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CLINICAL STUDY ON POSSIBILITY OF ANTI-NEOPLASTIC AGENTS INDUCED ADVERSE DRUG REACTIONS IN MALE AND FEMALE CANCER PATIENTS

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ABSTRACT

Adverse drug reactions (ADRs) are an important clinical issue and a serious public health risk. ADRs leading to hospitalization or occurring during hospital stay contribute significantly to cancer patient morbidity and mortality as well as representing an additional cost for healthcare systems. Chemotherapy, a multimodal approach to oncological treatment, involves highly complex regimens and hence accounts to high susceptibility toward ADRs. In the present scenario the death rate due to cancer is gradually increasing. It is one of the leading causes of death in adult aged under 65 years. It was widely noted that 80-90% of the human cancer may be attributable to environmental and life style factors. Estimations reveal that in the year 2000 over 6 million people died due to cancer and ADR is considered to contribute to the fatality rate. So there is a need to create awareness among the physicians towards ADR monitoring in cancer patients .Our present study is to analyze the pattern of Adverse Drug Reaction occurring in cancer patients treated with anticancer agents and to suggest useful interventions to reduce the incidence of ADR. The aim of the present study is to assess the adverse drug reactions in male and female cancer patients in Government Head Quarters, Krishnagiri. This clinical relevant study strictly states that the intervention of a clinical pharmacist in treatment team, which can limit, predict, monitor, prevent and treat the occurrence of ADR on ANAs. The study was conducted in the North eastern part of Tamilnadu with less literacy rate and high rate of incidence in sexually transmitted disease.

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INTRODUCTION

Cancer is a renegade system of growth that originates within a patient's bio system, more commonly known as the human body. There are many different types of cancers, but all share one hallmark characteristic unchecked growth that progresses toward limitless expansion. Cancer cells are also referred to as tumors or neoplasms. It is a heterogeneous group of diseases caused by the impairment of normal functioning of genes, which leads to genetic damage [1]. Many factors have been implicated in the origin of cancer. Some of the factors are as follows:

- Viruses, including Epstein - Barr virus (EBV), Hepatitis B virus (HBV) and human papilloma virus (HPV), human T-cell lymphotropic virus.
- Environmental and occupational exposure, such as ionizing and ultraviolet radiation and exposure to chemicals, including vinyl chloride, benzene and asbestos.
- Lifestyle factors, such as high-fat, low-fiber diet and tobacco use and ethanol.
- Medications, including alkylating agents and immune suppressants.
- Genetic factors, including inherited mutations, cancer causing genes (oncogenes) and defective tumor suppressor genes.
- Aging and cancer risk: Because a number of mutations usually must occur for cancer to arise, the chances of developing cancer increase as a person gets older because more time has been available for mutations to accumulate.
- People who develop AIDS after being infected with the human immunodeficiency virus (HIV0 are at high risk for developing a specific type of cancer called Kaposi's sarcoma.
- Heredity and cancer: cancer is not considered an inherited illness because most cases of cancer, perhaps 80-90%, occur in people with no family history of the disease. However, a person's chances of developing cancer can be influenced by the inheritance of certain kinds of genetic alternations [2].

MANAGEMENT

Many treatment options for cancer exist with the primary ones including surgery, chemotherapy, radiation therapy and palliative care. These treatments are used depending upon the type, location and grade of the cancer as well as the person's health and wishes [3]. Various strategic approaches of clinical pharmacist interventional

treatment managements were explained in table no.1.

CHEMOTHERAPY

Chemotherapy is the treatment of cancer with one or more cytotoxic antineoplastic drugs (chemotherapeutic agent) as part of a standardized agent. The term encompasses any of a large variety of different anticancer drugs, which are divided into broad categories such as alkylating agent and anti-metabolites.

ADVERSE EFFECTS OF ANTI-NEOPLASTIC DRUGS

Chemotherapeutic techniques have a range of side-effects that depend on the type of medications used. The most common combination of chemotherapy regimens observed during study period explained in table no. 2, that affect mainly the fast-dividing cells of the body, such as blood cells and the cells lining the mouth, stomach, and intestines. Clinical Pharmacist should inform the clinician about this adverse reaction during each administration time [4].

Chemotherapy-Induced Immunosuppression and Myelo Suppression

This occurs by paralyzing the bone marrow and leading to a decrease of white blood cells, red blood cells, and platelets. Anemia and thrombocytopenia, when they occur, are improved with blood transfusion. Neutropenia (a decrease of the neutrophil granulocyte count below 0.5 x 109/liter) can be improved with synthetic G-CSF (granulocyte-colony-stimulating factor, e.g., filgrastim, lenograstim).

Chemotherapy-Induced Typhlitis

Typhlitis is an intestinal infection which may manifest itself through symptoms including nausea, vomiting, diarrhea, a distended abdomen, fever, chills, or abdominal pain and tenderness. It has a very poor prognosis and is often fatal unless promptly recognized and aggressively treated.

Chemotherapy-Induced Gastrointestinal Distress

Nausea, vomiting, anorexia, diarrhea, abdominal cramps, and constipation are common side-effects of chemotherapeutic medications that kill fast-dividing cells. Malnutrition and dehydration can result when the patient does not eat or drink enough, or when the patient vomits frequently, because of gastrointestinal damage.

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Chemotherapy-Induced Anemia

Anemia in cancer patients can be a combined outcome caused by Myelo suppressive chemotherapy, and possible cancer-related causes such as bleeding, blood cell destruction (hemolysis), hereditary disease, kidney dysfunction, nutritional deficiencies and/or anemia of chronic disease. Treatments to mitigate anemia include hormones to boost blood production (erythropoietin), iron supplements, and blood transfusions. Myelo suppressive therapy can cause a tendency to bleed easily, leading to anemia.

Chemotherapy-Induced Alopecia

Hair loss (Alopecia) can be caused by chemotherapy that kills rapidly dividing cells; other medications may cause hair to thin. Severe hair loss occurs most often with drugs suchas doxorubicin, daunorubicin, paclitaxel, docetaxel, cyclophosphamide, ifosfamide and etoposide. Permanent thinning or hair loss can result from some standard chemotherapy regimens. Chemotherapy induced hair loss occurs by a non-androgenic mechanism, and can manifest as alopecia totals, telogen effluvium, or less often alopecia areata. Chemotherapy induces hair loss in women more often than men. Scalp cooling offers a means of preventing both permanent and temporary hair loss; however, concerns about this method have been raised.

Chemotherapy-Induced Infertility

Some types of chemotherapy are gonadotoxicity and may cause infertility. Chemotherapies with high risk include procarbazine and other alkylating drugs such as cyclophosphamide, ifosfamide, busulfan, melphalan, chlorambucil, and chloromethane. Drugs with medium risk include doxorubicin and platinum analogs such as Cisplatin and carboplatin. On the other hand, therapies with low risk of gonadotoxicity include plant derivatives such as vincristine and vinblastine, antibiotics such as bleomycin and dactinomycin, and antimetabolites such as methotrexate, mercaptopurine, and 5-fluorouracil. Female infertility by chemotherapy appears to be secondary to premature ovarian failure by loss of primordial follicles. This loss is not necessarily a direct effect of the chemotherapeutic agents, but could be due to an increased rate of growth initiation to replace damaged developing follicles [5].

Chemotherapy-Induced Teratogenicity

Chemotherapy is teratogenic during pregnancy, especially during the first trimester, to the extent that abortion usually is recommended if pregnancy in this period is

found during chemotherapy. Second- and third-trimester exposure does not usually increase the teratogenic risk and adverse effects on cognitive development, but it may increase the risk of various complications of pregnancy and fetal myelosuppression. In males previously having undergone chemotherapy or radiotherapy, there appears to be no increase in genetic defects or congenital malformations in their children conceived after therapy.

Chemotherapy-Induced Peripheral Neuropathy

Between 30 and 40 percent of patients undergoing chemotherapy experience chemotherapy-induced peripheral neuropathy (CIPN), a progressive, enduring, and often irreversible condition, causing pain, tingling, numbness and sensitivity to cold, beginning in the hands and feet and sometimes progressing to the arms and legs. Chemotherapy drugs associated with CIPN include thalidomide, epothilones, vinca alkaloids, taxanes, proteasome inhibitors, and the platinum-based drugs should be verify during medication history interview. Though the symptoms are mainly sensory, in some cases motor nerves and the autonomic nervous system are affected. CIPN often follows the first chemotherapy dose and increases in severity as treatment continues [6-8].

Chemotherapy-Induced Cognitive Impairment

Some patients report fatigue or non-specific Neuro cognitive problems, such as an inability to concentrate; this is sometimes called post-chemotherapy cognitive impairment, referred to as chemo brain by patients' groups.

Chemotherapy-Induced Organ Damage

- Cardio toxicity (heart damage) is especially prominent with the use of anthracycline drugs (doxorubicin, epirubicin, idarubicin, and liposomal doxorubicin). The cause of this is most likely due to the production of free radicals in the cell and subsequent DNA damage.
- Hepatotoxicity (liver damage) can be caused by many cytotoxic drugs.
- Nephrotoxicity (kidney damage) can be caused by tumor lysis syndrome and also due direct effects of drug clearance by the kidneys. Different drugs will affect different parts of the kidney and the toxicity may be asymptomatic (only seen on blood or urine tests) or may cause acute renal failure.

- Ototoxicity (damage to the inner ear) is a common side effect of platinum based drugs that can produce symptoms such as dizziness and vertigo.

Chemotherapy-Induced Other Adverse Effects

Less common adverse-effects include red skin (erythema), dry skin, damaged fingernails, a dry mouth (xerostomia), water retention, and sexual impotence. Some medications can trigger allergic or pseudo allergic reactions. Specific chemotherapeutic agents are associated with organ-specific toxicities, including cardiovascular disease (e.g., doxorubicin), interstitial lung disease (e.g., bleomycin) and occasionally secondary neoplasm (e.g., MOPP therapy for Hodgkin's disease) [9-11].

MATERIAL AND METHOD

This study was conducted at Government Head Quarters Hospital, Krishnagiri. It is a 200 bedded teaching hospital located in a socioeconomically backward region in Northeastern Krishnagiri, providing health care services in different specialties with highly qualified health professionals. The oncology department was selected for the study. This study is a prospective observational, single centered study conducted over a period of 6 months from December 2015 to May 2016. A prospective observational, single cantered study was carried out in the oncology department for 6 months data collection from December 2015 - May 2016. All the patients who attended the Oncology department during the study period subject to inclusion and exclusion criteria satisfying the inclusion and exclusion criteria were included [12-18].The data was collected from both outpatient and inpatient departments of Oncology [19-20]. The different sources of data used were:

- From the chemo-prescriptions of patients in case of Outpatients and from the patient case sheets in case of inpatients
- By communicating with the physicians during ward rounds
- By Medication history interview with cancer patients**.**

ADR Alert Form

After the cross check of patient data collection form ADR alert form filled by the clinical pharmacist to produce one copy to the physician and nursing staff and other one copy to attach to the patient data collection form. ADR alert form contains the patient details of diagnosis, suspected drugs with suspected ADR, observed ADR, Severity of ADR.

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RESULT ANS DISCUSSION

This study data was analyzed by using Microsoft Excel and SPSS. The P value and Chi square was analyzed for assessing the findings.

MOST COMMON SITES OF TUMOR IN THE CANCER PATIENTS

Out of 150 cases it was found that most commonly occurred was cervix cancer of ovarian cancers of 28.6% then breast cancer of 16.29% of the study population and the details given in table no:3.

TYPE AND GENDER WISE DISTRIBUTION OF ADVERSE DRUG REACTIONS

Table no 4 shows the type and gender wise distribution of adverse drug reaction in 150 cases of study population.

TOTAL NUMBER OF ADRs OBSERVED IN ONCOLOGY PATIENTS IN OUR HOSPITAL

In our clinical study we have selected 150 cases and here we reported the ADR occurring patients and the no.of ADR occurred in the patients and is given in table no: 5 and graphically in figure no: 1.From the table it was observed that in female patients more no: of ADRs was found with 216 ADRs. According to the given data in fig no: 1 it shows that ADR occurred more in females with 66.05% than in males with 33.95%.

CONCLUSION

The study population consists of 150 patients in total. Among them 54.6 % (n=82) of the patients were females. On classifying the patients on age 32 % (n=48) of the patients were of age group 50-59. From the total prescription 34.66% (n=52) patients were diagnosed as stage II cancer. From the total prescription 21.33 % (n=32) of the cases the site of the tumor was the cervix. As a part of the chemotherapy, the patients were prescribed with various anti-cancer drugs. Most frequently used anti-cancer drugs was 5-Fluorouracil.In 31.3 % (n=47) of patients with a combination of Cisplatin + 5 fluorouracil was prescribed. From the clinical pharmacist interventional study it may be concluded that chemotherapeutic index and dosage needed to achieve a therapeutic response usually proves toxic to the body's rapidly proliferating cells. Early modifications in dosage regimen of chemotherapeutic agents may minimize hazardous ADRs. This clinical study strongly sounds the importance of the role played by the clinical pharmacist regarding their targeted theraputic outcome strategies can

limit and manage ADR induced by ANA along with the medical team.

ETHICAL APPROVAL

The study was approved by the Institutional Ethical Committee of Government Head Quarters Hospital, Krishnagiri.

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Table.1: CLINICAL PHARMACIST INTERVENTIONAL TREATMENT STRATEGIES OF CHEMOTHERAPY		
1	Combined modality chemotherapy	The use of drugs with other cancer treatments, such as radiation therapy, surgery and/or hyperthermia therapy
2	Induction chemotherapy	The first line treatment of cancer with a chemotherapeutic drug. This type of chemotherapy is used for curative intent.
3	Consolidation chemotherapy	Given after remission in order to prolong the overall disease-free time and improve overall survival. The drug that is administered is the same as the drug that achieved remission.
4	Intensification chemotherapy	Identical to consolidation chemotherapy but a different drug than the induction chemotherapy is used.
5	Combination chemotherapy	Involves treating a patient with a number of different drugs simultaneously. The drugs differ in their mechanism and side-effects. The biggest advantage is minimising the chances of resistance developing to any one agent. Also, the drugs can often be used at lower doses, reducing toxicity.
6	Neoadjuvant chemotherapy	Given prior to a local treatment such as surgery, and is designed to shrink the primary tumor. It is also given to cancers with a high risk of micro metastatic disease
7	Adjuvant chemotherapy	Given after a local treatment (radiotherapy or surgery). It can be used when there is little evidence of cancer present, but there is risk of recurrence. It is also useful in killing any cancerous cells that have spread to other parts of the body. These micrometastases can be treated with adjuvant chemotherapy and can reduce relapse rates caused by these disseminated cells.
8	Maintenance chemotherapy	A repeated low-dose treatment to prolong remission.
9	Salvage chemotherapy or palliative chemotherapy	Given without curative intent, but simply to decrease tumor load and increase life expectancy. For these regimens, in general, a better toxicity profile is expected.

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Table. 2: COMMON COMBINATION CHEMOTHERAPY REGIMENS			
S.No.	Cancer Type	Acronym	Drug Combinations
1	Breast cancer	CMF	Cyclophosphamide, Methotrexate, 5-Fluorouracil
		AC	Doxorubicin, Cyclophosphamide
2	Hodgkin's disease	MOPP	Mustine, Vincristine, Procarbazine, Prednisolone
		ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
3	Non-Hodgkin's lymphoma	CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone
		RCHOP	Rithuximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone
4	Germ cell tumor	BEP	Bleomycin, Etoposide, Cisplatin
5	Gastric cancer	ECF	Epirubicin, Cisplatin, 5-Fluorouracil
		ECX	Epirubicin, Cisplatin, Capecitabine
6	Bladder cancer	MVAC	Methotrexate, Vincristine, Doxorubicin, Cisplatin
7	Lung cancer	CAV	Cyclophosphamide, Doxorubicin, Vincristine,
8	Colorectal cancer	FOLFOX	5-Fluorouracil, Folinic Acid, Oxaliplatin
9	Head and Neck cancer	CF	Cisplatin, 5-Fluorouracil

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TABLE NO.3: MOST COMMON SITE OF TUMORS IN THE CANCER PATIENTS

S.NO	SITE OF TUMORS	NO OF DIAGNOSIS	PERCENTAGE
1	Ovary	17	11.33
2	Breast	32	21.33
3	Tongue	3	2
4	Buccal Mucosa	2	1.33
5	Oropharynx	2	1.33
6	Cervix	23	15.33
7	Larynx	2	1.33
8	Hodgkin's Lymphoma	1	0.66
9	Penis	2	1.33
10	Anal	2	1.33
11	Rectum	9	6
12	Stomach	8	5.33
13	Lung	10	6.66
14	Vulva	1	0.66
15	Colon	4	2.66
16	Gallbladder	3	2
17	Endometrium	5	3.33
18	Chondrosarcoma	1	0.66
19	Mouth	2	1.33
20	Oral Cavity	2	1.33
21	Cheek	4	2.66
22	Hypopharynx	2	1.33
23	Submandibular	2	1.33
24	Urinary Bladder	4	2.66
25	Pancreas	4	2.66
26	Oesophagus	2	1.33
27	Leukaemia	1	0.66

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TABLE NO.4: TYPE AND GENDER WISE DISTRIBUTION OF ADR IN THE STUDY POPULATION

S.NO	ADR		FEMALE	MALE	TOTAL
1	Nausea, Vomiting		48	44	92
2	Alopecia		31	29	60
3	Stomatitis		10	3	13
4	Leukopenia		4	3	7
5	Thrombocytopenia		8	3	11
6	GI Ulceration		17	15	32
7	Neutropenia		14	11	25
8	Diarrhoea		27	19	46
9	Hyperpigmentation		14	8	22
10	Skin Rash		12	9	21
11	Amenorrhea		8	-	8
13	Abdominal Discomfort		14	7	21
14	Anorexia		13	11	24
15	Anemia		28	23	51
16	Dermatitis		2	3	5
17	Anaphylaxis		4	3	7
18	Local Inflammation		5	6	11
19	Pain	Headache	8	3	11
		Musculoskeletal Pain	5	3	8
		Injection Site Pain	3	2	5
20	Erythema		4	5	9
21	Peripheral Neuropathy		2	-	2
22	Myelosuppression		12	13	25
23	Mucositis		14	17	31
24	Constipation		16	14	30
25	Fever		4	5	9
26	Fatigue		8	15	23

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Table no.5: TOTAL NUMBER OF ADR OBSERVED IN THE ONCOLOGY WARD DURING THE STUDY DURATION

S.No.	GENDER	NUMBER OF ADR OCCURRED	PERCENTAGE OF ADR
1	Male	111	33.95
2	Female	216	66.05
	Total	**327**	**100**

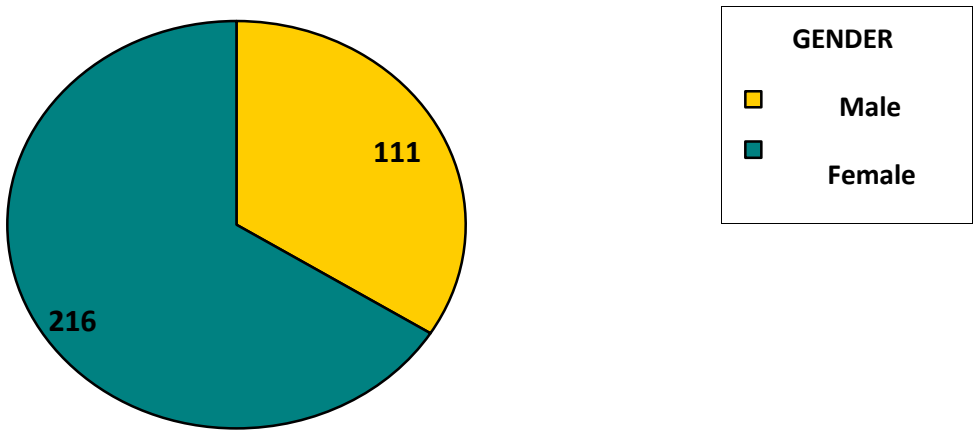

Figure No. 1: Total number of ADR observed in oncology patients in our hospital