaenia developed fever.

The median time to neutrophil recovery to ≥ 1.0 x 10^9/litre was three days with a mean of 4.3 days. The median time to neutrophil recovery to ≥ 1.5 x 10^9 /litre was also 3 days with a mean of 4.6 days. The level of platelets at the time of fever did not correlate with severity of neutropaenia (p=0.44) though overall thrombocytopaenia correlated with the level of neutropaenia (Table 5). Of 205 treatments evaluable, 19 (9.3%) required red blood cell transfusion to 'keep haemoglobin levels ≥ 10g/dl required for the next treatment.

Of the patients who died, one aged 32 years at the time of diagnosis had hepatocellular carcinoma. He had survived for 33 months from diagnosis. During this time he had been able to perform his duties fully until the last two weeks when his condition rapidly deteriorated. He died from complications of hyperkalemia in acute renal failure. The other one was a 56 year old male patient with breast carcinoma refractory to hormonal therapy, died after the 6th course of AC and had febrile neutropaenia. Another, a 23-year-old female with malignant neuroectodermal tumour (MNnet), died of progressive disease.

A 52 year old man with hormone refractory prostatic carcinoma was put on decetaxel and chlorambucil but died of severe haemorrhage

complicating thrombocytopaenia due to disseminated intravascular coagulopathy. Another 50-year-old dentist had hepatocellular carcinoma. He was treated with doxorubicin and cis-platin and was discharged, two days post chemotherapy. He developed intractable nausea and vomiting while at home but was reluctant to be readmitted until he became severely dehydrated with prerenal azotemia. He developed severe pancytopaenia and died from multiple organ failure. A 35-year-old patient with metastatic breast carcinoma with lumbar cord compression developed severe diarrhoea while undergoing concurrent chemotherapy and radiotherapy. She became septicaemic due to severe neutropaenia and died. Of the 14 patients with HIV non-Hodgkin's lymphoma all were treated with CHOP chemotherapy and one died from febrile neutropaenia.

Table 1

Types of cancers

Diagnosis	Number of patients
Breast carcinoma	50
Non-Hodgkin's lymphoma	
Non HIV related	33
HIV related	14
Kaposi's sarcoma	
HIV related	22
Non-HIV related	2
Carcinoma of the colon	19
Hepatocellular carcinoma	7
Ovarian carcinoma	7
Cervical carcinoma	7
Gastric carcinoma	5
Hodgkin's disease	5
Prostate carcinoma	5
Others	26
Total	202

Table 2

Protocol against Nadir Neutrophil count for the more frequently used protocol

	0		1		2		3		4	
Protocol	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
AC 60/600 (n = 61)	10	16.4	10	16.1	15	24.6	13	13.3	13	21.3
AC 50/500 (n = 20)	3	15	1	5	3	15	8	40	5	25
CHOP (n = 31)	9	29	0	0	4	12.9	11	35.5	7	22.6
CAF 600/60/600 (n = 10)	0	0	2	20	3	30	4	40	1	10
F/Plat (n = 5)	1	20	0	0	0	0	1	20	3	60
EDF (n = 6)	0	0	1	16.7	2	33.3	1	16.7	2	33.3
Tax/Dox (n = 8)	0	0	0	0	2	25	3	37.5	3	37.5

AC = Doxorubicin/cyclophosphamide
CHOP = Cyclophosphamide, doxorubicin, vincristine, prednisone
CAF = Cyclophosphamide, doxorubicin, 5-Fluorouracil
F/Plat = 5-Fluorouracil, cis-platin
EDF = Etoposide, doxorubicin, 5-Fluorouracil
Tax/Dox = Docetaxel/doxorubicin

Table 3

Nadir neutrophil grade against course of treatment (n = 218)

	Grade of neutropaenia									
	0		1		2		3		4	
Treatment course	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
1. (n = 77)	14	18.2	9	11.7	8	10.4	19	24	27	35.1
2. (n = 39)	5	12.8	5	12.8	15	38.5	7	17.9	7	17.9
3. (n = 35)	4	11.4	7	20	6	17.1	13	37.1	5	14.3
4. (n = 21)	1	1.8	3	14.3	7	33.3	7	33.3	3	14.3
5. (n = 21)	6	28.6	4	19.0	1	4.8	6	28.6	4	19.0
6. (n = 21)	1	4.8	3	14.3	2	9.5	8	38.1	7	33.3
n (n = 4)	0	0	0	0	0	0	1	25.0	3	75.0

n = Undetermined course in the second line in heavily pretreated patients
(P = 0.154)

Table 4

Occurence of fever according to degree of neutropaenia (n = 218)

	Gradient of neutropaenia											
	3		4_1		4_2		4_3		4_4		4_5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Fever present (n = 27)	6	10.3	10	22.2	4	66.7	2	100	2	100	3	75.0
No fever (n = 90)	52	89.7	35	77.8	2	33.3	0	0	0	0	1	25.0

(P < 0.001)

Grade of neutropaenia

4_1 0.1 – 0.499 x 10^9/litre
4_2 0.05 – 0.099 x 10^9/litre
4_3 0.25 – 0.049 x 10^9/litre
4_4 0.01 – 0.024 x 10^9/litre
4_5 <0.01 x 10^9/litre

Table 5

Nadir neutropaenia against Nadir thrombocytopaenia (n = 203)

	Grade of neutropaenia									
Grade of	0		1		2		3		4	
Thrombocytopaenia	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
0. (n = 180)	23	12.8	24	13.3	33	18.3	56	31.1	44	24.4
1. (n = 6)	1	16.7	0	0	2	33.3	0	0	3	50
2. (n = 5)	1	20	0	0	0	0	2	40	2	40
3. (n = 9)	0	0	1	11.1	1	11.1	0	0	7	77.8
4. (n = 3)	0	0	0	0	0	0	0	0	3	100

Table 6

Degree of neutropaenia and thrombocytopaenia at the start of neupogen in relation to death amongst patients who were admitted with severe neutropaenia (n = 27)

Platelet count x 10^9/litre	Absolute neutrophil count x 10^9/litre	Whether death occurred or not
91	0.018	No
41	0.06	Yes
20	0.005	Yes
93	0.153	No
154	0.396	No
186	0.0024	No
127	0.846	No
314	0.19	No
166	-	Yes
10	0.002	Yes
24	0.26	No
47	0.03	No
30	0.032	No
131	0.061	Yes
152	0.015	No
127	0.179	No
45	0.225	No
144	0.026	No
159	0.064	No
48	0.195	No
26	0.026	Yes
14	0.01	Yes
36	0.008	No
152	0.015	No
65	0.028	No
144	0.026	No
26	0.004	No
18	0.021	Yes

DISCUSSION

In delivering chemotherapy for chemosensitive/chemocurable neoplasms dose considerations are very important. The importance of dose intensity was first recognised by Frei and Canellos who demonstrated that a logarithmic increase in cytotoxicity could be achieved with a linear increase in chemotherapy dosage (8). Building on this, Hryniuk and others demonstrated in retrospective studies that an increased dose intensity of cytotoxic drugs within the conventional dose range may have a marked effect on breast cancer (9,10). Dose intensity of drugs in a given treatment should be as close as possible to those in the standard protocol. What limits the dose that can be delivered unfortunately is tissue toxicity to the rapidly proliferating cells, especially those derived from the bone marrow and gastrointestinal tract (GIT) epithelium. Lifetime accumulation of the two doses of certain drugs above certain levels is also detrimental to other organs. Examples are cardiotoxicity of anthracyclines, pulmonary toxicity by bleomycin and busulphan in particular.

It has been our policy to deliver chemotherapy to as near full doses as possible. Because of the pattern

of diseases as we see them, the AC protocol for breast carcinoma and the CHOP protocol for NHLs were most commonly used. In our earlier report on neutropaenia with the AC protocol, AC 60/600 was associated with grade 4 neutropaenia of 27.8% (11). In the current report grade 4 neutropaenia complicated 22.6% of treatments with CHOP and 21.3% of treatments with AC 60/600. It is paradoxical that AC 50/500 was associated with grade 4 neutropaenia more frequently than AC 60/600. The reason is that patients had doxorubicin/cyclophosphamide doses scaled downwards from 60/600 to 50/500 only if in the previous course they had had severe nadir cytopaenias. Many such patients went on to experience severe toxicity even at the lower dose. Overall, 25.7% of treatments were complicated by grade 4 neutropaenia. These levels of neutropaenia are much higher than those reported from NSABP B22 where grade 4 neutropaenia complicated 6.5% of treatments with AC at 60/600 (12). On the other hand, we also know that there are conflicting reports of the rates of grade 3 and 4 neutropaenia experienced with commonly employed chemotherapy regimens in primary breast cancer in particular. Dale and colleagues reported grade 3 and 4 neutropaenia in 78% of patients treated with CMF protocol and up to 100% of those treated with CAF or CEF (13).

For any given protocol in our study neutropaenia was worst in the first treatment and after repeated treatments but this did not reach statistical significance. Other studies have shown the degree of neutropaenia to be worst with the first two treatments (14). Patients who received prophylactic G-CSF following chemotherapy were protected from developing severe neutropaenia, but subgroup analysis was not carried out to find out the degree to which G-CSF was protective. The risk of febrile episodes correlated significantly with severity of neutropaenia. Those findings have long been established and hence the need to use prophylactic granulocyte or granulocyte macrophage colony stimulating factor (G-CSF or GM-CSF respectively) to prevent severe neutropaenia and the development of sepsis (15,16).

The mortality rate from septic neutropaenia was 21.4% in this study, much higher than 7% reported from other studies (17). Ease of communication could be a contributing factor. Patients who live far outside Nairobi were at higher risk of death if they developed febrile neutropaenia. Other reports have also shown mortality associated with gram negative sepsis in neutropenic patients to be between 10-30%, despite the prophylactic use of potent, broad-spectrum antibiotics.

Incidentally, patients infected with the human immune deficiency virus did not display outstanding mortality rates compared with non-HIV infected patients in this study, but again HIV infected patients were more likely to have received post chemotherapy prophylactic G-CSF.

Anaemia and thrombocytopaenia did not commonly complicate chemotherapy in this study. Depending on the tumour type, the incidence of anaemia at the time of diagnosis ranges from 20% to 60% (18). Chemotherapy and/or radiotherapy can also induce anaemia or aggravate that which already exists (2, 3). This usually is not a major problem as it is easily corrected with red blood cell transfusions or administration of recombinant human erythropoietin (rHuEPO). Only 9.3% of the patients had red blood cell transfusion. Bleeding from thrombocytopaenia is also prevented by transfusion of platelet concentrates to maintain counts above 20×10^9/litre.

Even though reduction in platelet numbers did not correlate with neutropaenia, patients with febrile neutropaenia tended to develop severe thrombocytopaenia. This is not unusual as fever tends to promote platelet destruction and febrile neutropaenia patients may also harbor some degree of disseminated intravascular coagulopathy, with attendant platelet consumption.

The median time to neutrophil recovery to $\geq 1.0 \times 10^9$ for patients admitted with grade 4 neutropaenia was three days with a mean of 4.3 days and that to $\geq 1.5 \times 10^9$/litre was three days with a mean of 4.6 days. This is fairly similar to a median of three days to recovery to ANC of $\geq 0.5 \times 10^9$/litre for those who were treated with filgrastin as opposed to five days of those who were on placebo as found by Mitchell and colleagues (19). Similar findings were also documented by Maher *et al* (20).

In both these studies however, shortening the duration of neutropaenia did not impact positively on survival.

CONCLUSION

Neutropaenia was the main haematologic toxicity complicating chemotherapy as observed in this

study. The risk of infection correlated with the severity of neutropaenia.

Prophylactic G-CSF post chemotherapy may have prevented the development of severe neutropaenia in a good proportion of the patients and also shortened the duration of severe neutropaenia by a few days. However, the mortality from febrile neutropaenia was very high, though quite comparable with findings in several other studies. Severe thrombocytopaenia and anaemia were not frequently encountered.

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