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Research Article

AN ANALYSIS OF UTILIZATION PATTERN OF ANTICANCER DRUGS IN DIAGNOSED CASES OF CARCINOMA IN A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT
Carcinoma is one of the common causes of death all over the world including India. Chemotherapy remains to be the main stay of treatment with other modalities in the management. Present study had been conducted to evaluate prevailing drug utilization pattern of anticancer drugs. An observational, retrospective record based drug utilization study was conducted in the oncology department of a tertiary care teaching hospital over a period of two and half years. Data of patients greater than 18 years and diagnosed as carcinoma were included in the study. Epidemiological data and details of prescribed drugs were recorded in a predesigned case record form. Out of 316 enrolled patients, majorities were male (234, 74.05%) and in the age group of 41-70 years (246, 77.85% patients). Carcinoma of the lung (91, 28.8%) was most commonly reported followed by pharynx (52, 16.45%), oral cavity (32, 10.13%) and breast (27, 8.5%). Chemotherapy was commonly used as combination regimens (299, 94.62%). 5-FU and platinum based combination were most frequently prescribed (124, 39.24%) especially in head and neck carcinoma (89, 28.16%). Platinum based combinations were also used in management of lung carcinoma. Chlorpheniremine maleate, dexamethasone, ranitidine, ondansetron, granisetron & furosemide with mannitol were used as palliative therapy either to prevent or manage adverse reactions of anticancer drugs. 5-FU and platinum based combination therapy were commonly used regimens except in carcinoma of breast. Antiemetic, antiallergic, antiulcer and corticosteroids were prescribed commonly as palliative therapy.

Keywords: *Carcinoma, Chemotherapy, Cisplatin, 5-FU*

INTRODUCTION
According to a survey by WHO, cancer is responsible for 13% of overall mortality in 2005 worldwide. In India, cancer is responsible for 10% of total mortality in 2002 which is expected to rise up to 25-50% by 2020 (WHO, 2003). Most frequent carcinomas reported in India are mouth/oropharynx, oesophagus, stomach and lungs/bronchus/trachea in males while carcinoma of cervix, breast, mouth/oropharynx and oesophagus in females (ICMR Report, 2006). Chemotherapy remains one of the integral components in the management of carcinoma. They are either used alone or in combination with other modalities of management (radiotherapy, surgery). Chemotherapy alone or as a component of multimodality approach has been shown not only to be effective but curative too in certain cases of squamous cell head and neck carcinoma, small cell and non-small cell lung carcinoma, breast carcinoma, cervix carcinoma, uterine carcinoma and colorectal carcinoma (Longo, 2012). The utilization pattern of anticancer drugs have changed significantly in the recent years because of better understanding of pathophysiology of carcinomas as well as introduction of newer drugs. Poorly defined pathophysiology of the carcinomas, significant variation in the response rate of individual anticancer drugs, availability of different regimens, intolerability of combination regimens necessitate to require observation and evaluation of cancer chemotherapy.

The therapeutic practice is expected to be primarily based on evidences provided by pre marketing clinical trials, but complementary data from post marketing period are needed to provide an adequate basis for improving drug therapy (Strom *et al.*, 1985). Drug utilization studies (DUS) are powerful exploratory studies to ascertain the role of drugs in society. Monitoring of prescriptions and DUS could identify the associated problems and provide feedback to prescribers (Shewade and Pradhan, 1998). Descriptive epidemiological drug utilization studies help to observe the prevailing prescribing pattern of anticancer drugs. By evaluating and comparing the prevailing pattern with the existing standards, necessary steps should be taken to optimize the drug therapy. Hence present study has been conducted with the aim to observe and evaluate the prescribing trends of anticancer drugs in diagnosed cases of carcinoma at tertiary care teaching hospital.

MATERIALS AND METHODS

An observational, retrospective record based drug utilization study was conducted in the oncology department of a tertiary care teaching hospital (PDU Govt. Medical College & Hospital), over a period of two and half years (30-9-2010 to 15-4-2013) after receiving the approval from institutional ethical committee. The study was conducted with the aim to analyse drug utilization pattern of anticancer drugs in a tertiary care teaching hospital setting.

The data of patients diagnosed as a case of carcinoma by oncologist with following inclusion and exclusion criteria were used in the study:

Inclusion Criteria:

1. Newly diagnosed and/or known case of carcinoma which required treatment with chemotherapy
2. Patients of either sex and age >18 years

Exclusion Criteria:

1. Patients diagnosed as having carcinoma who also required surgical intervention, radiotherapy or other modality of management
2. Patients suffering from other cancers like sarcoma, lymphoma, leukaemia etc.
3. Pregnant and lactating women

Case records of eligible patients from oncology department were taken and the data were entered into a pre-designed proforma which includes demographic details of patient, diagnosis, details of chemotherapy and other concomitant medication prescribed.

For defining drug use, we selected prescriptions containing at least one anticancer drug from the multiple prescriptions in the case records with follow-up visits. Thus, if the initial prescription was continued, it was regarded as the same prescription for the given duration. Any changes in that prescription was noted for calculating the drug consumption. Prescriptions containing drugs given along with chemotherapy agents were also recorded to measure the supportive therapy required.

Data Analysis

The data were subjected to analyze for:

1. Demographic details (Age and gender distribution)
2. Carcinoma diagnosis
3. Anticancer drugs prescribed
4. Concomitant medications prescribed

Results were expressed as percentage.

RESULTS

Out of 598 patients treated at oncology department during the study period, data of 316 (52.85%) patients' were analysed in the study. Data of patients who required surgery (213), radiotherapy (20) and diagnosed other than carcinomas like lymphoma (27), sarcoma (8), leukaemia (6), multiple myeloma (6) and others (2) were excluded from the analysis.

Of the enrolled patients, 234 (74.05%) patients were male and the rest were female. Majority of patients were in the age group of 41 to 70 years (246, 77.85%). Lung carcinoma was most commonly reported (91, 28.8%) followed by pharynx (52, 16.45%), oral cavity (32, 10.13%) & breast (27, 8.5%) carcinoma. Prevalence of carcinomas is mentioned in table 1 while gender and age group analysis are mentioned in table 2.

Table 1: Prevalence of carcinoma

Carcinoma	No. of patients (total= 316 patients)
Lung	91 (28.8%)
Pharynx (oro, naso, hypo)	52 (16.45%)
Oral cavity	32 (10.13%)
Breast	27 (8.5%)
Oesophagus	20 (6.33%)
Tongue	15 (4.75%)
Laryngopharynx	13 (4.11%)
Ovary	9 (2.85%)
Cervix, SCC, Hepatic (EACH)	6 (1.9%)
Prostate, Colorectal (EACH)	5 (1.58%)
Neck	4 (1.26%)
RCC, Maxillary sinus, Urinary bladder (EACH)	3 (0.95%)
Skin, Adenocarcinoma, Gall bladder, Pancreas (EACH)	2 (0.63%)
Middle ear, Penis, Cervical lymphnode, Tonsillar fossa, Pyriform, Upper chest, Axilla (EACH)	1 (0.32%)

Table 2: Gender and age group analysis of diagnosed cases of carcinoma

Epidemiology of carcinoma	Lung	breast	tongue	Oesophagus	Oral cavity	Pharynx	Larynx
Male/female	80/11	0/27	15/0	15/6	26/6	41/10	10/3
</=20 years	0	0	0	0	0	0	1
21-30	0	0	1	0	4	0	0
31-40	2	4	2	1	6	2	0
41-50	19	10	3	5	10	13	3
51-60	23	9	9	5	4	14	2
61-70	39	2	0	6	4	13	4
>70 years	8	2	0	4	4	9	3

Only small number of patients 17 (5.38%) were prescribed single anticancer agent. Two anticancer drugs were prescribed in 93 (29.43%) cases, three anticancer drugs were prescribed in 179 (56.65%) cases and four anticancer drugs were prescribed in 27(8.54%) cases. Among single agent chemotherapy, sorafinib was given in 7 cases, gemcitabine and docetaxel in 2 cases while gefitinib, etoposide, erlotinib, bicalutamide, 5-FU, carboplatin were given in one case. These were prescribed in renal cell carcinoma (4), lung carcinoma (4), hepatic carcinoma (3), prostate carcinoma (3), carcinoma of laryngopharynx (1), carcinoma of pharynx (1) and in pancreatic carcinoma (1).

Among the utilization of combination chemotherapeutic regimens, 5-FU and platinum based combinations were frequently prescribed (124, 39.24%). Utilization of these combinations in various carcinomas is depicted in table 3. Cisplatin was almost always given along with magnesium sulphate. In only two cases of carcinoma pharynx, one case of carcinoma laryngopharynx and two cases of carcinoma oesophagus cisplatin (along with magnesium sulphate) was prescribed alone while in rest of the cases cisplatin was prescribed in combination. Out of these, prescriptions of different combinations are cisplatin

+ etoposide (33), carboplatin + etoposide (24), carboplatin + paclitaxel (10), carboplatin + docetaxel (9) and carboplatin + gemcitabine (5). All of these platinum based combinations are given in carcinoma lung. In only one case of carcinoma laryngopharynx 5-FU alone was used while in the rest of the cases 5-FU was prescribed in combination. Among these, commonly used combinations were 5-FU + cyclophosphamide + doxorubin (7) and 5-FU + cyclophsosphamide+ epirubicin (3) and they were prescribed in the management of carcinoma breast. Other chemotherapeutic combinations used in carcinoma breast were cyclophosphamine + doxorubicin (9) and cyclophosphamide + doxorubicin + docetaxel (5).

Use of adjuvant drugs for the management of adverse effects of anticancer drugs was frequent and depicted in figure 1.

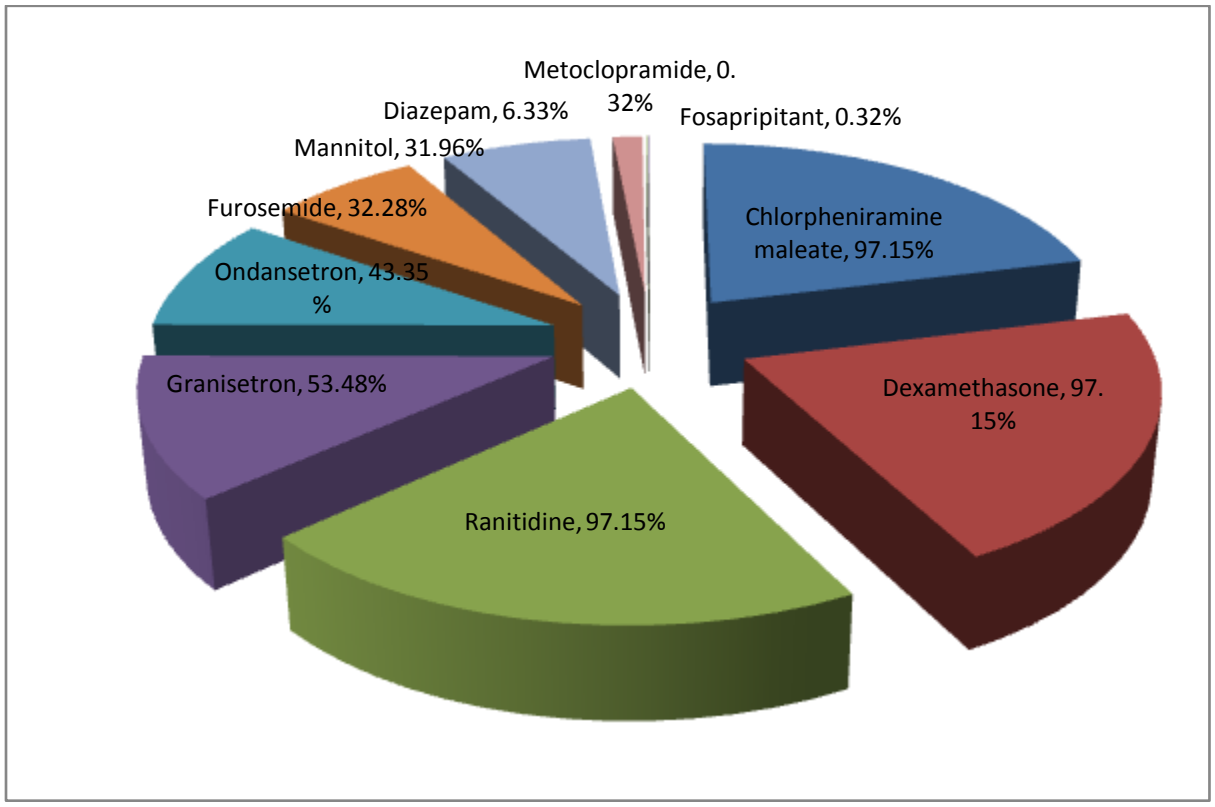

Figure1: Adjuvant drugs used for the management of cancer chemotherapy induced adverse effects

DISCUSSION

In the present study, usage of chemotherapy alone as management modality was observed in 52.85% of patients which is quite significant. As per Indian Council of Medical Research (ICMR) data, radiotherapy was the commonest modality of treatment at all stages; surgery was used for localized cancers and chemotherapy for patients having distant spread (ICMR Report, 2006). Carcinoma lung was the most commonly observed carcinoma in the present study. Other commonly observed carcinomas are of pharynx, oral cavity, breast, oesophagus, tongue and laryngopharynx. These findings are consistent with observations of various ICMR studies. Male to female ratio was high in this study (2.85) while according to ICMR, incidence rate is slightly higher in female as compared to male. In our study, 128 (40.5%) patients were above the age of 60 years. Out of these, majority of patients were in the age group of 61-70 years (90, 28.48%). Incidence of cancer increases as the age advances. According to the 1994 Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, over 50% of all cancers occur in patients who are older than 65 years of age (Corcoran, 1997).

Anticancer drugs were mostly prescribed in combination (299, 94.62%) in current study. This finding is consistent with the existing utilization pattern of anticancer drugs (Mayer and Janoff, 2007). Among combination chemotherapeutic regimens, 5-FU and platinum based combinations were commonly prescribed (124, 39.24%). Numerous experimental and clinical studies have revealed pronounced antitumor activity of cisplatin and 5-FU in various types of human cancers (Scanlon *et al.,* 1986; Lacave *et al.,* 1991).

Chemotherapy is especially required in advanced stages (III/IV) of head and neck cancers (Baur *et al.,* 2002; Paccagnella *et al.,* 1994; Pignon *et al.,* 2000). Cisplatin and continuous infusion of 5-FU have been established as the standard induction regimen for such advanced cases (Paccagnella *et al.,* 1994; Pignon *et al.,* 2000) with response rates of 20-50% (Paccagnella *et al.,* 1994; Lefebvre *et al.,* 1996; VALCS Group, 1991). In the present study, head and neck carcinomas were almost exclusively treated by this combination therapy of 5-FU and platinum compound. Docetaxel has proven to be an effective agent with response rate of 21-42% when used alone is patients with locally advanced, recurrent, and/or metastatic disease (Dreyfuss *et al.,* 1996; Catimel *et al.,* 1994; Couteau *et al.,* 1999). As docetaxel differs in mechanism of action from cisplatin and 5-FU, its addition to 5-FU and cisplatin seems to be effective theoretically and has also shown response rate of 90-95% in clinical practice (Janinis *et al.,* 2001; Posner *et al.,* 2001; Haddad *et al.,* 2003). Addition of taxane to 5-FU and platinum based regimens has been observed in 55 (56.7%) cases in this study.

For locally advanced oral cavity carcinomas, acceptable chemotherapeutic regimen for induction is combination of cisplatin, 5-FU and docetaxel/paclitaxel (Posner *et al.,* 2007; Lorch *et al.,* 2011; Vermorken *et al.,* 2007; Hitt *et al.,* 2005). Use of this combination therapy was reported in 19 (59.37%) cases in this study. Shibuya *et al.,* (2004) showed that docetaxel, cisplatin and 5-FU for tongue cancer was tolerated well and yielded an excellent response rate.

Carcinoma of oesophagus is one of the most common sites for carcinoma in India. Nearly 50% of patients with a diagnosis of oesophageal cancer present with overt metastatic disease, and chemotherapy is the mainstay of palliation in this setting (Ilson, 2008). With the increasing use of chemotherapy as an adjunct to surgical management, systemic chemotherapy will ultimately be used to treat the majority of patients with oesophageal cancer (Ilson, 2008).Cisplatin + 5-FU has been accepted as a treatment standard in squamous cell and adenocarcinoma of the oesophagus (Ilson, 2008). In present study, carboplatin and 5-FU along with taxane (Paclitaxel/docetaxel) was prescribed in majority of cases of carcinoma oesophagus. Carboplatin was found to be used more frequently in the management of oesophageal carcinoma in this study. Carboplatin, a second generation trivalent organic compound, has been used as a less toxic alternative to cisplatin in several cancer types (Sternberg *et al.,* 1985; Mannell *et al.,* 1989).

According to ICMR findings, carcinoma of lung is the most common cancer in males and it has shown in present study too (ICMR 4, 2001). Cisplatin is the most active and widely used drug and remains to be the standard component of combination chemotherapy for lung carcinoma (Johnson and O'Dwyer, 2005). In the present study too, cisplatin or carboplatin based combination therapy was used in majority of the cases of lung carcinoma. Among these, majority cases were prescribed cisplatin/ carboplatin along with etoposide while few cases were prescribed platinum along with taxanes. A regimen based on platinum agents and etoposide has proven efficacy and is considered to be the first line chemotherapy in small cell lung carcinoma (Sundstrom *et al.,* 1998; Mavroudis *et al.,* 2001).

Breast carcinoma is one of the most common neoplasms in women and is a leading cause of cancer-related deaths worldwide (Polyak, 2001). Anthracyclines rank among the most effective anticancer drugs ever developed (Weiss, 1992). FEC60, based on 5FU, cyclophosphamide, and epirubicin is now the most commonly used, effective, well tolerated FEC regimen as adjuvant treatment for breast cancer patients and has shown survival benefit too (Amin *et al.,* 2012; Russo *et al.,* 2013; Silva *et al.,* 2006). Consistent to these findings, 5-FU, cyclophosphamide and anthracycline combination usage for the management of breast carcinoma was most common in present study. 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 (Italian Multicentre Breast Study, 1988; Bonnadonna *et al.,* 1993). But in the present study usage of doxorubicin was considered to be significantly high as compared to epirubicin. Docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) as per its approved indication, is recommended as an option for the adjuvant treatment of women with early node-positive breast cancer. Taxanes are the fundamental drugs used in the treatment of breast cancer. Because of convenient pharmacokinetic parameters and consistent positive clinical results docetaxel is the preferred agent in this group. Addition of docetaxel or paclitaxel to the combination of doxorubicin and cyclophosphamide has been observed with nearly equal in frequency in the present study too (Crown *et al.,* 2004).

Nausea and vomiting are the most distressing side effects of cancer chemotherapy. Guidelines recommend the use of 5-HT_3 antagonists as pharmacological intervention for acute and delayed nausea and vomiting for moderately and highly emetogenic chemotherapy (Vrabel, 2007) and the same group was preferred in present study too. Evidence based medicine review databases have shown that ondansetron and granisetron have comparable antiemetic efficacy in reducing or eliminating chemotherapy induced nausea and vomiting (Vrabel, 2007). Hence for choice amidst 5-HT_3 antagonist, pharmacokinetic parameters, safety and cost should be considered. While considering the agent, cost, safety and pharmacokinetic parameters should be considered among 5-HT_3 antagonist. As ondansetron is oldest among all the agents in this group and cheaper too, it should be preferred. But in the present study, granisetron was more commonly prescribed as compared to ondansetron. Dexamethasone was given in nearly all the patients (307, 97.15%). Addition of dexamethasone to 5-HT_3 antagonists has been shown to improve the control of acute phase of chemotherapy induced vomiting (Barbour, 2012; Olver, 2005).

Chlorpheniremine was used in almost all patients (307, 97.15%). Plausible explanation for its use is to prevent and manage allergic reactions induced by anticancer drugs. But not all anticancer drugs are known to cause allergic reactions. Chlorpheniremine maleate has found to be effective, patient convenient and very useful in preventing allergic reaction due to paclitaxel (Harada *et al.,* 2008). Ranitidine was prescribed in all cases. It may be used to prevent development of stress induced ulcer but still its rationality in every case is questionable.

Nephrotoxicity is a well-known side effect of cisplatin (Dos Santos *et al.,* 2012), which can be managed by its rapid infusion (Tiseo *et al.,* 2007) as well as hydration therapy. Several researchers have shown that magnesium supplementation gives protection against cisplatin induced nephrotoxicity (Bodnar *et al.,* 2008; Willox *et al.,* 1986). In addition, Lajer *et al.,* reported that magnesium depletion enhances cisplatin-induced nephrotoxicity (Lajer *et al.,* 2005). In present study, cisplatin was used almost always with magnesium sulphate. Mannitol has nephroprotective action by causing osmotic diuresis and reducing the renal concentration of cisplatin (Hayes *et al.,* 1977; Frick *et al.,* 1979). Although other researchers have already reported the effect of furosemide on reducing the renal toxicity, its effect on the prevention of nephrotoxicity is still controversial (Cornelison and Reed, 1993). In fact, it has been reported that furosemide protects renal function, while it worsens renal histopathology (Lehane *et al.,* 1979). But in the present study, furosemide was always co prescribed with mannitol to reduce nephrotoxicity of cisplatin.

To summarise and conclude, anticancer drugs were almost always prescribed in combination. 5-FU and platinum based combination therapy was preferred in majority of cases except in carcinoma of breast and lung. In breast carcinoma, 5-FU, cyclophosphamide and anthracycline combination therapy was preferred while in lung carcinoma, platinum and etoposide combination was prescribed. H_2 antagonist (ranitidine), 5-HT_3 antagonists (ondansetron, granisetron), antiallergic (chlorpheniremine maleate) and corticosteroids (dexamethasone) were given in nearly all the cases to manage the adverse effects of anticancer drugs. Furosemide and Mannitol combination was given in some cases to reduce adverse effects of cisplatin.

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