Published in final edited form as:

Leukemia. 2018 November ; 32(11): 2495–2518. doi:10.1038/s41375-018-0120-2.

Ninety-Minute Daratumumab Infusion is Safe in Multiple Myeloma

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Keywords

CD38 antibody; multiple myeloma; infusion-related reactions

Daratumumab is a first-in-class anti-CD38 monoclonal antibody approved for relapsed and refractory multiple myeloma[1,2] and being tested in both smoldering[3] and newly diagnosed myeloma[4]. CD38 is expressed on airway smooth muscle cells, and infusion related reactions (IRRs) were marked by symptoms (cough, wheezing, rhinorrhea) similar to those of allergic rhinitis. Of all patients treated at 8mg/kg and 16 mg/kg in two pivotal trials, the proportion of patients that suffered an IRR was 65% (grade 1–2) and 3% (grade 3–4) in the GEN501 trial[1], and 59% (grade 1–2) and 4% (grade 3–4) in the SIRIUS trial[2]. A pooled analysis of SIRIUS and GEN501 data demonstrated that most IRRs (95.8%) occur during the first infusion, with a decreased incidence of IRRs during second (7%) and subsequent infusions (7%)[5]. There is no relationship between daratumumab serum levels and the development of IRRs[6].

The incidence and severity of IRRs has led to the recommended administration rates which result in infusion times for the first, second and subsequent infusions of 6.5, 4.5 and 3.5 hours respectively[7]. To decrease the IRR rate, one trial tested the addition of 10 mg of montelukast as a premedication prior to the first daratumumab infusion and found the IRR rate was one-third lower in patients who received this leukotriene inhibitor[8]. Beyond

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AUTHORSHIP CONTRIBUTIONS

HB, CCH wrote the protocol and the manuscript. YH designed the statistics. HB, JD, AW enrolled patients. HB, NS, NW, CCH prepared case report forms. Data analysis was performed by HB, NS, and NW. All authors reviewed and approved the final manuscript.

CONFLICTS OF INTEREST

Benson, Hofmeister, Efebera, and Rosko - research funding from Celgene, Janssen, Takeda, Roche, Karyopharm, Bristol-Myers Squibb; Hofmeister advisory board participation for Celgene, Adaptive Biotechnologies. No other disclosures from any other author.

slowing the infusion rate, no other clinical trial has successfully reported any intervention to decrease the IRR rate[9].

Because of the low incidence of infusion reactions after the first infusion, we hypothesized that increasing the infusion rate of the third and subsequent doses of daratumumab would not affect the safety profile. Previously this concept was studied with rituximab in which the second or subsequent infusion was given at a rapid 1 hour infusion rate[10]. This led to a rapid rituximab infusion protocol, where patients would be switched if they met certain rapid infusion criteria. With this experience, we developed an accelerated daratumumab infusion protocol with the hypothesis that increasing the infusion rate would not increase the IRR rate beginning with the third dose of daratumumab.

This was a prospective, single-center, open-label safety study of an accelerated daratumumab infusion in multiple myeloma patients. To be eligible, patients had to have received two or more doses of daratumumab at standard infusion rates; prior IRR's with daratumumab did not exclude patients. The infusion rate was calculated to deliver 20% of the dose over 30 minutes (200 mL/hr), and then the rate was increased to deliver the remaining 80% over 60 minutes (450 mL/hr). This resulted in a 90 minute estimated infusion time (total volume 550 mL). Per institutional policy, the total volume accounts for manufacturer overfill, and the tubing is primed with drug. Standard vital signs were collected prior to infusion start, every 15 minutes for 1 hour and finally at the end of the infusion. For the first accelerated infusion, patients were observed in the infusion suite for 30 minutes after infusion completion to assess for a delayed IRR. Existing premedication regimens were not altered for study purposes. Simon's two-stage optimal design was utilized based on the null hypothesis that the IRR-free rate was at most 85% and the alternative hypothesis that it's at least 98%. With a type I error rate of 0.05 and 80% power, the design allowed 7 patients to be treated in the first stage, and if no patient experienced grade 3 IRR, an additional 21 patients would be treated. At the end of the study, if none or only one patient out of the total 28 experienced grade 3 IRR, the regimen will be declared safe. IRRs and their respective symptoms were graded per the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE version 4.03). The protocol was approved by the Ohio State University cancer institutional review board (NCT02944565) and all patients consented prior to treatment.

Patients were enrolled beginning February 2017 and accrual of all 28 patients was completed in June of 2017. Baseline demographics can be found in Table 1. The median number of prior daratumumab infusions before study enrollment was five. Eight patients received the accelerated rate with their third daratumumab infusion, the earliest allowed per protocol. Eleven patients (39.3 %) had a history of reaction with their first dose with no history of recurrent reaction with their second dose. Premedication regimens with the accelerated dose varied including 5 patients who did not receive any steroid premedication and 3 who received reduced doses (less than 12 mg) of dexamethasone when the standard at our institution is 20 mg intravenous. The accelerated infusion was well tolerated among all 28 patients with no grade 3 or above IRRs.

The only treatment emergent toxicity was a single grade 2 hypertension event. This was felt to be related to the volume of fluid being infused over a shorter period of time as the patient had received 10 prior doses of daratumumab and had a history of hypertension requiring multiple antihypertensive medications. The accelerated infusion was paused and a diuretic resolved the hypertension. The patient resumed treatment at the previously tolerated rate and subsequently tolerated the accelerated rate. At the 4-week follow up point, all patients remained on the accelerated infusion with no additional toxicities.

The 90-minute daratumumab infusion was well-tolerated in multiple myeloma patients receiving their third dose or beyond and saved patients 2 hours of infusion time per dose. As depicted in Table 1, during the protocol accelerated infusion the most common premedication combination was acetaminophen, diphenhydramine, famotidine and dexamethasone. Since implementing the accelerated infusion as a new standard-of-care at our institution, the premedication strategy involves most standard medications for the first dose (acetaminophen 650 mg oral (po), diphenhydramine 50 mg intravenous (IV) or po, dexamethasone 20 mg IV, montelukast 10 mg po, and famotidine 20 mg IV), pruning the regimen to simply dexamethasone IV and montelukast po with the third dose (first accelerated), then dexamethasone IV only thereafter. Our current practice also avoids testing accelerated daratumumab in any patient whose most recent dose was prepared in the 1000 mL dilution due to moderate or severe IRR. Thus, patients must demonstrate tolerability of a 500 mL daratumumab infusion at the manufacturer recommended rates prior to receiving the accelerated infusion.

Preexisting chronic obstructive pulmonary disease (COPD) constitutes a specific risk factor for bronchospasm. Patients were excluded from daratumumab clinical trials if they had severe asthma or COPD with a forced expiratory volume in 1 second <60% of predicated. Additional pretreatment with short- and long-acting bronchodilators, or inhaled corticosteroids may further reduce the risk in this group that is at high risk of bronchopulmonary side effects. For our trial, patients with respiratory comorbidities were not excluded from the 90-minute infusion.

Because >90% of IRRs occur on the first infusion, the next step could be to test interventions that further decrease the risk of an IRR with the first dose. Anaphylactoid reactions are immediate non IgE-mediated systemic reactions[11]; for daratumumab, these are thought to be complement activation-dependent resulting from liberation of C3a, C5a, and C5b-9 that leads mast cells and basophils to release symptomatic vasoactive mediators[12]. Thus far antihistamines, corticosteroids, and reduction of the administration rate of pseudoallergenic drugs are the only available interventions, but of drugs that not yet entered the clinic, the complement inhibitor factor H could be considered in this setting[13]. Repeating this trial with the second rather than the third daratumumab infusion is likely to be successful with the majority of the reactions occurring with the first infusion.

Strategies such as this to decrease time in the infusion center reduce healthcare resources utilized and increase efficiency in advance of the future use of subcutaneous daratumumab, for which preliminary results have demonstrated decreased IRRs and higher trough levels in patients on chronic therapy[14].

Acknowledgments

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number P30CA016058. The content is solely the responsibility of the authors and does not represent the official views of the National Cancer Institute or the National Institutes of Health.

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Table 1

Baseline Characteristics	
Age, years	
Median (range)	67 (44–90)
Gender, n (%)	
Male	19 (67.9)
Female	9 (32.1)
Race, n (%)	
Caucasian	24 (85.7)
African American	3 (10.7)
Other	1 (3.6)
Number of prior daratumumab doses, n (%)	
2	8 (28.6)
3–5	7 (25)
6–9	0 (0)
10 or more	13 (46.4)
Median (range)	5 (2–26)
History of daratumumab reactions, n (%)	
First dose	11 (39.3)
Second dose	0 (0)
Premedication Use	
APAP + H1A + H2A + DEX, n (%)	15 (53.6)
APAP + H1A + H2A + LRA + DEX, n (%)	7 (25)
APAP + H1A + H2A, n (%)	4 (14.3)
APAP + H1A + H2A + LRA, n (%)	1 (3.6)
H1A + H2A + DEX, n (%)	1 (3.6)
Delayed Dexamethasone Use	
Yes, n (%)	10 (35.7)

Table abbreviations: APAP = acetaminophen; H1A = histamine₁ antagonist (diphenhydramine or hydroxyzine); H2A = histamine₂ antagonist (famotidine); LRA = leukotriene receptor antagonist (montelukast); DEX = dexamethasone