

Sensitizing the interdisciplinary team to desensitizations: An alemtuzumab case report

Matt G McKenzie¹ , Brittany D Bissell¹,
Margaret A Disselkamp², Gerhard C Hildebrandt³ and
Jessica N Cox¹

J Oncol Pharm Practice
0(0) 1–5

© The Author(s) 2019

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/1078155219865313

journals.sagepub.com/home/opp



Abstract

Introduction: We describe a case of alemtuzumab (Campath®) hypersensitivity requiring desensitization within the medical intensive care unit (MICU) in a patient with T-cell prolymphocytic leukemia.

Case report: We adopted a desensitization protocol from Gutierrez-Fernandez et al., which included three aliquots (0.15 mg intravenously (IV), 1.5 mg IV, and 28.5 mg IV) given approximately 1 h apart on day 1 followed by a full 30 mg dose IV on day 3. Unlike prior attempts to administer alemtuzumab to this patient, she tolerated the medication well and did not require any rescue medications.

Management and outcome: Successful plan development required a significant amount of strategic communication between hematology/oncology and MICU-related physicians, pharmacists, and nurses to ensure a safe and effective desensitization. The first step of planning required creation of a desensitization order set with directions for medication preparation and administration, premedications, and available medications in the event of an adverse reaction or anaphylaxis. Anaphylactoid-related medications were prepared at bedside and ready for administration prior to beginning the desensitization. Alemtuzumab was compounded in a chemotherapy-certified hood and verified by at least two chemotherapy-certified pharmacists. Foreword planning was also necessary to ensure multiple people were available or present at bedside for the desensitization, including a chemotherapy-certified nurse, a second chemotherapy-certified nurse for verification, a critical care-certified pharmacist, a pulmonary/critical care attending physician, and hematology attending physician.

Discussion: This case exemplifies the importance of clear and coordinated communication between different healthcare fields to safely and effectively complete extensive protocols such as desensitization strategies.

Keywords

Desensitization, alemtuzumab, intensive care unit, prolymphocytic leukemia, hypersensitivity

Date received: 29 May 2019; revised: 2 July 2019; accepted: 2 July 2019

Introduction

Alemtuzumab is a CD52-directed humanized monoclonal antibody that binds the CD52 antigen present on the surface of B and T lymphocytes. It can be used for a variety of conditions, although currently its only FDA approval is for the treatment of relapsing multiple sclerosis (Lemtrada®).¹ Alemtuzumab (as Campath®) was withdrawn from the market in 2012 and is available only through the manufacturer's distribution program. Off-label uses for this formulation include, but are not limited to, B-cell chronic lymphocytic leukemia, T-cell prolymphocytic leukemia (T-PLL), several T-cell lymphomas,

relapsed or refractory aplastic anemia, hemophagocytic lymphohistiocytosis, hematopoietic stem cell transplantation conditioning regimens, induction therapy for solid

¹Department of Pharmacy Practice, University of Kentucky Medical Center, Lexington, KY, USA

²Department of Pulmonary Critical Care and Sleep Medicine, University of Kentucky Medical Center, Lexington, KY, USA

³Department of Hematology and Bone & Marrow Transplantation, University of Kentucky Medical Center, Lexington, KY, USA

Corresponding author:

Matt G McKenzie, Department of Pharmacy Practice, University of Kentucky HealthCare, 800 Rose St, H110, Lexington, KY 40536, USA.
Email: matt.mckenzie@uky.edu

organ transplantation, and graft versus host disease prophylaxis and treatment.^{2,3}

The efficacy of alemtuzumab is closely tied with pathophysiology behind lymphocyte-related malignancies. The CD52 antigen maintains close proximity to the cell membrane and has minimal modulation upon antibody binding which allows for efficient depletion of lymphocytes.⁴ Further, studies have shown that T cells are depleted by antibody-dependent cellular cytotoxicity mediated by neutrophils and natural killer (NK) cells, whereas B cells are exhausted by cell lysis via activation of the complement cascade and subsequent apoptosis.^{5,6}

Infusion-related adverse drug reactions have been described previously with alemtuzumab. The most common reactions reported include skin rash (53%), headache (52%), urticaria (16%), pruritus (14%), and nausea (21%).² Serious infusion reactions occur in <3% of patients with even fewer experiencing true anaphylaxis. Of note, anaphylaxis and fatal infusion-related reactions are listed as a US Boxed Warning in the package insert.^{1,3}

Case

We describe the successful desensitization to alemtuzumab in one patient with T-cell promyelocytic leukemia (T-PLL).

This patient is a 59-year-old female with an oncologic history significant for what was then referred to as chronic lymphocytic leukemia with T-variant (T-CLL), which was originally diagnosed in 2014 at an outside facility with no indication for active treatment at that time. Other pertinent medical history included coronary artery disease with a history of percutaneous coronary intervention, congestive heart failure, diabetes mellitus type 2, endometriosis, hypertension, and hypothyroidism. Her family history was significant for both solid cancers as well as hematologic malignancies. Her allergy history at the time was notable for penicillins (edema, rash) and cephalexin (edema, rash).

Active surveillance for her T-CLL was continued until January 2018 when she began developing enlarged cervical and axillary lymph nodes. Soon after, she was started on an unspecified dose of subcutaneous alemtuzumab by her outside hospital oncologist. Minutes after administration of the first dose, she developed anaphylaxis and claimed “my throat started closing.” The patient required 0.1 mg of intravenous epinephrine to recover her airway. She was ultimately continued on alemtuzumab for several lower doses as part of a desensitization protocol, each time requiring 0.1 mg of intravenous epinephrine administration for respiratory distress.

Given the anaphylactoid response to subcutaneous alemtuzumab, the patient was initiated on

cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy in April 2018. She received one cycle prior to presenting with acute onset abdominal pain at which time she was noted to have small bowel obstruction and was transferred to our hospital for advanced care. Exploratory laparotomy identified excess scar tissue from prior abdominal surgeries as the cause of the obstruction.

During this admission, her significant findings included lymphocytosis ($19.3 \times 10^3/\mu\text{L}$) as well as cervical and axillary lymphadenopathy. Flow cytometry revealed T-cell prolymphocytic leukemia (T-PLL). Given the patient’s lack of response to prior outside treatment attempts, the patient continued to follow at our facility. Salvage therapy with fludarabine, mitoxantrone, and cyclophosphamide⁷ was initiated, but the patient’s lymphocytosis continued to worsen at two weeks after treatment. Alternative treatment options were discussed and included single-agent pentostatin⁸ (poor response rate) and re-trial of alemtuzumab as an intravenous infusion given the superior response in T-PLL when compared with subcutaneous administration.^{9,10} The team was hopeful but cautious given the high probability that alemtuzumab caused the patient’s prior hypersensitivity reaction based on a Naranjo score of 8 (Table 2). At this point, she was agreeable to re-trial alemtuzumab, this time as an intravenous infusion, with a desensitization approach. The manufacturer was notified of the re-initiation of therapy, and drug was requested for the following week.

When given for the treatment of T-PLL, alemtuzumab is typically given as an initial test dose of 3 mg and/or 10 mg followed by dose escalation to 30 mg three times per week for up to 12 weeks or until maximum response.¹¹ We employed a 12-step desensitization approach based on the protocol set forth by Gutierrez-Fernandez et al.¹² The protocol was reviewed with and agreed upon by our allergy and immunology physician group. Informed consent was obtained prior to protocol initiation. She received premedication 30 min prior to the start of the desensitization with diphenhydramine 25 mg IV, famotidine 20 mg IV, and lorazepam 0.5 mg IV. Alemtuzumab doses were then administered in a step-wise fashion without interruption (Table 1). The patient tolerated each infusion throughout all steps of the desensitization. She subsequently tolerated her first full dose while inpatient and was discharged without complications.

The patient continues to receive alemtuzumab 30 mg (full dose) IV three times per week without difficulty, now receiving doses at a facility closer to home. Her lymphocyte count reduced from $19.3 \times 10^3/\mu\text{L}$ prior to alemtuzumab treatment to $2.0 \times 10^1/\mu\text{L}$ at week six. She continues to be followed periodically and has been scheduled for repeat imaging and diagnostic

Table 1. Desensitization protocol.

Step	Solution used	Infusion Rate (mL/h)	Time of administration	Duration of infusion (min)	Volume infused (mL)	Administered dose (mg)	Cumulative dose (mg)
1	A	2	11:52	15	0.5	0.0015	0.0015
2	A	5	12:07	15	1.25	0.00375	0.00525
3	A	10	12:22	15	2.5	0.0075	0.01275
4	A	20	12:37	15	5	0.015	0.02775
5	B	5	12:54	15	1.25	0.0375	0.06525
6	B	10	13:09	15	2.5	0.075	0.14025
7	B	20	13:24	15	5	0.15	0.29025
8	B	40	13:39	15	10	0.3	0.59025
9	C	10	13:59	15	2.5	0.7125	1.30275
10	C	20	14:14	15	5	1.425	2.72775
11	C	40	14:29	15	10	2.85	5.57775
12	C	80	14:44	61.875	82.5 (remaining volume)	23.5125	29.09025

Solution A: alemtuzumab 0.15 mg in 50 mL (0.003 mg/mL); Preparation: Remove 5 mL of solution B (0.15 mg) and add 45 mL physiological saline solution.

Solution B: alemtuzumab 1.5 mg in 50 mL (0.03 mg/mL); Preparation: Remove 0.05 mL of drug solution from original alemtuzumab vial (1.5 mg) and add 49.95 mL physiological saline solution.

Solution C: alemtuzumab 28.5 mg in 100 mL (0.285 mg/mL); Preparation: Remove 0.95 mL of drug solution from original alemtuzumab vial (28.5 mg) and add 99.05 mL physiological saline solution.

Table 2. Naranjo Algorithm assessment.

Naranjo for hypersensitivity from alemtuzumab

Question	Yes	No	N/A
Are there previous conclusive reports of this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	−1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the drug was re-administered?	+2	−1	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0
Did the reaction reappear when a placebo was given?	−1	+1	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0
Naranjo Score	Probability		
≥9	Definite		
5–8	Probable		
2–4	Possible		
≤1	Doubtful		
Total score = 8-Probable			

Note: Significance of bolding indicates scores for case patient.

studies to assess treatment response. Treatment will be continued for up to 12 weeks and if at any point complete response has been obtained, an allogeneic hematopoietic stem cell transplant will be pursued as consolidative strategy.

Discussion

Our successful desensitization would not have been made possible without the exemplary communication and careful coordination of multiple individuals across several different fields of practice. Physicians, pharmacists, and nurses within our hematology/oncology and pulmonary/critical care teams worked diligently and strategically together to plan the desensitization to ensure both safety and efficacy of the treatment protocol. Our hematology/oncology physician and pharmacist group agreed upon and reproduced the protocol by Gutierrez-Fernandez et al. as defined in Table 1. Given the infrequency of anaphylaxis with alemtuzumab and the paucity of data surrounding desensitization of the drug, our allergy and immunology group was consulted and agreed with desensitization via the referenced protocol.

Additionally, prior to the day of admission, insurance authorization for the admission was obtained, a bed within the intensive care unit (ICU) was reserved, and all parties anticipated to be involved in the care of the patient were apprised of the situation. A chemotherapy-certified nurse was recruited to the ICU to administer the medication and monitor the patient for drug-specific reactions.

On the day of admission, pharmacy services were consulted to transcribe and verify written treatment orders to our electronic health record (including alemtuzumab orders, premedications, and potential adverse reaction medications), compound alemtuzumab in specialized aliquots for administration, and to have a clinical specialist at bedside to help monitor response. Multiple healthcare professionals were present at bedside for the desensitization: a chemotherapy-certified nurse, a second chemotherapy-certified nurse for verification purposes, and a critical care-certified pharmacist. The pulmonary/critical care attending physician and hematology attending physician as well as their respective teams, both rounded on the patient throughout the day. Both reaction and anaphylactoid-related medications were prepared at bedside and ready for administration if needed prior to beginning the desensitization protocol. The initial desensitization was performed in the intensive care setting with one-to-one nursing but could be considered in other care areas as nursing and care team availability allowed.

In contrast to Gutierrez-Fernandez et al.'s case report, our patient did not have any major reactions during the alemtuzumab desensitization process, owing to the safety and effectiveness of this method. A 12-step desensitization protocol allows a more progressive exposure to the allergen and for this reason, may be considered a safer alternative to shorter protocols. Similar strategies have been used for other anticancer agents and chemotherapy such as rituximab, paclitaxel, and carboplatin.^{13–17} Although much is published on how to administer and monitor medications during a desensitization, literature highlighting the creation, collaboration, and communication prior to and during the procedure is lacking. Our hope is to increase awareness of all steps required in a desensitization in order to be successful and ensure efficacy as well as safety.

Conclusion

The patient tolerated intravenous alemtuzumab without complications when given in an initial step-wise fashion as increasing doses and without interruption, adding to the available data on the safety of this protocol. This successful desensitization protocol utilized by our institution can be considered for future similar patients requiring toleration to first-line therapy. Additionally, this case exemplifies the importance of clear and coordinated communication between different healthcare fields to safely and effectively complete extensive protocols such as desensitizations.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Matt McKenzie, Brittany Bissell, Margaret Disselkamp and Jessica Cox: No conflicts of interest to disclose.

Gerhard C. Hildebrandt: Employment or leadership position: none; Consultant or advisory role: Pfizer, Kite Pharma, Incyte, JAZZ Pharmaceuticals; Stock ownership: Sangamo Bioscience, June Therapeutics, Kite Pharma, Novartis, Insys Therapeutics, Abbvie, GW Pharmaceuticals, Cardinal Health, Immunomedics, Endocyte, Clovis Oncology, Cellectis, Aetna, CVS Health, Celgene, Bluebird Bio, Bristol-Myers Squibb/Medarex Crispr Therapeutics, IDEXX laboratories, Johnson&Johnson, Pfizer, Procter & Gamble, Vertex, JAZZ Pharmaceuticals; Honoraria: none; Other remuneration: travel, expenses, accommodation: Kite Pharma, Incyte, Pfizer, Falk Foundation, JAZZ Pharmaceuticals, Astellas Pharma.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Matt G McKenzie  <https://orcid.org/0000-0003-1945-9471>

References

1. Lemtrada (Alemtuzumab) [package insert]. Cambridge, MA: Genzyme Corporation, 2014.
2. Alemtuzumab: Lexi-Drugs. Lexicomp. Riverwoods, IL: Wolters Kluwer Health, Inc., <http://online.lexi.com> (accessed 7 August 2018).
3. Campath (Alemtuzumab) [package insert]. Richmond, CA: Berlex Laboratories, 2003.
4. Clark SL, et al. Histopathologic spectrum of hypersensitivity reactions associated with anti-CD52 therapy (alemtuzumab). *J Cutan Pathol* 2016; 43: 989–993.
5. Clark RA, et al. Skin effector memory T cells do not recirculate and provide immune protection in alemtuzumab-treated CTCL patients. *Sci Transl Med* 2012; 4: 117ra7.
6. Jiang L, et al. Variable CD52 expression in mature T cell and NK cell malignancies: implications for alemtuzumab therapy. *Br J Haematol* 2009; 145: 173–179.
7. Hopfinger G, et al. Sequential chemoimmunotherapy of fludarabine, mitoxantrone, and cyclophosphamide induction followed by alemtuzumab consolidation is effective in T-cell prolymphocytic leukemia. *Cancer* 2013; 119: 2258–2267.
8. Mercieca J, et al. The role of pentostatin in the treatment of T-cell malignancies: analysis of response rate in 145 patients according to disease subtype. *J Clin Oncol* 1994; 12: 2588–2593.
9. Dearden C. How I treat prolymphocytic leukemia. *Blood* 2012; 120: 538–551.
10. Dearden CE, et al. Alemtuzumab therapy in T-cell prolymphocytic leukemia: comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. *Blood* 2011; 118: 5799–5802.
11. Dearden CE, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. *Blood* 2001; 98: 1721–1726.
12. Gutierrez-Fernandez D, et al. Hypersensitivity to alemtuzumab. A safe and effective desensitization protocol: a case report. *J Oncol Pharm Pract* 2019; 25: 1016–1020.
13. Bonamichi-Santos R and Castells M. Desensitization for drug hypersensitivity to chemotherapy and monoclonal antibodies. *Curr Pharm Des* 2016; 22: 6870–6880.
14. Castells MC, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008; 122: 574–580.
15. Feldweg AM, et al. Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. *Gynecol Oncol* 2005; 96: 824–829.
16. Goldberg A, et al. A modified, prolonged desensitization protocol in carboplatin allergy. *J Allergy Clin Immunol* 1996; 98: 841–843.
17. Lee CW, Matulonis UA and Castells MC. Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. *Gynecol Oncol* 2004; 95: 370–376.