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ORIGINAL ARTICLE

Acute infusion reactions to chemotherapeutic drugs: a single institute experience

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Summary

Purpose: Treating cancer often involves the use of chemotherapeutic agents. Due to the growing incidence of cancer worldwide and the expanding number of treatment options, it is important to understand the risks of adverse events associated with these treatments. In this study, we monitored the occurrence of acute infusion reactions in an outpatient chemotherapy center from April 2011 to April 2012.

Methods: For patients who developed infusion reactions, the causative 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 in accordance with NCI toxicity criteria. A reaction was considered as grade 1-2 (mild-moderate) if the patient experienced flushing, rash, fever, tremor, dyspnea, rigor, and mild hypotension. Symptoms such as severe hypotension, bronchospasm, cardiac dysfunction and anaphylaxis, requiring therapeutic intervention, were classified as severe, grade 3-4 reactions.

Results: Of the 2213 patients receiving chemotherapy during the study period, 138 (62%) developed an infusion reaction to the treatment. Among 138 patients most commonly treated types of carcinoma included breast (39.2%), lung (17.8%), colorectal (10%), and ovarian (8.5%) cancers. Docetaxel administration resulted in the largest number of infusion reactions, though most reactions were mild to moderate and did not require the cessation of treatment. Patients with mild to moderate reactions (89.2%) were able to continue treatment, while those who developed severe reactions (10.8%) could not continue treatment with the same agent.

Conclusion: 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 were of type 1 anaphylactic reactions, reactions against taxanes and monoclonal antibodies during the first infusion and in the following minutes suggest the activation of different mechanisms.

Key words: acute adverse reaction, chemotherapy, infusion, safety

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Introduction

Cancer patients can develop unexpected adverse reactions to the administered chemotherapeutic agents, which differ from the known toxicities of these drugs. These infusion reactions have been shown to occur with a wide range of drugs [1]. It is difficult to predict the reactions that an individual may experience upon exposure to a drug. Infusion reactions range from mild to life-threatening [2,3].

Infusion reactions are classified as standard infusion reactions (SIR) or anaphylactic reactions. Although clinical findings often overlap, the symptoms of SIR typically include fever, tremor, flushing, dyspnea, itching, and changes in heart rate and blood pressure. In contrast, anaphylactic reactions are characterized by urticaria, sudden nasal congestion, zonesthesia, changed voice due to laryngeal edema, shortness of breath, wheezing, hypotension, and loss of consciousness.

The National Cancer Institute (NCI) classifies hypersensitivity reactions from grade 1 to grade 5. In grade 1 reactions, temporary flushing and rash are observed, and fever is <38°C. In grade 2, rash, hives, dyspnea, and fever >38°C are also observed. In grade 3 reactions, hives that require parenteral intervention and allergy-related edema and hypotension are observed. Grade 4 reactions are defined as life-threatening anaphylaxis, and grade 5 reactions result in death [4].

The pathogenetic mechanisms of infusion reactions differ among different agents, and are not well-understood [5]. Most reactions that occur with the use of standard chemotherapeutic agents include type 1 hypersensitivity reactions [1,6,7]. True type 1 reactions are caused by the IgE mediated release of histamines, leukotrienes, and prostoglandins 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 basophiles 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.

Methods

Among patients who were treated in the outpatient chemotherapy unit at the Adana Baskent University, Medical Oncology department between April 2011 and April 2012, those who developed infusion reactions were enrolled in the study. All participants provided informed consent before enrollment. The study was approved by the ethics committee at Baskent University Adana hospital. In the outpatient unit, a median of 970 patients (range 845-1100) receive chemotherapy each month. The most common cancer types in our unit are lung (15.2%), breast (21%), and colorectal cancer (8.4%).

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 in accordance with NCI toxicity criteria. A reaction was considered as grade 1-2 (mild-moderate) if the patient experienced flushing, rash, fever, tremor, dyspnea, rigor, and mild hypotension. Symptoms such as severe hypotension, bronchospasm, cardiac dysfunction and anaphylaxis, requiring therapeutic intervention, were classified as severe, grade 3-4 reactions.

Before the use of a monoclonal antibody, each patient was given dexamethasone (16 mg) and premedication with ranitidine (50 mg) and pheniramine (45.5 mg) i.v. infusion as antihistaminics. Before the administration of cytotoxic drugs, dexamethasone (16 mg), raniditine (50 mg), and ondansetron (8 mg) i.v. were routinely given. Any patient who developed an infusion reaction was additionally given prednisolone (40 mg), pheniramine (45.5 mg) and, in the presence of shortness of breath and cyanosis, an inhaler solution of albuterol sulphate. In patients thought to have grade 1-2 reactions, the treatment drug was resumed at a lower infusion rate after the resolution of symptoms. In patients with grade 3-4 reactions, use of the treatment drug was not resumed. Alternative drug treatments were explored in these patients.

Results

In this study we monitored the occurrence of acute infusion reactions in the outpatient chemotherapy center from April 2011 to April 2012. Of 2213 patients receiving chemotherapy during the study period 138 (6.2%) developed an infusion reaction to the therapeutic agents administered. There were 94 (68.1%) female and 44 (31.9%) male patients with age range 32-79 years (median 56). Among the 138 patients, the most common cancer type was breast (39.2%), followed by lung (17.8%), colorectal (10%), ovarian (8.5%), and all others (28.5%). Of these reactions, 58.6% occurred during infusion of taxanes (docetaxel and paclitaxel), 23% occurred during the use of platinum agents (carboplatin, oxaliplatin, cisplatin), and 18% occurred during infusion of monoclonal antibodies (trastuzumab, rituximab).

Table 1 shows the percentages of allergic reactions developed by each drug.

Table 2 summarizes the number of subjects, the number of the cycles given, and the number and grade of reactions for patients during the 12-month study period.

While 64 of 67 (95.5%) patients who had developed allergies against docetaxel showed grade 1-2 reactions, 3 (4.5%) patients developed grade 3-4 reactions. Most (54 of 67; 80.5%) patients experienced the reaction during the first cycle, while 13 (19.5 %) patients experienced the reaction during cycles 2-3. In all patients, the reactions to docetaxel occurred within the first 1-5 min of the infusion. Patients who developed reactions were given prednisolone (40 mg) and pheniramine (45.5 mg). Therapy had to be discontinued in one patient with a grade 3-4 reaction. In all other patients, symptoms resolved and therapy was resumed. Of the patients who developed allergy to docetaxel, 53 (79.1%) did not receive standard premedication with oral prednisolone 12 and 1 hour prior to receiving chemotherapy. In contrast, 14 (20.9%) patients developed allergic reaction despite the standard premedication.

Thirty-two patients had an allergic reaction to platinum agents. None of the 18 patients with carboplatin allergy developed the reaction during the first cycle. Carboplatin reactions that developed during the third and following cycles were grade 1-2 in 12 patients (66.6%) and grade 3-4 in 6 (33.4%) patients.

Table 1. Distribution and percents of the allergic reactions by drug

Drugs	*Allergic reactions*	
	N	*%*
Docetaxel	67	48.5
Paclitaxel	14	10.1
Carboplatin	18	13.0
Oxaliplatin	10	7.2
Cisplatin	4	2.8
Trastuzumab	14	10.1
Rituximab	11	7.9
Total	138	100

Table 2. Percents of reactions along with the total number of cycles given and the number of patients

Drug	*Number of patients who received the drug*	*Number of cycles given*	*Number of reactions N*	*Grade 1-2 reactions N*	*Grade 3-4 reactions N*	*Percents within subject %*
Docetaxel	242	973	67	64	3	27.6
Paclitaxel	144	532	14	14	-	9.7
Carboplatin	162	814	18	12	6	11.1
Oxaliplatin	62	708	10	7	3	16.1
Cisplatin	183	1360	4	2	2	2.1
Trastuzumab	216	1872	14	13	1	6.4
Rituximab	61	416	11	11	-	18.0
Total	1070	-	138	123	15	-

In patients with grade 3-4 reactions, carboplatin therapy was not continued. In patients with grade 1-2 reactions, therapy was continued after resolution of symptoms. The adverse reaction occurred within the first 15 min in 6 patients and between 40th and 60th min in the others.

Of 4 patients who developed cisplatin allergy, 2 experienced grade 1-2 reactions after the 4th cycle, and 2 grade 3-4 reactions after the 3rd cycle of chemotherapy. One patient required intubation due to serious bronchospasm, hypotension, and respiratory arrest. Adverse reactions were observed 40 min after the initiation of therapy in one patient and 60-90 min after initiation of therapy in the others.

Of 10 patients who developed oxaliplatin allergy, one patient developed a reaction in the 2nd cycle, while the others developed the reaction during the 4th through 6th cycles. The time of onset of the reactions was 30-45 min after initiation of therapy. Seven patients developed grade 1-2 reactions and continued therapy after the resolution of symptoms. However, the other patients discontinued therapy due to grade 3-4 reaction. Upon development of the same grade reactions during repeated administrations, therapy was discontinued.

Rituximab, a monoclonal antibody, led to an infusion reaction in 11 (7.9%) patients. The reaction developed after the first infusion in 9 patients and after the second infusion in 2 patients. The time of onset of the reactions was 40-70 min after the initiation of infusion. Generally, grade 1-2 reactions, characterized by fever, tremor, nausea, headache, and abdominal pain were observed. None of the patients experienced grade 3-4 reactions. Therapy could be continued in all patients.

In 14 patients who received trastuzumab, infusion-related reactions were recorded. One patient developed respiratory and cardiac arrest following symptoms of severe bronchospasm, hives, and hypotension within 30 min of starting the infusion. After intervention, the patient was intubated and monitored in the intensive care unit. After 24 hours, he was extubated. Upon improvement of his general status, he was discharged. The remaining 13 patients developed grade 1-2 reactions between 30 and 60 min following the first infusion. In 13 patients, therapy could be continued after resolution of symptoms. No adverse events were seen with repeated infusions.

In total, 15 patients (10.8 %) developed grade 3-4 reactions and could not continue therapy. In contrast, 123 patients (89.2 %) showed grade 1-2 reactions and could continue therapy.

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 was 10.8 %. The majority of these reactions occurred against platinum compounds, while only 3 severe reactions were observed against taxanes.

Taxanes are very commonly used in both metastatic and adjuvant therapy protocols, either as a single-agents or in combined regimens. Taxanes may cause both SIR and anaphylactic reactions. Chromophore, which is present in the formulation of paclitaxel, and polysorbate 80, which 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 has been shown to be 5-20%, while the percentage of severe reactions, despite standard premedication, was 2% [14]. Nearly half (45%) of the allergic reactions seen in our outpatient unit were related to the use of docetaxel, and the percentage of reactions to docetaxel was 26%. In our study, nearly 80% of the patients developed this reaction during the first docetaxel infusion, within the first 1-5 min of infusion. These rates are consistent with the literature [14]. Although the reaction to docetaxel is very commonly observed in clinical practice, it is important to note that most patients experienced grade 1-2

reaction but were able to continue treatment. In our unit, the percentage of the reaction against paclitaxel was 10 %, 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 unit, platinum agents (carboplatin, oxaliplatin and cisplatin) produced an overall reaction rate of 29.3%. The highest rates of grade 3-4 reactions were caused by platinum agents.

The most commonly used platinum agent that caused reactions was carboplatin. Carboplatin is most commonly used to treat ovarian and lung cancer. 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]. Tamiya et al. [18] determined that the overall incidence of allergic reactions in lung cancer patients treated with cisplatin or carboplatin was 1.96%. Furthermore, in this study, a direct relationship was found between the number of platinum therapy 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]. In this study, the majority of reactions were mild to moderate and the rate of severe reactions was 6.1%. No patient with severe reaction continued treatment [9]. In our study, the rate of carboplatin allergy was 11.1%, 50% of which were grade 3-4 reactions that resulted in discontinuation of treatment. 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. 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 reactions were observed after the first 5 cycles. The percentage of grade 1-2 reactions was 23%, while the percentage of grade 3-4 was 37% [9,16,20,21]. In our study, 16.1% of the patients showed a reaction to oxaliplatin. Three patients (30% of the reacting ones) could not continue therapy due to a grade 3-4 reaction after the 4th and 5th cycles.

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 infusion [11]. Reactions are generally mild-moderate and rarely show a fatal course. Monoclonal antibodies cause both SIR and anaphylactic reactions, but anaphylaxis is rarely seen. With rituximab, 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, the rate of rituximab reactions was 18.7%. Since the reactions were grade 1-2, no drug discontinuation was needed.

The incidence of reaction during the first infusion of trastuzumab is 20-40% [30,31], with 0.3% of the reactions are grade 3-4. The incidence and severity of adverse reactions to trastuzumab is lower than that caused by rituximab [32]. In our unit, the rate of reaction caused by trastuzumab (6.4%) was lower compared with rituximab (18%), and one patient required intubation due to a grade 3-4 reaction during the first infusion of trastuzumab. She was discharged after being extubated. Other patients with grade 1-2

reactions could continue to use the drug safely.

The incidence of infusion reactions due to the administration of cetuximab varies by geographic region. While two studies conducted in Europe showed an incidence of grade 3-4 reactions as 2.5% and 3.5%, respectively [33,34], the incidence of grade 3-4 reactions increased to 20% in the southeast region of the USA [35]. No cetuximab allergy was encountered during our study.

Consequently, 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 was accounted for type 1 anaphylactic reactions, in contrast, reactions against taxanes and monoclonal antibodies during the first infusion and in the following minutes suggests 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, decrease of 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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