RESEARCH COMMUNICATION

Characteristics and Pattern of Mortality in Cancer Patients at a Tertiary Care Oncology Center: Report of 259 Cases

Gaurav Prakash[1*], Sameer Bakhshi[1], Vinod Raina[1], Sushma Bhatnagar[2], Atul Sharma[1], Lalit Kumar[1], NK Shukla[3], PK Julka[4], GK Rath[4]

Abstract

Background: Little is known about mortality statistics of hospitalised cancer patients from developing countries. This paper describes the distribution of causes of death in various malignancies, status of malignancy at the time of death, type and intent of therapy received by the cancer patient prior to death and nature of infections in terminal cancer patients who died in hospital. We also aimed to study discrepancies in mortality reporting in terms of death certificate at our center and tried to analyse possible causes. Results : Data for 259 consecutive deaths in hospitalized cancer patients in a calendar year were analysed. Of all these, 147 (57%) were cases of solid tumors, 107 (41%) were cases of hematological malignancies and 5 (2%) were other or undiagnosed cases. Median duration of hospital stay prior to death was 7 (1-106) days. Sepsis/multi organ dysfunction syndrome (MODS) was commonest immediate cause of death 118/259 (45.2%) followed by progressive malignancy in 64/259 (24.7%) cases. Only 13/267 (5%) patients died with controlled cancer. Some 184 (71.3%) deaths occurred within 90 days of any form of anticancer treatment of which more than three fourths (77.2%) occurred after chemotherapy. Among these chemotherapy related deaths, 63 were febrile neutropenic deaths, with the commonest site of infection in the lungs, and positive blood culture was found in 18 (28%) cases. There were discrepancies in information derived from death certificates and from case records in 84 (32%) cases. Most of these were due to the use of ambiguous terms like cardio-respiratory arrest as a cause of death in the death certificate. Conclusion: It is important to audit mortality data on a regular basis as this can provide valuable insight into hospital practice and may help to identify preventable causes of mortality. Mortality record keeping is another important aspect as variable practices in this area may have implications for cancer mortality reporting and this may ultimately lead to erroneous cancer epidemiology.

Keywords: Cancer mortality - death certificate - medical audit - neutropenic deaths

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Introduction

Cancer directed therapies, over last few decades, have evolved significantly in spectrum, effectiveness, usage and safety. There is parallel improvement in cancer treatment outcome and management of therapy-related complications. In spite of these advancements, inpatient deaths in oncology centers are common occurrence with majority dying due to advanced disease. A considerable number of patients die during course of treatment and many of these deaths are related to cancer treatment. Nevertheless, the issue of death and dying has received limited attention within the context of patient management. A medical audit is an important tool to look into the trends of such deaths and it may also identify areas in need of improvement during patient care. In the United Kingdom, National Confidential Enquiry into Peri-operative Deaths is an organisation established in 1988 for audits in health care (O'Brien et al., 2006; Mort et al., 2008). Its spectrum has evolved from initial inclusion of only peri-operative deaths to presently medical as well as surgical deaths. Guidelines issued by the same have led to meaningful changes in healthcare practice as well.

Large volume of published cancer mortality data is either in the form of clinical trial results or as an epidemiological account of mortality in an entire population. Specifically from oncology centers, focus has been on pattern of mortality in a particular cancer rather than on trends of inpatient mortality which is also a useful epidemiological parameter.

Mortality reporting discrepancies have been noted worldwide and cancer deaths are no exception (Moriyama et al., 1958; Steer et al., 1976). Use of ambiguous terminology in death certificates leads to erroneous mortality data of cancer patients. We audited the deaths of hospitalized patients in our center and present our

*[1]Department of Medical Oncology, [2]Unit of Anesthesiology, [3]Department of Surgical Oncology, [4]Department of Radiation Oncology, B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India *For correspondence : drgp04@gmail.com*

analysis which reflects hospital-based mortality pattern in oncology practice in a developing country. We also audited our death certificate in relation to primary cause of death mentioned by attending physician and inherent discrepancies in reporting.

Materials and Methods

Our center is a referral oncology center with medical, radiation and surgical oncology along with palliative care services. All services regularly treat patients on inpatient basis. The inpatient deaths are recorded in a mortality register and the medical records of all deaths are maintained in record section. Approximately 8,000 new cancer patients are seen annually and common cancers are breast, lung, head and neck, cervix, prostate, leukemia and lymphomas.

Primary objective of this study was to study characteristics of deaths, ante-mortem therapies and their complications. Our secondary objective was to assess the discrepancies in reporting cause of death in cancer patients in death certificate at our center.

Mortality records were retrieved for all inpatient deaths from 1st January 2008 to 31st December 2008. Source documents were hospital notes, nursing charts, and investigation reports. Along with demographic parameters we analysed type of therapy received by the patient (chemotherapy, radiotherapy, surgery, or stem cell transplant); lines of treatment (first or second/further lines of therapy); intent of treatment (curative or palliative); status of malignancy at time of death (controlled or uncontrolled disease); and causes of death with emphasis on neutropenic deaths. The cause of death was interpreted from the source documents, and the immediate cause of death was considered for analysis. Further we also noted the cause of death as recorded on the death certificate to see the discrepancies in mortality reporting.

Deaths occurring within 90 days of anticancer therapy were considered as mortality related to anticancer treatment. Status of cancer at the time of death, whether controlled or uncontrolled was recorded for all deaths. Controlled cancer in solid tumors was defined as clinical and radiological absence of disease for at least 1 month; for hematological malignancies, besides clinical and radiological response, hematological response was also considered to document the same. Non-responders and partial responders were grouped into uncontrolled malignancies.

Fever was defined as a single temperature of 38.3 °C or two temperature recordings greater than or equal to 38 oC recorded at least four hours apart. Neutropenia was defined as absolute neutrophil count less than 1000/mm^3 with falling trend. Documented focus of infection was considered based on symptoms pertaining to a particular system with or without culture positivity in case of HEENT (head, ear, eyes, nose and throat), gastrointestinal tract, skin and subcutaneous tissue infections. Pneumonia was defined as fever with new infiltrate on a chest radiograph, and respiratory symptoms with or without an organism being isolated from sputum. Fungal pneumonia was defined on characteristic findings of high resolution CT scan of chest. For a documented blood or urinary tract infection, culture had to be positive. First line antibiotics were defined as antibiotics used for first episode of fever as per departmental policy. Any subsequent addition or replacement of antibiotics was taken as use of second line antibiotics. Use of antifungal agents was defined as systemic antifungal therapy in therapeutic doses with intent of treatment; patients who received antifungal agents for prophylaxis were not considered in the same group.

Statistical analysis was carried out with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). This included descriptive analysis of demographic and clinical parameters.

Table 1. Baseline Characteristics of the 259 Cases

Median Age (Range)	46 years (2-83 years)
Male : Female	161:98
Type of Malignancies	
• Solid Tumors	147 (57%)
• Hematological Malignancies	107 (41%)
• Others/Undiagnosed*	5 (2%)
Treating Departments	
• Medical Oncology	126 (48.6%)
• Radiation Oncology	111 (42.8%)
• Surgical Oncology	10 (3.8%)
• Palliative Care Unit	12 (4.6%)
Age Group Distribution	
• ≤14 years	19 (7%)
• 15-24	34 (13%)
• 25-34	29 (11%)
• 35-59	126 (49%)
• ≥60	51 (20%)
Last Anticancer Therapy (within 90 Days of Death)	N=184
• Chemotherapy	142 (77%)
• Radiotherapy	26 (14%)
• Surgery	9 (5%)
• Stem cell transplant	7 (4%)
Median Duration of Hospital Stay Prior to Death (Range)	7 days (1-106 days)
Median Duration from Therapy to Death (Range)	13 days (1-90 days)

*3 cases of undiagnosed malignancies, 1 case of severe combined immunodeficiency, and 1 case of disseminated tuberculosis (admitted with provisional diagnosis of lymphoma)

Table 2. Profile of Deaths in Hematological Malignancies Versus Solid Tumors

Parameters	Solid (N= 147)	Hematological (N= 107)
Status of Disease at Death		
• Controlled	4 (2.7%)	9 (8.4%)
• Uncontrolled	143(97.3%)	98(91.6%)
Intent of Therapy		
• Curative	40 (27%)	71 (66%)
• Palliative	79 (54%)	21 (20%)
• Best Supportive Care Only	30 (20%)	15 (14%)
Curative Intent	(N=40)	(N=71)
• First Line of Therapy	38 (95%)	51 (70%)
• Second or Further Line	2 (5%)	22 (30%)
Palliative Intent	(N=79)	(N=21)
• First Line of Therapy	40 (51%)	5 (24%)
• Second or Further Line	39 (49%)	16 (76%)

Table 3. Distribution of Causes of Death with Various Malignancies

Cause of death	Leukemia	Lymphoma	Myeloma	Breast	Lung	H&N	Gyn	GIT	Sarcomas	Other	Total (%)
Sepsis/MODS	45 (69%)	20 (69%)	6 (46%)	5 (22%)	4 (20%)	9 (39%)	5 (33%)	16 (51%)	3 (30%)	5 (17%)	118 (45%)
Progressive Disease	5 (8%)	4 (14%)	2 (15%)	10 (44%)	12 (55%)	5 (20%)	5 (33%)	10 (32%)	4 (40%)	7 (24%)	64 (25%)
Hemorrhage	8 (13%)	2 (7%)	1 (8%)	1 (5%)	1 (5%)	3 (13%)	-	-		2 (7%)	18 (7%)
Acute Renal Failure	1	-	2	-	2	1	1	1		2	10 (4%)
Neurological causes*	3	1	1	2	1	3	1	1	1	7	21 (8%)
Cardiac causes+	1	-	-	-	1	-	-	1	-	2	5 (2%)
Pulmonary causes#	-	1	1	-	-	-	-	-	1	1	4 (1.8%)
Others$	2	-	-	1	-	-	-	1	-	1	5 (2%)
Insufficient Information	-	1	-	3		3	3	1	1	2	14 (5.4%)
Total (%)	65 (25%)	29 (11%)	13 (5%)	22 (8%)	22 (8%)	23 (8.5%)	15 (5.3%)	31 (11%)	10 (4%)	29 (11%)	259

*Raised ICP/CVA/status epilepticus; +Arrhythmia/MI/CHF; #ARDS/bleomycin or radiation toxicity; $Dengue/DKA/SVCO/intestinal obstruction; ARDS, adult respiratory distress syndrome; CHF, congestive heart failure; CVA, cerebrovascular accidents;DKA, diabetic ketoacidosis; GIT, gastrointestinal tract malignancies; Gyn, gynecological malignancies, H&N, head and neck malignancies; ICP, intracranial pressure, MI, myocardial infarction, MODS, multiorgan dysfunction syndrome; SVCO, superior vena cava syndrome

Categorical variables were summarised by frequency, and the quantitative variables were summarized by mean and standard deviation or median and range. Association for two-way tables, to assess difference between solid tumors and hematological malignancies was performed using the chi-square test. A P-value < 0.05 was considered significant.

Results

Baseline Characteristics and Basic Demography

From January 2008 to December 2008, there were total 22,916 admissions; of which there were 18,311 short admissions in day care facility, where no death was recorded. Of the 4605 admissions in the inpatient wards, there were 267 (5.8%) deaths in various departments. Data of 8 (3%) deaths was unavailable for analysis, and thus a total of 259 (97%) records were analyzed. The demographic parameters of these cases are shown in Table 1. Majority of deaths 126/259 (48.6%) were seen in age group 35-59 years. while 19/259 (7.3%) deaths were in pediatric age group and 51/259 (19.7%) in age group ≥60 years.

Of 259 deaths, 184 (71%) deaths occurred within 90 days of any form of anticancer treatment of which more than three-fourth (77%) occurred after chemotherapy. The status of malignancy was controlled in 4/147 (2.7%) deaths in solid tumors and 9/107 (8.4%) deaths in hematological malignancies (Table 2). Among all deaths, 40/147 (27%) cases of solid tumor and 71/107 (66%) cases of hematological malignancies were treated with curative intent.

Forty five (17.3%) patients, who died, were on best supportive care due to their poor performance status. Twelve of these cases had curable malignancy and were admitted with intention of administering curative therapy, but they were initially given best supportive care only, due to their extremely poor general condition at admission, which precluded administration of anticancer therapy.

Etiology of Mortality

Sepsis/multi organ dysfunction swyndrome (MODS) emerged as most common immediate cause of death as observed in 118/259 (45%) cases followed by progressive malignancy in 64/259 (25%) cases (Table 3). Sepsis was the leading cause among those who died with hematological malignancies and gastrointestinal cancers. Likewise progressive malignancy was the leading cause of death amongst patients who died with carcinoma breast, carcinoma lung, and sarcomas. Neurological causes were present in 21/259 (8%) cases and they were seen primarily in cases of brain tumor or in those with brain metastasis. Severe hemorrhage was main cause of death in 18/259 (7%) cases; majority of these being leukemia while amongst solid tumors massive bleeding was observed in head and neck cancer patients, in which 3/23 (13%) died of aspiration from torrential tumor bleed.

Thirteen (5%) deaths were seen in cases with controlled malignancy of which 9 cases were hematological malignancies and 4 solid tumors. Amongst eight cases of acute leukemia who were in complete remission, four died of sepsis and one each died of intracranial bleeding, acanthameba meningitis, acute left ventricular failure and cardiac arrhythmia during central venous catheterisation. Amongst solid tumor cases who died in controlled malignancy state, the death was attributed to dengue hemorrhagic fever, radiation pneumonitis, pneumonia and septicemia in one case each.

Neutropenic deaths

Of 149 deaths within 90 days of chemotherapy or hematopoietic stem cell transplant (HSCT); 63 (42%) were neutropenic deaths. Amongst these cases, 44 (70%)

Table 4. Analysis of Febrile Neutropenic Deaths

		Hematological (N=107)	Solid Tumors (N=147)	P value
Febrile neutropenic deaths		44 (41.5%)	19(12.9%)	0.04
Detectable infection focus		37 (84%)	13 (69%)	0.158
• Lung		32 (72%)	8 (42%)	0.02
• Skin and subcutaneous		6(13.6%)	3(15.8%)	0.80
• Gastro-intestinal tract		2 (4.5%)	3(15.8%)	0.13
• Genito-urinary tract		1 (2.3%)	1 (5.3%)	0.53
• HEENT		2 (4.5%)	1 (5.3%)	0.9
• Blood		2 (4.5%)	1 (5.3%)	0.03
No detectable focus		7 (16%)	6 (31%)	
Microbiology pattern		(N=17)	(N=1)	-
• Escherichia coli		5 (29%)	-	
• Klebsiella		5 (29%)	1(100%)	
• Pseudomonas		3 (18%)	-	
• MRSA		2 (12%)	-	
• Acenatobactor		2 (12%)	-	
• Enterococcus		1 (6%)	-	
• Salmonella		1 (6%)	-	
Antibiotics	First line only	7 (16%)	7 (37%)	0.06
	Second line	37 (84%)	12 (63%)	
Anti-fungal	Used	31(70.5%)	5 (26%)	0.001
	Not used	13(29.5%)	14 (74%)	
Disease status	Controlled	3 (6.8%)	2(10.5%)	0.71
	Uncontrolled	41(93.5%)	17(89.5%)	

Abbreviations: HEENT- Head Eye Ear Nose and Throat, MRSA- Methicillin Resistant Staphylococcus aureus

deaths were in hematological malignancies and 19 (30%) in solid tumors. Documented infection was present in 50/63 (80%) cases; 18/63 (29%) cases had a positive blood culture. Significantly higher number of septicemia and pneumonias were observed in the deaths occurring in hematological malignancies as compared to solid tumors (Table 4). Among 40 cases of pneumonia in neutropenic patients 8 (20%) were of fungal etiology and all these were patients of hematological malignancies. Use of second line of antibiotics and antifungal was also more frequent in hematological malignancies as compared to solid tumors.

Death certificate reporting

We noted that in 84/259 (32%) cases, cause of death could not be rightly assessed by death certificate alone. Amongst these 84 incomplete death certificate records, 23 (27%) had a phrase like cardio-respiratory arrest or cardio-respiratory failure, while in 32 (38%) only the name of the malignancy was recorded. In rest of 29 cases cause of death recorded on death certificate did not match with the cause found after study of case records.

Discussion

This audit describes results of inpatient mortality in cancer patients from an oncology center from a developing country. In 13/254 (5%) cancer deaths, malignancy was in complete remission while in remaining 241/254 (95%) cases disease was either uncontrolled or partially controlled. In latter group, there was active malignant disease present at the time of death which might have contributed in the death of patients. There was lack of sufficient data to clearly ascertain cause of death in 14 cases; however none of these 14 deaths occurred in patients with complete remission. In a similar report from Royal Marsden Hospital, London, etiology of deaths in hospitalized patients of various malignancies within 30 days of chemotherapy was primarily progression of underlying malignancy in 124/161 (77%) cases (O'Brien et al., 2006). Bouduer et al. from France reported progressive disease as primary cause of death in hospitalized patients in 56/81 (70%) cases (Bauduer et al., 2000). Terminal malignancy seems a logically correct most common cause of death in most cases but when it was studies in an autopsy series in a medical oncology center; cancer as a direct cause leading to death was found in only 9% of deaths. Most patients died of either sepsis or adult respiratory distress syndrome (Gerain et al., 1990). We also found that the sepsis was the commonest cause of death in 118/259 (45%) cancer patients. Similarly, a retrospective study of 267 elderly patients, with intermediate or high-grade Non-Hodgkin's lymphoma receiving CHOP chemotherapy demonstrated a chemotherapy-related death rate of 13%. Infection accounted for 82% of these chemotherapy-related deaths (Gomez et al., 1998).

We believe that these differences in etiology of mortality are due to different practice of terminal care and mortality reporting at various centers across the world. At our centers majority of the admitted patients with advanced malignancies were administered palliative anticancer treatments. Treatment related neutropenia might have lead to higher incidence of sepsis and ultimately sepsis related death which is reflected in reporting of sepsis as a most common direct cause leading to death. However from palliative care units terminal malignancy is more likely to be reported as a direct cause of death.

We found that neutropenic deaths due to septicemia and pneumonia were significantly more in hematological malignancies as compared to solid tumors (Table 4). Worldwide, now with increasing use of indwelling catheters and chemotherapy ports, incidence of gram-positive sepsis is increasing in neutropenic patients (Bullard and Dunn, 1996; Wolf et al., 2008). On the contrary we found that at our center 80% of the positive blood culture were gram-negative organisms, mainly Pseudomonas aeruginosa, Escherichia coli, and Klebsiella species. Amongst sites of documented infection, lung was the most common site in 40/63 (63.5%) cases; 8 of these were of fungal etiology and all these occurred in patients of hematological malignancies. This may be due to the fact that duration and severity of neutropenia is more in these patients and corticosteroids are common components of regimens for hematological malignancies, both of which predispose to increased risk of invasive fungal infection. Thus, the therapeutic use of antifungal agents was significantly more in hematological malignancies than in solid tumors (Table 4).

As compared to data from other center (O'Brien et al., 2006), where most deaths occurred after second or third line of treatment, our analysis showed that maximum deaths occurred after first line of treatment, both in curative and palliative setting. This difference reflects

the pattern of presentation of malignancies in advanced stage in our setup. Similarly, 12/45 (26%) cases, who died on best supportive care were admitted for definitive anticancer treatment. However their poor performance status at the time of admission precluded administration of anticancer therapy.

In the past, a number of authors have pointed out the inaccuracies of cancer death certificates by comparing the specified underlying cause of death to autopsy findings and to more specific hospital and pathologic information (Moriyama et al., 1958; Steer et al., 1976; Sington and Cottrell, 2002). Most of these studies dealt only with a small series of cases. In our analysis of data of 259 cases we found that 84/259 (32.4%) of death certificate were inconsistent with the likely cause of death. One reason of this variation can be differences in understanding of course of disease process among individual physicians. Another reason can be that more often than not, the physician attending patient at time of death and issuing death certificate was different from the main treating physician. Cardiac-arrest was used as cause of death mostly in cases who died following a course of advanced malignancy. Cardiac/respiratory failure was more often used as a generic term rather than a specific entity for congestive heart failure. Sington has reported discrepancies in cause of death mentioned on death certificate and the one found on necropsy in which the overall sensitivity of predicting correct cause of death from death certificate was 0.47, while sensitivity for all malignant causes of death was 0.65 (Sington and Cottrell, 2002). The relevance of these discrepancies is that they may significantly alter mortality data, which can have a bearing on cancer epidemiology. Documentation of cause of death and diagnosis as per ICD-10 classification can help to bring in more uniformity in mortality reporting.

At our canter 48.6% of deaths occurred in age group 35-59 years which is much lesser than 19.7 % of deaths seen in patients more than 60 years of age. Median age at our center was 46 years (range 2-83 years). While O'Brien et al reports median age of inpatient cancer deaths at 61 years (range 6-86 years) (O'Brien et al., 2006). It will be erroneous to infer that cancer deaths occur more frequently in younger population in developing countries. Actually, this reflects the larger number of referral of younger patients to tertiary care hospital in our setup. Elderly patients with advanced malignancy are less likely to be referred for higher centers in a resource constrained population and most such patient die at home.

A limitation of our study is that this is a single center data and mortality trend may be influenced by hospital admission policy. However this reflects current situation of cancer mortality from developing part of the world. In conclusions in the era of evidence based medicine and multi-center international research, we need to have more uniform ways of our record keeping and death reporting so that the comparisons can be more accurate. This study highlights the importance of medical audits, and their role is improving health care in the concerned hospital. A better knowledge of the profiles of dying patients in oncology departments is needed if we are to improve our approach in cancer epidemiology and management.

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