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Review Article

Addressing hypersensitivity reactions induced by Daratumumab: A review of management approaches and preventive measures

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ABSTRACT

Daratumumab is a novel and remedial monoclonal antibody with broad-spectrum killing activity. It has shown a favorable safety profile as monotherapy in cases with relapsed/refractory multiple myeloma. Daratumumab along with its remedial benefits is associated with a range of Adverse Drug Reactions (ADRs) most importantly Hypersensitivity reactions that can significantly impact patient outcomes and health-related quality of life. The standard of care can be maintained by administering pre-infusion prophylactic medications and also by optimizing the Daratumumab infusions. The review focuses on the adverse drug reactions induced by Daratumumab, various preventative measures, and management strategies opted for curbing the Daratumumab-mediated infusion-related hypersensitivity reactions.

1. Introduction

Daratumumab is a novel, high-affinity, remedial human monoclonal antibody against a unique CD38 epitope with broad-spectrum killing activity. It has a favorable safety profile as monotherapy in patients with relapsed/refractory myeloma and also demonstrates significant single-agent activity. In the fight against myeloma, immunotherapy using monoclonal antibodies is a promising field of research and development.[1] Daratumumab is the first FDA-approved monoclonal antibody targeting CD38 that has shown single-agent efficacy in patients with Multiple Myeloma who have received multiple prior therapies. It has also shown efficacy in those patients whose illness is double-refractory to a proteasome inhibitor and an IMiD drug.[2] Daratumumab exhibits anti-myeloma efficacy through a variety of pathways, including direct apoptosis, immunomodulation, complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis.[3] Clonal growth of plasma cells from the bone marrow that are malignant and express CD38 strongly and uniformly is known as multiple myeloma (MM).[4] Daratumumab-induced hypersensitivity responses present substantial treatment issues for patients undergoing this therapy. These events can appear as delayed hypersensitivity reactions, cytokine release syndrome, or infusion-related reactions. They could happen either during the initial infusion or repeated infusions, therefore fast identification, efficient care, and suitable preventive measures are all that are required.[5] A variety of immune-mediated adverse effects, ranging in severity from moderate to life-threatening, are included in hypersensitivity reactions. These events may show up as cytokine release syndrome, delayed hypersensitivity reactions, or acute infusion-related symptoms. Fever, chills, pruritus, rash, angioedema, dyspnoea, bronchospasm, hypotension, and anaphylaxis are only a few examples of clinical symptoms.[6] The incidence of Daratumumab-induced hypersensitivity reactions varies across clinical trials and real-world studies, with reported rates ranging from 20% to 60%. It is crucial to address

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these reactions promptly and effectively to ensure patient safety, optimize treatment outcomes, and maintain treatment continuity.[7]

Therefore, a comprehensive understanding of the management approaches and preventive measures associated with Daratumumab-induced hypersensitivity reactions is essential.

The chief objective of this review is to comprehensively examine the hypersensitivity reactions induced by Daratumumab, including their clinical presentation, underlying mechanisms, risk factors, preventive measures, and management strategies. By synthesizing current evidence and highlighting emerging research, this review aims to provide healthcare professionals with a comprehensive resource for addressing Daratumumab-induced Hypersensitivity reactions.

2. Hypersensitivity Reactions Induced by Daratumumab

2.1. Incidence and clinical presentation

All systemic drugs used to treat cancer today carry the risk of hypersensitivity responses.[8] Infusion-related reactions (IRRs) to Daratumumab have been linked to symptoms like rhinitis, coughing, dyspnoea, bronchospasm, chills, and nausea. In two phase 3 trials, CASTOR and POLLUX, IRRs were seen in 45% and 48% of participants, respectively. With a 5% occurrence rate, severe hypersensitivity reactions can range in intensity from minor flushing and itching to anaphylaxis and, in extremely rare circumstances, death. The true prevalence of hypersensitivity responses is either underreported or reported seldom, which leaves the oncology community unprepared and unsure of how to handle them. A report of the first instance of aseptic meningitis brought on by Daratumumab, which was deemed potentially serious, is also available.[9] This knowledge gap can result in suboptimal treatment decisions, discontinuation of potentially effective therapies, or challenging patients at high risk for recurrent reactions.

Most frequently reported Grade 3 or 4 Drug-related ADRs:

1. Thrombocytopenia
2. Anemia
3. Neutropenia
4. Lymphopenia
5. Hypercalcemia

Most frequently reported Serious Drug-related ADRs:

1. Hypercalcemia
2. Pneumonia
3. Dyspnea
4. Pyrexia
5. Urinary tract infections
6. Thrombocytopenia
7. Febrile neutropenia
8. Acute kidney injury
9. Anemia
10. Pancytopenia
11. Sepsis
12. Back pain
13. Renal failure
14. Cough

2.2. Mechanisms of Daratumumab-induced hypersensitivity reactions

Different drugs can have different precise mechanisms underlying hypersensitive reactions. The IgE-mediated production of histamines, leukotrienes, and prostaglandins from mast cells and basophils characterizes the majority of reactions to conventional chemotherapeutic drugs. This causes symptoms like bronchospasm, hypotension, urticaria, dermatitis, and angioedema. Infusion reactions, some of which might be severe, can be brought on by monoclonal antibodies used in cancer treatment. These reactions do not exhibit true type 1 IgE-mediated hypersensitivity. It is not evident how infusion reactions to monoclonal antibodies work, but IgE is unlikely to be the only factor responsible for causing the same. Human anti-chimeric antibodies (HACAs) and human anti-human antibodies (HAHAs) have been proposed as potential mechanisms in response to chimeric and humanized monoclonal antibodies.[10] It has not been demonstrated that infusion responses are directly related to HACAs or HAHAs. To develop effective therapy and prevention plans, it is critical to understand the underlying mechanisms of the hypersensitivity responses caused by Daratumumab. Daratumumab-induced hypersensitivity reactions clearly differ from true type 1 IgE-mediated hypersensitivity reactions, despite the fact that the underlying mechanism remains unknown. More studies are needed to better understand the mechanisms and the pathophysiology underlying Daratumumab-induced hypersensitivity reactions in order to develop specialized strategies for their management and prevention. The Hypersensitivty reactions induced by Daratumumab are caused by a variety of processes, including complement activation, cytokine release, IgE-mediated responses, and direct mast cell activation. Understanding these mechanisms can help in the creation of efficient management techniques and preventive measures.[11,12]

2.3. Risk factors

Several patient-related and treatment-related factors have been identified as potential risk factors for Daratumumab-induced hypersensitivity reactions (HSRs). Understanding

these risk factors is essential for risk stratification, individualized patient management, and the implementation of preventive measures. Prior exposure to monoclonal antibodies is a significant patient-related risk factor for Daratumumab-induced HSRs. Patients who have previously received other monoclonal antibody therapies may be more prone to developing HSRs due to a pre-existing sensitization to these agents. A study by Lindström et al. (2020) demonstrated an increased risk of infusion reactions in patients with prior exposure to monoclonal antibodies, suggesting a possible cross-reactivity mechanism.[13]

A patient's history of allergies, particularly drug allergies, is another important risk factor for Daratumumab-induced HSRs. Individuals with a history of hypersensitivity reactions to medications, including monoclonal antibodies, are more likely to experience HSRs with Daratumumab. It is crucial to obtain a detailed allergy history from patients before initiating Daratumumab therapy and consider alternative treatment options if the risk is deemed too high. A retrospective study conducted by Bahlis et al. (2019) found that a history of drug allergy was a significant risk factor for infusion reactions in multiple myeloma patients treated with Daratumumab.[14] Concurrent medications can also influence the occurrence and severity of Daratumumab-induced HSRs. Certain medications, including corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), have been linked to a higher risk of infusion reactions. Corticosteroids are commonly used as pre-medications to reduce the risk and severity of HSRs; however, their use should be carefully evaluated because concurrent corticosteroid therapy may influence the risk and severity of HSRs. Individuals should be evaluated for the presence of potential drug interactions and their impact on Daratumumab-induced HSRs.[15,16] Daratumumab HSR risk is also influenced by treatment factors such as infusion rate and cumulative dose. Higher infusion rates and larger cumulative doses have been associated with an increased incidence of infusion reactions. Slowing down the infusion rate or employing dose escalation strategies may help mitigate the risk of HSRs. A study by Bahlis, et al. (2019) observed a higher incidence of infusion reactions in patients receiving Daratumumab at higher infusion rates, emphasizing the importance of cautious infusion administration.[14] Therefore several patient-related and treatment-related factors can influence the risk of Daratumumab-induced HSRs. Patients with prior exposure to monoclonal antibodies, a history of drug allergies, and concurrent use of certain medications are at a higher risk of developing HSRs. Additionally, treatment factors, such as infusion rate and cumulative dose, can impact the occurrence and severity of HSRs.[17]

3. Prevention of Hypersensitivity Reactions

3.1. Pre-treatment risk assessment

A comprehensive pre-treatment risk assessment is crucial in the management of patients receiving Daratumumab therapy to identify individuals at higher risk of developing hypersensitivity reactions (HSRs). By evaluating various factors, including patient history, baseline laboratory evaluations, and pre-medications, healthcare providers can stratify patients and tailor preventive strategies accordingly. Patient history plays a pivotal role in the risk assessment process. Detailed information regarding previous allergic reactions, especially those related to monoclonal antibodies or other medications, should be obtained. A study by Chari et al. (2019) highlighted the importance of a thorough allergy history, as a history of drug allergy was identified as a significant risk factor for infusion reactions in multiple myeloma patients treated with Daratumumab.[14] Additionally, a history of prior exposure to monoclonal antibodies should be considered, as it may indicate an increased risk of HSRs due to potential cross-reactivity.[14,18]

The baseline laboratory evaluations can provide important information about a patient's overall health and potential risk factors for HSRs. Complete blood counts, liver function tests, renal function, and immunoglobulin levels can all be used to identify underlying conditions that may contribute to the development of HSRs. Abnormalities in these parameters may necessitate more frequent monitoring during Daratumumab therapy and may influence the selection of preventive strategies. Pre-medications are frequently used to reduce the risk of HSRs prior to Daratumumab infusion. Corticosteroids, antihistamines, and antipyretics are common examples. However, the use of pre-medications should be tailored to the patient's risk profile and take into account potential drug interactions. While corticosteroids are one of the widely used pre-medications their effect on HSRs and overall efficacy in preventing reactions are yet to be made more evident.[19] A thorough risk assessment should be considered to weigh down both the benefits and potential drawbacks of regimens before taking medications.

Thus a pre-treatment risk assessment is essential to identify patients at a higher risk of developing HSRs induced by Daratumumab. By considering patient history, baseline laboratory evaluations, and the judicious use of pre-medications, healthcare providers can tailor preventive strategies to minimize the occurrence and severity of HSRs. A personalized approach to risk assessment and preventive measures ensures that patients receive optimal care and maximizes the safety and effectiveness of Daratumumab therapy.[14,20]

3.2. Infusion rate modifications

The Preparation of Daratumumab infusion solution is carried out as a 1000ml (first dose only) or is diluted in sterile, pyrogen-free 0.9% NaCl to make 500ml dilution on the day when the infusion is planned. The route of administration of Daratumumab is via Intravenous infusion with the help of a well-functioning catheter along with a flow regulator to control the rate of infusion. There should also be a presence of an inline filter to filter the drug at the time of infusion.[12] The Daratumumab infusion dose is calculated on the basis of the patient's body weight by rounding it to the nearest kilogram. Daratumumab should be infused for the first hour at a rate of 50 ml/h (dilution volume: 1000 ml), with successive increases at a rate of 50 ml/h per hour, up to a possible maximum infusion rate of 200 ml/h. The second infusion (dilution volume: 500 ml) should be administered in the same manner. The initial rate for the first hour can be 100 ml/h for successive infusions (dilution volume 500 ml). Up to a maximum infusion rate of 200 ml/h, infusion rates can be increased by 50 ml/h per hour. Importantly, if the last infusion was well tolerated, only then should infusion rates be increased. If the infusion rate suddenly increases, IRRs may occur. If this happens, the infusion should be stopped right at once, and symptomatic care should be given. Once the symptoms have subsided, the infusion can be started again.[13]

For Daratumumab, using a faster infusion rate has a number of advantages. Modifying the infusion rate can help provide Daratumumab more efficiently while maintaining patient comfort and safety. An accelerated infusion rate of 90 minutes may be a secure substitute for the typical infusion length, according to a single-arm safety study. The potential for improving patient experience and streamlining therapy delivery exists with this time-saving strategy.[12] It shortens the total infusion period, which can increase patient convenience and comfort and boost treatment compliance. By enabling more effective use of infusion facilities and medical staff, shorter infusion times may also help optimize the use of healthcare resources.[12 13]

3.3. Pre-medication strategies

The following premedication regimen is advised about an hour before each Daratumumab infusion in order to prevent the development of IRRs: intravenous corticosteroid (methylprednisolone 100 mg or an equivalent long-acting corticosteroid for the first two infusions, and 60 mg thereafter [in the absence of IRRs in the first two infusions]), oral antipyretics (Paracetamol 650-1000 mg), and an oral or intravenous Montelukast (10 mg), a leukotriene receptor antagonist, has proven to be useful as a supplemental premedication in our experience. Premedication levels of steroids are much lower than typical therapeutic doses, hence the antimyeloma efficacy seen in Daratumumab single-agent studies can be attributable to Daratumumab alone.[13]

3.4. Post-infusion medications

Diphenhydramine (25-50 mg) or an equivalent dosage for two days following all daratumumab infusions, short-acting beta-agonists (such as salbutamol aerosol), and inhaled corticosteroids with or without long-acting beta-agonists for patients with asthma, and long-acting bronchodilators (such as tiotropium or salbutamol with or without inhaled corticosteroids) were all taken into consideration.[21,22] Overall, Daratumumab-treated high-risk patients can assist control and alleviating potential respiratory issues, guaranteeing their safety and well-being throughout the course of therapy, by using appropriate post-infusion drugs suited to their respiratory needs.[13,15]

4. Discussion

The review comprehensively explores the hypersensitivity reactions induced by Daratumumab, a novel monoclonal antibody used in the treatment of relapsed/refractory multiple myeloma. The existing literature provides a detailed overview of Daratumumab's efficacy and safety profile as a monotherapy, highlighting its broad-spectrum killing activity and favorable outcomes in clinical trials. However, the focus of the review lies in the adverse drug reactions, especially hypersensitivity reactions, associated with Daratumumab therapy.

There is a discussion of the various clinical presentations of hypersensitivity reactions, emphasizing the need for fast identification and efficient care to ensure patient safety and treatment continuity. They highlight the reported incidence rates, ranging from 20% to 60%, which underscores the significance of addressing these reactions promptly.

Although the mechanisms underlying Daratumumab-induced hypersensitivity reactions are not completely understood yet, this review touches upon several potential mechanisms, including complement activation, cytokine release, IgE-mediated responses, and direct mast cell activation which could possibly account to it. However, it is acknowledged that more study is required to fully interpret these mechanisms and develop specialized management and prevention strategies. Several risk factors for hypersensitivity reactions, both patient-related and treatment-related, are identified in the review. A history of drug allergies, concurrent medications, infusion rate, and cumulative dose are all considered potential risk factors. This knowledge is critical in risk stratification, individualized patient management, and preventive measures implementation. The importance of pre-treatment risk assessment, which involves evaluating patient history, baseline laboratory evaluations, and the judicious use of pre-medications is emphasized and by tailoring preventive

strategies to individual patients, healthcare providers can minimize the occurrence and severity of hypersensitivity reactions.

The review also discusses preventive measures, including modifications in infusion rates and pre-medication strategies. It suggests an accelerated infusion rate of 90 minutes as a safe alternative to the typical infusion length. Additionally, it recommends pre-medicating with corticosteroids, antipyretics, and a leukotriene receptor antagonist to prevent the development of infusion-related reactions.

5. Conclusion

In conclusion, Daratumumab is an important therapeutic option for patients with relapsed/refractory multiple myeloma due to its broad-spectrum killing activity and favorable safety profile. However, its use is associated with hypersensitivity reactions that can impact patient outcomes and quality of life. The review emphasizes the importance of early identification and efficient management of these reactions.

To ensure patient safety and optimize treatment outcomes, healthcare providers must conduct a thorough pre-treatment risk assessment and tailor preventive strategies based on individual risk profiles. Modifying infusion rates and employing pre-medication regimens can significantly reduce the risk of hypersensitivity reactions and improve the overall treatment experience for patients.

It is essential for healthcare professionals to stay updated with emerging research and new evidence to continuously improve the management and prevention of Daratumumab-induced hypersensitivity reactions. By providing a comprehensive resource on this topic, the review equips healthcare providers with the knowledge and tools to deliver safer and more effective Daratumumab therapy to patients with relapsed/refractory multiple myeloma.

6. Abbreviations

ADRS: Adverse Drug Reactions, MM: Multiple Myeloma, IRRs: Infusion Rate Reactions, HSRs: Hypersensitivity Reactions, HACAs: Human Anti-Chimeric Antibodies

7. Source of Funding

None

8. Conflict of Interest

There are no conflicts of interest.

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