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Abstract
Daratumumab is administered over a period of 4 to 5 hours, which is time-consuming. The study sought to demonstrate safety and cost benefits of administering daratumumab over a period of 90 minutes. A total of 100 patients were included. No difference in the incidence of infusion-related reactions was noted, and rapid daratumumab infusion provided cost savings.

Introduction: Daratumumab is approved for the treatment of multiple myeloma in both frontline and relapsed/refractory settings. Its major limitation is the long infusion time, especially with the first dose. Recent data demonstrated the feasibility of infusing daratumumab at an accelerated rate of 90 minutes starting from cycle 1 on day 15. Herein, we report the safety profile and cost associated with rapid daratumumab infusion protocol. Patients and Methods: A chart review was performed to identify patients who completed at least 1 cycle of daratumumab (single agent or in combination) from April 2016 to October 2018. Patients were divided into 2 cohorts: cohort 1 received rapid daratumumab infusion after its implementation in March 2018, whereas cohort 2 included patients treated with daratumumab administered at the standard rate. The primary endpoint was to compare differences in rates of infusion-related reactions (IRRs). An Excel (Microsoft)–based model was developed to estimate cost and productivity. Results: A total of 100 patients with relapsed/refractory disease were included in this study (53 in cohort 1 and 47 in cohort 2). Of the 53 patients in cohort 1, 18 (34%) received rapid daratumumab infusion starting with cycle 1. Overall, there was no statistically significant difference in rates of IRRs between cohort 1 and 2 (1.9% vs. 4.3%, P = .59); 1 patient in cohort 1 developed an IRR. The total costs estimated for a 52-week regimen of daratumumab infused at standard and rapid rates were $137,200 and $122,200 (P < .001), respectively. Conclusion: Our findings indicate that rapid daratumumab infusion is safe and tolerable and provides cost savings for patients with relapsed/refractory disease.

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Introduction
Daratumumab is an anti-CD38 monoclonal antibody currently Food and Drug Administration approved for the treatment of patients newly diagnosed with multiple myeloma who are transplant ineligible as well as those with relapsed/refractory disease.1 Daratumumab may be administered in combination with other agents or as monotherapy.2-9 Infusion-related reactions (IRRs) are a commonly reported side effect associated with daratumumab administration,1 which typically manifest as cough, chills, rigors, throat irritation, nasal congestion, wheezing, shortness of breath, and/or hypotension. These IRRs are likely attributed to targeting CD38, which is highly expressed on not only the multiple myeloma cells but also other tissues such as the upper airway smooth muscles. A pooled analysis of 1166 patients receiving daratumumab in the setting of monotherapy or combination treatment demonstrated that all grade IRRs occurred at an incidence of about 40% during the first infusion.1 Most of these IRRs were grade 1 to 2.1 Nonetheless, the rate of IRRs decreased significantly to 2% to 7% with repeated
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daratumumab dosing or exposure; fewer than 1% of patients experienced grade 3 IRRs with subsequent infusions.1,10 Because of the high IRR risk, the first daratumumab dose is administered slowly and titrated according to patient tolerability, thereby averaging 7 hours in duration.1 The duration of administration of the second and subsequent infusions is relatively shorter, ranging from 3 to 4 hours.7 Recent data demonstrated the feasibility of infusing daratumumab at an accelerated rate of 90 minutes starting with the third infusion (typically cycle 1 on day 15) where 20% of the dose is administered over 30 minutes and the remaining 80% over 60 minutes.11 This reduced the standard infusion time by approximately 2 hours.11 In light of these encouraging data, all daratumumab protocols at our institution were updated to implement the rapid infusion protocol in routine clinical care. Per protocol, all patients treated at our institute were eligible to receive daratumumab at the accelerated rate (rapid infusion) (ie, there were no predefined eligibility [inclusion/exclusion] criteria. Hence, the objective of this study was to assess the safety and tolerability of the rapid daratumumab infusion protocol typified by comparing the rates of IRRs among patients who received the standard daratumumab infusion (as recommended by the manufacturer) and those who received the rapid (accelerated) daratumumab infusion protocol. Moreover, pharmacoeconomic analysis was performed to evaluate the economic impact of adopting rapid infusion daratumumab in practice.

Patients and Methods

Study Design and Patient Selection

This was a retrospective, single-center, observational study from the prospectively collected Levine Cancer Institute Plasma Cell Disorders Database seeking to evaluate the safety profile and economic impact of rapid daratumumab infusion compared with the standard after the institute-wide implementation of the rapid (accelerated) infusion protocol in March 2018. An institutional review board—approved protocol was available before the start of this study, which allowed data collection on all daratumumab-treated patients who provided written informed consent.

A chart review was performed to identify all adult patients with plasma cell disorders who were treated with daratumumab or any daratumumab-containing regimen during the period of April 2016 through October 2018. Only patients who completed at least 1 cycle at the time of data collection were included in this study. Accordingly, patients were divided into 2 cohorts based on the rate of daratumumab infusion. Patients in cohort 1 received the rapid daratumumab infusion, whereas those in cohort 2 were treated with daratumumab administered at the standard infusion rate recommended by the manufacturer. Of note, daratumumab-naive patients in cohort 1 received the first 2 doses of cycle 1 at the standard infusion rate (per manufacturer’s recommendations) and were switched to the rapid rate starting with cycle 1 on day 15, even if they experienced IRRs with the first 2 infusions. For the remaining patients (previously exposed to daratumumab [ie, daratumumab experienced]) in cohort 1, the rapid daratumumab infusion protocol was instituted on the first day of the new or subsequent treatment cycle (Figure 1). Rapid daratumumab infusion was administered over a total of 90 minutes with 20% of the dose given over 30 minutes and the remaining 80% over 60 minutes as described by Barr et al.11 Patients in both cohorts received standard premedications 30 minutes before the initiation of daratumumab infusions, which encompassed acetaminophen 650 mg, diphenhydramine 25 mg, dexamethasone (dose ranging from 8-40 mg as recommended by provider), and montelukast 10 mg (only for the first 2 doses of the first cycle). Notably, inhaled corticosteroids or short-acting beta-2 agonists (bronchodilators) were not coadministered with any of these premedications. Daratumumab-related side effects were graded based on the Common Terminology Criteria for Adverse Events (CTCAE). In the event of an IRR, institutional guidelines were implemented that warranted the following measures: interruption of daratumumab infusion, medical management of the IRR.
(with diphenhydramine 50 mg, hydrocortisone 100 mg, and famotidine 20 mg; intramuscular epinephrine 0.3 mg and albuterol inhaler were reserved for hypotension along with airway obstruction), and resumption of daratumumab infusion after recovery from a mild-to-moderate IRR. The infusion was resumed at half the rate at which the IRR occurred and escalated afterward if there were no additional symptoms.

Study Endpoints

The primary endpoint of this study was to compare the rates of daratumumab IRRs after day 8 of cycle 1 between patients who received the rapid infusion protocol (cohort 1) and those who received daratumumab infusion based on the recommendations set forth by the manufacturer (standard infusion, cohort 2). Other endpoints included the differences in IRRs among the subset of patients in cohort 1 who received the rapid infusion protocol on day 15 of cycle 1 (daratumumab naive) and patients in cohort 2 (Figure 1). Drug and administration costs and productivity costs to patients and infusion suite staff were estimated based on clinical data.

Statistical Analysis

Baseline patient characteristics were described as either means (± SDs/range) or frequencies. The χ²/Fisher exact test with 1 degree of freedom was used to compare the rates of daratumumab-related infusion reactions between both cohorts. Previous studies indicated rates of daratumumab-related IRRs beyond day 1 of cycle 1 vary between 2% and 7%. For the purposes of this study, the rapid infusion protocol was deemed safe or well tolerated if the rates of IRRs did not cross the 7% threshold. The P value was set at .05 for statistical significance. All analyses were performed in SPSS version 25.0 (IBM Corp, Armonk, NY).

An Excel (Microsoft)—based model was constructed to reflect clinical practice, which provided estimates of infusion-associated costs and productivity cost or estimated lost wages to patients diagnosed with relapsed/refractory multiple myeloma and treated with either standard or rapid daratumumab infusion and to infusion suite staff. We estimated infusion-associated costs for the initiation and continuation of daratumumab during a 12-month period (Supplemental Figure 1). The clinical and infusion data of 100 patients with relapsed/refractory multiple myeloma treated at our institute from April 2016 to October 2018 were used to generate cost estimates from the societal perspective. Patient assignment to rapid or standard daratumumab followed the methods described earlier. Model inputs included drug cost and administration, staffing, patient salary, and travel distance and were conducted using the human capital approach. Drug administration reimbursement was obtained from the US Centers for Medicare and Medicaid Services 2018 Outpatient Prospective Payment System. Wholesale acquisition costs for drugs were obtained from AnalySource. Infusion staffing inputs were obtained from the institute administration. Patient salary and travel distance were mapped from the US Census based on patient zip code. The model assumed once patients switched to the rapid infusion rate on day 15 of cycle 1, they remained on rapid infusion rates. All costs were estimated in 2018 US dollars. Because of the short duration of the study period, discounting was not applied. Data inputs used in cost estimates were used in accordance with Consolidated Health Economic Evaluation Reporting Standards (CHEER).14

Results

A total of 100 patients were identified who completed at least 1 cycle of daratumumab as part of their treatment plan during the study period from April 2016 until October 2018; 53 were in the rapid daratumumab infusion arm (cohort 1), and 47 were in the standard infusion arm (cohort 2) (Figure 1). Of the 53 patients in cohort 1, 18 (34%) were daratumumab naïve. These patients were started on the rapid infusion protocol on the initiation of the first treatment cycle (day 15 of the first treatment cycle per protocol), whereas the rest in cohort 1 (daratumumab experienced: n = 35, 66%) received a median of 5 treatment cycles (range, 2-30) before subsequently switching to the rapid infusion protocol on the first day of the new treatment cycle. Baseline characteristics were comparable between the 2 treatment cohorts as shown in Table 1. Notably, 6 of the 100 patients included herein (5.7% in cohort 1 and 4.3% in cohort 2) received daratumumab for relapsed light-chain (AL) amyloidosis with 2 (1 in each cohort) having cardiac involvement and 1 (in cohort 2) with renal disease secondary to AL amyloidosis. The remaining 93 patients were treated with daratumumab for relapsed/refractory multiple myeloma. Furthermore, 2 patients (1 in each cohort) had a previous history of chronic obstructive pulmonary disease (COPD), and 7 (3 in cohort 1 and 4 in cohort 2) had asthma. All patients with asthma/COPD were already taking controller medications, which included a long-acting β2 agonist as monotherapy (salmeterol) or in combination (formoterol or vilanterol) with either an inhaled corticosteroid (fluticasone or budesonide) or a long-acting anticholinergic (umeclidinium), with the exception of 1 patient in cohort 2 who was on a short-acting β2 agonist (albuterol). None of these patients (with COPD or asthma) received additional premedications such as inhaled corticosteroids or bronchodilators before daratumumab infusion. Approximately one-third of the patients (in the entire cohort) were given single-agent daratumumab (13 [24.5%] in cohort 1 and 16 [34%] in cohort 2) (Table 1). The remaining patients in both cohorts were treated with daratumumab-containing drug combinations (ie, either an immunomodulatory agent or proteasome inhibitor). The most commonly used regimen (triple-drug combination) was daratumumab/pomalidomide/dexamethasone, which was administered to 75% (n = 40) of the patients in cohort 1 and 71% (n = 33) in cohort 2. Additionally, 17.5% (n = 9) in cohort 1 and 13% (n = 6) in cohort 2 received daratumumab/lenalidomide/dexamethasone. Daratumumab/bortezomib/dexamethasone was used in 4 (7.5%) and 8 (16%) of the patients in cohorts 1 and 2, respectively. All patients in this study were premedicated with acetaminophen 650 mg, diphenhydramine 25 mg, montelukast 10 mg (days 1 and 8 of the first cycle), and various doses of dexamethasone (all administered 30 minutes before daratumumab infusion). The mean dexamethasone dose was 17.4 mg (± 8.3) in cohort 1 and 21.6 mg (± 9.6) in cohort 2 (P = .2). Although not an endpoint of this study, it is worth noting that 17 patients (32%) in cohort 1 experienced a daratumumab IRR on day 1 of cycle 1 as opposed to 14 (30%) in cohort 2 (P = .83). There was no significant difference in the rates of IRRs after day 1 of cycle 1 between patients in cohort 1 and those in cohort 2 (1.9% vs.
4.3%, $P = .59$) (Figure 2A). Similarly, subgroup analysis, which included only daratumumab-naive patients in cohort 1 (ie, those who were given the rapid infusion on day 15 of cycle 1, n = 18 [34%]) suggested no difference in the rates of daratumumab IRRs relative to cohort 2 (5.5% vs. 4.3%, $P = .9$) (Figure 2B). In addition, all these IRRs were mild and manifested as chills, rigors, and/or throat itching, which were rated as grade 1 to 2 per CTCAE criteria. Most importantly, the daratumumab infusion was resumed after managing these reactions per institutional guidelines.

Including staffing, drug cost and administration, patient salary, and travel distance, the total cost estimated for a 52-week regimen of daratumumab infused at the standard rate was $137,200, whereas the total cost for the rapid infusion rate was $122,200 ($P < .001$) (Table 2). Drug and administration costs were similar between the standard and rapid cohorts ($112,300 vs. $110,600). Costs associated with staffing and patient productivity were greatest in the standard cohort (staff: $21,600 vs. $10,100; patient: $3300 vs. $1500).

**Discussion**

Findings from this study suggest that the implementation of the rapid daratumumab infusion protocol beyond day 8 of cycle 1 (ie, after the second dose) was a safe, well-tolerated, and convenient approach for treating patients with plasma cell disorders. These results are in line with those described by Barr et al.11 Furthermore, this approach might provide cost savings to both the patient and the health care system.

One of the major limitations of this study is that most of the patients in cohort 1 (rapid infusion arm) were daratumumab experienced. Of the 18 patients (daratumumab naive in cohort 1) who received the rapid infusion protocol with the first cycle, only 1 developed an IRR (chills and rigors, grades 1-2). It is worth noting that daratumumab was administered at the rapid or accelerated rate (over 90 minutes) on day 1 instead of day 15 of cycle 1 given the fact that this patient had a previous history of exposure to daratumumab (ie, daratumumab was restarted after 6 months of discontinuation). At the time of initiating the rapid infusion, the patient was also receiving blood products, which potentially raises some doubts as to whether the administration of daratumumab via this protocol contributed to the incidence of the IRRs. Fortunately, the IRRs were grade 1 to 2 per CTCAE criteria. Regardless, it is recommended that the daratumumab infusion be restarted at the standard rate (for the first 2 weeks) before switching to the rapid infusion if at least a 6-month period has elapsed since the last administered dose.

 Interestingly, there were 3 patients (a total of 6 in both arms) with AL amyloidosis and 6 with underlying comorbid conditions (heart failure, asthma, and COPD) who received the rapid daratumumab infusion. The presence of any cardiac, renal, or pulmonary disease may make clinicians reluctant to administer daratumumab via this rapid strategy. Based on our experience, the IRR occurrence rate, grades, and overall tolerability in this patient population were no different compared with the standard infusion cohort. Despite the small number of patients with cardiac or pulmonary diseases reported herein, our results suggest that the presence of organ dysfunction should not preclude patients from receiving daratumumab via the rapid or accelerated protocol.

Although our primary objective was to assess the safety of the rapid infusion protocol, it should be noted that the rates of IRRs observed in this study were lower than what has been previously reported in the literature, specifically with the first daratumumab infusion (day 1 of cycle 1). This could be attributed to the intense...
premedication regimen (diphenhydramine/acetaminophen/dexa-methasone/montelukast) that patients received before starting the daratumumab infusion. In addition, none of the patients in cohort 1 was premedicated with montelukast, inhaled bronchodilators, or corticosteroids at the time of switching from the standard to the rapid infusion (ie, either day 15 for daratumumab-naive patients or day 1 for daratumumab-experienced patients), which further substantiates the safety of this approach.

The prolonged administration time associated with the standard daratumumab infusion could be quite challenging for some cancer centers and infusion clinics where the long infusion hours significantly impact infusion chair and nursing availability. Furthermore, its administration (as recommended by the manufacturer) may be limited by infusion clinic operating hours. Split daratumumab dosing, which has been recently approved as an alternative administration strategy, may overcome some of these limitations; however, split dosing necessitates that patients come to infusion centers twice (2 consecutive days) a week, making it a less appealing or convenient option for some patients who are being treated with this medication.

Our cost model estimated savings for the daratumumab rapid infusion cohort, but beyond overall cost savings, we estimated that savings associated with the rapid infusion cohort could allow for a doubling of the infusion staff provided facilities had infusion chairs
for patients. Our analyses also estimated that patients incurred less productivity loss, thus enabling them to return to their normal lives when a part of the rapid infusion cohort. Considering relapsed/refractory multiple myeloma patients can be on daratumumab treatment for a long period of time, this attribute could be desirable to patients. Further exploration of patients and physician preferences could elicit optimal treatment paradigms for both parties. Another point for consideration is that there is no consensus among the health economic field for methodology of productivity quantification, especially for nonworking patients (eg, students, retired, elderly, etc). One could argue that because of mean patient age (eg, 65 years) (Table 1), patient productivity from our estimates should not be omitted. Because of the nature of the disease state, to be reflective of our patients’ age range (eg, 39-85 years), and for completeness of cost inputs from the societal perspective, we thought it was important to include productivity for our patient population.

There has been a growing interest in administering monoclonal antibodies (including daratumumab) via the subcutaneous route. A subcutaneous formulation of daratumumab (with recombinant human hyaluronidase) is currently under investigation. However, preliminary findings from the ongoing PAVO (Patients With Relapse or Refractory Multiple Myeloma) study showed that subcutaneous daratumumab (given at a flat dose of either 1200 mg or 1800 mg) was safe and effective; the overall response rates for the 1200-mg and 1800-mg doses were 25% and 42.2%, respectively, in patients with relapsed/refractory multiple myeloma. If this formulation becomes approved, it will most likely represent another convenient option for patients as well as health care providers, thereby posing a challenge for the rapid or accelerated infusion protocol. It is important to keep in mind that IRRs with the first dose of subcutaneous daratumumab occurred within the first 6 hours of the start of infusion (which takes about 20 minutes). Hence, close monitoring may be warranted at least initially for the first infusion. Because this formulation is yet to seek Food and Drug Administration approval, direct comparison of its cost benefits relative to the rapid infusion protocol is not feasible at this point.

**Conclusion**

The implementation of the rapid daratumumab infusion protocol did not predispose patients to a higher risk of IRRs. Given its safety, ease of administration, and financial benefits, every effort should be undertaken to make this approach accessible and available to all patients with plasma cell disorders.

**Clinical Practice Points**

- Infusion-related reactions are the most feared complications of daratumumab. In clinical practice, the first daratumumab dose is administered over 6 to 8 hours, whereas subsequent infusions are given over 4 to 5 hours. Such long infusion times may not be convenient to patients receiving treatment with daratumumab.
- The study sought to evaluate the following two objectives: (1) the safety of administering daratumumab at an accelerated rate over a total period of 90 minutes (starting from the third dose in daratumumab-naïve patients) compared with the standard approach recommended by the manufacturer and (2) the cost benefits associated with the implementation of the rapid daratumumab infusion protocol.
- A total of 100 patients were included in the study (53 in the rapid infusion arm and 47 in the standard arm). There was no difference in the incidence of infusion-related reactions between the 2 approaches. Furthermore, the rapid daratumumab infusion was associated with cost savings.
- These results suggest that implementation of the rapid daratumumab infusion protocol is feasible and should be adopted in clinical practice.

**Disclosure**

Dr. Usmani has received research funding from Amgen, Array, Biopharma, Celgene (BMS), Janssen, Merck, Pharmacemics, Sanofi, Takeda, GSK, Seattle Genetics, and Skyline Dx; consultancy fees from Amgen, Celgene (BMS), Janssen, Merck, SkylineDx, Takeda, and GSK; and served on the speakers bureau for Amgen, Celgene, Janssen, Sanofi, and Takeda. Dr. Voorhees has received consultancy fees from Celgene (BMS), GSK, Janssen, Novartis, and Oncopetides. Dr. Bhutani has received research funding from MedImmune, Janssen, and BMS and consultancy fees from Sanofi and Genzyme. Dr. Atrash has received consultancy fees from Takeda, Karyopharm, Sanofi, Cellectar, Jansen, GSK, and Celgene and served on the speakers bureau for Celgene (BMS). Dr. Paul has received honoraria from Celgene (BMS), consultancy fees from Janssen, and served on the speakers bureau for Amgen. Dr. Friend has served on the speakers bureau for Amgen. The remaining authors have stated that they have no conflicts of interest.

**Supplemental Data**

Supplemental figure accompanying this article can be found in the online version at [https://doi.org/10.1016/j.clml.2020.02.014](https://doi.org/10.1016/j.clml.2020.02.014).

**References**


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**Supplemental Data**

**Supplemental Figure 1** A Decision Tree Used to Estimate Costs Associated With Standard or Rapid Infusion of Daratumumab. Patient Characteristics Were Taken From the Institute Patient Population. The Probabilities of Occurring in Each Arm Were Estimated for Equal Distribution of Patients by Arm. Squares Represent the Decision node. Circles Represent Chance Nodes. Triangles Represent Terminal State.