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Positive Quality Intervention: Daratumumab (Darzalex®) for Multiple Myeloma

Description: Daratumumab injection is an anti-CD38 monoclonal antibody (mAb) FDA approved for use in a range of multiple myeloma patients including first line, transplant ineligible and relapse/refractory.[1] The subcutaneous formulation (DARZALEX *FASPRO®*) is not indicated for front-line transplant eligible patients but is indicated for varied multiple myeloma indications (review supplemental information for reference)[6]. This PQI will provide guidance for optimal administration and management of both daratumumab infusions and subcutaneous formulation.

Background: Daratumumab is administered as single agent or in combination with other multiple myeloma treatment options including proteasome inhibitors and immunomodulating agents and is dosed at 16mg/kg.[1] One of the most common adverse reactions of daratumumab is infusion reactions of any grade. The occurrence rate is observed at 37% with the first (16mg/kg, week 1) infusion[1] and one study observed occurrence rate rising to 58% in patients did not receive montelukast prior to their first infusion[5].The median time to onset of an infusion reaction is 1.5 hours (range 0-73 hours).[1] Infusion related reactions often present with symptoms similar to allergic rhinitis such as cough, wheezing and rhinorrhea due to CD-38 expression on airway smooth muscle cells.[2] In the CASSIOPEIA trial, when daratumumab was reinitiated post ASCT (at the rate/dilution volume used for the last dose), infusion reaction rates and severity were reported at rates consistent with week 2 (all 11%, Grade 3 or 4 <1%).[1] An option to manage infusion reactions is to split the first dose over 2 days. Daratumumab is administered at a dose of 8mg/kg on days 1 and 2.[1] DARZALEX *FASPRO®* utilizes flat dosing for subcutaneous injection at (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously into the abdomen over approximately 3 to 5 minutes according to recommended schedule.[6] For monotherapy, the corticosteroid may include methylprednisolone 100 mg or equivalent, with the option to reduce to 60mg after the second infusion. For combination therapy consider administering 20 mg dexamethasone or equivalent prior to every infusion. When dexamethasone is the background regimen corticosteroid, this will serve as the daratumumab premedication. Delayed infusion reactions have been noted with daratumumab, and it is recommended to administer corticosteroids the day or two after each daratumumab infusion, unless the background regimen-specific corticosteroid is administered the day after daratumumab. Consider prescribing post-infusion medications such as short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.[1] Due to the low incidence of infusion reactions after the first infusion, a 90-minute infusion of daratumumab has been shown to be safe in patients who have received at least 2 infusions of daratumumab.[2] Additional adverse events reported with daratumumab infusions include neutropenia and thrombocytopenia. These can be managed by dose delays. Dose reductions are not recommended. Supportive care with growth factors and transfusions can be considered. Herpes Zoster Virus and Hepatitis B Virus reactivation have both been reported in patients receiving daratumumab in 2-5% and 1% of patients respectively.

PQI Process: Prior to the first infusion:

- Verify concomitant medications to be given with daratumumab and determine the dosing frequency
  - Review Infusion rates, duration and dilution volumes (see *Supplemental Information*)[1,2]
- Ensure orders are placed for premedications - administer 1-3 hours before start of infusion[1]
  - Corticosteroid-intermediate or long acting such as methylprednisolone 100mg IV
  - Acetaminophen 650 -1000 mg PO
  - Diphenhydramine 25-50 mg IV or PO
- Consider adding an H2RA and LRA for the first 2-3 infusions[3]
  - Ex. Montelukast (Singular®) 10 mg PO x 1
  - Ex. Famotidine 20 mg IV

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PQI Process Continued:

- Determine duration and dose of post-infusion corticosteroids
- Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease
    - Discontinue after 4 infusions if the patient does not experience any major infusion reactions
- **To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is correct between either DARZALEX FASPRO® for subcutaneous injection or DARZALEX® for intravenous infusion**
- Determine if day 1 will be administered as a single dose or a split dose
    - Split doses can be considered for clinics with shorter hours of operation and may result in cost savings if full infusion is not able to be completed due to time constraints or reaction
- Patients experiencing grades 1-3 infusion reactions can be rechallenged
    - Permanently discontinue for the 3rd occurrence of a grade 3 or any grade 4 infusion reaction[1]
- Verify with immunohematology and laboratories/transfusion medicine departments that patient will be receiving CD38 mAbs and provide patient with a wallet card that specifies the blood profile (ABO, Rh and IST) * This should be determined before the first infusion of daratumumab
- Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting and continue for 3 months following completion of treatment
- Check hepatitis B status and advise that daratumumab administration could reactivate the virus
- Infusion set fitted with a flow regulator and an in-line sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (0.22 or 0.2 micrometer) is required
- Monitor patient for infusion reactions and manage infusion reactions per institutional standards
    - Infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions[1]

Prior to the second infusion (week 2)

- Determine if patient experienced an infusion reaction during the previous infusion
    - If no reaction, prepare daratumumab in the week 2 volume of 500mL and administer via the rate titrations listed below for week 2
    - If an infusion reaction occurred during the first infusion, use the dilution volume of 1,000 mL
- Check CBC for neutropenia and thrombocytopenia regularly during treatment

Prior to the third and subsequent infusions (week 3 and beyond)

- Determine if patient experienced an infusion reaction during the previous infusion and repeat prior infusion if reaction occurred
- If no infusion reaction during the second week infusion, rapid administration can be considered
    - Monitor vital signs prior to infusion, every 15 minutes for the first hour, and at the end of the infusion
    - Observe patient for signs and symptoms of an infusion reaction for 30 minutes following rapid infusion
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Patient Centered Activities:

- Counsel patient on disease state, treatment regimen, adverse reactions, and verify understanding
- Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting and continue for 3 months following completion of treatment
- Check hepatitis B status and advise that daratumumab administration could cause reactivation
- Provide patient with treatment calendar outlining planned treatment schedule
- Provide patient with wallet card detailing blood profile
    - This card should be carried throughout treatment and at least 6 months after treatment ends

References:

1. Darzalex® (daratumumab) [prescribing information]. Horsham, PA: Janssen Biotech; August 2020.
2. Barr, H., Dempsey, J., Waller, A. et al. Ninety-minute daratumumab infusion is safe in multiple myeloma. Leukemia 32, 2495–2518 (2018). https://doi.org/10.1038/s41375-018-0120-2
3. Moreau, P., van de Donk, N.W.C.J., Miguel, J.S. et al. Practical Considerations for the Use of Daratumumab, a Novel CD38 Monoclonal Antibody, in Myeloma. Drugs 76, 853–867 (2016). https://doi.org/10.1007/s40265-016-0573-4
4. Mateos MV, Nahi H, Legiec W, et al. Efficacy and safety of the randomized, open-label, non-inferiority, phase 3 study of subcutaneous (SC) versus intravenous (IV) daratumumab (DARA) administration in patients (pts) with relapsed or refractory multiple myeloma (RRMM): COLUMBA. Abstract #8005. Presented at the 2019 ASCO Annual Meeting, June 2, 2019; Chicago, IL.
5. Ajai Chari, Tomer M Mark, Amrita Krishnan, Keith Stockerl-Goldstein, Saad Z Usmani, Anil Londhe, Delores Etheredge, Hollee Parros, Sarah Fleming, Baolian Liu, Scott Freeman, Jon Ukropec, Thomas Lin, Ajay K Nooka; Use of Montelukast to Reduce Infusion Reactions in an Early Access Treatment Protocol of Daratumumab in United States Patients with Relapsed or Refractory Multiple Myeloma. Blood 2016; 128 (22): 2142.
6. Darzalex Faspro® (daratumumab and hyaluronidase-fihj) [prescribing information]. Horsham, PA: Janssen Biotech; May 2020.

Supplemental Information:

Infusion rates, duration and dilution volumes for daratumumab administrations[1,2]

	Dilution Volume	Initial Rate (1st hour)	Rate Increment (absence of reaction)	Maximum rate	Average Infusion Duration
Week 1					
Option 1 Single Dose (16 mg/kg)	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour	7 hours
Option 2 Split Dose					
Week 1 Day 1 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour	4.2 hours
Week 1 Day 2 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour	4.2 hours
Week 2 (16mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour	4 hours
Week 3 & Beyond (16mg/kg)					
Option 1, Standard Infusion	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour	3 hours
Option 2, 90 Minute Infusion	500 mL	200 mL/hour for 30 minutes (20% of dose)		450 mL/hour over 60 minutes (80% of dose)	90 minutes

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Indications[1,6]

Darzalex® (daratumumab) injection, for intravenous use	Darzalex Faspro® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use
For the treatment of adult patients with multiple myeloma: • in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy • in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant • in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant • in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy • in combination with carfilzomib and dexamethasone in patients who have received one to three prior lines of therapy • in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor • as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent	For the treatment of adult patients with multiple myeloma: • in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant • in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy • in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy • in combination with pomalidomide and dexamethasone in patients who have received at least one prior therapy including lenalidomide and a proteasome inhibitor • as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent