International Journal of Pharmacy and Biological Sciences
ISSN: 2321-3272 (Print), ISSN: 2230-7605 (Online)
IJPBS | Volume 8 | Issue 1 | JAN-MAR| 2018 | 482-487
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved| ज्ञान-विज्ञान विमुक्तये
|UGC Approved Journal |

A STUDY ON CHEMOTHERAPY INDUCED BIOCHEMICAL ABNORMALITIES IN PATIENTS WITH GYNAECOLOGICAL CANCERS

Leena Pavitha[1], Mandava Devi Akshitha[2], Vanitha Rani*, Anitha Ramesh[3], Thennarasu P [4], Sravan Prem[5]

[1, 2] Assistant Professors, CL Baid Metha College of Pharmacy, Chennai

[*, 4] Assistant Professors, Faculty of Pharmacy, Sri Ramachandra Medical College and Research Institute (Deemed to be University), Chennai

[3] Professor of Medical Oncology, Saveetha Medical College & Research Institute, Chennai

[5]Pharm D intern, Faculty of Pharmacy, Sri Ramachandra Medical College and Research Institute (Deemed to be University), Chennai

***Corresponding Author Email:** vanithak9@rediffmail.com

ABSTRACT

Aim: *The study was conducted to assess the incidence of biochemical abnormalities in patients with gynaecological cancers (Breast, Ovarian and Cervical) who were receiving chemotherapeutic regimen inclusive of corticosteroids.* ***Methods:*** *The study included 62 female patients, aged above 18 years, diagnosed with gynaecological cancers and admitted in the medical oncology unit for receiving cancer chemotherapy cycles inclusive of corticosteroids. Patients with pre-existing diabetes were excluded. Data including patients demographics, diagnosis, details of cancer chemotherapeutic cycles, cancer chemotherapeutic drug regimen, co-prescribed drugs, co-morbidities, surgical details, laboratory investigations including renal, liver, lipid and thyroid profiles, serum lactate dehydrogenase, calcium and blood glucose levels were obtained from the patient medical records and direct history interview of the patients. The data obtained were tabulated and analysed for the occurrence of biochemical abnormalities following cancer chemotherapy inclusive of steroids. Statistical analysis was performed using SPSS 16.0 version.* ***Results:*** *Of 62 patients included in the study, 59.6% females had breast cancer, 29% females had ovarian cancer, and 21.8% females had cervical cancer. Adriamycin + Cyclophosphamide + Taxane was given for 18 patients with breast cancer, of which 11 patients developed liver and 12 had renal function abnormalities. Taxanes + Platinums was given for 13 (72.2%) patients with ovarian cancer and 7 with cervical cancer, of which five and four patients developed liver function abnormalities respectively.* ***Conclusion:*** *The study identified liver, renal and electrolyte abnormalities with cancer chemotherapeutic regimens given for breast, ovarian and cervical cancers and hyperglycemia with regimens given for breast and cervical cancer.*

KEY WORDS

Cancer, Biochemical, Abnormalities, Gynecological

INTRODUCTION

The most common gynaecological cancers in women include breast cancer, cervical cancer and cancer of the ovaries. The increasing incidence of cancer in India has mirrored trends in developed countries, although the rates for major sites, such as female breast cancer have remained comparatively low. Cancer chemotherapy drugs are “cytotoxic” (cell killing) [1]. They are given orally or by injection and works systematically by killing cancer cells throughout the body.

The incidence of breast cancer increased over the 30-year period at the rate of 1.1% per annum. The changes

in rates were smaller within the latest 15-year period [2]. The magnitude and change of incidence rates in India were one-third of those seen in white women diagnosed with breast cancer in the United States [3].

The highly malignant nature of breast cancer dictates aggressive therapeutic regimens, often including multiple drug chemotherapy [2]. Although never used as the sole treatment for breast cancer, glucocorticoids are included in various combination chemotherapies. TAC (taxols + Adriamycin + cyclophosphamide), EC (epirubicin + cyclophosphamide), TC (taxols + capecitabine), TEC (taxols + epirubicin + cyclophosphamide), Trastuzumab regimen, with Prednisolone result in tumour regression in 50 to 80% of patients and complete response in 15 to 20% [4].

Cervical cancer is the fifth most common cancer in humans, the second most common cancer in women worldwide and the most common cancer cause of death in the developing countries [3]. The worldwide incidence of cervical cancer is approximately 510,000 new cases annually, with approximately 288,000 deaths worldwide. Unlike many other cancers, cervical cancer occurs early and strikes at the productive period of a woman's life [5, 6]. The current estimates indicate approximately 132,000 new cases diagnosed and 74,000 deaths annually in India, accounting to nearly 1/3rd of the global cervical cancer deaths. Indian women face a 2.5% cumulative lifetime risk and 1.4% cumulative death risk from cervical cancer [7]. The treatment regimen includes Cyclophosphamide + Topotecan, Taxols + Platinum, Doxorubicin + Platinum, Gemicitabine + Platinum, Capecitabine + Cyclophosphamide + Etoposide with prednisolone [8, 9].

Ovarian cancer is a cancer that begins in the ovary. The incidence of ovarian cancer, the trends vary according to geographic region – with decreasing rates in the United States and northern Europe but increasing rates in a few southern and eastern European countries and in Asian countries including Japan, China and Hong Kong. Although ovarian cancer rates in Mumbai were half of those in the United States in 1976 it ranked as the third most common neoplasm in Mumbai, women by the year 2000 and accounted for about 7% of the cancer incidence in the population [10]. The treatment regimen includes Taxol + platinum, 5-Flu+Platinum, 5-Flu+Platinum+Taxols with prednisolone [11].

Various side effects and toxicity profile has been reported and well documented for Cancer chemotherapeutic regimen [12-14] ^{are} enlisted below:

BIOCHEMICAL ABNORMALITIES DUE TO CANCER CHEMOTHERAPEUTIC REGIMEN

CHEMOTHERAPEUTIC REGIMEN	METABOLIC ABNORMALITIES
TAC (Taxols + Adriamycin + Cyclophosphamide)	• Impaired hepatic function • Impaired renal function • Elevated Aspartate transaminase (AST) • Elevated alkaline phosphatase • Elevated bilirubin
EC (Epirubicin + Cyclophosphamide)	• Elevated AST • Elevated alkaline phosphatase • Elevated bilirubin
TC (Taxane + Capecitabine)	• Elevated AST • Elevated alkaline phosphatase • Elevated bilirubin
TEC (Taxane + Epirubicin + Cyclophosphamide)	• Decreased haemoglobin • Elevation of AST • Elevation of bilirubin • Increased alkaline phosphatase
Cyclophosphimide + Topotecan	• Increased AST & ALT • Elevated bilirubin • Increased alkaline phosphatase
Taxols + Platinum	• Elevation in total bilirubin, AST and alkaline phosphatase • Elevation in serum creatinine • Elevation in blood urea nitrogen

Doxorubicin+ Platinum	• Hyperuricemia • Elevation in serum creatinine • Elevation in blood urea nitrogen
Gemicitabine+ Platinum	• Hyperuricemia • Reduced haemoglobin levels • Elevation in serum creatinine • Elevation in blood urea nitrogen • Increased Alanine transaminase & Aspartate transaminase
Capecitabine + Cyclophosphamide + Etoposide	• Severe hypertriglyceridemia • Hyperbilirubinemia
5-Flu+ Platinum	• Hypocalcemia • Hyponatremia • Hypokalemia • Elevation in serum creatinine • Elevation in blood urea nitrogen • Increased ALT or AST
5-Flu+Platins+Taxols	• Hypocalcemia • Hyponatremia • Hypokalemia • Elevation in serum creatinine • Elevation in blood urea nitrogen • Increased ALT or AST • Elevated bilirubin
Trastuzumab	• Mild elevation in serum creatinine • Elevation in blood urea nitrogen

Corticosteroids are strong anti-inflammatory drugs that form a part of all most all cancer chemotherapeutic regimens. Corticosteroids control and prevent nausea and vomiting caused by chemotherapy [15]. The study was conducted to assess the incidence of biochemical abnormalities in patients with gynaecological cancers (Breast, Ovarian and Cervical) who were receiving chemotherapeutic regimen inclusive of corticosteroids.

MATERIALS AND METHODS

This prospective observational study was carried out in Medical Oncology Unit of a tertiary care teaching hospital with the approval of the Institutional ethics committee and the consent of the study participants. 62 female patients, aged above 18 years, diagnosed with gynaecological (breast, ovarian, cervical) cancers and admitted in the medical oncology unit for receiving cancer chemotherapy cycles inclusive of corticosteroids were included in the study. Patients with pre-existing diabetes were excluded.

Data including patients demographics (age), diagnosis, details of cancer chemotherapeutic cycles, cancer chemotherapeutic drug regimen given for breast, ovarian, cervical cancers, co-prescribed drugs, co-morbidities, surgical details, laboratory investigations including renal profile (BUN, creatinine, sodium, potassium, bicarbonates, uric acid levels), liver profile (AST, ALT, total bilirubin, direct bilirubin), lactate dehydrogenase levels, calcium levels, lipid profile (cholesterol, HDL, LDL, triglycerides), thyroid profile (FT3, FT4, TSH) and blood glucose levels (RBS) were obtained from the patient medical records and direct history interview of the patients. The data obtained were tabulated and analysed for the occurrence of biochemical abnormalities following cancer chemotherapy inclusive of steroids in patients with breast, ovarian and cervical cancers. Statistical analysis was performed using SPSS 16.0 version. Categorical variables were explained as frequency and percentage analysis, continuous variables and were expressed as mean and standard deviation.

RESULTS

Of 62 patients included in the study, 37 (59.6%) females were diagnosed with breast cancer, 18 (29%) females were diagnosed with ovarian cancer, and 7 (21.8%)

females were diagnosed with cervical cancer. 1 (1.6%) female was between the age group of 18-25 years, 5 (8.06%) females were between the age group of 26-35 years, 16 (25.80%) females were between the age group of 36-45years, 24 (38.7%) females were between the age group of 46-55 years, 16 (25.80%) females were between the age group of 56-70 years. Of 62 patients included in the study, 46 (74.19%) females underwent surgery as a part of treatment; 60 (96.7%) patients were given curative type of treatment and 2 (3.3%) patients underwent palliative type of treatment.

In the present study, co morbidities were observed in 17 (27%) patients, which included 6 with hypertension and hypothyroidism each, 3 patients with asthma and one patient each with glaucoma and COPD.

Of 37 patients with breast cancer 18 (48.64%) were on AC*4-T*4 regimen (Adriamycin + Cyclophosphamide for 4 cycles– Taxane 4 cycles), 3 (8.1%) were on EC regimen (Epirubicin + Cyclophosphamide), 3 (8.1%) were on TC regimen (Taxane + Capecitabine), 6 (16.25%) were on TEC regimen (Taxane + Epirubicin or Adriamycin + Cyclophosphamide), 7 (18.9%) were on Trastuzumab + Taxane.

Of 18 patients with ovarian cancer, 13 (72.2%) were on Taxanes + Platinums regimen, 2 (11.11%) were on Liposomal Doxorubicin + Platinums, one (5.5%) was on Gemicitabine + Platinums, Cyclophosphamide + Topotecan, Capecitabine+ Cyclophosphamide+ Etoposide each. Of 7 patients with cervical cancer, 5 (71.4%) were on Taxanes + Platinums, one (14.2%) was on 5-Fluorouracil + Platinums, 5-Fluorouracil + Platinums + Taxanes each.

Anti-emetics were given for 62 patients which included, Ondansteron for 42 (67.7%) patients, 42 (67.7%) patients were prescribed with Metoclopramide, 42 (67.7%) patient was prescribed with Domperidone, 42 (67.7%) patients were prescribed with Prednisolone and 20(32.26%) patients were not on anti-emetics as they were on oral chemotherapy.

The liver function abnormalities in 37 patients with breast cancer are expressed in TABLE 1. The AST levels were found to be elevated in 11(61.1%) patients on AC*4-T*4 regimen, 4(66.7%) patients on TEC or TAC regimen and one (33.3%) patient on EC regimen. Bilirubin levels were found to be elevated in 5(27.8%) patients on AC*4-T*4 regimen. Alkaline phosphatase was found to be elevated in 4(22.2%) on AC*4-T*4 regimen, one (33.3%) patient on EC regimen, one (16.7%) patient on TEC or TAC regimen each.

The electrolyte abnormalities observed in 37 patients with breast cancer are expressed in TABLE 2. Hyperkalemia was observed in one (55.55%) patient on AC*4-T*4 regimen. Hypokalemia was observed in one (33.33%) patient on EC regimen, one (33.33%) patient on TC regimen, 3 (50.0%) on TEC or TAC regimen. Hyponatremia was found in one (33.33%) patient on EC regimen, one (33.33%) patient on TC regimen, one (16.66%) patient on TEC or TAC regimen.

The abnormalities in renal function of 37 patients with breast cancer were found to be elevated BUN and creatinine levels in 12(66.7%) patients on AC*4-T*4 regimen and 2(66.7%) patients on TC regimen. Of 37 patients with breast cancer, hyperglycaemia was found in one (16.66%) patient on TEC or TAC regimen, one (33.33%) patient on EC regimen.

Of 18 patients with ovarian cancer, the liver function abnormalities included an elevated AST levels in one (100%) patient on Cyclophosphamide + Topotecan regimen, 5 (38.46%) patients on Taxane + Platinum regimen, one (50%) patient on Liposomal doxorubicin + Platinum regimen, one (100%) patient on Gemicitabine + Platinum, one (100%) patient on Capecitabine + Cyclophosphomide + Etoposide regimen; elevated alkaline phosphatase levels in 1(100%) patient on Cyclophosphamide + Topotecan regimen, 2(15.38%) patients on Taxanes +Platinum regimen, one (50%) patients on Liposomal doxorubicin + Platinum regimen, one (5.5%) patients on Gemicitabine + Platinum (Table 3).

Of 18 patients with ovarian cancer, electrolyte abnormalities included, hypercalcemia in 2 (100%) patients on Liposomal doxorubicin + Platinum regimen, Hypocalcemia in 10 (76.92%) patients on Taxanes + Platinum regimen, one (100%) patient on Gemicitibine + Platinum regimen, hypokalemia in 3 (23.07%) patients on Taxanes + Platinum regimen, one (100%) patient on Capecitabine + Cyclophosphomide + Etoposide regimen, hyponatremia in one (100%) patient on Cyclophosphomide + Topotecan regimen, 4 (30.76%) patients on Taxanes + Platinum regimen (Table 4). Similarly of 18 patients, the renal function indicators BUN and creatinine were found to be elevated in 3 (23.07%) patients on Taxanes + Platinum regimen and in one (100%) patient on Cyclophosphamide + Topotecan regimen.

Of 7 patients with cervical cancer, the liver function abnormality observed included an elevated AST levels in 4 (80.0%) patients on Taxanes + Platinum regimen, one (100%) patients on 5- Flurouracil +platinum, One (100%) patient on 5-Flu + Taxanes (Table 5). The electrolyte abnormalities observed in 7 patients with cervical cancer included hypocalcemia in 3 (60%) patients on Taxanes + Platinum regimen, hypokalemia in 2 (40%) patients on Taxanes + Platinum, hyponatremia in one (100%) patients on 5- Flurouracil + Platinum (Table 6).

The abnormalities in renal function observed in 7 patients with cervical cancer were found in one (14.32%) patient on Taxanes + Platinums regimen and in one (14.2%) patient on 5- Flurouracil + Platinums + Taxanes. Hyperglycaemia was found to be elevated in one patient on 5- Flurouracil + Platinum regimen, of 7 patients with cervical cancer.

DISCUSSION

A prospective study was conducted to assess the incidence of metabolic abnormalities with cancer chemotherapy in 62 female patients with gynaecological cancers. Of the 62 patients in the study, majority were in the age range of 46-55 years with a mean age of 50.1 ± 12.08 years. The incidence of breast cancer (60%) was found to be high in the study population. A study done by Anne- Sofie Furberg, et al observed that the mean age of the study population was found to be 56.8 years. Majority of the patients were on curative therapy and only 2 8.5% of the study population had co-morbidities [14].

Patients with breast cancer were on five regimens namely: Epirubicin + Cyclophosphamide, Taxanes + Cyclophosphamide, Taxanes + Epirubicin or Adriamycin + Cyclophosphamide, Adriamycin + Cyclophosphamide + Taxanes, Trastuzumab + Taxanes. Majority of the patients with breast cancer were on the chemotherapeutic regimen of four cycles of (48.64%) of AC (Adriamycin + Cyclophosphamide) followed by four cycles of T (Taxane). This was followed by TEC 16.25% of (Taxane + Epirubicin or Adriamycin + Cyclophosphamide) regimen and 18.91% Trastuzumab + Taxanes regimen. The liver and the renal abnormalities observed in the study population with breast cancer was found to be higher with the chemotherapeutic regimen 61.11 % of AC (Adriamycin + cyclophosphamide) followed by four cycles of T (Taxane). Followed by this, patients receiving TEC (Taxane + Epirubicin or Adriamycin + cyclophosphamide) 33.33% regimen had liver abnormalities and patients on TC (Taxanes + Cyclophosphamide) 66.66 % had renal abnormalities. Of the electrolyte abnormalities, hypokalemia was observed with 16.66 % TEC (Taxanes + Epirubicin or Adriamycin + Cyclophosphamide) regimen and other electrolyte abnormalities were less observed. Of all the patients receiving Prednisolone, hyperglycemia was observed in only 2 (33.33%) patients with breast cancer on EC regimen and TEC OR TAC regimen each.

The chemotherapeutic regimens given for patients with ovarian cancer included Cyclophosphamide + Topotecan (5.5%), Taxanes + Platinums (72.22%), Liposomal doxorubicin + Platinums (11.11%), Gemicitabine + Platinums (5.5%) and Capecitabine + Cyclophosphamide + Etoposide (5.5%). Of 18 patients with ovarian cancer, liver abnormalities were observed with all the regimens; renal abnormalities were observed with Taxanes + Platinum (23.07%), followed by Cyclophosphamide + Topotecan (100%). Majority of the patients on Taxanes + Platinum presented with hypocalcemia (76.92%), followed by hyperkalemia (23.07%) and hyponatremia (30.7%). Hyperglycemia was not reported with any of the chemotherapy regimens given for patients with ovarian cancer.

The chemotherapeutic regimens given for patients with cervical cancer were Taxanes + Platinum (80%), 5-Fluorouracil + Platinum (100%), 5-Fluorouracil + Platinum + Taxanes (100%). Of these, liver abnormality of an increased AST levels were observed with all the regimens. Renal abnormality was observed with regimens Taxanes + Platinum (14.32%) and 5-Flurouracil + Platinum + Taxanes (14.2%). Patients on Taxanes + Platinum reported of hypocalcemia (60%) and hyperkalemia (40%). Hyperglycemia was observed with 5-Flurouracil + Platinum (100%) regimen.

The present study had attempted to identify the metabolic abnormalities occur with cancer chemotherapeutic regimens. All the identified metabolic abnormalities were corrected by appropriate interventions.

However, a smaller study population is a major limitation of the study. But to our knowledge, this is a first prospective study of its kind to assess the metabolic abnormalities due to cancer chemotherapy in gynecological cancers. The future objective of this study is to extend the study in larger number of samples and also to assess the possible role of these metabolic

abnormalities in the impairment of anabolic response to nutrition in cancer patients and thereby increasing the risk of malnutrition in them.

CONCLUSION

The study identified liver, renal and electrolyte abnormalities with cancer chemotherapeutic regimens given for breast, ovarian and cervical cancers and hyperglycemia with regimens given for breast and cervical cancer. It is recommended that all the patients on cancer chemotherapy may be regularly monitored for metabolic abnormalities and necessary interventions may be made for immediate correction of these abnormalities which may have a significant impact on achieving a better therapeutic outcome.

ACKNOWLEDGEMENT

The authors acknowledge the management and the faculty of Unit of Medical Oncology, Sri Ramachandra Medical Center and Hospital, Chennai.

REFERENCES

1. Wang YJ, Chu HY, Shu SG, Chi CS. Hyperglycaemia induced by chemotherapeutic agents used in acute lymphoblastic leukaemia: report of 3 cases. Zhonghua Sheng Wu Yi Xue Gong Cheng Za Zhi (Taipei) 1993; 51(6) : 457–461.
2. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973–1997. Int J Epidemiol 2005; 34: 405–412.
3. Minami Y, Takano A, Okuno Y, Fukao A, Kurihara M, Hisamichi S. Trends in the incidence of female breast and cervical cancers in Miyagi Prefecture, Japan, 1959-1987. Jpn J Cancer Res 1996; 87: 10–17.
4. Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, Gipson G, Burstein H, Lake D, Shapiro CL, Ungaro P, Norton L, Winer L and Hudis C: Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 over expressors and random assignment to trastuzumab or not in HER-2 non over expressors: Final results of cancer and leukemia group B protocol 9840. J Clin Oncol 2008; 26: 1642-1649.
5. Seow A, Duffy SW, McGee MA, Lee J, Lee HP. Breast cancer in Singapore: trends in incidence 1968–1992. Int J Epidemiol 1996; 25: 40–45.
6. Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013;132(5):1133-45.
7. Bosch FX, Lorincz A, Muñoz N, C J L M Meijer, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Path 2002; 55(4):244-265.
8. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. European Journal of Cancer 2013; 49, 1374-1403.
9. Baumann. K.H. A phase II trial (AGO 2.11) in platinum-resistant ovarian cancer: a randomized multicenter trial with sunitinib (SU11248) to evaluate dosage, schedule, tolerability, toxicity and effectiveness of a multi targeted receptor tyrosine kinase inhibitor monotherapy. Annals of Oncology 2012; 23: 2265–2271.
10. Juneja A, Sehgal A, Mitra AB, Pandey A. A survey on risk factors associated with cervical cancer. Indian J Cancer 2003; 40: 15–22
11. Tre´ dan O Carboplatin/cyclophosphamide or carboplatin/ paclitaxel in elderly patients with advanced ovarian cancer? Analysis of two consecutive trials from the Groupe d 'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. Annals of Oncology 2007; 18: 256–262.
12. Held-Warmkessel, Jeanne MSN, RN, AOCN, ACNS-BC Preventing & managing tumor lysis syndrome Oncology Times 2010;32(8):1-7.
13. Wanxing Duan, Xin Shen, Jianjun Lei, Qinhong Xu, Yongtian Yu, Rong Li, Erxi Wu, and Qingyong Ma et al. Hyperglycemia, a Neglected Factor during Cancer Progression. BioMed Research International 2014.
14. Anne-Sofie Furberg and Inger Thune Metabolic abnormalities (hypertension, hyperglycemia and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort International Journal of Cancer 2003; 104 (6): 669–676.
15. Gulliford M, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. Diabetes Care 2006; 29:2728-29.

***Corresponding Author:**
Vanitha Rani*
Email: vanithak9@rediffmail.com