Original Research Paper

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REPORTING OF ADVERSE DRUG EVENTS TO MONOCLONAL ANTIBODIES IN PATIENTS RECEIVING CHEMOTHERAPY IN A TERTIARY HOSPITAL OF CENTRAL INDIA

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ABSTRACT

INTRODUCTION: All drugs have side effects along with their desired effects. Understanding these may help to determine better safety profile. There is limited knowledge regarding the ADRs of Monoclonal Antibodies used for Cancer treatment.

AIM: The aim of this study is detection, assessment and reporting of Adverse Drug Reactions in cancer patients undergoing Monoclonal antibody therapy in Indian general patient settings.

MATERIAL AND METHOD: This is hospital based prospective observational study on 30 patients receiving the monoclonal antibodies with or without chemotherapy/radiotherapy for treatment of any type of cancer. Patients were interviewed as per CDSCO adverse drug event reporting form. Data was spread in Microsoft Excel 2010 and analysis was done on SPSS 16.

RESULT: Total number of Doses and ADEs observed in Bevacizumab group, Rituximab, Trastuzumab: 45, 30, 2 and 160, 80, 7 respectively.

CONCLUSION: The use of monoclonal antibody for cancer therapy is well tolerated and associated with minor adverse reactions that can be managed easily with supportive therapy.

KEYWORDS :

INTRODUCTION:

All medicines have side effects along with their desired advantages. It is important to monitor both the known and hitherto unknown side effects of medicines in order to determine any new information available to the safety profile [1].ADRs occur in 1-2.2% of hospitalised patients. The probability that a patient may experience an ADR during hospitalization ranges from 1-44% [2]. Adverse drug reactions, according to WHO, is defined as a response to a drug which is noxious & unintended, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function[3]. ADR related to anticancer drugs are important in view of mortality and morbidity as they injure the normal 2cities necessitate the requirement of monitoring, assessment and reporting of ADRs associated with anticancer drugs. This study is targeted to monitor suspected ADRs with Monoclonal Antibodies, in a focused manner and contribute to overall knowledge base regarding ADRs and dissemination of information to the physician, pharmacists and patients in the country.

MATERIAL AND METHOD:

Patient selection: All patients receiving the monoclonal antibodies with or without chemotherapy/radiotherapy for treatment of any type of cancer, during January 2015 to December 2017, at Hamidiya Hospital, Bhopal. The participants in this study had been offered to voluntary participate in this study and they had given the informed written consent before they were enrolled in this study.

Study Design: It was a hospital based prospective observational study with regular follow up during the study period.

Data collection: Patient data collection form used to interview the patients, was divided into two sections: 1.Patient proforma 2.CDSCO adverse drug event reporting form. Data were recorded: (1) by reviewing case sheets or treatment charts, (2) by interview with patient's caretaker. Thorough clinical examination was carried out after getting history to correlate with suspected adverse drug events. The biochemical, pathological and other laboratory tests were also reviewed to search adverse reactions leading to biochemical and pathological and other derangements. The pathological tests include Complete blood count including platelet count, renal function test and liver function test. The biochemical tests include electrolyte and blood sugar estimation and lipid profile. The diagnosis of the ADEs was based on history of drug ingestion, clinical finding and exclusion of other similar disorder. To establish the etiologic agent for a particular type of reaction, attentions was paid to the drug history, temporal correlation with the drug, duration of the reaction, improvement of reaction with time or on withdrawal of drug and recurrence of reaction on re-challenge further drug administration. The observed ADEs were monitored for the onset, duration and cessation of the reaction. All the monitored ADEs information was carefully recorded in CDSCO Suspected ADE reporting form and reported to higher centres.

Data analysis: Data was spread in Microsoft Excel 2010 and analysis was done. Causality assessment for ADEs was done on the basis of WHO-UMC CAUSALITY ASSESSMENT SCALE. The proportional of patients showing adverse reaction was expressed in percentage up to one decimal. Data was further analysed using the software SPSS 16 for windows for the following: 1. Age and sex distribution of patients.2.Drug utilization pattern.3.Adverse drug event pattern. 4. Causality assessment using WHO-UMC Criteria. 5. Assessment of severity by modified Hartwig and Siegel Scale. 6. Assessment of preventability by modified Schumock and Thornton scale.

Tools in the Study: 1.CDSCO Adverse Drug Event Reporting Form. 2. WHO-UMC causality assessment scale. 3. Modified Hartwig and Siegel scale. 4. Modified Schumock and Thornton scale.

RESULTS:

1. Demographic Data: AGE WISE DISTRIBUTION

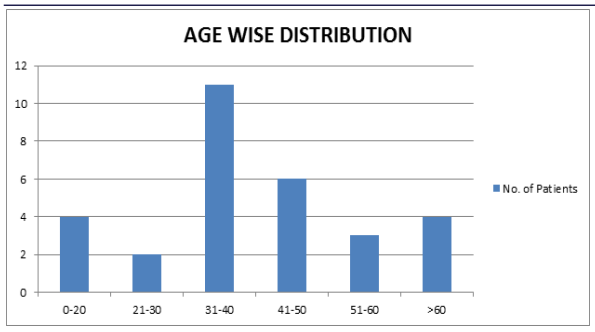

FIGURE 1

2. GENDER WISE DISTRIBUTION

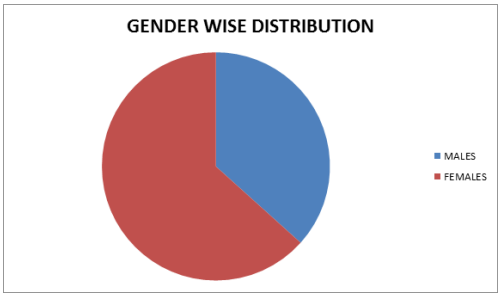

FIGURE 2

3.DRUG UTILIZATION PATTERN

TABLE 1

MONOCLONAL ANTIBODY(mAb)	mAb alone	mAb with CT	TOTAL
BEVACIZUMAB	2	17	19
RITUXIMAB	0	9	9
TRASTUZUMAB	2	0	2
TOTAL	4	26	30

4. ADE PATTERN WITH BEVACIZUMAB

TABLE 2

Drug	No. of pts. On mAb (Doses observed)	ADE	Total No. of ADE	Casualty Assessment			Severity Assessment			Preventability Assessment		
				Certain	Probable	Possible	Mild	Moderate	Severe	Definitely	Probably	Not Preventable
Bevacizumab alone	2 (5)	--	0	0	0	0	0	0	0	0	0	0
Bevacizumab with Chemotherapy	17 (40)	Nausea	40	0	8	32	28	12	0	0	24	16
		Vomiting	40	0	8	32	28	12	0	0	24	16
		Diarrhoea	10	0	2	8	7	3	0	0	6	4
		Muscle stiffness	10	0	2	8	7	3	0	0	6	4
		Fever	10	0	2	8	7	3	0	0	6	4
		Chills	20	0	4	16	14	6	0	0	12	8
		Anaemia	30	0	6	24	21	9	0	0	18	12
		Aggravation of burning pain over pre-existing haemorrhoids	0	0	0	0	0	0	0	0	0	0
TOTAL & Percentage	**19(45)**		**160 (100)**	**0 (0)**	**32 (20)**	**128 (80)**	**112 (70)**	**48 (30)**	**0 (0)**	**0 (0)**	**96 (60)**	**64 (40)**

5.ADE PATTERN WITH RITUXIMAB

TABLE-3

Drug	No. of pts. On mAb (Doses observed)	ADE	Total No. of ADE	Casualty Assessment			Severity Assessment			Preventability Assessment		
				Certain	Probable	Possible	Mild	Moderate	Severe	Definitely	Probably	Not Preventable
Rituximab with Chemotherapy	9(30)	Nausea	25	0	0	25	20	5	0	0	23	2
		Vomiting	20	0	0	20	16	4	0	0	18	2
		Anaemia	20	0	0	20	16	4	0	0	18	2
		Weakness	15	0	0	15	12	3	0	0	13	2
TOTAL & Percentage	**9(30)**		**80(100)**	**0(0)**	**0(0)**	**80(100)**	**64(80)**	**16(20)**	**0**	**0**	**72(90)**	**8(10)**

6.ADE PATTERN WITH TRASTUZUMAB

TABLE 4

Drug	No. of pts. On mAb (Doses observed)	ADE	Total No. of ADE	Casualty Assessment			Severity Assessment			Preventability Assessment		
				Certain	Probable	Possible	Mild	Moderate	Severe	Definitely	Probably	Not Preventable
Trastuzumab alone	2(2)	-										
Trastuzumab with Chemotherapy	0(0)	Diarrhoea	1	0	0	1	1	0	0	0	0	1
		Decreased appetite	1	0	0	1	1	0	0	0	0	1
		Fever	1	0	0	1	1	0	0	0	1	0
		Loss of hair	1	0	0	1	1	0	0	0	0	1
		Anaemia	1	0	0	1	1	0	0	0	1	0
		Raised SGOT & SGPT	2	0	0	2	1	1	0	0	0	2
TOTAL & Percentage	**2(100)**		**7**	**0**	**0**	**7(100)**	**6(85.7)**	**1(14.3)**	**0(0)**	**0(0)**	**2(28.5)**	**5(61.5)**

7. ADE PATTERN WITH ALL OBSERVED MONOCLONAL ANTIBODIES

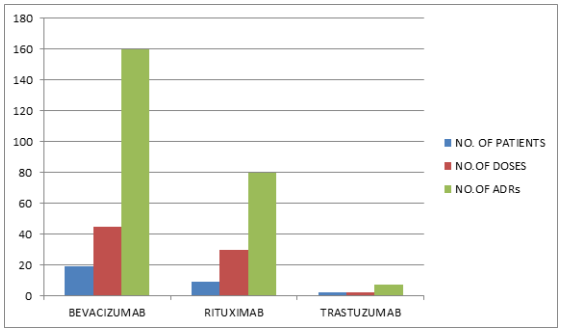

FIGURE 2

DISCUSSION:

Pharmacovigilance has an important role in the rational use of medicines by providing information about adverse drug reactions in the general population. There is a need to develop comprehensive ADR surveillance programme to detect, evaluate and develop mechanisms to identify and subsequently prevent associated morbidity and mortality and cost of treatment.

Adverse drug reactions are a cause of significant morbidity and mortality in patients of all areas of health care. Severe or potentially fatal reactions are detected after chemotherapy. Therefore it is important to have updated knowledge on trends of drug reactions and their management. Several factors predisposes to adverse drug reactions like (1) age of the patients [5, 6, 7, 8]. (2) Sex [9]. (3) Genetic and ethnic factors. (4) Previous history of adverse drug reaction [10]. (5) Underlying diseases [11]. (6) Route of drug administration [10], intravenous administration gives rise to more severe reactions [12, 13]. (7) Duration of treatment, being more common with chronic or frequent use rather than short term or intermittent use [10, 14]. (8) Polypharmacy or multiple drug use [15].

In our study, adverse events with possible relation to BEVACIZUMAB included nausea (mild grade 28, moderate grade 12), vomiting (mild grade 28, moderate grade 12), diarrhoea (mild grade 7, moderate grade 3), muscular stiffness (mild grade 7, moderate grade 3), fever (mild grade 7, moderate grade 3), chills (mild grade 14, moderate grade 6) and anaemia (mild grade 21, moderate grade 9). Overall, 70 %ADEs were of mild grade and 30% moderate grade. No unexpected adverse events were associated with BEVACIZUMAB was reported in our study and the results were in accordance with studies of Dhillon S [16], Raymond TS et al [17] and Zhang W et al [18].

Adverse events such as hypertension, proteinuria, bleeding, gastrointestinal perforations, thromboembolic events, were not reported with BEVACIZUMAB in our study, which were reported in studies of Dai F et al [19] and Hurwitz HI et al [20]. Our study is not in accordance with that of Hamilton E et al [21] and Cvetanovic et al [22] in terms of neutropenia and thrombocytopenia. Anaemia of moderate grade reported in our study due to combined effect of chemotherapy induced myelo-suppression and BEVACIZUMAB therapy.

In our study, adverse events with possible relation to RITUXIMAB included weakness (mild grade 12, moderate 3), anaemia (mild grade 16, moderate4), nausea (mild grade 20, moderate5) and vomiting (mild grade 16, moderate grade4). Overall 80% ADEs were of mild grade and 20% of moderate grade. Our findings are similar to those of Wood AM [23] and D' Arena et al [24] .Increased rate of infections were not observed in our study, which differ in opinion from that of Lindenmeyer LP et al [25] and Li F et al [26].

In our study, adverse events with possible relation to TRASTUZUMAB included diarrhoea (mild grade 1, moderate grade 1), decreased appetite (mild grade1), fever (mild grade 1), hair loss (mild grade 1), anaemia (mild grade 1) and raised SGOT and SGPT (mild grade 1, moderate grade 1). These findings differ from that of John M et al who observed ≥2 grade haematological toxicity [27]. Overall, 85.7%ADEs were of mild grade and 14.3%were of moderate grade. No adverse event related to cardiac toxicity was noted in our study while the study by Ismaili N et al [28] and Huszno J et al [29], showed cardiac toxicity as the predominant toxicity in the patients treated with chemotherapy. The alopecia appears to be due to concurrently used chemotherapeutic agents rather that due to therapy.

Preventability of the ADRs was evaluated using the criteria of Schumock and Thornton. In our study, overall 68.8 % reactions were considered probably preventable as they involve poor patient compliance, potential drug interactions, failure to do therapeutic drug monitoring or inadequate preventive measure. The remaining 31.1% reactions were regarded as not preventable.

Conclusion:

Majority of the patients with ADEs belonged to 31-40 years age group. Clinical patterns are almost similar to those observed on other studies with no major exceptions. This study suggests that the use of monoclonal antibody for cancer therapy is well tolerated and associated with less or minor adverse reactions that can be managed easily with supportive therapy.

Limitation of study:

Small sample size, single study centre and because of high cost of therapy for Indian general patients, statistically required sample size could not be achieved. Causality assessment had its share of uncertainty in polypharmacy cases and inherent underreporting of mild and self- limiting events.

REFERENCES:

1. Pharmacovigilence Program of India (PvPI) for Assuring Drug Safety, CDCSO, India.www.cdcso.nic.in/pharmacovigilence_intro.htm.
2. Hussein G, Bleidt B. Recognition, evaluation and reporting of adverse drug reactions. Clin.Reseach &Reg, affairs.1999:16(3):91-107.
3. The importance of Pharmacovigilance: Safety monitoring of medicinal products .Geneva, World Health Organization,2002. http://apps.who.int/medicinedocs/pdf/s4893e.pdf.
4. Lisa A. Ladewski, Steven M. Belknap, Jonathan R. Nebeker, Oliver Sartor, E. Allison Lyons, Timothy C. Kuzel, et al. Dissemination of information on potentially fatal adverse drug reactions for the cancer drugs from 2000 to2002: First results from the research on adverse drug events and reports project. J Clin Oncol.2003 Oct 15:21(20):3859-66.
5. Knight M. Adverse drug reactions in neonates. J Clin Pharma 1994; 34:128-35.
6. Van Arsdel PP. Allergy and adverse drug reactions. J Am Acad Dermatol 1982; 6:833-845.
7. Sullivan JR, Shear NH.Drug eruptions and other adverse drug effects in aged skin. Clin Geriatr Med 2002; 18:21-42.
8. Nolan L, O'Malley K. Adverse drug reactions in elderly. Sr J Hasp Mad 1989; 41:446-457.
9. Sharma VK, Sethuraman G. Adverse cutaneous reactions to drugs: an overview. J PostGrad Mad 1996; 42:15-22.
10. Schroeder DJ, Barone JA. Adverse drug reactions & drug induced disease. Clinical pharmacy & therapeutics.6th ed. New York: Williams & Wilkins 1996:21-32.
11. Peters BS, Carlin E, Weston RJ, Loveless SJ, Sweeney J, Weber J et al. Adverse effects of drugs used in management of opportunistic infection associated with HIV infection. Drugs Safety.1994; 10:439-54.
12. Nayak Surajit, Acharjya B. Adverse cutaneous drug reaction. Indian J Dermatol 2008:53(1):2-8.
13. Anderson JA, Adkinson NF Jr. Allergic reactions to drugs and biologic agents. JAMA 1987;258: 2891-9.
14. DeShazO RD, Kemp SF.Allergic reactions to drugs and biologic agents. JAMA 1997;278:1895-906.
15. Hoigne R. Risk factors for the adverse drug reactions: Epidemiological approaches. Eur J Clin Pharmacal. 1990; 139:321.
16. Dhillon S. Bevacizumab combination therapy: a review of its use in patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer. BioDrugs. 2013 Aug;27(4):375-92.
17. Taugourdeau-Raymond S1, Rouby F, Default A, Jean-Pastor MJ; French Network of Pharmacovigilance Centers. Bevacizumab-induced serious side-effects: a review of the French Pharmacovigilance database. Eur J Clin Pharmacol. 2012 Jul;68(7):1103-7.
18. Zhang W, Shen Z, Luo H, Hu X, Zheng L, Zhu X. The Benefits and Side Effects of Bevacizumab for the Treatment of Recurrent Ovarian Cancer. Curr Drug Targets. 2017;18(10):1125-1131.
19. Dai F, Shu L, Bian Y, Wang Z, Yang Z, Chu W, Gao S. Safety of Bevacizumab in treating metastatic colorectal cancer: a systematic review and meta-analysis of all randomized clinical trials. Clin. Drug Investig.2013 Aug 27.
20. Hurwitz HI, Tebutt NC, Kabbinavar F, Giantonio BJ, Guan ZZ, Mitchell L, Waterkamp D, Tabernero J. Efficacy and safety of Bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trails. Oncologist.2013; 18(9): 1004-12.
21. Hamilton E, Kimmick G, Hopkins J, Marcom PK, Rocha G, Welch R, Broadwater G, Blackwell K. Nab-paclitaxel/Bevacizumab/Carboplatin chemotherapy in first line triple negative metastatic breast cancer. Clin Breast Cancer.2013 Oct4.
22. Cvetanovic A, Vrbic S, Filipovic S, Pejcic I, Milenkovic D, Milenkovic N. Safety and efficacy of addition of Bevacizumab to Oxaliplatin based pre-operative chemotherapy in colorectal cancer with liver metastasis: A Single Institute Experience. J Boun.2013 Oct; 61(7): 1108-1114.
23. Wood AM. Am J Health Syst Pharm.2001. Rituximab: an innovative therapy for non-Hodgkin's lymphoma.Am J Health Syst Pharm.2001 Feb 1;58(3):215-29.
24. D'Arena G, et al. Adverse drug reactions after intravenous Rituximab infusion are more common in hematologic malignancies than in autoimmune disorders and can be predicted by the combination of few clinical and laboratory parameters: results from a retrospective, multicentre study of 374 patients.Leuk Lymphoma.2017 Nov;58(11): 2633-2641.
25. Lindermeyer LP, Hegele V, Caregnato JP, Wust D, Grazziotin L, Stoll P. Follow up of patients receiving Rituximab for diffuse large B cell lymphoma: An Overview of Systemic Reviews. Ann Hematol. 2013 Nov; 92(11): 1451-1459.

26. Li F, Yi SH, Yu Z, Xing LJ, Xu Y, Zhao YZ, Li ZJ, Qiu LG. Clinical efficacy and safety of chemo-immunotherapy with Rituximab, Fludarabine and Cyclophosphamide for chronic lymphocytic leukaemia. Zhonghua Xue Ye Xue Za Zhi.2013 May; 34 (5): 383-8.
27. John M, Hinke A, Stauch M, Wolf H, Mohr B, Hindenberg HJ, Papke J, Schlosser J, FAKT study group. Weekly Paclitaxel plus Trastuzumab in metastatic breast cancer pre-treated with anthracyclines: A Phase II multi-practice study. BMC Cancer.2012 May 4;12:165.
28. Ismaili N, Elmajjaoui S, Tahri A, Benjaafar N, Errihani H, Belbaraka R. Trastuzumab in early breast cancer. Presse Med.2013 Jul-Aug; 42(7-8):1069-80.
29. Huszno J, Les D, Danuta SS, Nowara E. Cardiac side effects of Trastuzumab in breast cancer patients-single centre experiences. Wspolczesna Onkol 2013; 17(2): 190-195.