CARBOPLATIN HYPERSENSITIVITY REACTIONS

BACKGROUND[1-4]

It is well-recognized that patients receiving carboplatin as second-line treatment of ovarian cancer have at least a modest risk for experiencing hypersensitivity reactions.[1] The onset of reactions is unpredictable and they could occur immediately upon initiation of the drug infusion or may not be seen until one half or more of the infusion has been administered to the patient. On the other hand, the onset of the reactions has also been reported in patients receiving more than six cumulative courses. The symptoms associated with the reactions range from a minor rash to diffuse erythroderma, pruritis, severe anxiety, dyspnea, tachycardia, hypotension, and in severe cases, death. Several management strategies[2-5] including heavy premedication, increased infusion time, intradermal skin testing[4], and desensitization have been suggested. Literature[2-5] has reported the success of continued carboplatin treatment via desensitization in patients who experienced moderate to severe hypersensitivity reactions.

TREATMENT ALGORITHM

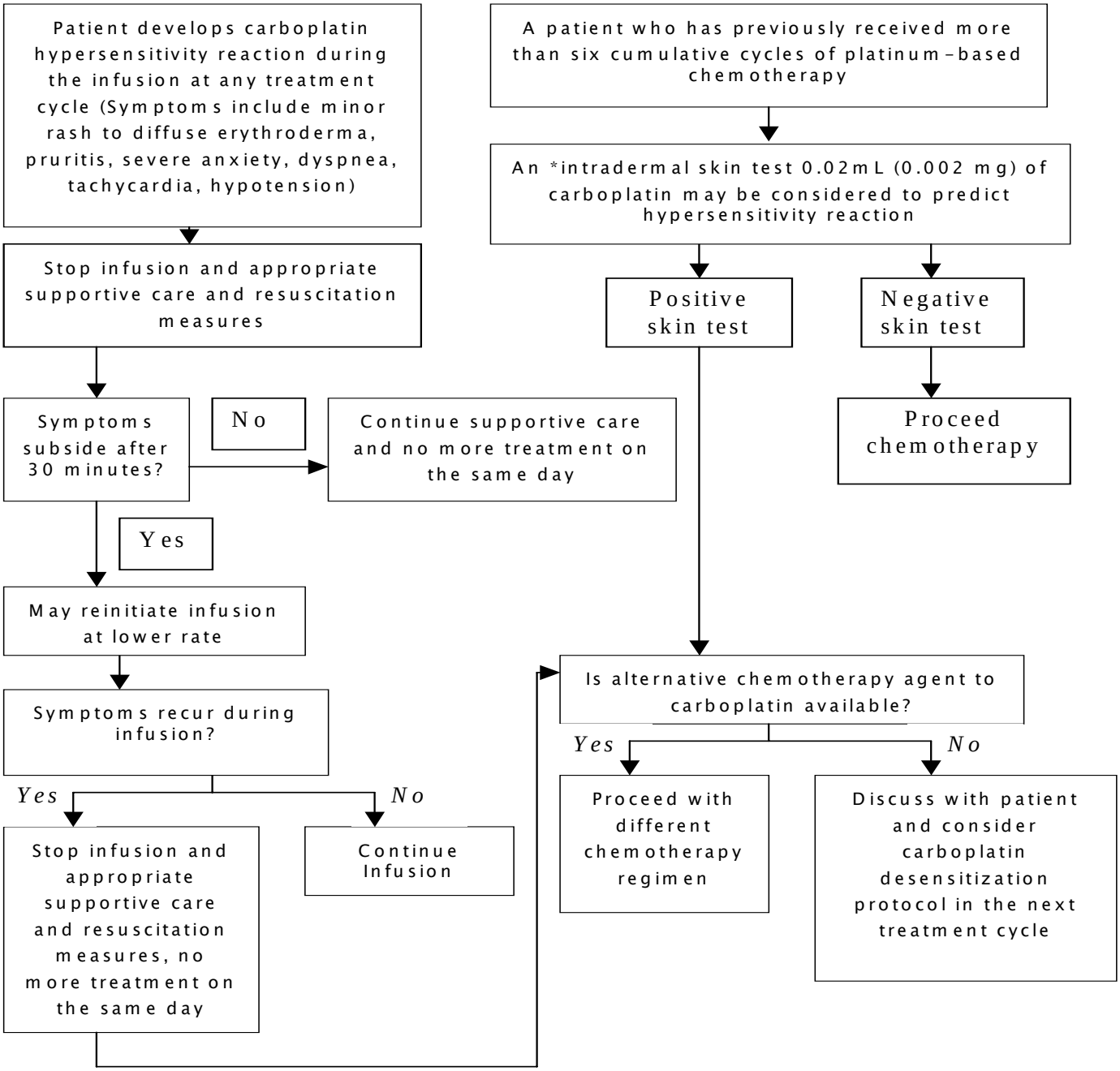
A. TREATMENT OF HYPERSENSITIVITY REACTIONS[1]

1. Discontinue infusion.
2. Administer 50 mg diphenhydramine IV and 100 mg hydrocortisone IV immediately.
3. If hypotension is present, administer epinephrine 0.35-0.5 mL IV every 15 - 20 minutes until the reaction subsides or a total of six doses are given.
4. If hypotension is present that does not respond to epinephrine, administer IV fluids.
5. If wheezing is present that is not responsive to epinephrine, administer 0.35 mL of nebulized albuterol solution.
6. Depending on severity of the reaction, the infusion may be reinitiated in 30 minutes after the symptoms have subsided.

B. DESENSITIZATION PROTOCOL[2-4]

For patients who experience a second hypersensitivity reaction after reinitiation of the carboplatin infusion, the clinician should discuss with their patients an alternative chemotherapy regimen if available or consideration of a carboplatin desensitization protocol (see protocols on next pages).

TREATMENT ALGORITHM FOR CARBOPLATIN HYPERSENSITIVITY REACTIONS



*A positive test is defined as an observation of at least a 5mm wheal with a surrounding flare after 15 minutes.

NOTE: Premedication schedule: dexamethasone 20 mg orally 12 hours, 6 hours, and 30 minutes before the infusion; 30 minutes prior to the desensitization administer diphenhydramine 50 mg IV and H_2 blockers (cimetidine 300 mg or ranitidine 50 mg IV).

CARBOPLATIN DESENSITIZATION PROTOCOL

Modified Dana Farber protocol for a Standard 3-solution, 12-step desensitization protocol over 6 hours for carboplatin [4]

Total dose	[a]Prescribed dose	Solution concentration (mg/mL)	Dose in each solution (mg)
Solution A	500 mL	0.01	5
Solution B	500 mL	0.1	50
Solution C	Depending on the prescribed dose	1	Prescribed dose

Step	Solution	Rate (mL/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	A	4	15	0.01	0.01
2	A	10	15	0.025	0.035
3	A	20	15	0.05	0.085
4	A	40	15	0.1	0.185
If the patient continues without reactions at this point, proceed to step 5. Solution B may be started.					
5	B	10	15	0.25	0.435
6	B	20	15	0.5	0.935
7	B	40	15	1	1.935
8	B	80	15	2	3.935
If the patient continues without reactions at this point, proceed to step 9. Solution C may be started.					
9	C	20	15	5	8.935
10	C	40	15	10	18.935
11	C	80	15	20	38.935
If the patient is still without reactions at step 11, proceed to step 12. The remaining solution may be infused over 3 hours					
12	C		180	Prescribed dose	Prescribed dose plus 3.935 mg [a]
			Total time=5.8 h		Total dose= prescribed dose plus 3.935 mg [a]

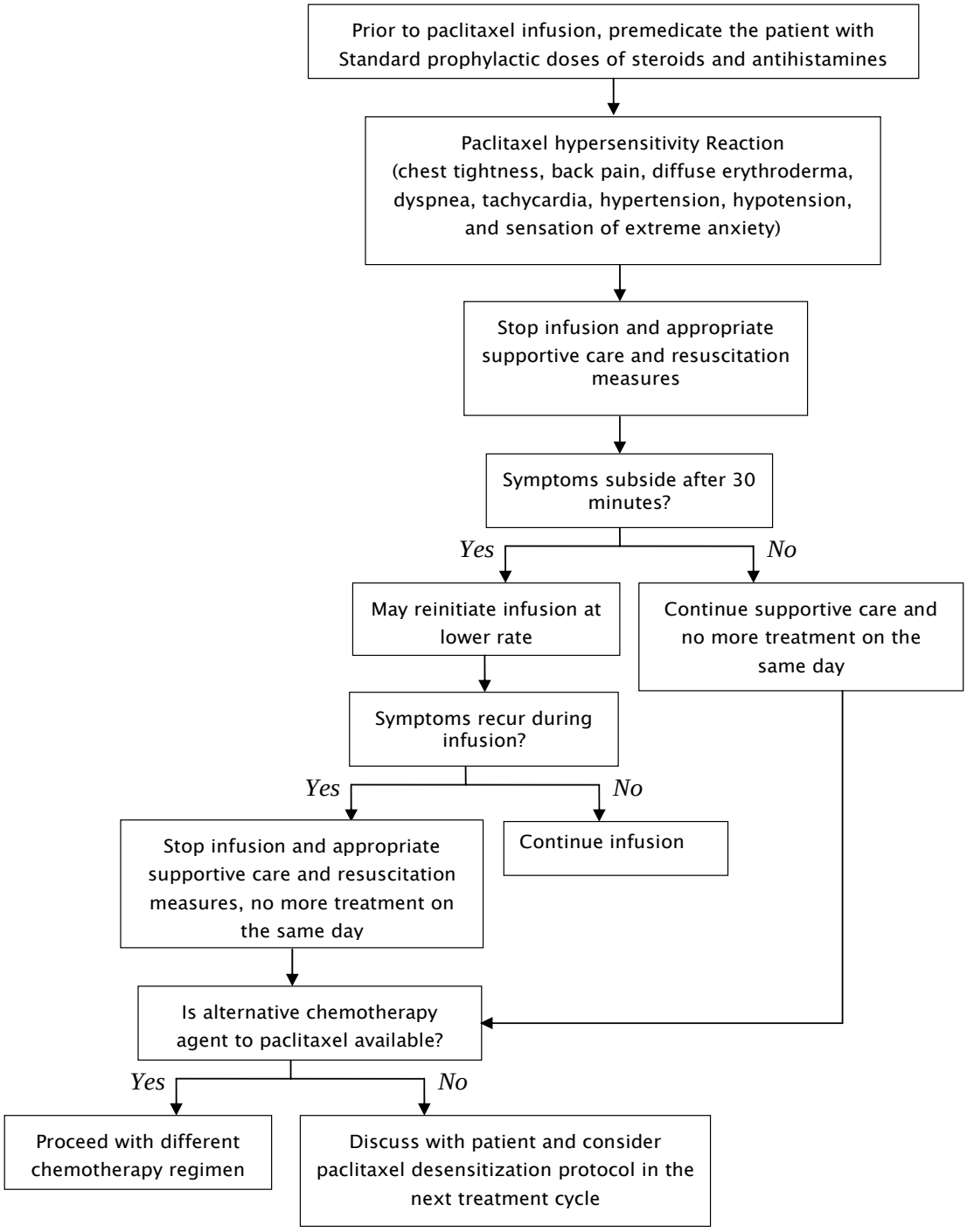
[a] 3.935 mg represents the administered dose from solution A and B, which it is considered negligible. In this protocol, 10 patients participated and they all successfully completed 35 planned courses of desensitizations with a median of 5 courses, 31 of which were without reactions (89%).

REFERENCES:

1. Markman M, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999;17:1141 - 45.
2. Markman M, et al. Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: carboplatin-hypersensitivity reactions. *J Cancer Res Clin Oncol* 2004;130:25 - 8.
3. Rose PG, et al. Successful administration of carboplatin in patients with clinically documented carboplatin hypersensitivity. *Gyn Oncol* 2003;89:429 - 33.
4. Markman M, Zanotti K, Peterson G, et al. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003;15:4611 - 4.
5. Lee CW, et al. Carboplatin hypersensitivity: 1 6-h, 12-step protocol effective in 35 desensitizations in patients with gynecologic malignancies and mast cell/IgE-mediated reactions. *Gyn Oncol* 2004;95;370 - 6.

PROPHYLAXIS AND TREATMENT OF PACLITAXEL HYPERSENSITIVITY REACTIONS

A. PROPHYLACTIC AND TREATMENT ALGORITHM



B. PROPHYLAXIS[1-2]

1. FOR Q3 WEEK (135-225 mg/m^2) PACLITAXEL INFUSIONS, 30 MINUTES PRIOR TO INFUSION, THE PATIENT SHOULD RECEIVE:

A) 20 mg dexamethasone orally 12 hours and 6 hours before taxane (for paclitaxel only) and 20 mg IV before treatment.
B) 50 mg diphenhydramine IV before treatment.
C) H_2 blocker (cimetidine 300 mg IV or ranitidine 50 mg IV) before treatment.
D) Slowly withdraw the patient (if possible) from any beta-blocker medication that could potentiate a reaction or make it harder to treat.

2. FOR WEEKLY (50-90 mg/M^2/WEEK) PACLITAXEL INFUSION, 30 MINUTES PRIOR TO THE 1ST WEEKLY DOSE:

A) 10 mg dexamethasone before treatment.
B) 25 mg diphenhydramine IV before treatment.
C) H_2 blocker (cimetidine 300 mg IV or ranitidine 50 mg (V) before treatment.

NOTE:
If no hypersensitivity reactions occur, all premedications can be deleted for subsequent weekly paclitaxel doses.
If hypersensitivity reactions occur, every 3-week premedication protocol should be followed.

C. TREATMENT OF REACTIONS[1]

If the hypersensitivity reaction occurs:

A) Discontinue infusion.
B) Administer 50 mg diphenhydramine IV and 100 mg hydrocortisone IV immediately.
C) If hypotension is present, administer epinephrine 0.35-0.5 mL IV every 15-20 minutes until the reaction subsides or a total of six doses are given.
D) If hypotension is present that does not respond to epinephrine, administer IV fluids.
E) If wheezing is present that is not responsive to epinephrine, administer 0.35 mL of nebulized albuterol solution.
F) Depending on severity of the reaction, the infusion may be reinitiated in 30 minutes, after the symptoms have subsided.

D. Desensitization protocol[3-5]

For patients who experienced a second hypersensitivity reaction after reinitiating the paclitaxel infusion – A discussion with the patient about switching to other alternative chemotherapy regimen if available. Otherwise, a paclitaxel desensitization protocol may be considered. (See protocols on next pages).

PACLITAXEL DESENSITIZATION PROTOCOL

Modified Dana Farber protocol for a Standard 3-solution, 12-step desensitization protocol over 6 hours for paclitaxel[4]

Total dose	[a]Prescribed dose	Solution concentration (mg/mL)	Dose in each solution (mg)
Solution A	500 mL	0.006	3
Solution B	500 mL	0.06	30
Solution C	Depending on the prescribed dose	0.6	Prescribed dose

Step	Solution	Rate (ml/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	A	4	15	0.006	0.006
2	A	10	15	0.015	0.021
3	A	20	15	0.03	0.051
4	A	40	15	0.06	0.111
If the patient continues without reactions at this point, proceed to step 5. Solution B may be started.					
5	B	10	15	0.15	0.261
6	B	20	15	0.3	0.561
7	B	40	15	0.6	1.161
8	B	80	15	1.2	2.361
If the patient continues without reactions at this point, proceed to step 9. Solution C may be started.					
9	C	20	15	3	5.361
10	C	40	15	6	11.361
11	C	80	15	12	23.361
If the patient is still doing fine without reactions at step 11, proceed to step 12. The remaining solution may be infused over 3 hours					
12	C		180	Prescribed dose	Prescribed dose plus 2.361 mg [a]
			Total time=5.8 h		Total dose=prescribed dose plus 2.361 mg [a]

[a]2.361 mg represents the administered dose from solution A and B, in which it is considered negligible.
In this protocol, 17 patients participated and they all successfully completed a total of 77 desensitizations with a median of 5 courses, 72 of which were without reactions (94%).

REFERENCES:

1. Weiss RB, et al. Hypersensitivity reactions from Taxol. *J Clin Oncol* 1990;8:1263 - 8.
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3. Peereboom DM, et al. Successful re-treatment with Taxol after major hypersensitivity reactions. *J Clin Oncol* 1993;11:885 - 90.
4. Feldweg AM, et al. Rapid desensitization for hypersensitivity reactions to paclitaxel and doxcetaxel: a new standard protocol used in 77 successful treatments. *Gynecol Oncol* 2005;96:824-9.
5. Markman M, et al. Paclitaxel-associated hypersensitivity reactions: Experience of the gynecologic oncology program of the Cleveland Clinic Cancer Center. *J Clin Oncol* 2000;18:102 - 5.