Study of prescription pattern and adverse drug reactions of antineoplastic drugs in patients with breast cancer in a tertiary care teaching hospital

Renuka L. Kadam[1], Vijay M.Motghare[2,*], Smita Sontakke[3], Vijay Mahobia[4], A.K. Diwan[5]

[1]Post Graduate Student, [2]Professor & HOD, [3]Associate Professor, Dept. of Pharmacology, GMC, Nagpur, [4]Assistant Professor, [5]Associate Professor & HOD, Dept. of Radiotherapy, GMC, Nagpur.

***Corresponding Author:**
Email: vm.motghare@gmail.com

Abstract

Introduction: To study current prescription pattern of drugs and adverse drug reactions (ADRs) in patients of carcinoma breast.

Methodology: This observational, cross-sectional study was carried out in Radiotherapy department of a tertiary care teaching hospital for a period of two months. Patients diagnosed with breast carcinoma and attending Radiotherapy department for chemotherapy were included. Prescriptions were analysed and details of drugs prescribed were recorded. Patients were enquired about occurrence of any ADRs and details were recorded. Preventability and severity of ADRs were assessed by modified Schumock and Thornton scale and modified Hartwig and Siegel scale respectively.

Results: A total of 70 patients were included in the study. Cyclophosphamide was the most commonly used chemotherapeutic agent (77.14%), followed by Doxorubicin (68.57%) and 5-FU (44.29%). Most commonly prescribed regimen was Cyclophosphamide + 5FU + Doxorubicin followed by Cyclophosphamide + Doxorubicin. Nausea was the most commonly reported ADR followed by alopecia, vomiting and blackening of nails. Maximum ADRs were reported with Cyclophosphamide + Doxorubicin + 5 FU combination followed by Cyclophosphamide + Doxorubicin combination. Out of the total ADRs 60.11% belonged to the category of "definitely preventable" while 74.15% of ADRs were of less severity categorized as "mild level 1" severity.

Conclusion: Cyclophosphamide was the most commonly prescribed drug. Highest incidence of ADRs was observed with Cyclophosphamide + Doxorubicin + 5 FU. Inspite of prophylactic antiemetic treatment majority of patients had nausea and vomiting which indicates that more vigorous measures to prevent emesis need to be undertaken since these ADRs of antineoplastic drugs are usually preventable.

Keywords: Carcinoma breast, Anticancer drugs, Adverse drug reaction.

Introduction

Breast cancer is the most common cancer among women, with an estimated 1.67 million new cases diagnosed in 2012 (about 25% of all cancers). About 70,218 women died of this cancer in the year 2012 (mortality of 21.5% of all cancer cases), mortality rate being 12.7 per lac population, ranking it the number one killer in women.(1)

Chemotherapy alone or as a part of multimodality approach has been shown not only to be effective but curative too in certain cases of carcinomas including breast carcinoma.(2) Utilization pattern of anticancer drugs has undergone tremendous change over the last few years mainly due to enhanced knowledge of pathophysiology of carcinomas resulting in development of newer drugs.(3)

Evaluation of prescribing patterns of anticancer drugs is essential due to availability of different regimens, variable response rate with different drugs and intolerability of combination regimens. Drug utilization studies(DUS) provide an useful tool to assess appropriateness of therapy, identify areas that need improvement so as to make medical care rational, cost effective and of standard quality.(4) By evaluating and comparing the prevailing pattern with existing standards, necessary steps can be taken to optimize anticancer therapy with improved efficacy and minimal toxicity.(5) Drug utilization research can thus help to set priorities for the rational allocation of health care budgets.(4)

Chemotherapy regimens are highly complex and associated with intolerable adverse effects. In a study of ADRs due to chemotherapeutic agents in Oncology patients highest incidence of ADRs was reported in patients treated for breast carcinoma (39.1%).(6)

Epidemiological research performed in Australia shows 11% of adverse drug reactions(ADRs) in Australian Hospitals were associated with anticancer drugs and immunosuppressive drugs with anticancer drugs being the most common agents responsible for medication-related hospitalizations.(7) ADRs place a high financial burden on the health sector. ADR reporting and its management will enhance the effectiveness of therapy and reduce the side effects which ultimately will reduce the rate of mortality.(8)

Hospital-based ADR monitoring and reporting programs can help in identifying and assessing the risks associated with the use of drugs. This data may help prescribers to identify ADRs and deal with them more efficiently, and also help in preventing the occurrences of these ADRs in future.(9) There is scarcity of studies related to evaluation of prescription pattern as well as ADRs in patients of breast carcinoma specifically in central India. Hence, this study was undertaken with the objective to evaluate the prescription pattern of anticancer drugs as well as ADRs associated with these

drugs in patients of breast cancer in a tertiary care teaching hospital in Central India.

Materials and methods

This prospective, observational, cross-sectional study was carried out in Radiotherapy department of a tertiary care teaching hospital for a period of two months after approval from institutional ethics committee.

Women diagnosed with breast cancer and attending Radiotherapy department for chemotherapy, aged > 18 years of age were included in the study. Patient receiving first cycle of chemotherapy, those on concomitant radiotherapy and suffering from any other malignancy were excluded. Patients were approached after they received their chemotherapy cycle. Those meeting the selection criteria were briefed about the study and written informed consent was obtained from those willing to participate. Their prescriptions were analyzed and the following data was recorded: demographic characteristics, diagnosis, number of drugs prescribed, route of administration, dosing frequency, duration, prescription by generic/brand name. Patients were enquired about occurrence of any ADRs during the previous cycle of chemotherapy using a pre designed standardized proforma. Preventability and severity of ADRs were assessed by modified Schumock and Thornton scale, modified Hartwig and Siegel scale respectively.[10,11]

Data was analysed by using Graph pad prism version 5.0 software.

Results

Table 1 shows the general characteristics of study patients. Average age of study population was 49.27 ± 9.41(mean ± SD) years. Majority of patients were in 41 – 50 years of age group. Mean weight was 49.50 ± 8.26 (mean ± SD) Kg.

Table 1: Demographic characteristics of study patients (n=70)

Characteristics		No of patients	Percentage
Age in years (mean± SD): 49.27 ± 9.41		-	-
Age group	31-40	15	21.4
	41-50	29	41.4
	51-60	17	24.3
	61-70	8	11.4
	>70	1	1.4
Weight in Kg (mean± SD): 49.50 ± 8.26		-	-

Table 2 shows the chemotherapeutic agents used in study patients. Cyclophosphamide was the most commonly used chemotherapeutic agent (77.14%), followed by Doxorubicin (68.57%) and 5-FU (44.29%).

Table 2: Chemotherapeutic agents used in study patients (n=70)

Chemotherapeutic agent	No. of patients	Percentage
Cyclophosphamide	54	77.14
Doxorubicin	48	68.57
5 FU	31	44.29
Docetaxel	10	14.29
Paclitaxel	09	12.86
Epirubicin	06	8.57
Capecitabine	06	8.57
Trastuzumab	04	5.71
Gemcitabine	03	4.29
Cisplatin	02	2.86
Gafitinib	01	1.43

Fig.1 shows the different chemotherapeutic regimes used in study patients. Most commonly prescribed regimen was Cyclophosphamide + 5FU + Doxorubicin followed by Cyclophosphamide + Doxorubicin.

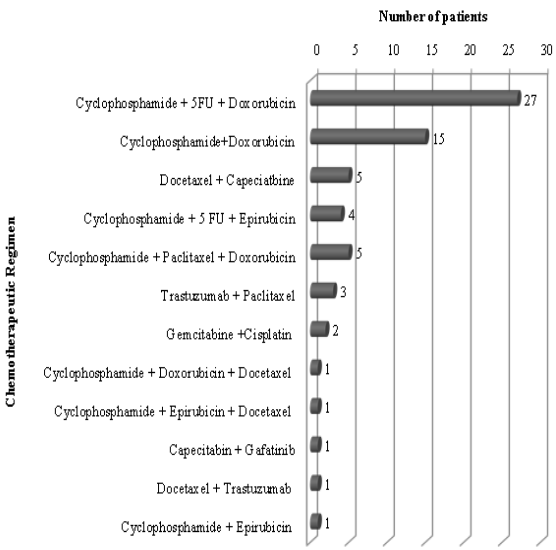

Fig. 1: Chemotherapeutic regimen used in study patients

Table 3 shows adverse drug reactions in study patients with different combination chemotherapies. Maximum adverse drug reactions were seen with Cyclophosphamide + Doxorubicin + 5 FU combination followed by Cyclophosphamide + Doxorubicin combination.

Table 3: Adverse drug reactions in study patients with different chemotherapeutic regimes

Combination chemotherapies	Adverse drug reactions (ADRs) N=70 (Percentage of patients)				
	Nausea	Vomiting	Alopecia	Blackening of nails	Total number of ADRs
Cyclophosphamide + 5FU + Doxorubicin	23(32.85)	14(20)	26(37.14)	16(22.85)	79
Cyclophosphamide + Doxorubicin	14 (20)	10 14.29)	8(11.42)	0 (0)	32
Docetaxel +Capecitabine	4 (5.71)	3(4.29)	2 (2.86)	2 (2.86)	11
Cyclophosphamide + 5FU + Epirubicin	3(4.29)	4 (5.71)	2 (2.86)	2 (2.86)	11
Cyclophosphamide + Paclitaxel + Doxorubicin	5 (7.14)	4 (5.71)	3 (4.28)	0 (0)	12
Trastuzumab + Paclitaxel	2 (2.86)	2 (2.86)	2 (2.86)	0 (0)	06
Others	06(8.57)	06(8.57)	06(8.57)	01(1.42)	19

(Others include: Gemcitabine + Cisplatin, Cyclophosphamide + Doxorubicin + Docetaxel, Cyclophosphamide + Epirubicin + Docetaxel, Capecitabine + Gafitinib, Cyclophosphamide + Epirubicin)

Fig. 2 shows the magnitude of individual adverse drug reactions. Nausea was the most commonly reported adverse drug reaction followed by alopecia and vomiting.

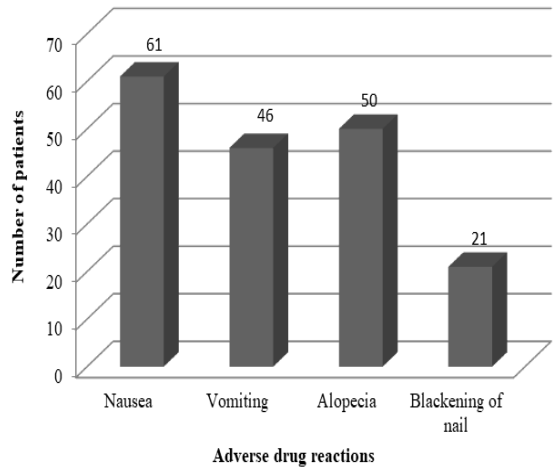

Fig. 2: Magnitude of adverse drug reactions in study patients

Preventability of the ADR was assessed by modified Schumock and Thornton scale. ADRs like nausea, vomiting belonged to the category of "definitely preventable (60.11%) while ADRs like alopecia, blackening of nails belonged to the category of "not preventable"(39.88%). Based on modified Hartwig and Siegel scale of severity assessment majority of the ADRs were of less severity categorized as "mild level 1" severity (74.15%), however, vomiting was categorized as "moderate level 3" severity(25.84%).

Discussion

With huge advances in anticancer medicines treatment is now available for many malignancies which were previously considered fatal. This has resulted in improved survival and reduced disease recurrence. But in spite of these advances, use of anticancer drugs always has its limitations due to the associated ADRs.[12] This study aimed at evaluating the prescription pattern and study ADRs associated with the use of anticancer drugs in patients of carcinoma breast. In this study majority of patients were found to be in the age group of 41 – 60 years and this is in accordance with age incidence of breast cancer in other similar studies performed.[3,5,13]

Cyclophsophamide and Doxorubicin were the most commonly used chemotherapeutic agents in this study and are prescribed in combination with other chemotherapeutic agents. Similar findings are reported in a study conducted by Khan SAS et al.[13]

Anthracyclines rank among the most effective anticancer drugs ever developed.[14] FAC, based on 5FU, Cyclophosphamide, and Adriamycin is now the most commonly used, effective, well tolerated FAC regimen as adjuvant treatment for breast cancer patients and has also shown survival benefit.[15,16,17] Similarly in this study this was the most commonly used combination chemotherapy second to follow being Cyclophosphamide and Doxorubicin combination. But in a study conducted by Pentareddy MR et al Adriamycin + Cyclophosphamide (4 cycles) followed

by Paclitaxel(4 cycles) was the most common combination chemotherapy while 5-FU+ Adriamycin + cyclophosphamide was second commonly used combination.[5] As an anthracycline, epirubicin ranks among the most effective agents in breast cancer and it has been reported to have a more favourable toxicity profile than its parent compound, doxorubicin.[18] But in the present study usage of doxorubicin was considered to be significantly high as compared to epirubicin. Higher use of doxorubicin is also reported in another study.[3] The most probable cause of higher use of doxorubicin compared to epirubicin might be lower cost of the former.

Taxanes are amongst the fundamental drugs being used in the management of breast cancer. Docetaxel and Paclitaxel are the most preferred drugs in this group due to excellent clinical outcome and desirable pharmacokinetic properties.[5] They were found to be fourth and fifth most commonly used drugs in our study.

Nausea (87.14%) was the most common side effect, which is in accordance with previous studies.[6,8] Alopecia (71.42%) was noted to be higher than vomiting, which is a different observation compared to other similar studies[6,8] in which nausea and vomiting have been found to be the commonest adverse effects of anticancer drugs. In our study vomiting was third commonest ADR to be reported. Inspite of pre-medication with parenteral dexamethasone, ondansetron and ranitidine in each study patient, nausea and vomiting were still encountered in high frequency. Nevertheless, with the use of 5-hydroxytryptamine-3 antagonists, the incidence of nausea and vomiting has significantly decreased though they have failed to prevent this completely. This indicates that current ADR prevention and management practices need to be revised.[6]

Blackening of nails was also a frequent (30%) ADR in our study and was commonly associated with Cyclophosphamide+5FU+Doxorubicin combination. Nail pigmentation is caused by chemotherapeutic agents like cyclophosphamide, doxorubicin, hydroxyurea, and bleomycin. Cyclophosphamide has been reported to cause diffuse black pigmentation. Two published case reports suggested blackening of nails as an ADR reported in patients who received cyclophosphamide containing chemotherapy regimen.[19,20] Out of the total ADRs 60.11%(mostly nausea and vomiting) were categorized as "definitely preventable". This appears to be a matter of concern and suggests that more vigorous strategies need to be employed to reduce the occurrence of these ADRs which should mainly include more stringent antiemetic regimes. This would greatly help in reducing the suffering of these patients who already are in great distress due to the disease and its treatment.

Our study selectively targeted breast cancer subjects those were exclusively on chemotherapeutic regime (without concomitant radiotherapy). This excludes the major bias that is associated with other studies. Patients receiving first cycle of chemotherapy were excluded because: this being a cross-sectional study patients were approached only once. If they were interviewed on the day when they received first cycle of chemotherapy, delayed ADRs occurring after the first cycle would have been missed.

We conclude that combination chemotherapy including Cyclophosphamide, 5 FU and Doxorubicin was the most commonly prescribed combination chemotherapy for carcinoma breast. Nausea is the commonest ADR in breast cancer patients on chemotherapy to be followed by alopecia and vomiting. Blackening of nail is also encountered with fair frequency.

References

1. K. Park. Park's Textbook of Preventive and Social Medicine. 23edition. Jabalpur: Banarasidas Bhanot; 2015.P. 389
2. Longo DL. Cancer cell biology and angiogenesis. Harrison's Principles of Internal Medicine 18th ed.2012. 693.
3. Dave DJ, Pillai A, Shah DV, Agarwal S and Goel A. An analysis of utilization pattern of anticancer drugsin diagnosed cases of carcinoma in a tertiary careteaching hospital. International Journal of Basic and Applied Medical Sciences 2014;4 (1):251-9
4. Sjoqvist F, Birkett D. Drug utilisation. WHO Booklet. Chapter 10. Sweden, Australia: WHO; 2003.
5. Pentareddy MR, Suresh A.V.S., Shailendra D, Subbaratnam Y, Prasuna G, Naresh D.T.V., Rajshekar K. Prescription Pattern of Anticancer Drugs in a Tertiary Care Hospital. Journal of Evidence based Medicine and Healthcare 2015; 2(20):3001- 9.
6. Chopra D, Rehan HS, Sharma V, Mishra R. Chemotherapy-induced adverse drug reactions in oncology patients: A prospective observational survey. Indian J Med Paediatr Oncol 2016;37:42-6
7. Mrugank BP and Hareesha RP: Prospective Observational, Non-Randomized, Parallel Sequence study for assessment of Adverse Drug Reactions due to Chemotherapeutic treatment in different types of Cancer patients. Int J Pharm Sci Res 2013;4;386-91.
8. Thapaliya K, Shrestha A, Prajapati S, Subedi R, Giri S. Study of pattern of adverse drug reaction due to cancer chemotherapy and their management in hospitalized patient in BP Koirala Memorial Cancer Hospital. J Chitwan Med Coll. 2014;4:24–8.
9. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. Br J Clin Pharmacol. 2008;65:210–16.
10. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. HospPharm. 1992;27:538.
11. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992;49:2229-32.
12. Chabner BA, Amrein PC, Druker BJ. Antineoplastic agents. In: Bruntan LL, Lazo JS, Parker KL, editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. USA: MaGraw-Hill Companies, Inc.; 2006. p. 1315.

13. Khan SAS, Ilyaz M, Manasa K. The Pharma Innovation Journal 2015; 4(8): 12-18.
14. Weiss RB 1992 the anthracyclines: will we ever find a better doxorubicin? Seminars in Oncology 19(6): 670-86.
15. Amin KA, Mohamed BM, El-wakil MA and Ibrahem SO (2012). Impact of Breast Cancer and Combination Chemotherapy on Oxidative Stress, Hepatic and Cardiac Markers. Journal of Breast Cancer 15(3):306-312.
16. Russo F, Linsalata M, Clemente C, D'Attoma B, Orlando A, Campanella G, Giotta F and Riezzo G (2013). The effects of fluorouracil, epirubicin, and cyclophosphamide (FEC60) on the intestinal barrier function and gut peptides in breast cancer patients: an observational study. BMC Cancer 1356.
17. Silva MF, Tosello C, Laloni MT, Andrade CM, Bertozzi A, Vernaglia P, Correa FM, Moraes RP and Goes JS (2006). FEC 60 adjuvant chemotherapy (AdCT) in breast cancer (BC) patients (Pts): 10- year follow-up results. Journal of Clinical Oncology 24(18S).
18. Italian multicentre breast study with epirubicin, Ambrosini G, Bali M, Garusi G et al. Phase III randomized study of flurouracil, epirubicin, and cyclophosphamide v flurouracil, doxorubicin, and cyclophosphamide in advanced breast cancer: an Italian multicentre trial.J Clin Oncol.1988Jun;6(6):976-82.
19. Kumar S, Dixit R,Karmakar S, Paul S.Unusual nail pigmentation following cyclophosphamide containing chemotherapy regimen. Indian J Pharmacol 2010Aug;42(4):243-244.
20. Prajapati VB, Madhyastha S, Acharya R, Gopalaswamy V, Doddamani A. Cyclophosphamide and doxorubicin induced melanonychia:A case report.J Clin Diagn Res2017Jan;11(1):OD04-OD05.