

Cyclophosphamide desensitization in patients with severe hypersensitivity reactions to bendamustine

Bradley Figgins^{1,2}, Brian Primeaux¹ , Brandon R Shank¹,
Sheree E Chen¹, Donna M Weber³ and Huifang Lu⁴

J Oncol Pharm Practice

0(0) 1–4

© The Author(s) 2019

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/1078155219867127

journals.sagepub.com/home/opp



Abstract

Introduction: Cyclophosphamide is a nitrogen mustard alkylator employed in the treatment of many malignancies and autoimmune disorders. Despite reports of cyclophosphamide hypersensitivity ranging from rash to anaphylaxis, no cases of desensitization have been reported in the oncologic setting.

Case report: We report a cyclophosphamide desensitization protocol used for two patients who experienced severe hypersensitivity to bendamustine, a structurally related drug with potential cross immunogenicity.

Management and outcome: An interdisciplinary approach including immunologist, oncologist, and clinical pharmacists resulted in the development of a multi-step desensitization protocol for cyclophosphamide. The desensitization protocol described enabled the safe administration of cyclophosphamide for the two patients with limited treatment alternatives.

Discussion: To the authors' knowledge, this is the first report of cyclophosphamide desensitization in the oncologic setting. Two patients with advanced hematologic malignancies were able to receive cyclophosphamide with minimal adverse effects, despite experiencing previous severe hypersensitivity to another nitrogen mustard analogue.

Keywords

Bendamustine, cyclophosphamide, desensitization, hypersensitivity

Date received: 20 June 2019; revised: 8 July 2019; accepted: 8 July 2019

Introduction

Cyclophosphamide is a nitrogen mustard alkylator employed in the treatment of many malignancies and autoimmune disorders. Despite the approval of several novel agents in recent years, hyperfractionated cyclophosphamide-based regimens remain viable options for patients with relapsed or refractory hematologic malignancies. In this setting, cyclophosphamide is used at 300–350 mg/m² intravenously every 12 h for three or four days.^{1,2}

Hypersensitivity reactions, ranging from urticaria to anaphylaxis, have been reported with varying doses of cyclophosphamide.^{3,4} In cases where treatment options may be limited for patients with advanced disease, such complications may preclude use of other agents in the same drug class and adversely affect outcomes. Reports of desensitization to antineoplastics have

been primarily limited to platinum, taxanes, and monoclonal antibodies.⁵ We present two cases of cyclophosphamide desensitization in patients with prior

¹Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, USA

²Department of Pharmacy, Memorial Sloan Kettering Cancer Center, New York, USA

³Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, USA

⁴Department of General Internal Medicine, Section of Rheumatology and Clinical Immunology, The University of Texas MD Anderson Cancer Center, Houston, USA

Corresponding author:

Brian Primeaux, Division of Pharmacy, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 377, Houston, TX 77030, USA.

Email: primeaux.brian@gmail.com

severe hypersensitivity to bendamustine, a nitrogen mustard with potential cross immunogenicity due to the presence of a shared dual 2-chloroethyl functional group (Figure 1).

Case one

A 61-year-old female with a history of diverticulitis and allergic rhinitis was diagnosed with multiple myeloma in 2012. Over subsequent years, her disease progressed through multiple lines of treatment. In March 2016, on day one, cycle five of carfilzomib–bendamustine–dexamethasone, the patient became hypotensive and developed chest tightness, palpitations, and lip/tongue swelling while receiving bendamustine. Hydrocortisone, epinephrine, and diphenhydramine were administered and the patient was immediately referred to the emergency center, where her symptoms resolved within a few hours. She was not re-challenged with bendamustine and subsequently received an alternative chemotherapy regimen.

In November 2016, her disease progressed and a hyperfractionated cyclophosphamide-based regimen with dexamethasone (dex) was selected for rapid cytoreduction. Considering the potential for immunologic cross-reactivity between bendamustine and cyclophosphamide, the immunology service recommended desensitization.

Case two

A 70-year-old female with a history of depression was diagnosed with mantle cell lymphoma in February 2016. While receiving cycle two of bendamustine–rituximab, she developed severe flushing, a widespread rash, chest tightness, and swelling of the lip and tongue within a few minutes after starting the first dose of bendamustine. On the following day, she received a second dose of bendamustine and developed recurrent

symptoms. Due to this intolerance, therapy was changed to ibrutinib.

In February 2017, the patient was admitted to receive hyperfractionated cyclophosphamide and dexamethasone for relapsed disease. The immunology service was consulted and recommended desensitization due to the severity of the previous reaction to bendamustine.

Management and outcomes

An interdisciplinary approach including immunologist, oncologist, and clinical pharmacists resulted in the development of a multi-step desensitization protocol for cyclophosphamide (Table 1).

Patient one was admitted to the intensive care unit (ICU) for close monitoring; each of the eight cyclophosphamide doses ($350 \text{ mg/m}^2/\text{dose}$) were administered through four successive doses of increasing concentration. Several premedications were administered prior to the first bag of each desensitization. The patient tolerated all doses without significant complications, developing only transiently elevated blood pressure. One month later, she received the second cycle. This time, after tolerating the first dose in the ICU, she was transferred to a general floor to receive the remaining doses by desensitization. After two cycles, the patient's disease progressed, requiring a change in therapy.

Patient two was admitted to the ICU for six doses ($300 \text{ mg/m}^2/\text{dose}$) of cyclophosphamide, which were administered over three days according to the same protocol as in case one (Table 1). The patient developed pruritus and mild chest pain on day two; the treatment was otherwise well tolerated and the patient was discharged with supportive medications, including allopurinol.

Four days later, the patient was admitted after presenting with a widespread pruritic, petechial rash.

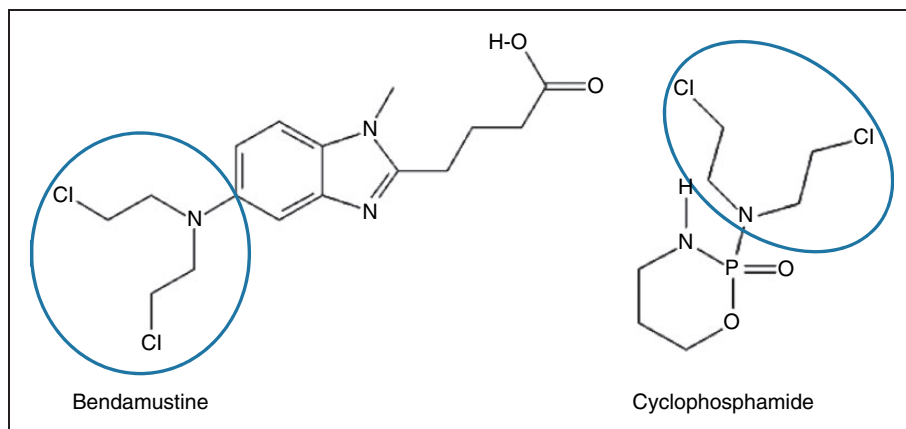


Figure 1. Comparative chemical structures.

Table 1. Cyclophosphamide desensitization protocol.

Bag #	Cyclophosphamide dose ^{a,b} (% of total dose)	Infusion time
1	0.1%	First dose: 1 hour; Subsequent doses: 0.5 hour
2	1%	First dose: 1 hour; Subsequent doses: 0.5 hour
3	10%	First dose: 1 hour; Subsequent doses: 0.5 hour
4	88.9%	All doses: 2 hours
Premedication regimen		
Drug	Scheduling	
Dexamethasone 20 mg IV	Given 30 min prior to the administration of bag #1 of each dose	
Hydrocortisone 50 mg IV		
Diphenhydramine 25 mg IV		
Famotidine 20 mg IV		
Ondansetron 8 mg IV		
Montelukast 10 mg by mouth daily	Initiated one day prior to starting cyclophosphamide and continued through the final dose of cyclophosphamide	
Cetirizine 10 mg by mouth daily		

Note: Mesna was provided as a continuous IV infusion on each day of cyclophosphamide using a 1:1 ratio.

^aAll bags were prepared in 100 mL 0.9% sodium chloride.

^bNext bag administered immediately after previous bag finished.

Since symptoms took seven days to appear after starting cyclophosphamide, the immunology and dermatology services believed the likelihood of immediate drug hypersensitivity was low. A skin biopsy was not performed since the symptoms resolved with steroids, antihistamines, and discontinuation of allopurinol. She then received a second cycle of cyclophosphamide without complications, but experienced disease progression.

Discussion

To the authors' knowledge, this is the first report of cyclophosphamide desensitization in the oncologic setting. Two patients with advanced hematologic malignancies were able to receive cyclophosphamide with minimal adverse effects, despite experiencing previous severe hypersensitivity to another nitrogen mustard analogue.

Currently, the literature supporting this practice is limited to a single case report of a pediatric patient who received cyclophosphamide for lupus.⁶ The first dose of cyclophosphamide was successful in treating the patient's disease, but was complicated by angioedema, dyspnea, and hypotension. A 12-step desensitization protocol previously developed by Castells et al. was

used for subsequent cyclophosphamide doses (1200 mg) with no adverse effects.⁵ Additionally, a case of desensitization to melphalan, another nitrogen mustard, was reported for a patient with multiple myeloma undergoing high-dose conditioning prior to stem cell transplantation.⁷

The protocol developed in the current series successfully desensitized both patients using a graded four-step approach, mirroring a previous protocol for platinum analogue desensitization.⁸ The premedication regimen was designed to target multiple mediators of allergic reactions and was well tolerated by both patients. Both patients tolerated each dose of cyclophosphamide with mild adverse effects and no signs of acute hypersensitivity.

Neither patient underwent dermatologic testing to confirm the presence of type I hypersensitivity to bendamustine or cyclophosphamide; however, data supporting such testing for these agents are limited.⁹ In both cases, the reactions to bendamustine occurred while receiving doses beyond the first cycle, suggesting that priming of the immune system by initial exposure may have been involved in the development of drug-specific antibodies. Notably, the first patient was previously exposed to cyclophosphamide during chemomobilization prior to stem cell collection. It is possible that the lack of hypersensitivity to cyclophosphamide in this patient may be the result of impaired immune reconstitution following transplantation. The probability of hypersensitivity to carfilzomib, which was concurrently administered with bendamustine, is low due to the patient's tolerance of the drug in subsequent regimens.

In conclusion, the presented desensitization protocol enabled the safe administration of cyclophosphamide for two patients with limited treatment options. Development of further protocols for other antineoplastics is warranted to expand access to treatment for patients with hypersensitivity reactions.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Brian Primeaux  <https://orcid.org/0000-0002-6553-0155>

References

1. Dimopoulos MA, Weber D, Kantarjian H, et al. HyperCVAD for VAD-resistant multiple myeloma. *Am J Hematol* 1996; 52: 77–81.

2. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. *J Clin Oncol* 2005; 23: 7013–7023.
3. Lakin JD and Cahill RA. Generalized urticaria to cyclophosphamide: type I hypersensitivity to an immunosuppressive agent. *J Allergy Clin Immunol* 1976; 58: 160–171.
4. Rosas-Vargas MA, Casas-Becerra B, Velazquez-Armenta Y, et al. Cyclophosphamide hypersensitivity in a leukemic child. *Ther Drug Monitoring* 2005; 27: 263–264.
5. Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008; 122: 574–580.
6. Lee YJ, Toh J, Jerschow E, et al. Successful cyclophosphamide desensitization in a pediatric patient with systemic lupus erythematosus and anaphylaxis after initial exposure. *Annal Allergy Asthma Immunol* 2016; 117: 329–331.
7. Ganetsky A, Takach PA, Lynch DM, et al. Melphalan desensitization following immediate hypersensitivity in a patient undergoing conditioning for autologous hematopoietic cell transplantation. *J Allergy Clin Immunol Pract* 2016; 4: 555–556.
8. Robinson JB, Singh D, Bodurka-Bervers DC, et al. Hypersensitivity reactions and the utility of oral and intravenous desensitization in patients with gynecologic malignancies. *Gyn Oncol* 2001; 82: 550–558.
9. Popescu NA, Sheehan MG, Kouides PA, et al. Allergic reactions to cyclophosphamide: delayed clinical expression associated with positive immediate skin tests to drug metabolites in five patients. *J Allergy Clin Immunol* 1996; 97: 26–33.