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Incidence of Infusion Reactions to Anti-Neoplastic Agents in Early Phase Clinical Trials: The MD Anderson Cancer Center Experience

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Abstract

Background—Infusion reactions (IRs) to anti-neoplastic agents require prompt recognition and immediate treatment to avert significant complications.

Methods—We conducted a retrospective review of the medical records of consecutive patients who received anti-neoplastic therapy in the outpatient treatment center of the Department of Investigational Cancer Therapeutics from January 1, 2013 to November 30, 2013.

Results—Of the 597 patients who received treatment, 9 (1.5%) had IRs (all grade 2). The most common IRs observed on first occurrence were chills (n=5), itching, rash, and facial flushing (n=3

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Compliance with Ethical Standards

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each). There were no IR-related deaths. All the IRs were reversible with appropriate symptomatic treatment and the therapy was completed after temporary cessation of infusion in 7 of the 9 patients. The infusion was stopped in 2 patients due to symptoms suggestive of IgE-mediated allergic reaction and cytokine storm. Five of the 8 patients who were re-challenged with the same therapy developed a similar reaction. However, the infusion was completed in 4 of the 5 patients after administration of intravenous diphenhydramine and/or hydrocortisone, or slowing the rate of infusion and subsequently cycles with the same agents were uneventful.

Conclusion—IRs to anti-neoplastic agents are rare. Though the clinical presentations are overlapping, most IRs are not IgE-mediated allergic reactions. Appropriate premedication and slow rate of infusion facilitates uneventful administration of the anti-neoplastic agents in subsequent cycles. Further study in a larger cohort of patients to identify biomarkers of hypersensitivity is warranted.

Keywords

anti-neoplastic agent; cytokine reaction; hypersensitivity; infusion reaction; monoclonal antibody; phase I

Introduction

Patients receiving repeated courses of chemotherapy are prone to develop infusion reactions (IRs), defined as unexpected reactions that cannot be explained by the known toxicity profile of the drug [1]. IRs can vary based on the type of agent administered, as well as, the duration, frequency of infusion and prior exposure to the inciting agent [2–7]. Some of the IRs are allergic reactions, which are typically IgE-mediated; while others are cytokine-mediated anaphylactoid reactions, generally referred as systemic infusion reactions (SIRs) [8]. IgE-mediated allergic reactions release proinflammatory mediators such as histamine and prostaglandin following prior sensitization to the same agent, and therefore manifest after six or seven courses of the therapy [9]. On the other hand, cytokine-mediated IRs are independent of prior sensitization and they usually manifest with the first or second infusion of the agent [10,9]. Anti-neoplastic agents that are commonly associated with IRs are platinum based compounds (cisplatin, carboplatin, oxaliplatin), taxanes, procarbazine, asparaginase or epipodophyllotoxins (teniposide, etoposide) [6,8,11].

Platinum based compounds are likely to cause acute IRs with extensive exposure. For example, oxaliplatin causes an acute reaction in 0.5%–25% of cases [8,12], which is usually mild to moderate and is life-threatening in <1% of reactions [8,12,13]. Most of these reactions occur after receiving the drug seven to eight times [2] as is the case with most IgE-mediated IRs. Most of them occur within the first few minutes of infusion and may progress rapidly from mild to severe IRs such as severe erythema, bronchospasm, and hypotension when re-challenged with the same agent [8,12].

On the other hand, IRs due to taxanes are mostly anaphylactoid reactions. They normally occur in 30% of patients; and with pre-medication decreases to <4% [8]. These reactions are dose dependent, and occur mostly within few minutes of infusion at first or second exposure, suggesting a non-IgE-mediated mechanism [14]. It has been postulated that these IRs may

be due to the effect of the drug on mast cells and basophils. Cremophor EL, the solvent in paclitaxel is also thought to be partially responsible, as it is known to induce histamine release and hypotension [8,15]. When drugs are infused in combination with each other, it becomes more difficult to identify the triggering agent. For example, taxanes can be administered with platinum-based drugs. However carboplatin related reactions vary in the timing and severity compared to taxanes [8].

More recently, recombinant antibodies have been developed for treatment of various cancers [16,17]. Chimeric antibodies are >50% human, humanized antibodies are >90%, and fully humanized antibodies are 100% human [8]. Though monoclonal antibodies are better tolerated than cytotoxic chemotherapeutic agents, some of them such as rituximab and trastuzumab can cause non-allergic IR within the first hour of infusion [8]. The incidence of IR due to monoclonal antibodies was highest for rituximab (77%), followed by trastuzumab (40%) and cetuximab (12%) [9]. They are cytokine-mediated [18]. Most of them occur 30 minutes to two hours into the infusion and unlike typical IgE-mediated reactions are usually mild [19]. However, in the rare event of cytokine-release syndrome, hypotension, bronchospasm, and urticaria that are typical of IgE-mediated allergic reactions have been reported with monoclonal antibodies, although the onset is generally much quicker in IgE-mediated allergic reactions, within minutes of starting the infusion [20]. The incidence of IR usually decreases with repeat infusions of monoclonal antibodies [19].

Patients who experience mild to moderate IRs, usually with taxanes or monoclonal antibodies are more likely to tolerate re-challenge with slower infusion rate and use of appropriate premedication than patients who experience severe IRs [8]. Disruption of therapy may be required for IR to platin compounds as more than 50% of the patients experience IR when re-challenged despite premedication [10]. This underscores the need for accurate assessment of IRs as physicians are often challenged to make treatment decisions such as discontinuation of an otherwise effective therapy versus face the risk of fatal IRs when re-challenged. Since the phase I program at The University of Texas MD Anderson Cancer Center is one of the largest for treating patients with advanced, refractory cancers, with the unique ability to capture IRs associated with use of conventional and novel cancer therapeutics, we conducted a retrospective chart review of the 597 consecutive patients with advanced cancer treated at The Clinical Center for Targeted Therapy (CCTT) to assess the prevalence and clinical presentation of IRs in phase I population.

Methods

We conducted a retrospective review of the electronic medical record of 597 consecutive patients with advanced cancer who were treated at the CCTT (outpatient treatment center) of the Department of Investigational Cancer Therapeutics (phase I clinical trials program) at The University of Texas MD Anderson Cancer Center from January 1, 2013 to November 30, 2013. This retrospective study was approved by the MD Anderson Cancer Center Institutional Review Board (IRB). All patients provided written informed consent before enrollment on a clinical trial during this period, and all the clinical trials were approved by the MD Anderson Cancer Center IRB.

We reviewed the electronic medical records of all the 597 patients who were seen and given chemotherapy orders in the CCTT and identified 9 patients who were ordered the Adult Hypersensitivity and Allergic Reaction order set from the Phase I Investigational Cancer Therapeutics clinic. In addition, 45 random patients who did not experience IRs were selected from the data set to serve as controls.

The study was designed to characterize the IRs patients develop to anti-neoplastic agents and to determine if re-challenge with the same drug is feasible with pre-medications prior to administration of the anti-neoplastic agents and/or slowing the rate of infusion. Therefore, data on the anti-neoplastic agents administered, lines of therapy, type of infusion reactions, rate of infusion at the time of reaction, duration of the infusion administered, pre-medication status, known drug allergies, prior reaction to the same agent, intervention used to treat IRs, dose modifications due to IRs, IRs associated with re-challenge with the same anti-neoplastic agent were collected besides demographic data such as age, gender, and primary tumor type. We assessed the severity of the IR based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [21].

Data Analysis

Patient characteristics were summarized using descriptive statistics. The Fisher's exact test or Wilcoxon rank sum test, as appropriate, was used to evaluate the association between the variables and occurrence of IR. All statistical tests were 2-sided, and $p = 0.05$ was considered statistically significant. Statistical analyses were carried out using SPSS (version 22.0; SPSS, Chicago, IL, USA)

Results

Patients

A total of 597 consecutive patients (Table 1) received anti neoplastic therapy, either targeted therapy (small molecules and/or monoclonal antibody), immune therapy, conventional chemotherapy, or a combination of these therapies, in the outpatient treatment center of the Department of Investigational Cancer Therapeutics (phase I clinical trials program) from January 1, 2013 to November 30, 2013. Of the 597 patients who received anti-neoplastic agents during this interval, 9 (1.5%) experienced IRs, as identified by the activation of Adult Hypersensitivity and Allergic Reaction order set from the Phase I Investigational Cancer Therapeutics clinic. In addition, 45 patients who did not experience IR were randomly selected to serve as controls. Demographic and baseline characteristics of these patients are summarized in Table 2.

Treatment

Of the 54 patients (cases, $n=9$; controls, $n=45$), 47 (87%) received targeted therapy either alone or in combination with chemotherapeutic agents (cases, $n=7$; controls, $n=40$). Of the remaining 7 patients, 5 received chemotherapeutic agents only (cases, $n=2$; controls, $n=3$), 1 patient received antibody drug conjugate (control), and 1 patient received vaccine (control).

Of the nine patients who experienced IRs, 7 (78%) received targeted therapy, either alone or in combination with chemotherapeutic agent, and 2 (22%) received conventional chemotherapy (Table 3). Of the seven patients who had IRs with a treatment that included a targeted agent, six (86%) received treatment with a monoclonal antibody (single agent, n=3; combination of monoclonal antibody therapies, n=2; combination of monoclonal antibody and chemotherapeutic agents, n=1). Of the 6 patients who received monoclonal antibody, 5 of them received anti-VEGF therapy.

Infusion Reactions

The IRs were observed during the first cycle of therapy in seven of the nine patients (except patient #1 and 9). IR was seen during the seventh cycle in patient #1, typical of patients receiving oxaliplatin therapy, and in the second cycle in patient #9, who also received oxaliplatin. The IRs observed in the nine patients on first occurrence were chills (n=5), itching, rash, and facial flushing (n=3 each), shortness of breath, hypertension, and hives (n=2 each), and nausea, rigor, abdominal cramps, dizziness, tachycardia, chest tightness, and prolonged QTc (n=1 each). The severity of all the IRs by CTCAE v4.03 criteria were either grade 1 or 2. There were no deaths reported due to IRs.

On an average, the IR's were observed 52 minutes (range, 23–80) after initiating the therapy in 7 patients, and in 2 patients (patient #6 and 8), 5 and 15 minutes after completion of therapy respectively. Besides stopping the infusion, all the patients except 1 (patient #8) were treated with intravenous diphenhydramine and hydrocortisone; patient # 8 was treated with intravenous atropine for abdominal cramps. In addition, a patient (patient #6) was treated with nasal oxygen and intravenous metoclopramide for shortness of breath and nausea respectively. All the IRs were reversible with appropriate symptomatic treatment. Among the seven patients in whom the infusion was temporarily held, the infusion was reinitiated at a slower rate (except patient #7) and completed in five of them (except patient #1 and 2). Patient #1 had facial flushing and rash in the arms and neck 65 minutes after starting oxaliplatin (7th cycle). Despite resolution of the reaction within an hour of stopping the infusion, the infusion was not resumed in this cycle in view of the well-established occurrence of IgE-mediated allergic reaction to oxaliplatin after 5 cycles of therapy [22]. Patient #2 had chills, shortness of breath, tachycardia, hypertension and prolonged QTc interval on EKG, 44 minutes into the infusion with anti-TGFβRII monoclonal antibody. Though the patient recovered from the IR, the drug was held by the sponsor due to a cytokine-storm like reaction observed in another patient at a different site. The IRs observed in nine patients and their management is presented in Table 3.

Re-challenge with the same agent

Eight out of nine patients were re-challenged with the same agent (Table 3). One patient (patient #9) was not re-challenged as the patient came off the treatment for progression of disease. Three patients (patient #1, 4, and 6) completed subsequent cycles with the same therapeutic agents uneventfully. Five of the eight patients (patient #2, 3, 5, 7, and 8) developed similar reactions when re-challenged with the same agent. However, four of the five patients (except patient #7) completed therapy following administration of additional medications such as intravenous diphenhydramine and/or hydrocortisone, or slowing the rate

of infusion. The one patient for whom infusion was stopped (patient #7) was transferred to emergency care for observation after administration of intravenous diphenhydramine, hydrocortisone and nasal oxygen for severe itching, facial swelling and chest tightness. Nevertheless, the symptoms resolved two hours after stopping the infusion and the patient completed three more cycles of the same therapy uneventfully but with adequate premedication, before the patient was taken off the treatment for disease progression. Four of the five patients who failed re-challenge initially (except patient #2) received more cycles of therapy with the same agent with appropriate premedication. The fifth patient (patient #2) did not receive further therapy due to progression of disease and was referred to hospice.

Factors associated with IR

The distribution of baseline demographic, clinical, laboratory, and treatment characteristics of 9 patients who had IR and 45 patients who served as controls have been tabulated (Table 2). There appeared to be no statistically significant difference in characteristics between patients who had IR and the control group to suggest identification of a possible risk factor for IR. However, there is increased occurrence of an IR in patients who received a treatment that included a targeted agent (7 of 9 patients who had IR; $p=0.068$), more specifically a monoclonal antibody (6 of 7 patients who received a targeted agent and had an IR).

Discussion

In the recent past, the therapeutic arsenal for advanced cancer has evolved dramatically leading to the increased investigation of targeted agents and monoclonal antibodies [23]. Though serious drug-related toxicity and death is reportedly low in phase I trials, 10.3% and 0.4% respectively [24], many intravenous anti-neoplastic agents have the potential to cause IRs [19]. Therefore, it is important to have an expanded knowledge base regarding IRs, and strategies to prevent and/or manage them.

In our experience at the CCTT, we observed that the occurrence of IRs was relatively low (1.5%; 9 of 597 patients). Effective use of premedication and institution of standing orders that outline the next steps of immediate intervention in the rare event of an IR may have attributed to the low rate of IR in our institution. The IRs were grade 2, non-fatal and were managed by administration of antihistamines, corticosteroids and reinitiating the infusion at a slower rate after a temporary cessation of infusion in majority of the patients.

Consistent with previously published reports of IRs in 77% of patients treated with rituximab, 40% with trastuzumab, 16–19% with cetuximab, and 5% with panitumumab [15], 20% (6 out of 30) of the patients who received treatment in our center that included a monoclonal antibody had IR. Six of the nine (66%) patients with IRs received monoclonal antibodies (fully human monoclonal antibodies, $n=3$; combination of fully human and recombinant monoclonal antibody, $n=2$; and, recombinant monoclonal antibody, $n=1$) either as single-agent or as a combination. The IRs occurred during the first course of the therapy. Though they were mild and benign in nature, they did not follow a characteristic pattern. Patient #5 and 6 received single-agent monoclonal antibody. While patient #5 had mild reactions like itching, chills and facial rash, patient #7 in addition had chest tightness, shortness of breath, hypertension and dizziness. However, the reaction resolved within an

hour of stopping the infusion, though nasal oxygen was used besides the conventional antihistamine and corticosteroid to treat this patient. Hypertension was a known side effect of the anti-VEGF therapy the patient was receiving. Patient #3 and 7 who received a combination of monoclonal antibodies had similar IRs, itching, rashes, and hives. Though the clinical presentation was indistinguishable from the IgE-mediated allergic reaction, the symptoms resolved within an hour of temporary cessation of therapy and the management of IR remained the same. Anecdotally, patient #2 had shortness of breath, chills, tachycardia, hypertension, and prolonged QTc 44 minutes after initiating an infusion with monoclonal antibody. Though the patient recovered from the IR with conventional administration of antihistamine and corticosteroid and cessation of infusion, the drug was held by the sponsor due to a cytokine-storm like reaction observed in another patient at a different site. Invariably IRs related to monoclonal antibodies are due to release of cytokines into circulation [25]. In some instances however, massive amount of tumor necrosis factor (TNF)- α and interleukin (IL)-6 may be released into the circulation during the first infusion precipitating life threatening IRs that characterize a cytokine storm [9] as seen in patient #2. Interestingly, patient #2 developed IR to fully human monoclonal antibody. It appears that the occurrence of IR to monoclonal antibody may not be related to the humanized content as evident from our experience (patient #2, 5, and 6). Similar IR to fully human monoclonal antibody has also been described by Ostensborg et al, where Ofatumumab, a fully human monoclonal antibody, was associated with infusion-related adverse events on the first day of infusion in 46% of 59 patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab and in 38% of 79 patients with bulky fludarabine-refractory disease [26]. When the treatment was re-initiated in 5 of the 6 patients after administration of diphenhydramine/hydrocortisone, and/or slowing the infusion, all of them were able to tolerate the therapy. It has been hypothesized that the mediators of hypersensitivity depleted during the initial reaction could not be replenished in the short interval of time, facilitating completion of therapy without further IR [27,28]. Patient #8, who received a combination of chemotherapeutic agent and a monoclonal antibody, had abdominal cramps shortly after completion of the infusion, which was intermittent in nature. Though the Adult Hypersensitivity and Allergic Reaction order set was activated for this patient, classifying it as IR was uncertain. The multi-specialty work-up initially attributed the abdominal cramp to constipation associated with use of narcotic analgesics. However, following imaging studies, it was concluded as chronic referral pain consequent to pleural disease. Despite the overlap in the clinical presentation, based on our experience in CCTT and documentation by several others in literature [15,19], the management of IR is the same. The importance of close monitoring and the need to respond immediately with temporary cessation of the infusion and appropriate medical intervention cannot be emphasized enough.

In our center, of the eight patients re-challenged with the same therapeutic agent, five of them (patient #2, 3, 5, 7 and 8) had IRs similar to the reaction during initial exposure and all the five had IR to monoclonal antibodies. Though re-challenge with the monoclonal antibody is a reasonable option as majority of IRs to monoclonal antibodies is not an IgE-mediated allergic reaction, the addition of appropriate premedication and/or slowing of infusion appears to be a requirement. However, routine administration of premedication prior to infusion of monoclonal antibodies has been a subject of debate. Timoney et al [29]

advocated the cessation of diphenhydramine after the initial two cycles of cetuximab as no severe life threatening reactions occurred when 746 doses of cetuximab was given in 115 patients without premedication with diphenhydramine [29]. Contrary to this finding, we observed that patient #5 who did not receive any premedication and patient #7 who received only antihistamine as premedication during re-challenge had IRs similar to the initial cycle. But, with use of both antihistamine and corticosteroid as premedication the subsequent cycles were uneventful. Our experience is remarkably consistent with the observations made by Siena et al [30], who have reported that IR was 1% in patients who received both antihistamine and corticosteroid premedication compared to 4.7% among patients who received antihistamine alone. Despite these discrepancies, premedications are often recommended to prevent cytokine-release syndrome [19]. The IRs appeared to subside with each subsequent dose and all of them received three to six courses of the same therapy without further complications, except patient #2, who had to come off the study due to disease progression. None of them were required to discontinue the therapy. This declining reaction to subsequent dose is possibly due to a reduction in the tumor burden resulting in proportionate drop in cytokine release [31].

IRs with platins and taxanes are well documented and therapeutic recommendations including successful desensitizing protocols have been described for management of IRs [32,6,28,10]. In our experience mild IRs were reported in two patients (patient # 1 and 9) following administration of oxaliplatin in combination with 5 fluorouracil, folinic acid and lenalidomide. The first patient (patient #1) presented with IRs characteristic to platin compounds [12]; facial flushing and rash in the arms and neck observed 65 minutes into the seventh cycle of the therapy. Though the infusion was discontinued for this cycle based on the assumption of an IgE-mediated allergic reaction, the patient received seven additional cycles of therapy at reduced dosage and slow infusion rate. On the contrary, the second patient (patient #9) reported chills and rigors 80 minutes into the second course of the therapy. Though this patient completed the cycle on re-initiating at a slower rate, came off the study immediately thereafter for progression of disease.

In the absence of predictive risk factors to suggest association with IR, it is important to exercise vigilance while administering these agents to cancer patients as quick recognition of symptoms and astute management can prevent the evolution of IR to more complicated, sometimes fatal events. Certain preventive measures that may be beneficial are elicitation of thorough medical history including history of allergies and prior exposure to the same agent. Interestingly, information on geographic location may be important as anaphylactic reactions have been reported within few minutes of initiating the first course of cetuximab in patients from North Carolina, Arkansas, Missouri, Virginia, and Tennessee [33]. This was attributed to the presence of IgE antibodies against galactose- α -1,3-galactose from prior tick bite. This compound is also found on the Fab segment of the cetuximab antibody and allows for efficient cross-linking of IgE receptors on mast cells [33]. Further, skin testing may serve as a risk-assessment tool to diagnose hypersensitivity to certain drugs such as platin compounds [34,28,10].

This study is not without limitations. The incidence of mild IRs in our study population may be an underestimation for several reasons. We had included only those patients who received

anti-neoplastic therapy in the outpatient treatment center of our department. IR was not clearly defined and minor IRs such as itching and redness may have been missed due to lack of standard reporting method. Data was collected by performing a query of the Adult Hypersensitivity and Allergic Reaction order set generated for outpatients receiving treatment with a phase I protocol in the ambulatory treatment centers. As a result we may have failed to capture some patients who had IRs. Further, administration of premedication as a standard procedure to minimize the risk for infusion reactions may have abrogated the occurrence of some mild to moderate IRs. Due to rapid progression of the disease in phase I population, patients may have come off the study after two cycles, whereas IgE-mediated IRs are more likely to occur after five or six cycles of therapy. In addition, the small sample size and significant overlapping of symptoms made it difficult to characterize the IR. Moreover, skin testing was not done and serum tryptase levels were not assessed at the time of the IR to distinguish between IgE-mediated allergic reaction and cytokine-mediated IR. Ideally, serum tryptase levels $>11.4\text{ng/mL}$ within 3 hours of the event, which is indicative of mast cell degranulation, may help to distinguish IgE-mediated allergic/anaphylactic reactions from non-IgE-mediated reactions [35,36].

In conclusion, based on our experience in CCTT, phase I trials is a relatively safe option for patients with advanced, refractory cancer as the occurrence of IR is relatively low at 1.5% (9 of 597 patients). Most of the IRs were not IgE-mediated allergic reaction, but were cytokine-mediated IRs to monoclonal antibodies. However, the risk of developing IRs should not be underestimated as more novel compounds are being investigated. Despite premedication and our best efforts, IRs are unavoidable. As mild reactions have the propensity to rapidly progress to fatal incidents, it is imperative for clinicians to recognize the symptoms, make accurate assessment and initiate prompt action. Moreover, similar clinical presentations despite mechanistic differences make it difficult for the physicians to differentiate between an IgE mediated and non-IgE-mediated IR. Nevertheless, adequate knowledge of underlying mechanisms, accurate grading, and preparedness to manage a potential IR will help the physician to differentiate between IgE-mediated allergic reaction and non-IgE-mediated reaction, accomplish a risk benefit analysis, and make an informed decision on desensitization and re-challenging the patient with an otherwise beneficial same therapeutic agent. Considering the heterogeneity of the IRs, further study in a larger cohort of patients to identify biomarkers of hypersensitivity is warranted.

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Table 1

Baseline patient and treatment characteristics of the study population (n=597 patients)

Variable	Group	N (%) n=597
Age, n (%)	60 years	340 (57)
	>60 years	257 (43)
Sex, n (%)	Female	324 (54)
	Male	273 (46)
Tumor type, n (%)	Upper GI	30 (5)
	Colorectal	59 (10)
	Gynecologic	87 (15)
	Head and Neck	58 (10)
	Lung	42 (7)
	Pancreas	14 (2)
	Other	151 (25)
	Breast	70 (12)
	Gastrointestinal	26 (4)
	Genitourinary	39 (7)
	Hepatocellular	21 (4)
ECOG PS, n (%)	0	101 (17)
	1	455 (76)
	2	41 (7)
Combination therapy, n (%)	Yes	464 (78)
	No	133 (22)
Treatment type, n (%)	Chemotherapeutic only	37 (6)
	Targeted only	245 (41)
	Chemotherapeutic + Targeted	273 (46)
	Other	42 (7)
Targeted therapy (n=518) that included a monoclonal antibody, n (%)	Yes	329 (64)
	No	189 (36)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; PS, performance status

Table 2

Baseline patient and treatment characteristics of 9 patients with IRs and 45 controls

Variable	Group	Cases (n=9)	Controls (n=45)	p-value
Age (years)	Median (Range)	59 (36–69)	60 (20–79)	
Age, n (%)	60 years	5 (56)	23 (51)	1.000
	>60 years	4 (44)	22 (49)	
Sex, n (%)	Female	5 (56)	23 (51)	1.000
	Male	4 (44)	22 (49)	
Tumor type, n (%)	Upper GI	2 (22)	3 (7)	0.355
	Colorectal	1 (11)	2 (4)	
	Gynecologic	1 (11)	8 (18)	
	Head and Neck	1 (11)	3 (7)	
	Lung	1 (11)	4 (9)	
	Pancreas	1 (11)	0 (0)	
	Other	2 (22)	14 (31)	
	Breast	0 (0)	4 (9)	
	Genitourinary	0 (0)	4 (9)	
	Hepatocellular	0 (0)	3 (7)	
ECOG PS, n (%)	0	3 (33)	7 (16)	0.427
	1	6 (67)	34 (76)	
	2	0 (0)	4 (9)	
Combination therapy, n (%)	Yes	5 (56)	37 (82)	0.098
	No	4 (44)	8 (18)	
Treatment type, n (%)	Chemotherapeutic only	2 (22)	3 (7)	0.068
	Targeted only	6 (67)	17 (38)	
	Chemotherapeutic + Targeted	1 (11)	23 (51)	
	Other	0 (0)	2 (4)	
Targeted therapy that included a monoclonal antibody (n=47; cases, n=7; controls, n=40)	Yes	6 (86)	24 (60)	0.396
	No	1 (14)	16 (40)	
Hemoglobin (g/dL)	Median (Range)	12.4 (10.6–13.8)	11.4 (8.3–16.8)	0.390
White blood count (K/ μ L)	Median (Range)	5.1 (2.8–15.8)	6.2 (1.9–30.2)	0.862
Absolute neutrophil count (K/ μ L)	Median (Range)	3.3 (1.5–14.3)	3.7 (0.9–28.4)	0.754
Absolute basophil count (K/ μ L)	Median (Range)	0.02 (0.01–0.03)	0.02 (0.00–0.09)	0.924
Absolute eosinophil count (K/ μ L)	Median (Range)	0.09 (0.02–0.37)	0.08 (0.00–0.80)	0.917

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; IR, infusion reaction; PS, performance status

IRs reactions observed at first occurrence in 9 patients treated at CCTT

Table 3

Patient #	Anti-neoplastic agent	Pre-medication given	Duration of infusion prior to reaction (minutes)	Symptoms of reaction	CTCEA grade	Treatment given	Next cycle	# of infusions prior to this reaction	# of infusions post reaction ^a	Infusion reaction with re-challenge
1	Chemotherapy (combination)	diphenhydramine, dexamethasone, acetaminophen, famotidine, palonosetron	65	facial flushing, rash to arms and neck	2	diphenhydramine, hydrocortisone, infusion stopped	Oxaliplatin dose was decreased and duration of infusion increased from 2 to 3 hours	6	5 +	no
2	Targeted- Monoclonal antibody (single-agent)	diphenhydramine, dexamethasone, acetaminophen, famotidine	44	chills, shortness of breath, tachycardia hypertension, EKG: prolonged QT c	2	diphenhydramine, hydrocortisone, infusion stopped	dose of dexamethasone increased	none	1	yes
3	Targeted- Monoclonal antibody (combination)	none	59	Itching, hives	1	diphenhydramine, hydrocortisone	premedication added	none	4+	yes
4	Targeted- Small molecule (single-agent)	none	23	facial flushing	1	diphenhydramine, hydrocortisone, reinitiated at a slower infusion rate	slower rate of infusion	none	2+	no
5	Targeted- Monoclonal antibody (single-agent)	none	35	itching (arms, thighs, and abdomen), chills, rash	1	diphenhydramine, hydrocortisone, deneroxol, reinitiated at a slower infusion rate	premedication added to third cycle and beyond	none	6	yes
6	Targeted- Monoclonal antibody (single-agent)	none	completed (60 min) and 5 min after infusion	chest tightness, shortness of breath, facial flushing, chills, nausea, hypertension, dizziness	2	diphenhydramine, hydrocortisone, metoclopramide, nasal oxygen	premedication added	none	3	no
7	Targeted- Monoclonal antibody (combination)	none	55	Itching, redness, hives	1	diphenhydramine, hydrocortisone	premedication added	none	4	yes
8	Monoclonal antibody + chemotherapy	dexamethasone, ondansetron	completed (90 min) and 15 minutes after infusion	abdominal cramps	1	atropine		none	6	yes
9	Chemotherapy	dexamethasone, ondansetron	80	chills and rigors	2	diphenhydramine, hydrocortisone, reinitiated at a slower infusion rate		1	none	-

^a+, ” sign indicates patient is continuing on the therapy at the time of data cut off.

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events; EKG, electrocardiogram