RESEARCH ARTICLE

Hematologic Toxicity in Patients Undergoing Radical Anti-cancer Therapy: A Cross-Sectional Analysis of Patients in an Oncology Ward in India

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Abstract

Burden of cancer is progressively increasing in developing countries like India which has also led to a steep rise in toxicity due to anti-cancer therapy. A cross-sectional analysis was here conducted for patients with different malignancies (except leukaemia) who while undergoing radical anti-cancer therapy were admitted to our oncology ward from January-July 2013. In a total of 280 patients, the total number of toxicity events was 473. Nine patients expired over this time period. Among the events, grade 2 anaemia the most common (n=189) while the most common grades of neutropenia and thrombocytopenia were grade 4 (n=114) and grade 2 (n=48), respectively. Among the tracable microbial etiologies, gram negative bacteria were the most commonly found pathogens. Treatment interruptions took place in 240 patients (median duration=8.8 days). Prolonged hospital admission, intensive care and artificial ventilation support was needed to be given in 48, 7 and 13 patients respectively. Advanced NSCLC, KPS <70, pancytopenia and artificial ventilation requirement were found to have a significant impact on death. Such studies show the prevailing practice from institutes of our country and may guide us formulating a guideline for managing such toxicities for this part of the world.

Keywords: Haematological toxicities - non-haematological malignancies - radical anti-cancer therapy

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Introduction

Burden of cancer is progressively increasing in economically developing countries like India. Globally, the burden of new cancer cases in 2000 was estimated to be around 10.1 million (Murthy et al., 2008). Developing world shares 53% of this load which already has taxed its limited resources. With increasing burden more number of patients are now a days undergoing cancer directed therapy, which is essentially a sign of increasing awareness and advancement of oncologic facilities in this part of the world. This has led to a steep rise in toxicities of anti-cancer therapy in these countries. We tried to introspect into the occurrence of haematological toxicities which force us to admit patients, undergoing curative anti-cancer therapy in the form of chemotherapy, radiotherapy or a combination of chemo-radiation in our institute in our oncology in-patient ward over a period of seven months.

Materials and Methods

We did this cross-sectional analysis over a period of seven months (January-July 2013) for all those patients who while undergoing anti-cancer therapy in our institute with a curative intent got admitted to our oncology in-patient ward with some sort of haematological toxicity. Before starting this analysis we took informed consent from our institutional ethical committee. The demographic data including age, sex, performance status (Karnofsky's performance status score) and socio-economic background of all these patients were collected. We also reviewed the diagnosis and the on-going treatment details of these patients. As some of the patients got admitted multiple times with one or other type of haematological toxicity, we calculated each admission with its cause as an event. Sometimes there were two toxicities present simultaneously in one patient, so we have reported them in combination and separately also. Grading of toxicity was done using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

For all these patients we did a baseline laboratory work-up after admission which included a complete blood count (CBC) and liver function tests (LFT) and kidney function tests (KFT). CBC was repeated daily while LFT and KFT were done when and as required.

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All the patients with grade 2 anemia with haemoglobin (Hb) level ≥9g/dl were initially treated with hematinic along with treating the cause of anemia if possible like bleeding etc. For all those who did not regain their Hb even after three days or those who showed a down-sliding of Hb level and those with baseline Hb level <9g/dl were supplemented with PRBC along with hematinic replenishment. For those patients who could not be supplemented with PRBC for some other contra-indications were given a single shot of injection: erythropoietin.

For all those patients who admitted with grade 3/4 neutropenia with or without leukopenia the baseline temperature was noted and if the patient was found to be febrile, we immediately sent blood for bacterial culture and sensitivity (CS) and chest X-ray. Temperature charting, every two hourly was done for all these patients. If the patients were afebrile at baseline we sent blood samples for CS whenever there was a spike of fever. Till the report of blood CS was available, we started the patients on empirical intravenous antimicrobial agents. We changed the antimicrobial agents if the fever did not subside even after 72 hours of antibiotic administration or the report of CS showed resistance to that drug, whichever took place earlier. If the patients remained febrile even after seven days of antibiotic therapy we used to send blood samples for fungal CS and started on empirical antifungal therapy. Sputum samples for fungal CS were also sent if the chest X-ray showed features suggestive of fungal pneumonia. Urine, CSF and stool for CS were sent depending on patients' symptomatology. If the cultures came out to be negative in spite of unremitting fever the modification to initial empirical therapy was guided by assessment of risk for infection with the following antibiotic resistant organisms like MRSA i.e. methicillin resistant staphylococcus aureus (early addition of vancomycin or linezolid), VRE i.e. vancomycin resistant enterococcus (addition of linezolid or daptomycin), ESBL i.e. extended-spectrum beta-lactamase forming gram negative bacteria (addition of imipenem or meropenem) or KPCs i.e. Klebsiella pneumoniae carbapenemase (addition of colistin or tigecycline).

Growth factors (Granulocyte-Colony Stimulating Factors/Peggylated G-CSF i.e. Peg G-CSF) were administered when there was febrile neutropenia, any grade 4 neutropenia or leukopenia when absolute neutrophil count (ANC) showed a decreasing trend with or without persistent infections in spite of CS based antibiotic therapy. We also advocated use of growth factors and empirical antifungals if the patients were clinically septic and/or hypotensive, or had organ dysfunction. The G-CSF was continued till the ANC rose up to 10,000/cmm. Antiviral treatment for HSV or varicella-zoster virus (VZV) infection was only indicated if there was clinical or laboratory evidence of active viral disease. Hand hygiene, maximal sterile barrier precautions were practiced routinely. Antibiotic therapy was stopped when there was improvement in clinical picture or blood CS report came out to be sterile or patient expired.

In patients with thrombocytopenia only observation was done with close vigilance for any bleeding manifestation if the platelet counts were more than 20000/cmm. For any platelet count below this mark or for those who showed a progressively decreasing platelet count over consecutive three days or anybody with platelet count over this mark but having bleeding manifestations platelet rich plasma (PRP) transfusion were done. The indications of single donor platelet transfusion (SDP) were: patients with severe bleeding manifestations leading to complications, no improvement or decrease in platelet counts in spite of 10 units of PRP transfusion.

For every patient any singe admission for managing any of these toxicities was considered to be a single event and so the total number of toxicity events was higher than total number of patients. We also took a single event of pancytopenia as a single event of anemia, neutropenia and thrombocytopenia and similarly any combination of two toxicities were split into one each while calculating the total number of toxicity events. We analysed the frequency of all the events with the grade distribution. We analysed our practice of first line empirical antibiotic and antifungal administration in these patients. We noted the pattern of supplementation of growth factors and blood components; we also recorded and studied the effects of these toxicities in these patients like interruption in treatment, infection rate, prolonged hospital admission i.e. hospital admission more than one week, ICU admission and ventilation support, death. We studied the effect of different variables like age, sex, KPS, treatment regimen, primary malignancy, infectious organism on the outcomes like different grade 3 or 4 toxicities, ICU admission and death. We also analysed the impact of ICU admission and ventilation support on death. Chi square test was used to calculate the odds ratio (OR) with 95% confidence interval (CI). Two sided p value was also calculated. We used SPSS 17 for statistical analysis.

Results

Patient demographics

A total of 280 patients were found eligible for analysis, the total number of toxicity events being 473. 154 patients were female while 126 were male. A total of 124 patients were in the age group above 40 years while 156 patients belonged to an age group less than or equal to 40 years. 101 patients were having a KPS score of blow 70 while 156 patients were having a KPS score in the range of 80-70. Only 23 patients were having a KPS score of more than 80. 115 patients were below poverty line according to Indian economic stratification system while rest belonged to a class above poverty line (Table 2). Distribution of primaries in these patients have been shown in Table 1.

Among a total 215 events of anaemia the distribution of grades was as follows: Grade 2: 189; Grade 3: 23; Grade 4: 3. Similar distribution of grades for neutropenia and thrombocytopenia has been furnished in table 3. Among the neutropenic events the most common grade was Grade 4 (with or without fever) (n=114). Grade 2 thrombocytopenia was most common (n=48) followed by grade 4 (n=35) and grade 3 (n=22).

The blood CS report (n=105) did not reveal the etiology in most of the cases (n=58). In those where an

Table 1. Showing the Distribution of Malignancies in the Patients with Different HematologicToxicities

Toxicites, Primary Malignancies	
Anemia alone (n=159)	
Carcinoma cervix IIIB	65
Carcinoma cervix stage IIB	38
Early Carcinoma breast (Stage I/II)	11
Advanced Carcinoma breast (stage III/IV)	16
E-SCLC	2
NSCLC Stage IV	16
NSCLC Stage III	2
Carcinoma Gall bladder stage III	1
Carcinoma bladder stage IV	2
Neuro-endocrine tumours	2
NHL stage IV	1
Locally advanced HNSCC (stage III/IV)	1
ODG	1
Sarcoma	1
Granulocytopenia alone (n=71)	
Carcinoma breast (Early)	18
Advanced carcinoma breast	13
NSCLC	13
E-SCLC	2
Sarcoma	12
Medulloblastoma	4
NSGTC stage IV	2
Pineal dysgerminoma	2
Metastatic carcinoma esophagus	2
Metastatic carcinoma prostate	1
Multiple myeloma	1
Supratentorial PNET	1
Thrombocytopenia alone (n=34)	
Advanced NSCLC (stage III/IV)	16
Sarcoma	4
Advanced carcinoma breast	5
Early Carcinoma breast	3
GBM	3
Thymoma	1
Carcinoma cervix	1
NSGCT	1
Combination of any two (n=58)	
Advanced Carcinoma breast	24
Advanced NSCLC	13
Granulocytopenia+thrombocytopenia	33
Sarcoma	9
Anemia+granulocytopenia	18
Early carcinoma breast	4
Anemia+thrombocytopenia	7
Medulloblastoma	3
Carcinoma cervix IIIB	2
ODG	1
GBM	1
Carcinoma stomach	1
NSGCT	1
Pancytopenia (n=31)	
Advanced NSCLC	9
Advanced carcinoma breast	8
Sarcoma	8
Carcinoma unknown primary with multiple brain metastasis	2
E-SCLC	1
Locally advanced HNSCC	1
Carcinoma cervix IIIB	1
Malignant Melanoma	1

Table 2. Showing the Demographic Data in Our Study Cohort (n=280)

Parameters	Group	No.
Age	<20	16
	20-40	140
	>40-60	92
	>60	32
Sex	Female	154
	Male	126
KPS (Karnofsky Performance Score)	>80	23
	80-70	156
	<70	101
Socio-economic status	Below poverty line	15
	Above poverty line	175

Table 3. Showing the Distribution of Grades of Different Haematological Toxicities

Toxicity	Grade	No.
Anemia (n=215)	2	189
	3	23
	4	3
Granulocytopenia (n=153)	3	39
	4 without fever	19
	Febrile Neutropenia	95
Thrombocytopenia (n=105)	2	48
	3	22
	4	35

etiologic agent could be traced, gram negative bacteria (GNB) were the most commonly found agents followed by mixed infections (Table 6). Among the gram negative bacteria Klebsiella pneumoniae was the most commonly detected pathogen (n=11) followed by Pseudomonas aeruginosa (n=7). ESBL (extended spectrum beta lactamase) pattern of resistance could be detected in 18% of GNB while KPC was found in one case. Among the GPB methicillin resistant staphylococcus aureus (MRSA) was the most commonly detected pathogen (50% of all GPB). Documented fungal infection and viral infection were noted in two cases each.

We studied our practice of first line empirical antibiotic therapy in patients of febrile neutropenia. The most commonly used antibacterial combination was a polytherapy using cefoperazone-sulbactum along with amikacin while most commonly used empirical antifungal agent was fluconazole while acyclovir was the only antiviral which was used in our study cohort. In 46 patients we changed on to a second line antibiotic therapy due to resistance (depending on CS report or clinical deterioration) while in 59 patients the patients responded to the first line antibiotic therapy (Table 4). The median duration of antibiotic therapy in our study cohort was 9.4 days (range 3-27 days). The most commonly used second-line antibiotic was a piperacilin-tazobactum along with imipenem combination (46%) with or without other antimicrobials followed by vancomycin-tobramycin combination (21%) with or without other antimicrobials. Colistin was required to be used in two patients.

The summary of blood components, growth factors and hematinic supplementation has been shown in Table 5. The median number of packed red blood cell (PRBC) requirement was 2 (range: 1-6). Only two patients were given a single injection of erythropoietin (4000u subcutaneously). In 36 cases of neutropenia G-CSF administration was not required. The median number of days G-CSF administered has been 6 days (range: 3-10 days). The median number of units of PRP required was 4.8 (range: 2-12). SDP administration was required only in 4 patients and only one of them required more than 2 units (3 units).

Table 4. Showing the First Line Antibiotics Used in the Patients with Infections

	Antibiotics		No. of patients	
First line	Antibacterial	Cefoperazone-Sulbactum (CS)+Amikacin	68	Response evaluation
		CS+Amikacin+Metronidazole	13	No response/resistance=46
		Tazobactum-Piperacilin+Metronidazole	5	
		CS+Amikacin+Clindamycin	12	
		Augmentin+Metronidazole	7	Response=59
	Antifungal	Fluconazole (empirical/based on sensitivity report)	39	
		Voriconazole	2	
	Antiviral	Acyclovir	2	

Table 5. Showing the Requirement of Blood Component or Growth Factor Supplementation for These Events of Toxicity

Mode of supplementation	Quantity	Frequency
Packed red blood cells	Nil	43
	1-2units	154
	>2units	16
Single injection of erythropoietin		2
Granulocyte-Colony stimulating factor	Nil	36
(5μg/kg body weight)	3-5 days	39
	5-7 days	56
	7-10 days	18
	>10 days	2
Peggylated G-CSF	1 day	1
	>1 day	1
Platelet rich plasma	<5units	15
	5-10units	9
	>10units	2
Single donor platelet	1-2units	3
	>2units	1

Table 6. Showing the Adverse Effects of Toxicities

Adverse effects	Details	No.
Treatment interruptions	<1 week	85
	1-2 week	109
	>2 weeks	46
Congestive heart failure from severe anemia		3
Infections	Bacterial:	47
	GPB	12
	GNB	21
	Mixed	14
	Fungal	2
	Viral	2
	Unknown/cryptogenic	58
Life threatening bleeding comlications		
	Intra-articular bleeding leading to arthropathy	1
	Intracranial bleeding	1
	Pulmonary haemorrhage	1
Dose reduction in chemotherapy		217
Hospital admission	>1 week	48
Intensive care provision	<1 week	5
	≥1 week	2
Ventilation support		13
Death		9

Treatment interruptions took place in 240 patients due to any of these toxicities, the median duration of interruption being 8.8 days. Congestive heart failure due to severe anemia took place in three patients. Severe bleeding manifestations were observed in three patients (Table 6). In 217 patients dose reduction in chemotherapy was done to avoid further toxicities but radiation dose was kept unchanged in all of those who were undergoing radiotherapy. More than one week of hospital admission was required in 48 patients. Intensive care was need to be given in seven patients and 13 patients required artificial ventilator support as a result of some complications owing to these toxicities. Overall nine patients expired during this period due to some direct or indirect complications of haematological toxicity. Seven patients were having pancytopenia while one patient was having intracranial bleeding with grade 4 neutropenia and in one patient the death could be attributed to severe infection in febrile neutropenia.

We found that age more than 60 years (OR: 1.3; 95% CI: 1.1-1.9; p=0.04), KPS less than 80 (OR: 1.4; 95% CI: 1.2-1.9; p=0.002), concurrent chemo-radiation (OR: 2.1; 95% CI: 1.1-2.6; p=0.04), CSI (OR: 1.3; 95% CI: 1.1-2.1; p=0.02) and advanced primary disease (OR: 1.9; 95% CI: 1.2-2.6; p=0.002) had a significant negative impact on incidence of grade 3 or 4 toxicities. Age more than 60 years (OR: 1.4; 95% C.I: 1.1-2.1; p=0.03), KPS less than 70 (OR: 1.8; 95% C.I: 1.1-2.4; p=0.003), requirement of SDP (OR: 1.9; 95% CI: 1.4-2.1), sarcoma as a primary malignancy (OR: 1.1; 95% CI: 1.02-1.31; p=0.003) and infection by gram positive bacteria (OR: 1.6; 95% CI: 1.1-2.2; p=0.007) was significantly associated with intensive care requirement. Artificial ventilation support was significantly associated with severe bleeding manifestations (OR: 1.6; 95% CI: 1.1-2.3; p=0.003), documented fungal infection (OR: 1.5; 95% CI: 1.1-2.8; p=0.04) and advanced non-small cell lung cancer (NSCLC) (OR: 1.6; 95% CI: 1.1-2.4; p=0.009).

Advanced NSCLC as a primary (OR: 1.9; 95% CI: 1.4-2.4; p=0.003), KPS less than 70 (OR: 1.4; 95% CI: 1.1-2.4; p=0.03), pancytopenia (OR: 4.1; 95% CI: 1.8-7.5; p=0.003), MRSA infection (OR: 4.1; 95% CI:3.8-5.4; p=0.0002) and artificial ventilation requirement (OR: 2.6; 95% CI: 1.2-3.2; p=0.005) was having a significant association with death.

Discussion

This study, a cross sectional analysis of 280 patients over seven months, from an oncology ward of a tertiary cancer care centre of India provides us with a glimpse of hematologic toxicities in cancer patients undergoing radical anti-cancer treatment in a real world situation in

a developing nation. It shows the pattern of hematologic toxicities in patients undergoing radical anti-cancer therapy for which they merit admission and in-patient care in our country. A total of 473 toxicity events took place over this period of which 215 were anemia, 153 granulocytopenia and 105 events of thrombocytopenia. We analysed their demographics including socio-economic strata, primary malignancy, pattern of care provided to them, their impact upon patients' outcome in terms of infection, prolonged (more than one week) hospital admission, intensive care provision, artificial ventilation support, severe ventilation support, congestive heart failure and finally death. Also looked upon were the etiologic pathogens and practice of antibiotic therapy in these patients.

Our management of anti-cancer therapy induced anemia, febrile neutropenia or thrombocytopenia deviates substantially from the European, ASCO (American society of Clinical Oncology) guidelines (Groopman et al., 1999; de Naurois et al., 2010; Freifeld et al., 2011; Flowers et al., 2013). Though we did not analyse the MASCC score routinely in our study cohort, some of the important prognostic factors related to adverse outcome resembles the findings of other studies (Klastersky et al., 2000; Osmani et al., 2012).

It has also been seen that G3/4 leucopenia and decrease of platelets are independent risk factors for the occurrence of chemotherapy induced anemia (CIA). Moreover, G3/4 leucopenia, decrease of platelet and G3/4 thrombocytopenia were found to be also associated with the severity of CIA (Cheng et al., 2012). Though the current study failed to derive such relationship but it has shown the adversities related to advanced NSCLC. One cannot deny the fact that we might have over treated our patients in some instances keeping in mind the poor socio-economic background, inadequate nutritional status and finally the non-compliance rate observed in our patients (Mohan et al., 2008; Malik et al., 2013).

A similar prospective observational study from our Institute showed an overall mortality rate of 8% (Ghosh et al., 2012). A similar study on febrile neutropenic patients from Thailand showed an overall mortality rate of 14% (Chindaprasirt et al., 2013) while in our cohort it was around 5%. The above study was done on patients with leukaemia and undergoing hematopoietic stem cell transplantation (Ghosh et al., 2012). The use of antibiotic was uniform in that study and mortality was associated with a nadir leukocyte count <200/μl and an abnormal chest radiograph. The source of infection could be documented in 30% cases while in our series it was documented in 44.76% cases. With evolution of modern techniques and advancement in the field of clinical and translational research the overall disease specific outcomes have improved over the decades but the lacunae still persist which may be the attributable cause of this burden of toxicity in our part of the world (Murthy et al., 2008; D'souza et al., 2013). In spite of having its own limitations in the form of heterogeneity in the study cohort, management protocols and interpersonal variability such studies may enlighten us in the way we can avoid such toxicities with proper patient selection, modify our course of management of these toxicities including judicious use of antimicrobial agents, blood components along with growth factors and hematinics taking into account the scarcity of health resources in these developing nations. Finally one must not overlook the cost: benefit ratio of such treatment approach in these patients and should incorporate palliative care whenever possible in the plan of action from the very beginning.

In conclusion, treatment related toxicities result in interruptions of the proposed therapeutic regimen; they can be fatal at times. Hematologic toxicity is one of the major concerns for those undergoing radical anti-cancer therapy in developing nations. Patients' poor performance status, low socio-economic background and heavy disease burden in such countries may negatively impact the overall picture. Last but not the least, due to difficult terrain, inaccessible medical facilities and inability to reach hospital within 24 hours of onset of fever many international guidelines are flouted and importance of India centric innovative measures is paramount. Studies like this may show the prevailing practice from different institutes from our country and may form the stepping stone of guidelines suitable for managing such toxicities in patients from this part of the world where overall burden of cancer has already taken a toll on our limited health resources.

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