Assessment of safety of a rapid desensitization regimen for patients with hypersensitivity reactions to chemotherapy infusions

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Background Hypersensitivity reactions (HSRs) to chemotherapy agents occur with relatively high frequency with some of the most widely used chemotherapeutic drug classes. Desensitization using a standard 12-step protocol has been successful, but takes about 6.5 hours. Limited studies have shown that a faster protocol may also be safe.

Objective To determine when desensitization could be safely speeded up.

Methods Patients with documented HSRs (n = 24) were desensitized initially with the standard 12-step protocol for 1 or 2 treatments, for a total of 180 desensitizations. Those patients who had negative skin testing and who tolerated the desensitizations were switched to the more rapid desensitization protocol (n = 16).

Results All 16 patients were successfully desensitized, having received the full dose of their chemotherapy. Eight patients were not advanced to the rapid protocol because they had reactions during initial desensitizations or they had a positive skin test; all of them were successfully desensitized using the 12-step protocol at the slower rate of infusion. These data present criteria for defining which patients may be safely transitioned to a rapid desensitization protocol.

Limitation Most of the patients in the study (21 of 24) were women.

Conclusions Patients with HSRs to chemotherapy agents, who tolerate an initial 12-step desensitization and have a negative skin test, can be advanced to a more rapid protocol. It is likely that patients with HSRs to the taxanes can be started on the more rapid protocol without starting on the 12-step protocol.

Platinum compounds (carboplatin, cisplatin, and oxaliplatin) and taxanes (paclitaxel, docetaxel, and cabazitaxel) are widely used in first- and second-line treatments of many solid tumors, including ovarian, lung, breast, esophageal, colon, and prostate cancers. The monoclonal antibodies include rituximab and trastuzumab. Rituximab is the standard of care, alone or in combination with chemotherapy, for the management of CD20-positive lymphoproliferative conditions such as B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia. Trastuzumab is used for human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

Observed hypersensitivity reactions in patients who receive chemotherapy range from mild (itching, flushing, and rashes), to life threatening (hypotension, dyspnea, and seizures), to fatal.[1-6] HSRs can involve the skin (itching, flushing, rash), the respiratory tract (dyspnea, wheezing, hypoxia, and airway blockage due to angioedema), the cardiovascular system (hypotension, arrythemia, and myocardial infarction), and the gastrointestinal system (nausea, vomiting, and diarrhea). The reactions are common. In one study, carboplatin was found to cause HSRs in more than 27% of patients who received more than 7 treatments, and one half of those reactions were moderate to severe and included wheezing and hypotension.[2] Paclitaxel causes HSRs in 40% of patients on the first infusion, although it can be reduced to less than 10% with premedication with dexamethasone.[7] In addition, fatal reactions can occur, even with adequate premedication. For instance, docetaxel has caused fatal HSRs, even in patients who received the recommended 3-day dexametha-

Manuscript received November 6, 2012; accepted January 16, 2013.

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Disclosures The authors have no disclosures.

Commun Oncol 2013;10:42-46

sone premedication.[8,9] The platins and rituximab have also caused documented deaths.[3,4,10]

The goal of this study was to define the criteria for using a rapid desensitization protocol to safely treat patients who had previous HSRs.

Methods

For the past 3 years, the outpatient cancer treatment center at Dekalb Medical Center in Decatur, Georgia, has successfully used a 12-step protocol,[11-14] developed by Dr. Mariana Castells, to treat patients with a history of HSRs to their chemotherapy medications.[15] In the current study, all patients who had documented HSRs and who were referred to our center for desensitization were treated initially with the 12-step protocol for 1 or 2 treatments. Briefly, the procedure consisted of administering 3 10-fold dilutions of the chemotherapy agent, each in 250 ml of diluents, in 12-16 steps, over a period of 6.5 to 8 hours. Systemic reactions during an infusion were treated by stopping the infusion temporarily and then restarting at the same point. On subsequent infusions, that step could be extended or an additional step inserted at that point to slow the infusion. If needed, additional H1 antihistamine was used. Epinephrine was used if needed.

A sample protocol, used for a patient who was allergic to carboplatin and was to receive a dose of 555 mg, is shown in Tables 1 and 2. Total time for the desensitization protocol was 339.38 minutes (5.66 hours). A previous study, using the 12-step protocol with 100 ml bags, has shown that the use of a more rapid desensitization protocol can be safely administered.[16] In our study, patients who tolerated the initial infusions without any symptoms and for whom skin tests were negative, were advanced to this more rapid desensitization protocol.

TABLE 1 Formulation of carboplatin dilutions

	ml per bag	mg per ml	mg per bag
IV Bag 1	250	0.022	5.550
IV Bag 2	250	0.222	55.500
IV Bag 3	250	2.203	550.632[a]

[a]Total dose is about 555 mg because Bag 1 and Bag 2 are only partially administered.

TABLE 3 Carboplatin dilutions for rapid protocol using 100 ml bags

	ml per bag	mg per ml	mg per bag
IV Bag 1	100	0.056	5.550
IV Bag 2	100	0.555	55.500
IV Bag 3	100	5.441	544.080[a]

[a]Total dose is about 555 because Bag 1 and Bag 2 are only partially administered.

The more rapid protocol was done by adding the chemotherapy to diluents to make a total volume of 100 ml, in each of the 3 bags, instead of the usual 250 ml total volume of each bag. These calculations are shown for a patient receiving a total carboplatin dose of 555 mg in Tables 3 and 4. The total time for the desensitization was reduced to 226.88 min (3.78 hours).

For some infusions, the use of 100 ml for each bag would have resulted in a concentration that would be too viscous for easy infusion. In these cases, the 250 ml total for each bag was used but a more rapid infusion rate

TABLE 2 Protocol for administration of 555 mg carboplatin

Step	Bag	Rate, ml/hr	Time, min[a]	Volume infused, ml	Dose administered, mg	Cumulative dose, mg
1	1	2.0	15	0.500	0.011	0.011
2	1	5.0	15	1.25	0.028	0.039
3	1	10.0	15	2.5	0.056	0.094
4	1	20.0	15	5.0	0.111	0.205
5	2	5.0	15	1.25	0.278	0.483
6	2	10.0	15	2.5	0.555	1.038
7	2	20.0	15	5.0	1.110	2.148
8	2	40.0	15	10.0	2.220	4.368
9	3	10.0	15	2.5	5.506	9.874
10	3	20.0	15	5.0	11.013	20.887
11	3	40.0	15	10.0	22.025	42.912
12	3	80.0	174.38	232.5	512.088	555.000

[a]Total time, 339.38 min (5.66 h).

TABLE 4 Rapid protocol for the administration of 555 mg of carboplatin using 100 ml bags

Step	Bag	Rate, ml/hr	Time, min[a]	Volume infused, ml	Dose administered, mg	Cumulative dose, mg
1	1	2.0	15	0.500	0.028	0.028
2	1	5.0	15	1.25	0.069	0.097
3	1	10.0	15	2.5	0.139	0.236
4	1	20.0	15	5	0.278	0.513
5	2	5.0	15	1.25	0.694	1.207
6	2	10.0	15	2.5	1.388	2.595
7	2	20.0	15	5	2.775	5.370
8	2	40.0	15	10	5.550	10.920
9	3	10.0	15	2.5	13.602	24.522
10	3	20.0	15	5	27.204	51.726
11	3	40.0	15	10	54.408	106.134
12	3	80.0	61.875	82.5	448.866	555.000

[a]Total time, 226.88 min (3.78 h).

TABLE 5 Carboplatin dilutions for rapid protocol using 250 ml bags

	ml per bag	mg per ml	mg per bag
IV Bag 1	250	0.022	5.550
IV Bag 2	250	0.222	55.500
IV Bag 3	250	2.203	550.632[a]

[a]Total dose is about 555 because Bag 1 and Bag 2 are only partially administered.

resulted in the same total time for the desensitization. This is shown in Tables 5 and 6.

Patients were given H1 and H2 antihistamines to take the night before and the morning of the procedure. Other premeds, including steroids, antileukotriene agents, and antiprostaglandins were individualized for each patient. However, the maximum steroid dose consisted of 1 dose of prednisone 20 mg the night before the infusion and whatever the protocol was for the drug being administered on the morning of the infusion.

Results

In all, 24 patients were enrolled in the study, of whom 16 were advanced to the rapid protocol. All 16 were successfully desensitized, having received the full dose of their

TABLE 6 Rapid protocol for the administration of 555 mg of carboplatin using 250 ml bags

Step	Bag	Rate, ml/hr	Time, min[a]	Volume infused, ml	Dose administered, mg	Cumulative dose, mg
1	1	2.0	15	0.500	0.011	0.011
2	1	5.0	15	1.25	0.028	0.039
3	1	10.0	15	2.5	0.056	0.94
4	1	20.0	15	5.0	0.111	0.205
5	2	5.0	15	1.25	0.278	0.483
6	2	10.0	15	2.5	0.555	1.38
7	2	20.0	15	5.0	1.110	2.148
8	2	40.0	15	10.0	2.220	4.368
9	3	25.0	15	6.3	13.766	18.134
10	3	50.0	15	13.0	27.532	45.665
11	3	100.0	15	25.0	55.063	100.728
12	3	200.0	61.875	206.3	454.272	555.000

[a]Total time, 226.88 min (3.78 h).

TABLE 7 Patients advanced to rapid infusions

Patient number	Age, y	Cancer type	Drug	No. of desensitizations[a]	Reactions
1	65	Breast	Taxotere	4	Itching, flushing, dyspnea
2	76	Ovarian	Taxol	15	Flushing, dyspnea
3	51	Ovarian	Carboplatin	18	Hypotension, stomach pain, vomiting
4	47	Breast	Taxotere	5	Flushing, dyspnea
5	64	Lung	Taxotere	25	Flushing, back pain, severe dyspnea
6	68	Lung	Taxol	5	Flushing, dyspnea, chest tightness
7	50	Breast	Trastuzumab	20	Dyspnea, back pain, shaking chills
8	67	Ovarian	Taxol, taxotere	8	Flushing
9	44	Ovarian	Taxol, taxotere	4	Tingling, numbness
10	70	Fallopian tube	Taxotere	7	Flushing, dyspnea, cough, back pain
11	64	Colon	Oxaliplatin	5	Dyspnea, anxiety, chest tightness
12	45	Breast	Taxotere	2	Vomiting
13	73	Uterine	Taxol	2	Flushing, back pain
14	71	Colon	Oxaliplatin	7	Flushing, dyspnea
15	53	Breast	Trastuzumab	7	Flushing, dyspnea, chest tightness
16	50	Ovarian, uterine	Carboplatin	2	Flushing, decreased oxygen saturation

[a]Total no. desensitizations, 136.

chemotherapy. They received a total of 136 desensitizations. The details are summarized in Table 7. Eight patients were not advanced to the rapid protocol because they had reactions during their initial desensitizations or because they developed a positive skin test. They received a total of 44 desensitizations. All were successfully desensitized using the 12-step protocol at the slower rate of infusion. The details for the patients who were not advanced are summarized in Table 8.

Discussion

This paper presents the results of 23 consecutive patients who were referred for documented HSRs and 1 patient who was referred for a positive skin test to carboplatin. Of the 24 patients, 16 met the criteria to be advanced to a more rapid desensitization. They were all successfully desensitized, receiving 136 desensitizations. Most of the desensitizations were to the taxanes, with only 2 each of carboplatin and oxaliplatin. It is

TABLE 8 Patients not advanced to rapid infusions[a]

Patient number	Age, y	Cancer type	Drug	No. of desensitizations	Reactions
1	74	Ovarian	Carboplatin	7	Flushing, respiratory distress
2	58	Colon	Oxaliplatin	7	Nausea, vomiting, severe back pain
3	54	Ovarian	Carboplatin	2	Flushing, severe itching, dyspnea, nausea, rash, diaphoresis
4	57	Ovarian	Carboplatin	6	Unavailable
5	63	Ovarian	Carboplatin	6	Positive skin test
6	50	Ovarian	Carboplatin	2	Intense burning of skin, rash
7	59	Ovarian	Carboplatin	12	Flushing, itching, cough, nausea
8	59	Endometrial	Carboplatin	2	Cough, nausea

[a]Total no. desensitizations, 44.

interesting that all those who could not be advanced, were taking carboplatin or oxaliplatin. This suggests that the more rapid protocol might be applicable to all taxane reactions. This will now be the desensitization used for all patients referred to our center for desensitization to the taxanes.

This research shows that patients who have HSRs to chemotherapy agents, who tolerate an initial 12-step desensitization, and who have a negative skin test, can be advanced to a more rapid protocol. It also seems likely that all patients with HSRs to the taxanes can be started on the more rapid protocol, even without starting on the 12-step protocol. Further research is needed to determine if patients with a systemic reaction to carboplatin or trastuzumab, who tolerate a standard 12-step protocol for desensitization, but then develop a positive skin test, can still be advanced to a more rapid infusion.

Acknowledgments

The authors wish to thank Dr. Mariana Castells for her pioneering work in establishing protocols for desensitization of patients with allergic reactions to chemotherapy and for her advice and encouragement. We also wish to thank our referring physicians, Dr Cheryl Jones, Dr Rodolfo Bordoni, Dr Lynn Zemsky, Dr Jayanthi Srinivasiah, Dr Simbo Anduloju, Dr Kristina Bowen, Dr Pradeep Jolly, and Dr Crain Garrot (Georgia Cancer Specialists); Dr Hiba Tamim (Atlanta Cancer Care); Dr Barry Yaffe and Dr Harvey Hamrick (Kaiser Permanente); Dr Sarah Hosford (Midtown Gyn Oncology); Dr Allan Freedman (Suburban Hematology-Oncology Associates) for trusting us with the care of their patients.

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