International Journal of Preventive Medicine Research
Vol. 1, No. 1, 2015, pp. 12-16
http://www.publicscienceframework.org/journal/ijpmr

Characteristics of Ischemic Heart Disease Patients Dying with Drug Induced Bone Marrow Suppression

Muhammad Irfan[1, *], Ghulam Mustafa Aftab[2], Muhammad Arif Nadeem[1], Irfan Bhatti[1], Tariq Suleman[1], Khalil Ahmed[1], Muhammad Naseem Akhtar[1], Attique Abou Bakr[1]

[1]Medicine department, Services Institute of Medical Sciences, Services Hospital, Lahore, Pakistan
[2]Medical Student, CMH Medical College, Lahore, Pakistan

Abstract

Objective: To determine characteristics of Ischemic Heart Disease (IHD) patients dying with drug induced bone marrow suppression. *Study Design:* Cross-sectional Study. *Place and Duration of Study:* Medical Unit 3, Services Hospital Lahore, from December 2011 to February 2012. *Methodology:* Patients of IHD taking medication from Punjab Institute of Cardiology (PIC), Lahore presented with mucosal bleeding (PIC syndrome). The clinical data and laboratory assessment was made, analyzed and Fisher exact test applied to find any significance at 5% level. *Results:* Amongst 86 patients with Platelet count <100,000/mm^3, 25.6% patients died while 74.4% discharged. Death group of patients had statistically significant association with Fever ($p = 0.002$), Diabetes Mellitus ($p = 0.002$), abnormal ALT ($p = 0.000$) and abnormal serum creatinine ($p = 0.026$), while recovered group had significant association with current no use of clopidogrel ($p = 0.000$), calcium channel blockers ($p = 0.000$) and nitrates ($p = 0.017$). However, gender, age, bleeding, past history of Dengue, Hemoglobin, White cell count, Platelet count, INR, current use of aspirin, beta-blockers, ACE inhibitors and statins had no significance with hospitalization outcome. The risk of bleeding was >4.115 times in patients using calcium channel blockers. *Conclusion:* A large number of IHD patient had died during the epidemic of drug induced bone marrow suppression and death was common among patients with diabetes, fever, abnormal ALT and abnormal creatinine. However recovery was more among patients not using clopidogrel, calcium channel blockers and nitrates. The risk of bleeding was positively correlated with use of calcium channel blockers.

Keywords

Ischemic Heart Disease, PIC Syndrome, Bone Marrow Suppression, Death

Received: March 10, 2015 / Accepted: April 2, 2015 / Published online: April 6, 2015

1. Introduction

Bone marrow failure[1] is a group of disorders that may manifest as either single cytopenia (e.g., erythroid, myeloid, or megakaryocytic) or pancytopenia.[2] It can be either inherited or acquired.[3] Acquired bone marrow failure can be caused by drugs,[4] chemicals,[5] radiation,[6] viral infection[7], vitamin deficiencies, immune dysfunction and idiopathic.

Because the bone marrow is the manufacturing factory of blood cells[8], the suppression of its activity causes their deficiency. This condition can rapidly lead to life-threatening infections, as the body cannot produce leukocytes in response to invading bacteria and viruses, as well as anemia due to a deficiency of red blood cells and spontaneous severe

* Corresponding author
E-mail address: Irfanmed3@yahoo.com (M. Irfan)

bleeding due to lack of platelets.

The incidence of acquired aplastic anemia in Europe and North America is estimated to be two per million populations per year as compared to its higher rates in Asia.[9]

In December 2011, hundreds of Ischemic Heart Disease (IHD) patients taking free medicines from Punjab Institute of Cardiology (PIC) started presenting in emergency department of Services Hospital, Lahore with bicytopenia or pancytopenia, and related complications and a significant number of these patients died. The drug induced bone marrow suppression was suspected and the condition was then labeled as "PIC Syndrome". Later Pyrimethamine contamination in Nitrate was found as the culprit drug.[10]

This study was conducted to reveal the characteristics of Ischemic Heart Disease patients dying with drug induced bone marrow suppression after receiving medicines from PIC, so that some significant predictors to death can be found that may help the doctors in future during such disaster.

2. Methodology

This study was carried out at the Medical unit3, Services Hospital, Lahore from December 2011 to February 2012. Purposive sampling technique was used and all the admitted 86 patients of both sexes with history of Ischemic Heart Disease and taking free medications from the PIC and having bone marrow suppression of short duration were included. On the other hand, patients with past history of bone marrow suppression of long duration were excluded. Informed consent was taken from patients recruited and their demographic data was recorded.

The clinical as well as laboratory assessment was made. Oral medications provided from the PIC were withdrawn. Complete blood count along with renal function tests and liver function tests were performed. The collected data was analyzed on SPSS version 15.

The descriptive analysis of the collected data was done. Age, Hemoglobin concentration, White cell count , Platelet count, serum creatinine, ALT and INR were quantitative variables, while gender, fever, bleeding, history of diabetes mellitus, hypertension, past history of Dengue, current use of aspirin, clopidogrel, calcium channel blockers, nitrates , diuretics, beta-blockers, ACE inhibitors, statins and hospitalization outcome were the qualitative variables. Investigational data was interpreted in negative or positive values. For quantitative variables, means and standard deviations were calculated and for qualitative variables, frequencies and percentages were computed. Chi-square test (Fisher exact test) was applied to find any association of factors at 5% level of significance. The means of quantitative variable were compared with Hospitalization outcome through Independent T test.

3. Results

All admitted 86 patients of Ischemic Heart Disease (IHD) with platelet count below 100,000/mm^3 were enrolled, 59 were males and 27 females. The mean age (years) of patients was 59.47 ± 9.76, the mean hemoglobin (g/dl) 10.32 ± 2.41, the mean white cell count (x 10^3/mm^3) 2.89±2.38, the mean platelet count (x 10^3/mm^3) 23.24 ± 19.82, the mean ALT (IU/ml) 28.00 ± 17.63, the mean serum creatinine (mg/dl) 1.10 ± 0.65 and the mean INR was 1.18 ± 0.41 (table 1).

Amongst 86 patients, 22 patients (25.6%) were died during hospitalization while remaining 64 (74.4%) were recovered and discharged (table 2a).

The group of patients who died during hospitalization was statistically correlated with the age of patients, gender, history of fever, bleeding, diabetes mellitus, hypertension, past history of dengue, hemoglobin concentration, white cell count, platelet count, ALT, serum creatinine, INR, use of aspirin, clopidogrel, diuretics, beta-blockers, ACE-inhibitors, calcium channel blockers, nitrates and statins.

On comparing the means of quantitative variable with hospitalization outcome through Independent T test (table 1), we found that the mean creatinine of expired patients group (1.36 ± 1.06) was more than the mean creatinine of discharged patients group (1.01 ± 0.41), and the association was statistically significant (p=0.026). The comparison of the rest of the quantitative variables with hospitalization outcome was statistically insignificant. However, the mean age of expired patients (62.50 ± 10.84) was more than the mean age of discharged patients (58.42 ± 9.22) with p value of 0.091.

Among patients who had fever, 52.2% (12 out of 23) died during hospitalization, while among those who had no fever, 84.1% (53 out of 63) got recovered and were discharged. The association was statistically significant (p=0.002).

Among diabetic patients, 52.2% (12 out of 23) died during hospitalization, while among non-diabetic patients, 84.1% (53 out of 63) got recovered and were discharged. The association was also statistically significant (p=0.002).

Among patients who had abnormal ALT, 56.7% (17 out of 30) died during hospitalization, while among those who had normal ALT, 91.1% (51 out of 56) got recovered and were discharged. The association was statistically significant (p=0.000).

Among patients who were not using clopidogrel, 95.5% patients (42 out of 44) got recovered and were discharged from hospital, while 4.5% (2 out of 44) died. The association was also statistically significant (p=0.000).

Among patients who were not using calcium channel blockers, 91.5 % patients (43 out of 47) got recovered and were discharged from hospital, while 8.5% (4 out of 47) died. The association was also statistically significant (p=0.000)

Similarly, among patients who were not using nitrates, 100% patients (14 out of 14) got recovered and were discharged from hospital, while none died. The association was also statistically significant (p=0.017).

The risk of bleeding was 4.115 times more in group of patients who were using calcium channel blockers. However, use of aspirin and clopidogrel, history of dengue and hypertension, low platelets and deranged INR did not favor the risk of bleeding in these patients. (Table 3)

Table 1. Comparison of quantitative variables with Hospitalization outcome through Independent-Samples T test (n=86).

Quantitative variables	Minimum	Maximum	Discharged Patients	Expired Patients	Total	p-value
			Mean ± SD	Mean ± SD	Mean ± SD	
Age of patients (years)	36	80	58.42±9.22	62.50±10.84	59.47±9.76	0.091
Hemoglobin conc. (g/dl)	0.6	15.4	10.55±2.50	9.68±2.06	10.32±2.41	0.147
WBC count (x10^3/mm^3)	0.6	13.0	3.06±2.49	2.38±1.98	2.89±2.38	0.252
Platelet count (x10^3/mm^3)	1	99	24.14±20.65	20.64±17.37	23.24±19.82	0.478
Serum Creatinine (mg/dl)	0.1	5.3	1.01±0.41	1.36±1.06	1.10±0.65	0.026
INR	0.1	3.7	1.16±0.40	1.25±0.42	1.18±0.41	0.373

Table 2a. Qualitative Factors associated with Deaths of Ischemic Heart Disease patients dying with Drug induced bone marrow suppression (n=86).

Qualitative variables	Discharged patients (n=64)	Died patients (n=22)	Likelihood Ratio	p-value
Gender:				
Male	17 (63.0%)	10 (37.0%)	2.613	0.116
Female	47 (79.7%)	12(20.3%)		
Fever:				
Yes	11 (47.8%)	12 (52.2%)	10.831	0.002
No	53(84.1%)	10 (15.9%)		
Bleeding:				
Yes	51 (70.8%)	21 (29.2%)	3.676	0.104
No	13(92.9%)	1 (7.1%)		
Past history of Dengue:				
Yes	1 (100%)	0 (0%)	0.595	1.000
No	63(74.1%)	22 (25.9%)		
Hypertension:				
Yes	38 (70.4%)	16 (29.6%)	1.289	0.314
No	26(81.2%)	6 (18.8%)		
Diabetes mellitis:				
Yes	11 (47.8%)	12 (52.2%)	10.831	0.002
No	53 (84.1%)	10 (15.9%)		
ALT				
Abnormal	13 (43.3%)	17 (56.7%)	23.052	0.000
Normal	51 (91.1%)	5 (8.9%)		

Table 2b. Qualitative Factors associated with Deaths of Ischemic Heart Disease patients dying with Drug induced bone marrow suppression (n=86).

Qualitative variables	Discharged patients (n=64)	Died patients (n=22)	Likelihood Ratio	p-value
Current use of Aspirin:				
Yes	54 (71.1%)	22 (28.9%)	6.350	0.058
No	10 (100%)	0 (0%)		
Current use of Clopidogrel:				
Yes	22 (52.4%)	20 (47.6%)	23.404	0.000
No	42 (95.5%)	2 (4.5%)		
Current use of Diuretics:				
Yes	11 (61.1%)	7 (38.9%)	1.987	0.222
No	53 (77.9%)	15 (22.1%)		
Current use of Beta-blockers:				
Yes	42 (73.7%)	15 (26.3%)	0.048	1.000
No	22 (75.9%)	7 (24.1%)		
Current use of ACE Inhibitors:				
Yes	34 (75.6%)	11 (24.4%)	0.064	0.810
No	30 (73.2%)	11 (26.8%)		
Current use of Calcium channel blockers:				
Yes	21 (53.8%)	18 (46.2%)	16.610	0.000
No	43 (91.5%)	4 (8.5%)		

Qualitative variables	Discharged patients (n=64)	Died patients (n=22)	Likelihood Ratio	p-value
Current use of Nitrates:				
Yes	50 (69.4%)	22 (30.6%)	9.173	0.017
No	14 (100%)	0 (0%)		
Current use of Statins:				
Yes	56 (72.7%)	21 (27.3%)	1.289	0.437
No	8 (88.9%)	1 (11.1%)		

Table 3. Qualitative Factors predicting the bleeding in Ischemic Heart Disease patients with Drug induced bone marrow suppression (n=86).

Qualitative variables	Occurrence of Bleeding		Likelihood Ratio	p-value
	Yes (n=72)	No (n=14)		
Current use of Aspirin:				
Yes	65 (85.5%)	11 (14.5%)	1.349	0.356
No	7 (70.0%)	3 (30.0%)		
Current use of Clopidogrel:				
Yes	37 (88.1%)	5 (11.9%)	1.168	0.384
No	35 (79.5%)	9 (20.5%)		
Current use of Calcium channel blockers:				
Yes	3 (7.7%)	36 (92.3%)	4.115	0.077
No	11 (23.4%)	36 (76.6)		
Past history of Dengue:				
Yes	1 (100.0%)	0 (0.0%)	0.358	1.000
No	71(83.5%)	14 (16.5%)		
Hypertension:				
Yes	44 (81.5%)	10 (18.5%)	0.551	0.556
No	26(87.5%)	4 (12.5%)		
Platelet count:				
$\geq$10000/mm^3	55 (82.1%)	12 (17.9%)	0.643	0.726
<10000/mm^3	17(89.5%)	2 (10.5%)		
INR				
$\geq$1.5	10 (83.3%)	2 (16.7%)	0.002	1.000
< 1.5	62 (83.8%)	12 (16.2%)		

4. Discussion

The clinical presentation of drug induced cytopenia is variable and symptoms and signs are due to involvement of either of the three cell lineages.[11] The drugs responsible for bone marrow suppression include phenylbutazone, chloramphenicol,[12] gold[13], sulfonamides, Felbamate[14], nifedipine[15], methotrexate[16], pyrimethamine[17] and many more drugs. Pyrimethamine causes, as it was found the culprit,[10] reversible pancytopenia (megaloblastic anemia, leucopenia, agranulocytosis, and thrombocytopenia) secondary to depletion of folic acid stores, generally prevented with co-administration of leucovorin.[18]

In our study, it was found that cytopenias were not directly related with death of these ischemic heart disease patients, rather comorbid illnesses like diabetes mellitus and failure of vital organs like liver and kidneys during that event of bone marrow suppression were important. Anemia, leucopenia and thrombocytopenia were statistically not significant in patients who died (p=0.130, p=0.759, p=1.000 respectively). However, diabetic patients died more significantly (p=0.002). We found that presence of leucopenia (WBC<4000/mm^3) was not significant in death group. However, fever, in the occurrence of which leucopenia may had played a role, was statistically significant in those patients died (p=0.002).

Among liver function tests[19], abnormal ALT had played a significant role in deaths of these patients (p=0.000), while abnormal INR was not statistically significant (p=0.494). This might be due to increase in ALT caused by liver injury and increase in INR in majority of these patients might be iatrogenic caused by anticoagulant medicines used like marevan. Similarly, increased serum creatinine was significant in death group (p=0.026). All these facts had indicated that vital organ involvement like liver and kidneys had played significant role in deaths of these IHD patients.

The mean age of died patients was more than discharged patients, as it was difficult for these old patients to sustain the stress of bone marrow suppression.

Absence of some of these drugs in the management of these IHD patients had played a role in hospitalization outcome. Among patients who were not using clopidogrel, 95.5% recovered and discharged, while 4.5% died (p=0.000). Among patients who were not using calcium channel blockers, 91.5% recovered and discharged, while 8.5% died (p=0.000) and similarly patients who were not using nitrates, 100%patients got recovered and discharged, while none died (p=0.017). These findings were indicative of a fact that those patients who were not using these medicines had survived.

It was found that anti-malarial drug, Pyrimethamine contamination in nitrate was responsible[10] for bone marrow suppression, however our study showed that cytopenia was not significantly related to deaths and survival of these

patients, rather diabetes, fever, vital organ damage and no use of some of these drugs had played the role in deaths and survival of these patients.

Scientifically the forensic analysis[20] including postmortem of these died patients and chemical studies of the specimens would have been carried out to assess the exact cause of death but practically it was not done and only toxic levels of the contamination i.e. Pyrimethamine was assessed and its clinical implications were noted.

5. Conclusion

A large number of patients with history of Ischemic Heart Disease and taking oral medications from the PIC, Lahore died during that event of drug induced bone marrow suppression. Death was more likely among patients who were diabetic, and had fever, abnormal ALT and abnormal creatinine. However recovery was more common among patients who were not using clopidogrel, calcium channel blockers and nitrates. The risk of bleeding in our patients was positively correlated to the use of calcium channel blockers. In future the strict vigilance on the system of purchase, storage, periodical inspection and dispensing of the drugs in the hospital pharmacy must be carried out to avoid such disasters.

References

[1] Bunch C. Bone marrow failure. *Medicine International* 1995; 10: 495-9.

[2] Rehman H, Fazil M, Khan FM. The etiological pattern of pancytopenia in children upto 15 years. *Pak armed forces med J* 2003; 53: 183-7.

[3] Guinan EC. Acquired aplastic anemia in childhood. *Hematol Oncol Clin North Am* 2009; 23:171.

[4] Handoko KB, Souverein PC, van Staa T. Risk of aplastic anemia in patients using antiepileptic drugs. *Epilepsia* 2006; 47:1232.

[5] Powars D. Aplastic anemia secondary to glue sniffing. *N Engl J Med* 1965; 273:700.

[6] Lange RD, Wright SW, Tomonaga M. Refractory anemia occurring in survivors of the atomic bombing in Nagasaki, Japan. *Blood* 1955; 10:312.

[7] Hadzic N, Height S, Ball S. Evolution in the management of acute liver failure-associated aplastic anaemia in children: a single centre experience. *J Hepatol* 2008; 48:68.

[8] Wilson A, Trumpp A. Bone-marrow haematopoietic-stem-cell niches. *Nat Rev Immunol* 2006; 6:93.

[9] Young NS, Kaufman DW. The epidemiology of acquired aplastic anemia. *Haematologica* 2008; 93:489.

[10] Cox A. Pyrimethamine Poisoning in Pakistan. Available at: http://www.blacktriangle.org/blog/pag 2420.

[11] Young NS, Bacigalupo A, Marsh JC. Aplastic anemia: pathophysiology and treatment. *Biol Blood Marrow Transplant* 2010; 16:S119.

[12] Wallerstein RO, Condit PK, Kasper CK, et al. Statewide study of chloramphenicol therapy and fatal aplastic anemia. *JAMA* 1969; 208:2045.

[13] Kay AG. Myelotoxicity of gold. *Br Med J* 1976; 1:1266.

[14] Brodie MJ, Pellock JM. Taming the brain storms: felbamate updated. *Lancet* 1995; 346:918.

[15] Laporte JR, Ibanez L, Ballarin E. Fatal aplastic anaemia associated with nifedipine. *Lancet* 1998; 352:619.

[16] Unena SG, Molina JF, Garcia CD. Espinoza LR. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. *Arthritis Rheum* 1996; 39 (2): 272-6.

[17] Waxman S, Herbert V. Mechanisms of pyrimethamine-induced megaloblastosis in human bone marrow. *N Engl J Med* 1969; 28*:* 1316–1319.

[18] Chute JP, Decker CF, and Cotelingam J. Severe Megaloblastic Anemia Complicating Pyrimethamine Therapy. *Ann Intern Med* 1995; 122(11):884-5.

[19] Limdi J K, Hyde G M. Evaluation of abnormal liver function tests. *Postgrad Med J* 2003; 79: 307–12

[20] Carrier B. Data Analysis. In: File System Forensic Analysis. 1st ed. Indiana: Crawfordsville; 2005:16-7.