IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

A Clinical Study to Assess the Drug Utilization Pattern and Expenditure of Multi-drug Therapy in Breast Cancer Patients

Rohit Kumar Kumawat[1]*, Rajesh Asija[2] and Mahendra Kumar Chauhan[3]
[1]Research Scholar, Maharishi Arvind Institute of Pharmacy, Jaipur, India- 302020.
[2]Principal, Maharishi Arvind Institute of Pharmacy, Jaipur, India- 302020.
[3]Associate Professor, Maharishi Arvind Institute of Pharmacy, Jaipur, India- 302020.

Abstract :
Anticancer drugs resistance is a complex process that arises from altering in the drug Targets. Advances in the DNA microarray, proteomics technology and the development of Targeted therapies provide the new strategies to overcome the drug resistance. Although a design of the new chemotherapy agents is growing quickly, effective chemotherapy agent has not been discovered against the advanced stage of cancer (such as invasion and Metastasis). The cancer cell resistance against the anticancer agents can be due to many Factors such as the individual's genetic differences, especially in tumoral somatic cells. Also, the cancer drug resistance is acquired, the drug resistance can be occurred by different Mechanisms, including multi-drug resistance, cell death inhibiting (apoptosis suppression), Altering in the drug metabolism, epigenetic and drug targets, enhancing DNA repair and gene amplification. In this review, we outlined the mechanisms of cancer drug resistance and in following, the treatment failures by common chemotherapy agents in the different type of cancers..

INTRODUCTION

By providing advances in the cancer research, our knowledge of the cancer biological characteristics is updating every day. Cancer causes the uncontrolled Growth of abnormal cells and dynamic altering in the Genome (which cause cancerous features in normal Cells). The cancer progression impairs the normal biological process of healthy cells which achieved by the Invasion of nearby tissues and metastasize to distant Tissues.[1]
In addition to, common cancer treatments such as Surgery, radiation therapy, chemotherapy, combination therapy and laser therapy; the selective therapies are based on the better conception of the biology and Molecular genetics in the tumor progression used for the Promising treatments. Todays, despite these advances, The promising option for cancer treatment is Chemotherapy. Currently, 90% of failures in Chemotherapy are during the invasion and metastasis of Cancers related to drug resistance. In the chemotherapy, By following the administration of a certain drug, a large Number of patient tumor cells become resistant to the Drug. So, the drug resistance appears as a serious Problem in the field of cancer.4 There are many problems In the cancer therapy, such as cytotoxic agents resistance And toxic chemotherapy. The novel cancer treatments by studying on the molecular targets of oncogenes, tumor Suppressor genes and RNA interference (RNAi) are expanded.[2]
The purposes of these therapies include 1. The kinases inhibition that involved in the cell Proliferation, 2. Improving the rapid immune responses In cancer, 3. Specializing the medications, 4. Drug Delivery into cancer cells and 5. Reducing the side effects Of anticancer drugs, etc. 7 There are several mechanisms Including inactivation of the drug, multi-drug resistance, Inhibiting cell death (apoptosis suppression), changes in Drug metabolism, epigenetic and drug targets, enhance DNA repair and gene amplification that cause the Resistance to the chemotherapy.[3]

NEED OF THE STUDY.

A few of the Family history, obesity, the use of processed foods, physical inactivity, postponing childbearing, having fewer children, an earlier age at menarche, and a shorter nursing period are all risk factors for cancer. The care of patients and their quality of life have improved as a result of recent developments in the treatment of breast cancer patients. It is critical to use anticancer therapy properly since, despite their toxicity, they have been proved to improve patients' prognoses. Receiving pharmaceuticals with the best possible indication, regimen, and price is considered rational drug usage. However, irrational drug usage can have detrimental implications, such as inadequate treatment, overprescription of medications, the emergence of drug

resistance, unfavourable side effects, and a financial burden on patients and hospitals. Drug use evaluation is one strategy to guarantee sensible drug use (DUE). 23 DUE is a comprehensive drug use assessment that will guarantee sensible medicine use for each patient, especially in light of potential medical, social, and financial repercussions (Introduction to drug utilisation research., 2003). DUE have been utilised all across the world to facilitate access to medications for all people. Healthcare decision-makers can learn more about total drug usage by gender, comorbidities, and age group by analysing medication use and spending. Additionally, it can reveal which medications contributed most to budget expenditures. Additionally, assessing whether a medication has been over- or under-prescribed, if it adheres to the treatment protocol and guidelines, and the effect of policy changes on medication use can all be helpful. Action is frequently taken in response to the DUE and may include changing the drug's classification or placing restrictions on its usage, as well as creating a need for greater education and awareness campaigns. Prior literature research indicate that both the pattern of anti-cancer medication use among cancer patients and the relationship between drug use and clinical outcome are understudied. DUE may help us in detecting the pattern of prescription chemotherapeutic drugs for treating breast cancer as well as early warning indicators of irrational drug use in order to give intervention tools to improve medication consumption and realise the continual development of treatment quality

RESEARCH METHODOLOGY

Study Design- Prospective, Observational study

Study Subject

The investigation was carried out in a tertiary care hospital with beds that was outfitted with contemporary diagnostic and medical facilities. Patients at this facility come from many geographical areas.

Study Duration.

Duration of study was 5 months.

Sampling

The study was carried out on 91 patients.

Inclusion Criteria

- Patients aged >18 years
- Patients of either sex diagnosis with any malignancy.
- Patients prescribed a muti drug therapy.

Exclusion Criteria

- Patients who is not willing to participate in the study.
- patients with a carcinoma diagnosis who additionally needed surgery, radiation, or another type of care.
- patients with additional malignancies, such as sarcoma, lymphoma, leukaemia, etc.
- women who are expecting or lactating

Method Of data collection

The patient's progress record, treatment chart, laboratory results, patient history record, and other documents were used to collect the patient's demographic data, current medicines, laboratory results, prior medical and pharmaceutical history, and other data.

During the study period, the patients data was collected 4 times in 30days of interval, which include drug therapy regimen, costing and ADRs was recorded.

Age, sex, and weight are among the patient's demographic details that were gathered.

All medications, their dosages, routes of administration, frequency, and dates of beginning and ending use are included in the current medication data.

The past medical and pharmaceutical history information that was gathered included the patient's prior allergies, co- morbidities, and medications that they had taken.

The appropriate laboratory studies carried out to confirm the ADR were included in the laboratory data that was gathered.

The pattern of drug regimen for the treatment was be recorded and side effect observed will be noted. The cost of drug therapy in each visit was noted

The study objectives and process were explained to the patient or their relatives in their own language to obtain informed consent. Patients who consented to participate were then interviewed to collect relevant data. The data were collected in a case record form (CRF) specifically designed for the study.

Evaluation of Data

Recorded data based on a structured questionnaire was evaluated using computer software and categorized and analyzed individually with the drug.

IV. RESULTS AND DISCUSSION

Table 6.1: Demographic details of the patients

Demographic Details		**Prospective phase N = 91; [n (%)]**
Gender	Male	00 (00)
	Female	91 (100)
Age	21 – 30	3 (3.3)
	31 – 40	15 (16.5)
	41 – 50	32 (35.2)
	51 – 60	28 (30.8)
	61 – 70	10 (10.9)
	71 – 80	3 (3.3)
Menopausalstatus	Pre-menopausal	31 (34.1)
	Peri-menopause	4 (4.4)

	Post-menopausal	54 (59.3)
Age at menarche	Less than 15	64 (70.3)
	15 or above	27 (29.7)
Co-morbid condition(s)	None	58 (63.7)
	Diabetes mellitus	18 (19.8)
	Hypertension	25 (27.5)
	Hypothyroidism	5 (5.5)
	Ischemic heart disease	1 (1.1)
	Seizures	1 (1.1)
Clinicalstage ofdisease	Stage I	5 (5.5)
	Stage II A	18 (19.8)
	Stage II B	16 (17.6)
	Stage III A	24 (26.4)
	Stage III B	10 (10.9)
	Stage III C	5 (5.5)
	Stage IV	13 (14.3)
Endocrinestatus of tumour	ER positive	21 (23.1)
	ER negative	58 (63.7)
	PR positive	15 (16.5)
	PR negative	64 (70.3)
	Unknown	12 (13.2)
	HER positive	13 (14.3)

HER 2 status	HER 2 negative	63 (69.2)
	Equivocal but not confirmed with FISHtest	3 (3.3)
	Not tested for HER 2over expression	12 (13.2)

ER : Estrogen Receptor ; PR : Progesterone Receptor ; HER 2: HumanEpidermal Growth Factor Receptor

It was observed from the data that the entire study population was female whereas prospective phase comprised of 100% female (n=91 respectively). The most vulnerable age was 41-50 years in both the phases, thus majority of the population was post menopausal (51% and 59.3%). It was also seen that that the age of menarche was less than 15 years in majority of thecases (100% in retrospective phase and 70% in prospective phase). Majority of the study population did not report any co-morbid conditions (62% in retrospective phaseand 63.7% in prospective phase) whereas hypertension was the most prevalent disease in the patients reporting co-morbidity (32% and 27.5%). It could also be observed that breast cancer was majorly being diagnosed in stage 3 in the study population (Retrospective phase 54% cases and Prospective phase 42.8%). Onanalyzing the endocrine receptor status of the tumor it was observed majority of the study population was hormone receptor negative and it was not assessed in 13% of the cases in both retrospective and prospective phases. It was also noted that majority of the study population was negative for HER-2 receptor (75% and 69.35) and as not evaluated in 13% of the cases.

6.2: Treatment patterns

Table 6.2: Treatment protocols followed in the patients

Treatment Protocol	Regimen Details	n (%)
Single Chemotherapy Regimenc	Pacli	1 (1.1)
	FEC	3 (3.3)
	AC	1 (1.1)
	TAC	1 (1.1)
Combination of Chemotherapy Regimens	AC – Pacli	8 (8.8)
	FEC – Doce	4 (4.4)
Combination of Chemotherapy and Radiation	FAC	3 (3.3)
	FAC – Pacli	1 (1.1)

	FEC	1 (1.1)
	AC – Pacli	25 (27.5)
	FEC – Doce	3 (3.3)
Combination of Chemotherapy and Hormonal / Targeted therapy with or without Radiation	AC – Pacli – Tamox	12 (13.2)
	AC – Pacli – Anas	8 (8.8)
	AC – Pacli – Anas – Tamox	1 (1.1)
	AC – Pacli – Tras	1 (1.1)
	AC – Pacli – Tras – Anas	1 (1.1)
	Pacli – Anas	1 (1.1)
	FEC – Tamox	2 (2.2)
	FEC – Anas	3 (3.3)
	FEC – Tamox – Anas	1 (1.1)
	FEC – Doce – Anas	2 (2.2)
	FEC – Letrozole	1 (1.1)
	FEC – Doce – Tamox	5 (5.5)
	FAC – Tamox	2 (2.2)

The most common treatment approach followed was a combination of surgery, chemotherapy and radiation therapy which accounted for 80% cases in both retrospective and prospective phases. The most commonly used protocol was a combination of anthracyline with taxane with or without surgery and / orradiation therapy (95% in retrospective phase and 97.80% in prospective phase) [Table 6.2]

Table 6.3: Appropriateness of treatments in study patients

Parameter	Prospectivephase/Post intervention		Chi^2 P Value	Statistical Significance in the difference observed
	Compliance n (%)	Non- Compliance n (%)		
Selection of anticancer Agents	617 (85.1)	108 (14.9)	0.028	Significant
Selection of endocrine therapy forendocrine responsive tumors	20 (95.2%)	1 (4.7%)	0.586	Not Significant
Selection of treatment for HER 2 positive patients	8 (50%)	8 (50%)	0.114	Not Significant
Dosing of anticancer agents(s)	597 (82.3)	128 (17.66)	0.001	Significant

It was seen that the compliance to the standard had risen from 63.5% to 86.9% for the administration of anticancer agents and anti-emetics administration compliance increased from 50% to85.1%.

Table 6.4: Assessment of QALY in the enrolled patients

Status of QALY	Stage	n(%)
Degraded	4	8 (8.79)
	1A	3 (3.29)
	2A	10 (10.98)
	2B	7 (7.69)
	3A	7 (7.69)
	3B	6 (6.59)
	3C	4 (4.39)
	4	4 (4.39)
	1A	2 (2.19)
	2A	8 (8.79)
	2B	9 (9.89)
	3A	16 (17.58)
	3B	4 (4.39)
	3C	1 (1.09)
	4	1 (1.09)
	3A	1 (1.09)

It was observed that average QALY at the beginning of the treatment in breast cancer patients was 0.04035 $\pm$ 0.009960 whereas it dropped down to 0.03949 $\pm$ 0.007594 at the end of the treatment. The QALY had gone down as per the score calculated from the EQ-5D scale, but it

was not considered statistically significant (p value 0.276).

Table 6.5: Assessment of VAS scale in the enrolled patients

Status of VAS	Stage	n(%)
Degraded	4	6 (6.59)
	1A	2 (2.19)
	2A	12(13.18)
	2B	10 (10.98)
	3A	15 (16.48)
	3B	7 (7.69)
	3C	4 (4.39)

Improved	4	4 (4.39)
	1A	2 (2.19)
	2A	2 (2.19)
	2B	5 (5.49)
	3A	3 (3.29)
	3B	2 (2.19)
No Improvement	4	3 (3.29)
	1A	1 (1.09)
	2A	4 (4.39)
	2B	1 (1.09)
	3A	6 (6.59)
	3B	1 (1.09)
	3C	1 (1.09)

Furthermore, on analyzing the VAS scale it was observed the average VAS score in the beginning of the treatment was 83.516 $\pm$ 15.6435 and at the end of the treatment was 78.520 $\pm$ 12.3337. It could be assessed the score had decreased corresponding to the degradation in the quality of life of the patients and it was statistically significant (P value 0.000). [Table 6.4 and Table 6.5]

The data was also assessed individual patient wise. The assessment showed thatthe QALY had degraded in 49.45% (n=45) and improved in 48.35% (n=44) cases. Onthe other hand VAS score had degraded in 61.54% (n=56) but improved in 19.78% (n=18) cases.

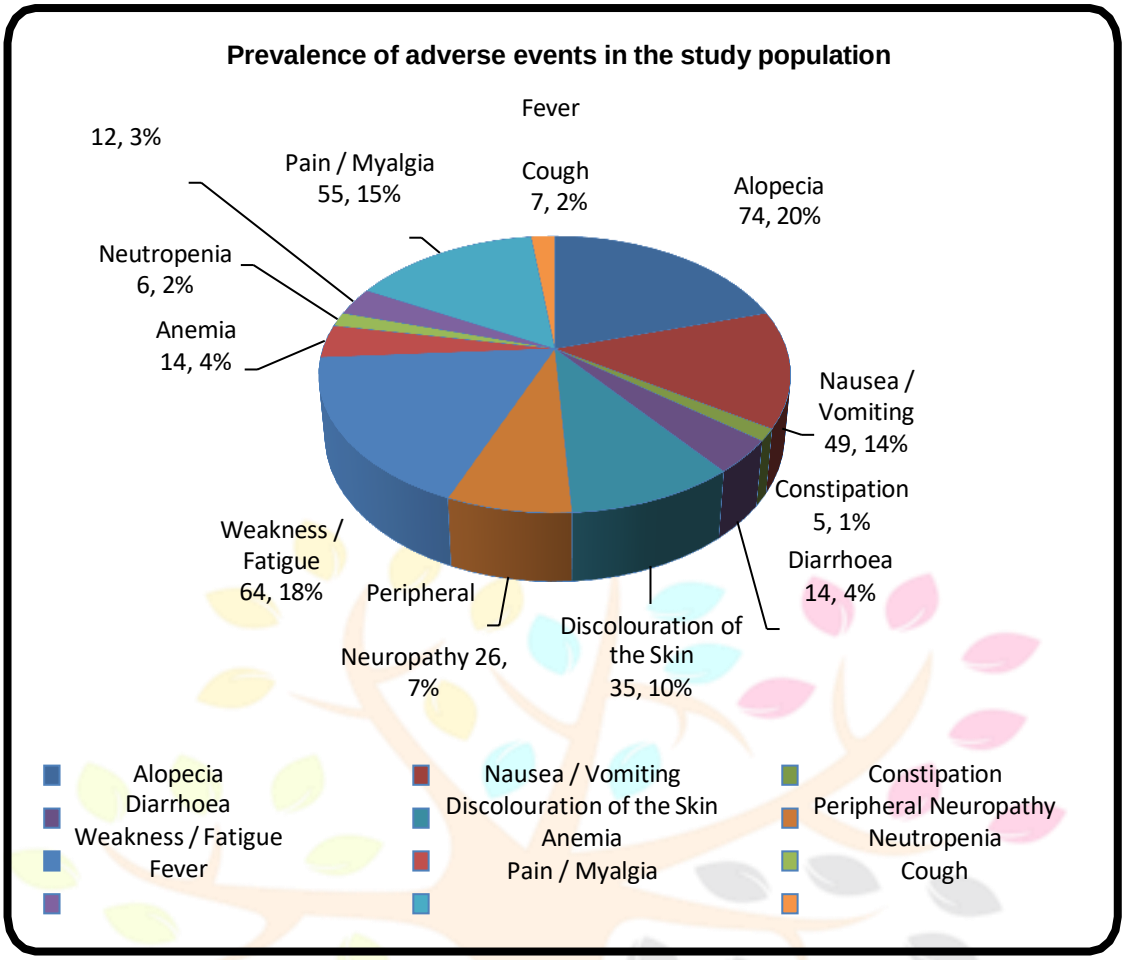
Table 6.6: Economics evaluation of the various regimens practiced in the study

Regimen (n)	Average Baseline QALY	Average QALYat theend of treatment	AverageBaseline VAS	Average VAS at the endof thetreatment	Cost of Treatment	Change InQALY	Change InVAS
AC (1)	0.029285	0.043496	100	90	14773.68	0.014211	-10
AC-Pacli (55)	0.040729	0.039243	83.91	79.32	84143.36	-0.001486	-4.59
AC-Pacli-Tras (2)	0.057534	0.035815	97.5	84.67	Cost of 1 tras = 75000	-0.043438	-12.83
FAC (5)	0.034080	0.038364	90	82.67	22453.92	0.004284	-7.33
FEC (11)	0.040397	0.039810	80.45	71.74	61590.12	-0.000586	-8.71
FEC-Doce (14)	0.039812	0.041905	81.79	78.93	149912.82	0.002094	-2.86
TAC (1)	0.025523	0.026178	60	65	107955.68	0.000655	5
Weekly Pacli (2)	0.041529	0.037685	75	75	151607.04	-0.003844	0

AC: Doxorubicin + Cyclophosphamide ; Pacli: Paclitaxel ; Tras: Trastuzumab ; FAC: 5-Fluorouracil + Doxorubicin + Cyclophosphamide ; FEC: 5-Fluorouracil + Epirubicin + Cyclophosphamide ; Doce: Docetaxel ; TAC: Docetaxel +Doxorubicin + Cyclophosphamide

The most commonly used regimens in Breast cancer were anthracycline based alongwith / without taxane and radiation therapy. Some of the patients were also prescribed with weekly paclitaxel. Table 6.6 above describes the most common regimens practiced and the change in QALY along with the total treatment cost for the regimen.

6.7: Prevalence and types of adverse events observed in breast cancer patients



The most commonly seen adverse events were alopecia (20%), followed by weakness/fatigue (18%) and pain/myalgia (15%). The least commonly seen adverse event were neutropenia and cough prevalent in 2% of the cases each. [Figure6.7]

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