

## Rational Use of Carboplatin in the Treatment of Non-Small-Cell Lung Cancer (NSCLC)

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### Abstract:

**Aims:** To observe chemotherapy of non-small-cell lung cancer patients receiving carboplatin for the parameters of rational use of carboplatin. **Methods:** In our observational study, a total of 25 chemotherapy-naïve patients, of both sexes, of histologically and cytologically confirmed NSCLC were studied. A performa was designed to collect data related to the patient's chemotherapy. **Results:** A large majority of the patients were smokers and all of them presented at either Stage III b or Stage IV. Cough was the most common presenting complaint and adenocarcinoma was the most common histological type. Carboplatin (AUC of 5.0 mg/ml/min-Calvert's formula) was administered in combination with either Etoposide or Gemcitabine. All drugs were given on day 1 of a 21-day cycle for a maximum of 6 cycles. Premedications and post-medications were also administered. Myelosuppression was the most common adverse effect observed. There was no involvement of a pharmacist in the chemotherapy of patients. Nurses and other hospital staff were unaware of the risks associated with handling and disposal of cytotoxic agents. The calculations of doses of the antineoplastic drugs were done by the oncologists and there was no double check on them. **Conclusion:** There is a need for pharmacist intervention in the chemotherapy of patients and to train nurses about the safety precautions required for the safe handling, administration and disposal of antineoplastic agents and the hazards associated with it.

**KEY WORDS:** *carboplatin, non-small-cell lung cancer, rational use.*

### INTRODUCTION:

Lung cancer is the leading cause of cancer death world wide [1]. Bronchogenic carcinomas are classified into two broad groups: small cell lung cancer (SCLC) and non small cell lung cancer (NSCLC) [2]. Together, non-small-cell lung cancers, or NSCLCs, make up about 75% of all lung cancers. Each type is named after the types of cells that were transformed to become cancer. The following are the 3 most common types of NSCLC: Adenocarcinoma/bronchoalveolar - 35-40%, Squamous cell carcinoma - 25-30%, Large-cell carcinoma - 10-15%. Non small cell lung cancer usually spreads and grows more slowly than small cell lung cancer ([http://www.emedicinehealth.com/non-small-cell\\_lung\\_cancer/article\\_em.htm](http://www.emedicinehealth.com/non-small-cell_lung_cancer/article_em.htm)). For non-small cell lung cancer, surgery offers the best chance for long-term survival and cure, if the tumor is confined to the lung and is operable. Unfortunately the majority of patients present at an advanced stage and are unresectable [3]. Some of the symptoms of NSCLC include cough, hemoptysis, shortness of breath, wheezing, chest pain, loss of appetite, weight loss and fatigue, hoarseness of voice,

swallowing difficulty and bone pain (<http://www.nlm.nih.gov/medlineplus/ency/article/007194.htm>).

Tests and procedures to detect, diagnose, and stage non-small cell lung cancer are often done at the same time. Tests and procedures used for diagnosis may include physical exams and tests, chest X rays, CT scan, PET scan, Sputum cytology, fine needle aspiration (FNA), bronchoscopy and thoracoscopy ([http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/Patient\\_national\\_cancer\\_institute](http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/Patient_national_cancer_institute))

Chemotherapy uses drugs to kill cancer cells and stop new ones from growing. Chemotherapy alone is often used when the cancer has spread (stage IV). It may also be given before surgery or radiation to make those treatments more effective. Chemotherapy may be given after surgery (called adjuvant therapy) to kill any remaining microscopic areas of cancer

(<http://www.nlm.nih.gov/medlineplus/ency/article/007194.htm>).

Unlike cisplatin there is much less renal toxicity with carboplatin so there is no need for

vigorous hydration schedule or forced diuresis. Reduced creatinine clearance reduces carboplatin clearance and increases toxicity. Corticosteroids and Antihistamines can be employed to reduce or prevent infusion reactions. The commonest dose limiting adverse effect of carboplatin is myelosuppression, anemia or granulocytopenia. Red blood cell transfusions or epoetin may be required. Nausea and vomiting are common but not as frequent or severe as with cisplatin. Liver function abnormalities are common. Gastrointestinal pain is occasional. Peripheral neuropathy, allergic reactions and cardiovascular effects are uncommon with carboplatin [4, 5].

The American Society of Clinical Oncology made several recommendations, regarding treatment with platinum combinations. Recommendations were based on treatment strategies that improve overall survival. Treatments that improve only progression-free survival prompted scrutiny of toxicity and quality of life. For first-line therapy in patients with performance status 0 or 1, a platinum-based two-drug combination of cytotoxic drugs is recommended. Non-platinum cytotoxic doublets are acceptable for those with contraindications to platinum therapy. For patients with performance status 2, a single cytotoxic drug would be sufficient. First-line cytotoxic chemotherapy at disease progression, or after four cycles in patients who are not responding to treatment should be stopped. Two-drug cytotoxic chemotherapy at six cycles even in patients who are responding to therapy should to be stopped (<http://www.asco.org/guidelines/nsclc>).

Carboplatin and either paclitaxel, docetaxel, or gemcitabine have become the three most commonly used drug regimens in the United States for NSCLC. Furthermore, carboplatin plus paclitaxel was chosen as the standard treatment arm for the Eastern Cooperative Oncology Group (ECOG) study 4599, the randomized trial that demonstrated a statistically significant improvement in response rate and survival when bevacizumab was added to the doublet as first-line treatment

of patients with nonsquamous NSCLC [6]. Oncologists in the United States have embraced carboplatin as their favorite platinum drug for the first-line treatment of patients with metastatic non-small-cell lung cancer (NSCLC) [7].

Two North American phase III trials have compared carboplatin plus paclitaxel with cisplatin-based combinations and demonstrated similar efficacy but lower rates of nausea, leukopenia, and nephrotoxicity with the use of carboplatin [8, 9]. Treatment with cisplatin was not associated with a substantial increase in the overall risk of severe toxic effects. The vomiting is arguably more troubling to patients than thrombocytopenia, which is largely asymptomatic, and few would argue that carboplatin is logistically much easier to administer [7].

When you are hoping to cure NSCLC, cisplatin combinations are recommended. In contrast, for patients with stage IV NSCLC in whom the goal is not cure but symptom and disease control, avoiding toxicity becomes more important, especially when there is little difference in survival when using a less toxic regimen. Even in this setting, however, for otherwise fit patients with severe cancer-related symptoms—such as cough, shortness of breath, or pain—that cannot be relieved by a local intervention, the potential increased response rate offered by cisplatin over carboplatin results in a better chance at tumor shrinkage and related symptom improvement [7].

In most developed countries, death rate due to all malignancies except lung cancer, have shown a decline in the last 20 years. During this period, death rate due to lung cancer showed an increase. Recently there is a declining trend. In the developing countries like Pakistan, however, death rate due to lung cancer continues to accelerate. The true incidence of lung cancer is not known in Pakistan due to lack of available data. Recently collected data from SKMCH & RC tumor registry shows that it accounts for <10% of the cancers disposed at our institution. A retrospective analysis of 182 diagnosed patients with lung cancer at SKMCH was conducted.

The data were analyzed with respect to age, history, clinical symptoms, stage at presentation and history of smoking. The most common occurrence of lung cancer was in patients above the age of 50 years and non small cell lung cancer was the most common histology. Majority were found to have cough, chest pain and haemoptysis. Approximately 75% had positive history of smoking [10].

Cancer is a disease that requires long term treatment and intensive monitoring. Patients who receive chemotherapy should receive advice on side effect management and proper self-care to properly cope with drug related problems and ultimately obtain the maximum benefits from the treatment. Pharmacist intervention based on chemotherapy counseling improved knowledge and satisfaction in oncology inpatients and reduced adverse events following chemotherapy treatment. By utilizing this pharmaceutical care activity, pharmacists will be able to serve as valuable health care staffs who can ultimately improve the quality of oncology care in the future [11].

Cytotoxic drugs are frequently used in oncology practice. They are mainly administered intravenously and require reconstitution and dilution. Preparation, administration and disposal of chemotherapeutic agents require a specialized, skilled and highly knowledgeable professional practice [12].

Cytotoxic drugs are potentially hazardous to personnel and patients and appropriate waste disposal is necessary. The issue of safe handling of hazardous wastes must be addressed in all health care settings.

Exposure to chemotherapy of health care professionals may occur during drug preparation, administration, or disposal of equipment, or when human excreta is handled either by inhalation, absorption through direct skin contact, or ingestion route [13].

#### **Aims:**

- Observe chemotherapy of non-small-cell lung cancer patients receiving carboplatin in combination with other chemotherapeutic agents

- Study the adverse effects of the prescribed regimens.
- Observe the parameters of rational use of carboplatin in non-small-cell lung cancer patients.

#### **MATERIALS AND METHODS:**

This is a prospective observational study conducted in INMOL (Institute of Nuclear Medicine and Oncology), Lahore from 14<sup>th</sup> June to 14<sup>th</sup> July, 2010. A total of 25 patients of both sexes of histologically or cytologically confirmed non-small-cell lung cancer were studied, who received carboplatin at a dose calculated to produce an area under concentration-time curve of 5.0 milligrams per milliliter per minute (Calvert's formula). A performa was designed to collect data related to the patient's symptoms, diagnosis, treatment plan, drugs given prior to and after the chemotherapy and side effects experienced by the patient after a cycle of chemotherapy.

#### **Inclusion criteria:**

Patients who were prescribed Carboplatin in combination with other antineoplastic agents and who had not received chemotherapy before (chemotherapy-naïve) were chosen for our study.

#### **Exclusion criteria:**

Patients receiving radiotherapy were not included.

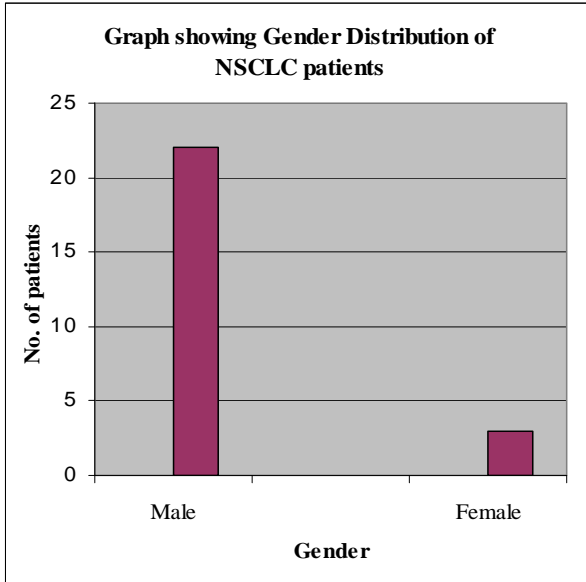
#### **RESULTS:**

Of the 25 chemotherapy-naïve patients, 22 were male and 3 were female (Figure 1). The female patients were non-smokers while 76% of the male patients were smokers (Figure 2).

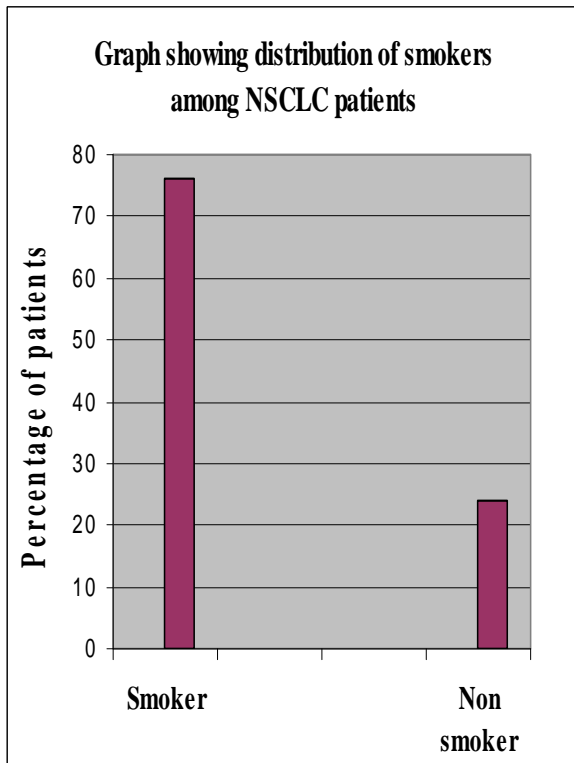
The most common presenting complaint in these patients was cough (80%), other complaints included hemoptysis (50%), dyspnoea (70%), chest pain (30 %), hoarseness of voice (40%) and fatigue (60%) (Figure 3). The duration of symptoms varied from 3 months to 2 and half years.

Before undergoing treatment, a complete clinical history was taken of each patient

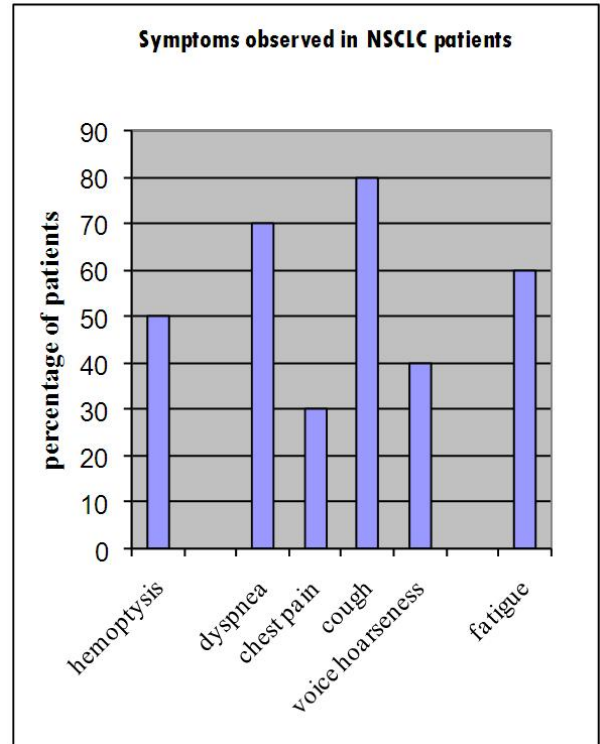
together with a physical exam including performance scale evaluation, CT scans, ultrasounds, X-Rays, histology of the primary tumour, blood reports and biochemical tests including renal and hepatic function parameters.



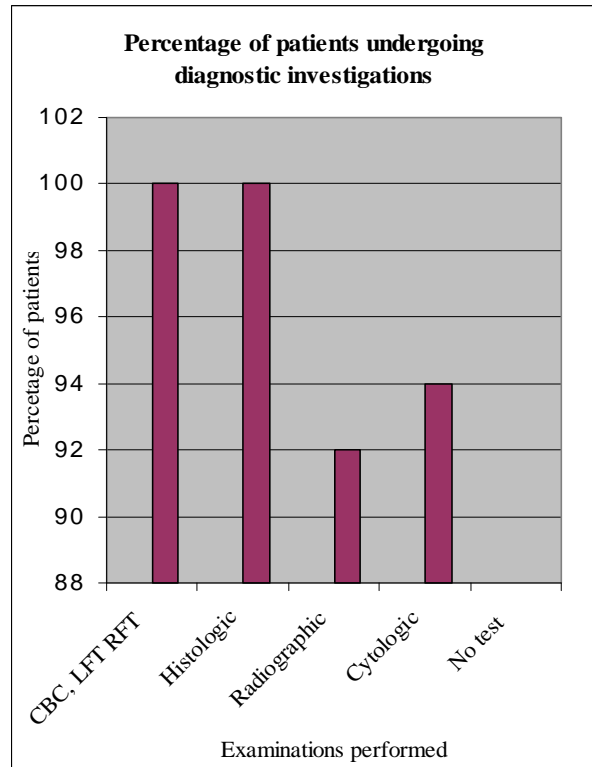
**Figure 1.** Gender distribution of NSCLC patients



**Figure 2.** Prevalence of smoking in NSCLC patients



**Figure 3.** Symptoms observed in NSCLC patients



**Figure 4.** Investigations carried out for diagnosis.

All 25 patients had taken blood tests, histologic examinations, 92% of the patients underwent radiologic examinations and 94% underwent cytologic examinations (Figure 4).

40% of the patients presented with Stage III b and 60% with Stage IV non-small cell lung cancer (Figure 5). Histological types were adenocarcinoma in 36%, squamous cell carcinoma in 64% of the patients. No patient was diagnosed with Large cell carcinoma (Figure 6).

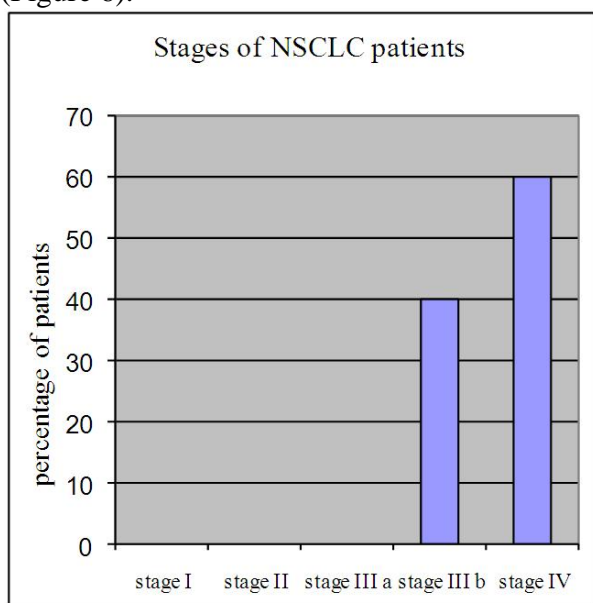


Figure 5. Stage of NSCLC

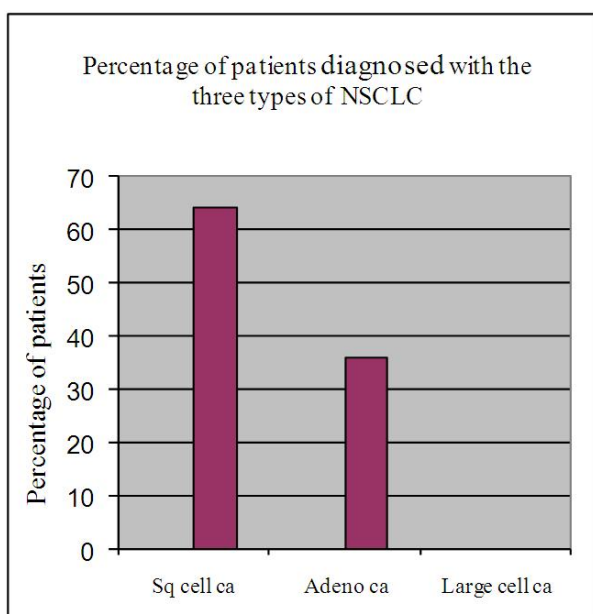


Figure 6. Type of NSCLC

Carboplatin at a dose calculated to produce an area under the concentration-time curve of 5.0 milligram per milliliter per minute (Calvert's formula) was administered intravenously as a one hour infusion diluted in 0.9% normal saline solution. 52% of the patients received carboplatin in combination with Etoposide and 48% were administered Carboplatin in combination with Gemcitabine (Figure 7).

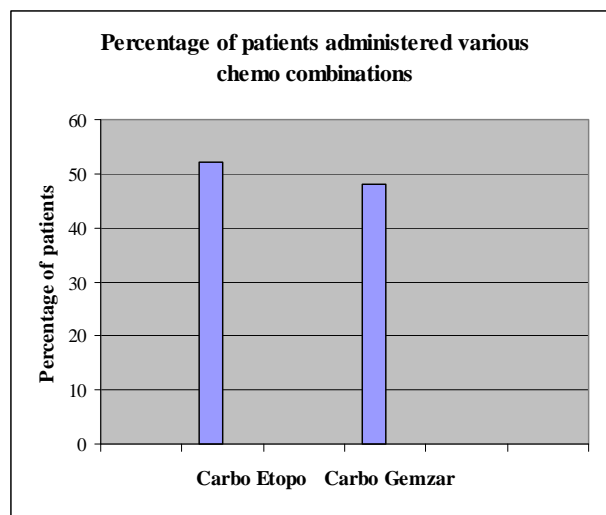
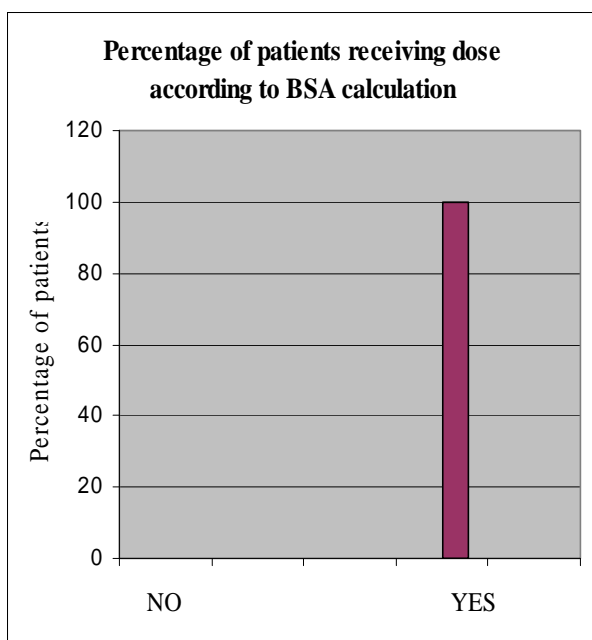


Figure 7. Chemotherapy combinations administered in NSCLC patients

Gemcitabine (Gemzar) or Etoposide was administered at the completion of the carboplatin infusion diluted in 0.9% normal saline. All drugs were given on day 1 of a 21-day cycle for a maximum of 6 cycles. The chemotherapy was administered in an outpatient department. Premedications including anti-emetics (Onset), anti-histamine (Avil), and Dexamethasone (Decadron) were administered in all 25 patients to reduce the side effects of antineoplastic agents. All 25 patients were prescribed post medications. These included Ranitidine (76%), Ondansetron (88%), Maxolon (88%), Gravinat (28%), Flagyl (0.2%), Toradol (0.16%).

The dose of drugs given in combination with Carboplatin was calculated according to the body surface area (BSA) in all 25 patients (Figure 8).



**Figure 8.** Dose calculation according to BSA

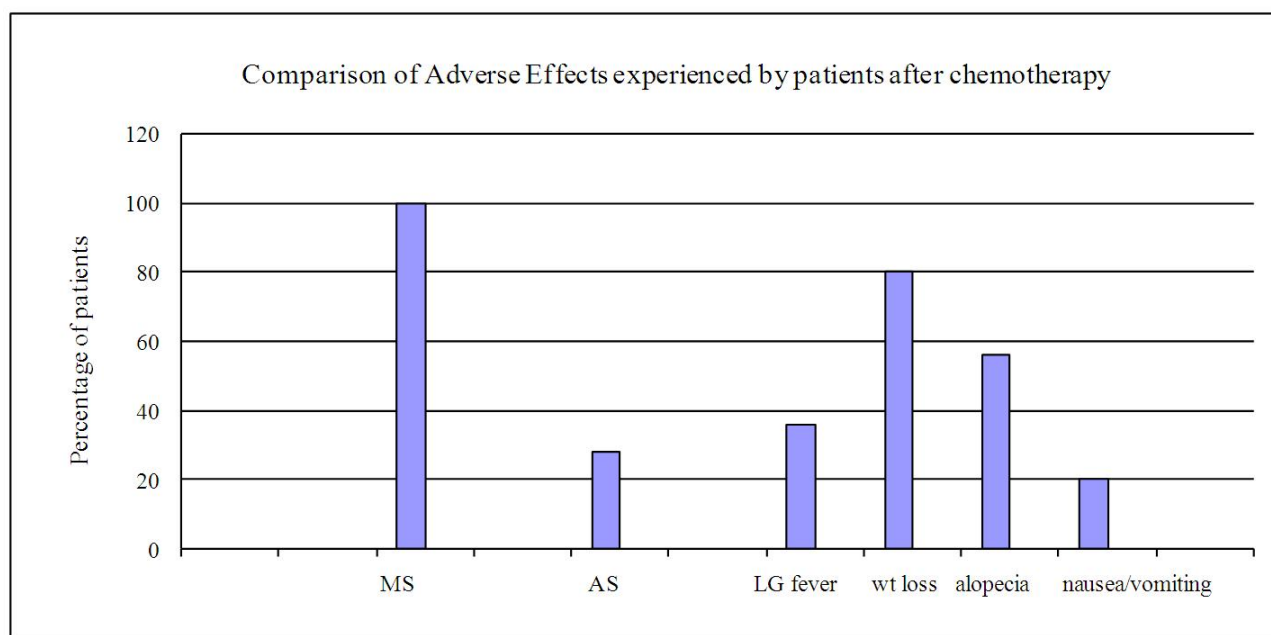
After receiving a cycle of chemotherapy all 25 patients experienced myelosuppression (Grade 2-3 neutropenia and thrombocytopenia) which is a documented adverse effect of carboplatin, 28% experienced appetite suppression, low grade fever was reported by 36% of the patients, weight loss was observed in 80% of the patients, Grade 1 alopecia was observed in

56% of the patients and Grade 1 nausea and vomiting in 20% of the patients (Grading according to the WHO grading of acute and subacute toxicity) (Figure 9).

**DISCUSSION:**

Many chemotherapeutic agents are effective against both small-cell and non-small-cell lung cancer. Among the most active are those of the platinum family: cisplatin, which cross-links DNA, and carboplatin, a cisplatin analogue. Most studies suggest that carboplatin is as efficacious as cisplatin but less toxic. However, published data do not support the frank substitution of carboplatin for cisplatin in patients with curable disease [14, 15].

76% of the male patients in this study were smokers. Tobacco products kill more than 450,000 Americans each year, and another 50,000 die of the effects of secondhand smoke. A tobacco-free environment would greatly improve the health of our society and would reduce the rates of death from coronary artery disease, lung cancer, and chronic lung disease [16].



**Figure 9.** Frequency of different adverse effects experienced by patients during chemotherapy.

The adverse effects of chemotherapy can be severe but are generally manageable and reversible. Major effects include nausea, vomiting, alopecia, myelosuppression, nephrotoxicity, neuropathies, high-pitch hearing loss, and electrolyte depletion [17]. Carboplatin, a second generation platinum complex, is less nephrotoxic and emetogenic than its parent compound. Carboplatin-etoposide combination is not more active, but clearly much less toxic than cisplatin-etoposide in NSCLC [18].

Gemcitabine/cisplatin is among the most widely used regimens in Europe for first-line treatment of non-small-cell lung cancer (NSCLC). Problems with cisplatin use in this setting include significant nonhematologic toxicity and difficulty of use in outpatients. Carboplatin constitutes a reasonable alternative to cisplatin in this combination, since it shows synergy with gemcitabine *in vitro*, is easier to use in ambulatory patients, and has a better nonhematologic toxicity profile [19].

In this study we observed that all drugs were administered on day 1 of 21-day cycle for a maximum of 6 cycles. The combination of gemcitabine (Gemzar) and carboplatin (Paraplatin) was initially hampered by unacceptable platelet toxicity. However, the use of a 21-day schedule with the administration of gemcitabine on days 1 and 15 or the use of a 28-day schedule with the omission of day-15 gemcitabine has clearly been well tolerated and active. This regimen is well tolerated and easily administered on an outpatient basis. It therefore represents an excellent “platform regimen” for the addition of new agents, particularly those associated with minimal myelotoxicity. Three-drug regimens consisting of gemcitabine/carboplatin and a taxane have been evaluated both with concurrent and sequential administration of the drugs [20].

All 25 patients of NSCLC in this study were prescribed anti-emetics before and after chemotherapy. The concern for vomiting has become less with the use of improved anti-nausea medications [21].

The current treatment of advanced small-cell and non-small-cell lung cancer with

combination chemotherapy is nonspecific, nonselective, and toxic. New combinations of chemotherapy are not likely to make substantial improvements in survival. However, prevention, early detection, and the use of specific biologic targets offer optimism and hope that mortality from this disease may be reduced [16].

During our study we observed that there was no involvement of a pharmacist in the prescribing or administration of chemotherapy to the cancer patients. The patients were not counseled on how to manage side effects of their chemotherapy. While technological advances in cancer therapies mean more treatments are available for more patients with more complex forms of the disease, the drugs are often highly toxic. Management of the risks and costs associated with cancer therapies requires the involvement of pharmacists in the production of chemotherapy and in the provision of advice to maximize patient safety [22, 23]. Advice given by pharmacists has been found to improve patients' control over chemotherapy side effects [24]. The contribution of pharmacists needs to be evaluated at each stage of the treatment of oncology patients to assure quality of services [25, 26].

The nurses wore gloves while administering drugs to the patients but the empty vials and ampoules of chemotherapeutic agents were disposed off along with other kinds of hospital waste. Since there was no pharmacist present in the wards, the nurses tallied medicines with the chemotherapy flow sheets in the patients' files but the doses once calculated by the oncologist were not checked by anyone.

The containers of cytotoxic drugs were disposed off along with other hospital waste. The hospital staff was unaware of the risks associated with handling and disposal of cytotoxic chemotherapy.

Since 1983, guidelines concerning exposure to chemotherapy of health care professionals during administration of drugs or disposal of empty containers and equipment have been developed. Guidelines and recommendations have been published in the USA by the

Occupational Safety and Health Administration (OSHA), the American Society of Hospital Pharmacists (ASHP), the Oncology Nursing Society and by various groups in Canada, New Zealand, Australia, Europe and more recently in Italy. The overall purpose of the specific guidelines for the safe handling and disposal of antineoplastic agents is to protect health-care personnel, patients and the environment from unnecessary exposure to potentially hazardous substances. Although these guidelines are not identical, they are similar in their recommendations to reduce aerosolization and direct contact to chemotherapeutic agents. The cornerstone of all these guidelines is the education and training of health professionals, patients and their family, and the use of supplies and equipment to reduce exposure [27].

#### **CONCLUSION:**

Rational use of Carboplatin in the treatment of non-small cell lung cancer involves not only prescribing of carboplatin to patients who cannot withstand Cisplatin but also includes dosage calculation of carboplatin according to a standard formula (Calvert's formula in this case) as well as calculation of the dose of antineoplastic agents given in combination with Carboplatin according to the patient's body surface area. In our study we observed that dosage calculations were done correctly by the oncologist but there was no system of double check before administering the drug to the patients. There was no involvement of a pharmacist in the chemotherapy of patients, his role was confined to filling prescriptions in the hospital pharmacy. The nurses were unaware of the risks associated with preparing, handling, administering and disposing off of cytotoxic agents. The patients were counseled by the nurse about their post medications and many patients came back for the treatment of their side effects.

#### **RECOMMENDATIONS:**

The success of public health programmes in detecting cancer early depends on the allocation of resources, availability of qualified

specialists, and access to follow-up treatment. (Global action against cancer Updated 2005 World Health Organization and International Union Against Cancer). There is a need for initiating large-scale screening programs in Pakistan to detect preclinical cancer in asymptomatic individuals in the general population to provide earlier and thus more effective treatment.

In Pakistan the government should start a nation wide awareness program educating people about lifestyle factors like tobacco, dietary and exercise habits and infectious agents that lead to the development of cancer. This program should be based on the principle approaches to cancer control laid down by the National Cancer Control Programme (Policies and managerial Guidelines, 2<sup>nd</sup> Edition, World Health Organisation, 2002, available at <http://www.who.int/cancer/nccp/nccp/en/>)

The four principal approaches to cancer control are:

- Prevention
- Early detection
- Diagnosis and treatment
- Palliative care

There is a need for pharmacists in chemotherapy wards to ensure safe and effective treatment with minimal interactions and side effects. They can also perform a double check on dosage calculations.

There is also a need for the implementation of recommended guidelines for storage, transport, administration and waste disposal of chemotherapeutic drugs, in the event of a spill and during administration of chemotherapy in an outpatient setting. There should be educational programs to educate doctors, pharmacists and nurses about these guidelines and their importance in ensuring optimal and safe patient care.

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