Mortality among cancer patients within 90 days of therapy in a tertiary hospital of Tanzania: is our pre therapy screening effective?

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Abstract

Background A high mortality has been reported during the first ninety days of cancer therapy and is more pronounced in patients with febrile neutropenia. Bugando Medical Center, oncology department offers cancer diagnosis and treatment services to the population of lake-zone of Tanzania with limited data on the 90 days outcome. Here, we report the 90 days mortality and factors associated with it among cancer patients attending oncology department of the tertiary hospital in Tanzania. Methodology Enrolled participants underwent baseline physical examinations and functional status assessment using Karnofsky score. On each clinic visit, FBP was taken and patients were investigated for infections. Data were entered in Microsoft Excel and analyzed using STATA version 13. Results A total of 102 participants were enrolled. Their median age was 50 years [38-60]. The majority of study participants were females 76(75%) and 82(80.4%) had primary school education. The majority of patients had solid cancer 96(94.1%). A total of 12 (11.8%) patients died within 90 days of starting therapy. Having low hemoglobin level before starting cancer therapy (p=0.001), having Karnofsky score below 80% (p=0.001) and using 5-fluorouracil containing therapy (p=0.004) were found to be associated with mortality within 90 days of therapy among cancer patients. Conclusion About 10% of cancer patients die within 90 days of therapy. Anemic patients, with poor performance status and on 5-Fluorouracil regimen are more likely to die within 90 days of cancer therapy.

Background

Cancer is the second leading cause of death worldwide [1], with more than 60% of cases being reported from Africa, Asia, Central and South America. These regions account for about 70% of cancer deaths worldwide [2]. It is estimated that between 2000 and 2020 there will be 75% increase of cancer incidence in resource limited countries [3]. Mortality rate due to cancer is more in resource limited countries than in developed countries [4]. It is estimated that by 2020, about 70% of deaths associated with cancer diseases will be from resource limited countries and cancer survival rate will be 50% less than that of the developed countries [5].

In Tanzania, by the year 2008 there were 21,180 new cases of cancer per 42.5 million people [6]. In a 2014 report, deaths due to cancers were reported to be 9,100 and 10,800 for men and women, respectively [7]. Cervical and breast cancers were leading causes of death among women while esophagus and head and neck cancers were leading cause of death among male[7]. Mortality among cancer patients on therapy is reported to be much higher within the first 90 days [8, 9] and the incidence is reported to be 10.3 times higher in patients with one comorbidity (renal disease, heart disease, chronic bronchitis, and mucositis) while increasing to even 24.1 times higher with the increase in number of comorbidity [8]. Other factors associated with mortality among cancer patients on therapy include the type of cancer, anticancer regimen, age, performance status, anemia, neutropenia [8, 10-13]. Furthermore, outpatients have been reported to have higher mortality rate than the inpatients which is associated with the lack of supportive care among out patients [8, 10].

The number of cancer patients receiving medication at the oncology department of Bugando Medical Centre (BMC) has increased due to the availability of chemotherapy, diagnostic techniques and improved infrastructure for cancer management. However, data on mortality and its associated factors within 90 days of starting chemotherapy is limited. Here we are reporting mortality and factors associated with it within 90 days of therapy among cancer patients attending oncology department of BMC. The spectrum of bacterial pathogens causing infections among these patients have also being determined.

Methods

This was a hospital-based cross-sectional study with a follow-up component which was conducted from August 2017 to May 2018 at the oncology department of the BMC. The unit caters for around 100-150 cancer patients per month and receives up to 25 new patients per month (http://www.bugandomedicalcentre.go.tz/index.php?bmc=24). The study enrolled all patients with age above 12 years, histologically confirmed to have cancer and scheduled to start chemotherapy.

The minimum number of patients to be enrolled in the study was obtained using calculation for the precision of a single parameter, Kish and lisle of 1965. The prevalence of mortality among cancer patients of 8% was substituted and the minimum number of patients obtained was 82 [9].

Data collection: A total of 114 patients were eligible to start cancer therapy at oncology department of BMC during the study period, however we enrolled 111 patients beacause 3 patients withdraw the concept of participatng in the study.

At enrollment physical and clinical examination were done; blood pressure was measured using a digital blood pressure monitor CHU 304 (CITIZEN SYSTEMS JAPAN CO.LTD) that has been clinically validated by the European Society of Hypertension protocol of 2010. Body temperature was measured by a digital thermometer MDD 93/42/EEC, ”0197” (Holding Corp. GmbH (Hamburg)) and body weight and height were measured using DETECTO machine (WEBB CITY, MO U.S.A). The data on type, stage of cancer, treatment regimen and duration of therapy were recorded from the patients’ file. At each visit patients were evaluated for signs and symptoms of infections, especially fever.

At baseline, the following investigations were done: Full blood picture (FBP), urine and blood culture as per BMC management protocol. Another FBP were taken during follow up visit and for patients who had signs and symptoms of infections blood and urine were collected for culture following the standard operating procedures of accredited microbiology laboratory of BMC. Blood cell counts were analyzed by the use of Cell-Dyn 1800 automated hematology analyzer, (Abbott Diagnostics. Drug susceptibility testing was done using Kirby Bauer disk diffusion technique and interpreted using the Clinical and Laboratory Standard Institute (CLSI) guidelines[14].

Data management and analysis: Laboratory data were recorded in laboratory workbook and then entered onto excel spreadsheet for cleaning and coding before being transferred to STATA version 13 for analysis. Continuous data like blood pressure, body weight, Karnofsky score, temperature, white blood cell count and neutrophil count were presented as medians and interquartile ranges and compared by Wilcoxon rank-sum test. Categorical variables such as sex,

marital status, occupation, and level of education were presented as frequency (percent) and compared by Chi-square or Fisher's exact test. A p value of < 0.05 was considered statistically significant.

Results

Social demographic and baseline clinical data: Out of 111 enrolled patients, 102 were included in the final analysis. A total of 5 patients could not start cancer therapy due to financial reasons, two were lost to follow up one died before started on therapy and one shifted to anaother center in Dar es saalam for cancer management (Ocean road cancer institute).

The median age [IQR] of the study population was 50[30-60] years. The majority were females 76(74.5%) and 82 (80.3%) had primary school education. The slightly majority 70 (68.6%) were married. The majority of patients had solid cancers (94.1%) and about one-third of patients reported at oncology department while at cancer stage IV. Regarding various clinical parameters, the median body temperature [IQR] was 36.2°C [35.6-36.6], median neutrophil [IQR] count of $3.0x10^9$/L [2.1-4.1] and median HB 11.6g/dl [10.2-12.6]. Out of 102 patients, 19 (18.6%) were HIV positive.

Types of cancer diagnosed: The commonest type of cancer diagnosed was gynecological cancer 47 (46.1%), followed by head and neck cancer 12 (11.8%). Breast cancer was disgnosed in 11(10.8%) (Table 1).

Mortality within 90 days of starting chemotherapy: Mortality within 90 days of starting therapy among cancer patients at the oncology department was 12(11.8%). The age of those died ranged between 33 and 76 years. All patients who died in the current study had solid cancer and anemia at baseline with hemoglobin range from 7.3-11.4 g/dl . The majority 11 (91%) reported at the oncology departement at advanced stage i.e cancer stage 3 and 4 . A total of 9 (75%) had a performance status below 80% by karnofsy score (Table 2).

Culture results and mortality within 90 days of starting chemotherapy: Among the 102 blood cultures done at baseline, 7(6.9%) were culture positive. *S. aureus* 4(3.9%) was the most frequently detected, followed by *E. coli* and *Pseudomonas aureginosa*, 2(1.9%) and 1(1%), respectively. Regarding urine culture, 13/102(12.7%) patients had significant bacteriuria at baseline. *S. aureus* 7(6.9%) was the predominant bacteria followed by *E. coli* 5(4.9%) and *Pseudomonas aureginosa* 1(1%). Out of patients with bacterial infections either UTI or blood stream infections 3/18(16.6%) died compared to 9/84(10.8%) without bacterial infection who died, p=0.244. of patients with bacterial infections who died, One patient 1/7(14.3%) had *S. aureus* blood stream infection and two had significant bacteriuria due *P. aureginosa* and *E. coli* 2/13(15.4%).

Factors associated with mortality: Significant proportion of patients with head and neck cancer died compared to patients with other type of cancers (33.3%, 4/12 vs. 8.9%, 8/90, P=0.014). The median hemoglobin level of patients who died was significantly lower than the median hemoglobn level of patients who survived (10 [9.3-10.8] g/dl vs. 11.8 [10.5-12.7] g/dl, P=0.001).

Discussion

Mortality within 90 days of starting chemotherapy among cancer patients in the current study was found to be 12% and was similar to 11% that was reported by Kudere *et al.* from the United States among cancer patients on therapy in 2006 and slightly higher than 8% which has currently being reported from South Africa[8, 15]. Additionally, similar mortality was reported in the study done in West Africa 8 years ago which reported the mortality of 10% [16]. Together with cancer itself which compromises the immune system the toxicity brought by the therapy collectively compromise the health of the patients and might lead to high mortality observed.

As previously reported in the world cancer report of 2012 [17], the current study found solid cancers to be the predominant cancers in our centre. Contrary to the world report were the commonest solid cancer was lung cancer [18, 19] our study found the commonest solid cancer to be cervical cancer. Cervical cancer have been known to be the leading type on cancer in Tanzania for the past one decade [20, 21]. The national campaign in screening for cervical cancer which has raised the alarm for most of women to test for cervical cancer could explain the findings but regarding lung cancer has received little attention therefore it might be underreported. Contrary to what was observed and reported in several studies[8, 22], in our study all patients with hematological malignancy survived. Hematological malignancy is known to have higher mortality than solid cancer, the reason being that, hematological malignancies are associated with depletion of neutrophil and neutrophil function due to cancer itself and the toxicity of therapy [22-24]. Neutropenia has been associated with increased mortality in many studies [22-24]. Of current, the use of granulocyte colony stimulating factors among patients with reduced number of neutrophil before starting therapy which stimulate the neutrophil production have reduced mortality in this cohort.

The toxicity induced by 5-fluorouracil such as stomatitis, mucositis, and diarrhea [25] could partly explain the observation of high mortality in this group of patients in the current study. Similar findings of high mortality among patients in 5-fluorouracil have been reported in United States and Greece [26]. As observed in a previous study in France, [27] patients with carcinoma of head and neck had two times odds of dying than patients with other cancers. The increased mortality in head and neck cancer patients may be associated with the proximity of disease to vital organs which impairs one's ability to swallow and breath [28]. Additionally, significantly high mortality among patients with head and neck cancers in this study could be contributed by late stage presentation at the oncology department, advance age and poor performance status. Late stage presentation has been documented as the main predictor of mortality [28]. Furthermore, advance age has been noted as the poor prognostic factor among patients with head and neck cancer [29].

As it was documented in a meta-analysis where anemia was found to be the leading cause of mortality [30], in the current study all patients who died had anemia at the baseline. This could be due to the fact that, anemia leads to the hypoxic state which reduces the amount drug delivered to the cell and hence reduces the therapy response [31-33]. Anemia has also being reported as the independent predictor of mortality among cancer patients in previous studies [34-

36]. Furthremore, anemia is associated with fatigue which causes inability to perform the daily activities among cancer patients and hence reduces the quality of life of patients and hence increase mortality [31-33].

The mortality data for patients with hematological malignancy in the current study should be carefully being interpreted due to the limited number of patients.

Conclusions

Mortality of cancer patients within 90 days of therapy was slightly higher than in South Africa and more pronounced in patients with anemia at baseline, use of 5-Fluorouracil, poor performance status and diagnosis of head and neck cancers. A multicenter study among patients with hematological malignancy should be conducted to determine the 90 days treatment outcome and factors associated.

Abbreviations

BMC	Bugando Medical Centre
CLSI	Clinical and Laboratory Standard Institute
FBP	Full blood picture
IQR	Interquartile range

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study was given ethical clearance by the Joint CUHAS/BMC ethics and scientific review committee with certificate number CREC/228/2017. Permission to carry out the study was also sought from the management of the Bugando Medical Centre and the Oncology department. Written informed consent was obtained from participants after being informed about the study objectives and procedures. For all participants aged less than 18 years consents were sought from parents/guardians and assent was requested from the participant.

CONSENT FOR PUBLICATION

Written informed consent was obtained from patient

Availability of data and material

The data is available upon request and the request should be made to the Director of Research and Innovation, Catholic University of Health and Allied Sciences.

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Competing interest

None declared

Authors' contributions

MJC, MFM, SEM and BL designed the work. MJC, MFM, VS and SEM patients recruitment, performed laboratory investigations and results interpretations. MJC and BL manage the patients. MFM, RK and SEM analyzed and interpreted the data. MFM wrote the first draft of the manuscript which was critically reviewed by RK, VS, SEM and BL. All authors read and approved the final version of the manuscript.

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Tables

Table 1: Description of type of cancer seen during the study period

Variable	Frequency(N)	Percent (%)
Gynecological cancers	47	46
Cancer of Cervix	40	39
Uterine cancer	5	4.9
Ovarian cancer	1	1
Choriocarcinoma	1	1
Head and Neck Cancers	12	12
Squamous cell carcinoma of head and neck	5	4.9
Adenocarcinoma of Head and Neck	3	2.9
Retinoblastoma	2	2
Nasopharyngeal cancer	1	1
Sinonasal cancer	1	1
Connective tissue cancers (sarcoma)	12	12
Kaposi's sarcoma	6	6
Malignant melanoma	2	2
Malignant phyllodes	1	1
Fibro sarcoma	1	1
Osteosarcoma	1	1
Chondrosarcoma	1	1
Breast cancer	11	11
Gastrointestinal Cancers	10	10
Hepatocellular cancer	4	4
Pancreatic cancer	2	2
Colon cancer	2	2
Esophageal cancer	1	1
Biliary rhabdomyosarcoma	1	1
Hematolymphoid malignancies	6	6
Hodgkin lymphoma	2	2
Chronic myeloid leukemia	1	1
Acute myeloid leukemia	1	1
Burkitt's lymphoma	1	1
Nonhodgkin lymphoma	1	1
Genital and reproductive cancer	2	2
Perianal cancer	1	1
Prostate cancer	1	1
Lung cancer	1	1

Table 2: Baseline characteristics for patients who died within 90 days

Variable	*Patient identification*									
	1	2	3	4	5	6	7	8	9	10
Age(years)	76	71	52	43	65	50	49	62	51	51
BMI(kg/m^2)	18	29	22.2	25	21	25	27.7	23.2	25.2	22.8
Cancer type	Nasopharyngeal cancer	Breast cancer	GIT metastatic cancer	Malignant melanoma	Cancer cervix	Pancreatic cancer	Sinal nasal cancer	Adenocarcinoma of nose	Cervical cancer	Cerv canc
Type of therapy Type 1 Type 2 Type 3	5-Fluoro uracil Cisplatin Paclitaxel	Carboplatin	Docetaxel Dexamethasone	Carboplatin	Cisplatin Dacarbazine	Gemcitabine 5-Fluoro Uracil	Cisplatin Radiotherapy	Cisplatin	Cisplatin Radiotherapy	Cisp 5-Flu Urac
Stage of cancer	3	4	4	3	3	3	4	4	2	3
Baseline neutrophil (x10^9/L)	3.51	19.7	3.2	2.38	2.94	5.65	0.75	2.83	5.79	3.21
Neutrophil 1(x10^9/L)	2.9	19.8	2.87	3.92	1.09	5.17	1.65	2.6	5.8	2.25
Neutrophil 2(x10^9/L)	-	-	1.35	2.41	1.08	-	1.41	1.6	7.46	-
Neutrophil 3(x10^9/L)	-	-	-	1.13	-	-	-	3.17	2.69	-
Neutrophil 4(x10^9/L)	-	-	-	-	-	-	-	3.07	3.91	-
Neutrophil 5(x10^9/L)	-	-	-	-	-	-	-	1	-	-
Baseline Hb (g/dl)	9.6	11.1	11	9.9	10.1	9	9.1	10.5	7.3	10.3
Baseline WBC(x10^9/L)	6.14	4.58	4.8	4.29	5.33	8.37	2.92	4.8	8.84	5.1
Karnofsky score (%)	80	20	60	80	90	70	90	70	80	90
Blood culture	No growth	No growth	No growth	No growth	No growth	No growth	No growth	No growth	No growth	No grov
Urine culture	No growth	*P. aureginosa*	No growth	No growth	No growth	No growth	No growth	No growth	No growth	No grov
Body temperature(^{o}C)	36	38.2	37.1	36.3	36.8	37.2	37	35.2	35.5	36.7

Table 3: Factors associated with mortality within 90 days of therapy

Variable	*Dead* *Number (%) Median[IQR]*	*Alive* *Number (%) Median [IQR]*	*P-value*
HIV status			
Unknown(21)	3 (14.3)	18 (85.7)	
Negative(62)	9 (14.5)	53 (85.5)	
Positive(19)	0 (0)	19 (100)	0.211
Baseline body temperature (^0C)	36.2 [35.4-36.4]	36.2[35.7-36.7]	0.4023
BMI	23.8 [21.7-25]	22.9[20.2-25.9]	0.453
Cancer type			
Others (90)	8(8.9)	82(91.1)	
Head &neck (12)	4(33.3)	8(66.67)	0.014
Therapy type			
Cisplastin(50)	7(14.0)	43 (86.0)	0.492
5-Fluorouracil(10)	4(40.0)	6 (60.0)	0.004
Paclitaxel(22)	1(4.5)	21(95.5)	0.235
Carboplatin(9)	2(22.2)	7 (77.8)	0.308
Darcabazine(4)	1(25.0)	3 (75)	0.402
Docetaxel(6)	2(33.3)	4(66.7)	0.091
Karnofsky score (%)	80 [70-85]	90 [80-90]	0.001
Baseline Hb(g/dl)	10 [9.3-10.8]	11.8[10.5-12.7]	0.001
Baseline white blood cell($x10^9/L$)	4.9 [4.4-5.7]	5.2 [4-6.7]	0.226
Baseline neutrophil($x10^9/L$)	3.1 [2.6-4.6]	3 [2-4.1]	0.653
Body temperature visit (°C)			
Visit1	36.6 [36.1-37]	36.4[35.9-36.8]	0.852
Visit2	36.7 [36-36.9]	36.2[35.8-36.8]	0.677
Visit3	36.1 [36.1-36.3]	36.3[35.8-36.8]	0.565
Visit 4	36.3 [35.5-37.1]	36.2[35.7-36.6]	0.758
Visit 5	35.2 [35.2-35.2]	36.4 [35.9-37]	0.490