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ACUTE INFUSION REACTIONS OCCURRING IN A CHEMOTHERAPY WARD- A SOUTH INDIAN TERTIARY CANCER CENTER STUDY

Oncology

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ABSTRACT

Objectives: To determine the incidence and characteristics of infusion reactions that developed during treatments with chemotherapeutic drugs in the daycare ward of our institute. Also to study any patient or chemotherapy-related factors causing acute adverse reactions. **Materials and Methods:** Acute infusion reactions in patients on chemotherapy that occur in the daycare chemotherapy ward between September 2021 and August 2022 were studied. For patients who developed infusion reactions, the causal drug, chemotherapy regimen, and grade /severity of the reaction were documented. NCI CTCAE classification was used to grade the severity of the reaction. **Results:** Of the 33,140 chemotherapy administrations, 388 (1.17%) were incidence of acute infusion reactions (>/=Gr 2). The median age of patients who had infusion reactions was 55 years. A higher proportion of females experienced reactions. Taxanes were the most common cause of reactions overall, followed by Platinum agents. Taxane reactions occurred during the initial cycles of chemotherapy. Platinum drug infusion reactions most commonly occurred in later lines and cycles of chemotherapy. Infusion reactions occurred more commonly in combination regimens. Reaction time most commonly for taxanes and rituximab was within 5 minutes of starting chemotherapy. However, for platinum agents, the reaction occurred at a median time of around 45 minutes after starting chemotherapy. **Conclusion:** The use of chemotherapy comes with the risk of toxicity in the form of acute infusion reactions. Different classes of drugs have different risks and patterns of hypersensitivity which may range from mild to severe reactions or sometimes even death. Pharmacovigilance of these drugs needs to be explored, and the use of preventative measures (like adequate premedication, adequate time gap after premedication, and specific drug infusion rates) needs to be enhanced to reduce the incidence and severity.

KEYWORDS

Acute, Infusion Reaction, Hypersensitivity, Chemotherapy

INTRODUCTION

Cancer patients undergoing chemotherapy may develop infusion reactions to the administered chemotherapeutic agents, sometimes despite using adequate precautions. It is difficult to predict the patient subgroup which is more susceptible to reactions and also the nature and severity of reaction that an individual may experience upon exposure to a drug. Infusion reactions could range from mild to life-threatening [2,3].

Infusion reactions are classified as standard infusion reactions (SIR) or anaphylactic reactions. The symptoms of SIR typically include fever, tremors, flushing, dyspnea, itching, and changes in heart rate and blood pressure. Anaphylactic reactions, on the other hand, are characterized by urticaria, sudden nasal congestion, change in voice due to laryngeal edema, shortness of breath, wheezing, hypotension, and loss of consciousness. However, there is an overlap in the clinical picture between the two. The National Cancer Institute (NCI) CTCAE v5 classifies hypersensitivity reactions from grade 1 to grade 5 based on severity [4].

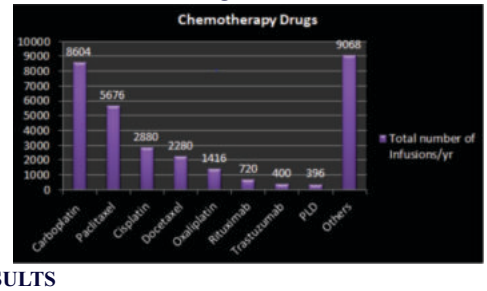
The mechanisms of infusion reactions vary between different agents and are not completely understood [5]. Most reactions that occur with the use of standard chemotherapeutic agents are type 1 hypersensitivity reactions [1,6,7]. Type 1 reactions are caused by the IgE-mediated release of histamines, leukotrienes, and prostaglandins from mast cells in tissue and basophils in peripheral blood [7,8]. Reactions related to platinum-based compounds such as carboplatin and oxaliplatin are considered type I IgE-mediated reactions [9,10].

Metabolites of some chemotherapeutic agents may cause anaphylactic reactions by directly affecting mast cells and basophils without the mediation of IgE [1]. Taxanes (docetaxel and paclitaxel) in particular can lead to clinical manifestations similar to type 1 hypersensitivity reactions [9,10]. In this study, we determined the incidence and characteristics of infusion reactions that developed during treatments with chemotherapeutic drugs and monoclonal antibody therapies. We also studied to see if any patient characteristics influence infusion reactions.

Methods

All patients receiving chemotherapy on OPD (daycare) basis were studied between September 2021 and August 2022. More than 33 thousand administrations occurred during this time. The most common drug infused was carboplatin. The most common regimen was paclitaxel + carboplatin. Before the administration of cytotoxic drugs, suitable premedication based on the chemotherapy regimen was used. Any patient who developed an infusion reaction was additionally given hydrocortisone (100 mg) IV, pheniramine (45.5 mg) IV, and, in the presence of shortness of breath, an inhaler solution of levosalbutamol and budesonide was used. In patients with grade 1 or 2 reactions, the treatment drug was resumed at a lower infusion rate after the resolution of symptoms. In patients with grade 3-4 reactions, the treatment drug was not resumed. For patients who developed infusion reactions, the causal drug, the dose and number of treatments received, the onset time of the reaction, the duration of the reaction, blood pressure, pulse, level of oxygen saturation during the reaction, and other symptoms were recorded. The severity of reactions was determined by CTCAE infusion-related reaction criteria v5.

Table 1- Individual Total Drug Administered



RESULTS

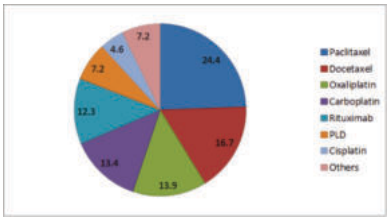
Of 33140 infusions of chemotherapy during the study period, 2054 (6.19%) was the overall incidence of acute infusion reactions (>/=Gr

1). There were 18015 (57.3%) female and 13425 (42.7%) male chemotherapy administrations with an age range of 18-78 years (median 55).

The most common drug infused was carboplatin (25.9% of all infusions), and taxanes (paclitaxel and docetaxel) together accounted for 24% of all infusions.

Among all patients, cancer types receiving chemotherapy included head and neck, cervical, breast, colorectal, lymphoma, ovarian, and others. Of these reactions, 41.1% occurred during infusion of taxanes (docetaxel and paclitaxel), 31.9% occurred during the use of platinum agents (carboplatin, oxaliplatin, cisplatin), and 18% occurred during infusion of monoclonal antibodies (trastuzumab, rituximab). The remaining 9% of infusion reactions occurred with other chemotherapeutic agents. However, it was observed that more severe (Gr 3 and Gr 4) reactions were attributable predominantly to platinum agents.

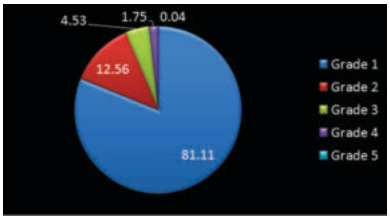
Table 2- Proportion Of Acute Drug Infusion Reaction



Percentage of Female to Male Administrations was 57.3 % (18015) vs 42.7% (13425)

71% of acute infusion reactions occurred in females and the remaining 29% occurred in males. Females in general seemed to be more susceptible to acute infusion reactions in our study.

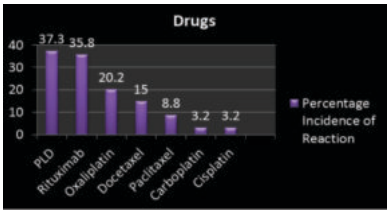
Table 3- Overall Grades Of Infusion Reaction



Platinum drug infusion reactions most commonly occurred in later lines and cycles of chemotherapy. Taxane reactions occurred during the initial cycles of chemotherapy. Infusion reactions occurred more commonly in combination regimens. Reaction time most commonly for taxanes and rituximab was within 1-5 minutes of starting chemotherapy. However, for platinum, the reaction occurred at a median time of around 45 minutes after starting chemotherapy.

The toxicity rate of individual drugs concerning the total infusion of the same drug has been summarized in table 5 as follows. The maximum incidence rate of acute infusion reactions was seen with Pegylated Liposomal Doxorubicin (37.3% of total PLD infusions), followed by rituximab (35.8%). The least incidence rate was seen with cisplatin.

Table 4- Percentage Incidence Of Individual Drug Hypersensitivity



DISCUSSION

In cancer treatment, hypersensitivity reactions may develop with the use of nearly all types of systemic agents (cytotoxics and monoclonal antibodies). With the worldwide increasing incidence of cancer, the use of these drugs has also increased significantly. In the literature, the majority of infusion reactions (95%) have been reported to be of grade 1-2, or mild to moderate [11]. In our study, the percentage of severe reactions (>/=Gr 3) out of all grades of reactions was 6.2 %. The majority of these severe reactions (49.23%) occurred against platinum compounds, while taxanes accounted for 36.92%. Taxanes are very commonly used in both metastatic and adjuvant therapy protocols, either as a single agent or as combination regimens. Taxanes may cause both SIR and anaphylactic reactions. Cremophor EL, a formulation vehicle used to improve the solubility of various poorly water-soluble drugs, which is present in the formulation of paclitaxel, and polysorbate 80, a surfactant that is present in the formulation of docetaxel, are a major cause of these reactions. Adverse reactions caused by paclitaxel seem to be caused by complement activation, mast cell/basophil activation, and classical IgE-mediated anaphylaxis [12]. The pathogenesis of reactions caused by docetaxel has not been fully characterized [13]. The percentage of reactions that resulted from docetaxel is 5-20%, while the percentage of severe reactions, despite standard premedication, was 2% [14]. In our study, around 15% of the patients who received docetaxel had an acute infusion reaction. Nearly 90% of the patients developed this reaction during the first two cycles of docetaxel. Most of these patients receiving docetaxel had acute infusion reactions within the first 5 min of infusion. These rates are consistent with the literature [14]. The percentage incidence of the reaction against paclitaxel was 8.8% in our study, consistent with the range of 8-45% that has been reported [15].

The incidence of any grade reaction to platinum compounds has been reported to be 12-20% [9,10,16,17]. In our study, the incidence of acute infusion reaction was 20.2% for oxaliplatin, 3.2% for Carboplatin, and 3.2% for cisplatin. Platinum agents (oxaliplatin, carboplatin, and cisplatin) produced an overall reaction rate (proportion) of 34.45% (out of all reactions). Oxaliplatin and carboplatin accounted for around 14% and 13% of reactions respectively. Carboplatin was the most commonly used chemotherapeutic drug at our center. Carboplatin was used to treat Ovarian, Head and neck cancer, and Cervical and Lung cancer most commonly among others. A study reported that the incidence of any type of reaction to carboplatin was 12% [17]. In the same study, 27% of the patients who received 7 or more cycles with carboplatin developed reactions, compared to approximately 1% in those who received less than 7 cycles [17].

In our study, around 65% of the patients who developed a severe reaction to Carboplatin were patients who were rechallenged with Carboplatin in patients with Ovarian carcinoma (Platinum Sensitive relapse). Tamiya et al. [18] determined that the overall incidence of allergic reactions in lung cancer patients treated with cisplatin or carboplatin was 1.96%. This study also showed a direct relationship between the number of platinum cycles and the occurrence of hypersensitivity reactions. In the literature, 50% of patients who developed an infusion reaction against platinum agents went on to develop reactions to repeated drug administrations, despite premedication [20, 22-24]. A fatal case related to the use of cisplatin was reported [25]. Cross-allergy exists between cisplatin and carboplatin, but its incidence is not known [26]. Therefore, if a platinum compound will be re-used, desensitization is recommended [27-29]. Due to the increasing use of carboplatin as both a first- and second-line therapy for ovarian cancer, the incidence of allergic reactions also increased. Polyzos et al. reported that the incidence of allergic reactions in ovarian cancer patients treated with carboplatin was 16%, mostly after the 4th course [9]. Our study also had 1 acute infusion reaction leading to death in a patient receiving Carboplatin in the recurrent setting of Ovarian cancer. No patient with severe reaction continued treatment [9]. In our study, the incidence rate of carboplatin allergy overall was 3.2%. In a retrospective study, it was reported that increasing the duration of carboplatin infusion from 30 min to 3 hours decreased the number and severity of reactions [19]. With the growing use of oxaliplatin in the Folfox and Xelox regimens for the treatment of colorectal cancer, the incidence of hypersensitivity reactions has incrementally increased. More patients have been receiving Xelox Regimen at our center on a daycare basis due to ease of administration and logistic convenience for the patients. Although there are more case reports about oxaliplatin allergy, a study published in 2006 showed that 15% of 108 patients showed an allergic response. The rate of severe reactions was 2.2% over 5 years. When oxaliplatin was readministered to 14 patients who developed reactions, recurrent development of the allergy was seen [20]. In a subsequent large-scale study, 308 of 1224 patients (25%) developed oxaliplatin allergy. Most of these reactions occurred after the first 5 cycles of chemotherapy. The

percentage of grade 1-2 reactions was 23%, while the percentage of grades 3-4 was 37% [9,16,20,21]. In our study, 20.2% of the patients who received oxaliplatin had an infusion reaction. Forty-four patients (15% of all with oxaliplatin reaction) could not continue therapy due to a grade 3-4 reaction. Around 60% of patients who had an infusion reaction to oxaliplatin had the incidence at 3rd or higher cycle of chemotherapy. Overall the proportion of total patients who had an infusion reaction to oxaliplatin was 13.9%.

Table 5 Individual Drugs With Severity.

Grade of reaction	Paclitaxel	Docetaxel	Oxaliplatin	Carboplatin	Rituximab	PLD	Cisplatin	TOTAL Individual Grade of reaction
Gr 1	420	322	194	208	207	119	60	1530
Gr 2	40	14	48	54	42	20	28	246
Gr 3	38	3	37	3	3	3	6	93
Gr 4	3	4	7	10	6	6	0	36
Gr 5	0	0	0	1	0	0	0	1
Total Individual Drug Reaction	501	343	286	276	258	148	94	

The cause for an increase in severe reactions with platinum as compared to taxanes could be due to several reasons. One may be due to increased vigilance with the use of taxanes and the adequate dose of steroid premedication and the time gap after premedication. Another factor could be the use of H1 and H2 receptor antagonist premedication with taxane unlike with platinum.

While infusion reactions to monoclonal antibodies are typically seen within the first 30 to 120 min after initiation of infusion, the majority of reactions occur during the first and second infusions [11]. Reactions are generally mild-moderate and rarely show a fatal course. With rituximab, studies have shown that more than 50% of the reactions were seen during the first infusion. These reactions were proportional to the levels of CD20 cells in the blood. In our study, 13.53% of all reactions were attributable to rituximab. The incidence of rituximab reaction was 35.8%. However, only 3.4% of all rituximab reactions were severe and required patients not to be rechallenged with the drug.

The incidence of reaction during the first infusion of trastuzumab is 20-40% [30,31], with 0.3% of the reactions being grade 3-4. The incidence and severity of adverse reactions to trastuzumab are lower than that caused by rituximab [32]. In our study, trastuzumab reaction was seen in only 3 patients (0.14%), lower compared with rituximab (13.53%). No cetuximab allergy was encountered during our study. One of the limitations of our study, however, is the fact that only chemotherapy administered in our daycare ward has been studied here. The patients who have received chemotherapy on an in-patient basis including those who have received monoclonal antibodies after admission have not been included in this study.

Although severe reactions are rare, the incidence of mild to moderate reactions against taxanes, platinum compounds, and monoclonal antibodies is quite high. Clinical symptoms do not vary widely among the agents, though the onset time of symptoms does vary. While reactions against platinum agents accounted for type 1 anaphylactic reactions, reactions against taxanes and monoclonal antibodies during the first infusion and in the following minutes suggest the presence of different mechanisms. It is important to accurately determine the grade of adverse reactions. While mild-moderate reactions (grade 1-2) tend to present with fever, skin rash, flushing, tremor, itching, and dyspnea, severe reactions (grade 3-4) tend to present with serious hives, bronchospasm, wheezing, zonesthesia, and voice alterations. Mild-moderate reactions can be controlled by temporary discontinuation of treatment and administration of symptomatic supportive therapy. Although the same drug can be continued after complete resolution of the symptoms, subsequent administrations should include premedication, a decrease in the infusion rate, and/or a desensitization protocol. In severe reactions, the infusion should be discontinued and supportive therapy should be initiated. In such events, the drug should be changed if possible, and if it is necessary to continue with the same drug, a desensitization program should be applied.

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