

Infusion reactions associated with use of biologic medicines in cancer therapy

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ABSTRACT

Biologic medicines, such as monoclonal antibodies are gaining popularity for prevention and treatment of diseases. Due to their binding specificity for the molecular target of interest, or other biochemical pathways in human system, they provide benefits of lowering the unwanted systemic effects with an increase in efficacy. Studies on expression of molecular targets bestows one disadvantage of targeted therapies as molecular target of interest expresses in many instances on the normal cells as well, thereby disrupting normal cellular function and causing varying grades of toxicity. Though severe reactions are not common, mild-to-moderate infusion reactions has been associated with treatment with monoclonal antibodies. For achieving the treatment goal and future decisions, the proper assessment and evaluation of severity and nature of infusion reactions is required. Inappropriate assessment of adverse infusion reactions can affect the treatment decisions and prove to be life threatening.

This review discusses the selected monoclonal antibodies which are used for treatment of life threatening conditions such as cancer. We have discussed the infusion reactions associated with both the monoclonal antibodies as well as monoclonal antibody-drug conjugates used for treatment of cancer.

Keywords: Infusion reactions, Biotherapeutics, Monoclonal antibody, Hypersensitivity

How to cite this article

Singh A, Singh DK, Bhorla U. Infusion reactions associated with use of biologic medicines in cancer therapy. *Oncocytology* 2014;4:10–18.

Article ID: 100006OCYAS2014

doi:10.5348/OCY-2014-6-RA-2

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Received: 25 July 2014

Accepted: 30 August 2014

Published: 29 September 2014

INTRODUCTION

Biologic medicines including monoclonal antibodies are complex molecules which are the backbone of targeted therapies [1]. The biologic medicines are developed for targeting specific cells or biochemical pathways in human system, thereby reducing the other unwanted systemic effects and increasing efficacy [2]. These were initially considered to be associated with limited potential for side effects. Now in use since some years, they have shown previously unknown and unexpected adverse drug reactions and infusion reactions.

The appropriate assessment and understanding of the severity and nature of infusion reactions is important for determining the best current treatment as well as for taking the future decisions about the treatment. Failure to assess adverse infusion reactions can negatively affect

the treatment decisions. The treatment goal is dependent about the appropriate assessment of the course of treatment, by continuing active treatment in patients who may be safely re-challenged and also discontinuing the treatment in patients who are at high risk for experiencing a second reaction with the drug. When administering therapy it is important to be aware of the possibility of infusion reactions and proper prevention, management and procedures should be readily available in hand to counter these untimely and unwanted events.

This article reviews the general description and infusion reactions associated with selected monoclonal antibodies used for treatment of cancer. A PUBMED/MEDLINE search was conducted for studies and reviews of infusion reactions to biologic medicines. More information was obtained from the product information provided for each agent on company website and package inserts. Objective of this review is to discuss the infusion reactions of biologics used for treatment of cancer. Both monoclonal antibodies and monoclonal antibodies-drug conjugates are discussed with an emphasis placed on how the occurrence of these reactions affects further treatment.

Infusion reactions

Humanized monoclonal antibodies (MoAbs) represent a significant addition to therapeutic options for a variety of malignancies [3]. Generally the monoclonal antibodies are well tolerated but many adverse events including infusion reactions, overlapping with other chemotherapeutics have been reported. The infusion reactions generally occur with the first dose [4]. The infusion reactions with monoclonal antibodies are mostly mild but if not managed appropriately, they may prove life threatening. Infusional toxicity is defined as any event within 24-hours of an infusion described as allergic reaction or anaphylactoid reaction, or any event occurring on the first day of dosing described as allergic reaction, anaphylactoid reaction, fever, chills, or dyspnea [5].

Though the pathophysiology of infusion reactions with monoclonal antibodies is not very well understood, efforts to elucidate the mechanisms are underway. Infusion reactions can be broadly categorized by their immunologic mechanisms into anaphylaxis and anaphylactoid reactions. Anaphylaxis is a systemic, immediate hypersensitivity reaction mediated by factors released from interactions between immunoglobulin E (IgE) and mast cells that produce an antigen-antibody reaction [6]. Anaphylactoid reactions can be differentiated from anaphylaxis by the fact that they are not IgE-mediated but rather cytokine-mediated [7]. Despite the mechanistic disparities, there are no significant differences in clinical manifestations from anaphylaxis and anaphylactoid reactions and the immediate management of both reactions is the same. They can involve cutaneous, respiratory, gastrointestinal, or cardiovascular systems. Both terms are often used interchangeably in literature when describing

severe infusion reactions. One difference, however, is that patients who experience cytokine-mediated anaphylactoid reactions, which are commonly less severe, can be re-challenged using stronger premedication and slower infusion rates.

For infusion reactions, the clinical manifestations require prompt, accurate assessment and management to avoid severe adverse events, including fatality. Prompt identification and management of infusion-related reactions can help optimize therapy.

This review summarizes the characteristics of infusion reactions and further discusses the reactions that occur with individual monoclonal antibodies used for cancer treatment.

Characteristics of infusion reactions

To make a better understanding and delineating hypersensitivity reactions and infusion reactions induced by cytokine release on one global platform, the National Cancer Institute Common Toxicity Criteria (NCI-CTC) came up with criteria to distinguish between the two [8]. The proven mechanism to infusion reactions to monoclonal antibodies is still debatable, as these reactions are unlikely to be true, type 1 IgE-mediated hypersensitivity reactions [9]. At therapeutic dose, all infusion reactions involve the immune system. The two classes of reactions include anaphylactic which are allergic in nature and are generally mediated by IgE, and other which include anaphylactoid which are not true allergic reactions and are not mediated by IgE. The infusion reactions to chimeric and humanized monoclonal antibodies may be a result of their ability to elicit human antichimeric antibodies (HACAs) and human anti-human antibodies (HAHAs), respectively [10–13].

As per the NCI-CTC grading criteria, mild-to-moderate reactions (Grades 1 and 2) are characterized by flushing, rash, fever, rigors, chills, dyspnea, and mild hypotension. Severe reactions (Grades 3 and 4) are associated with bronchospasm and hypotension requiring treatment, cardiac dysfunction, anaphylaxis, and other symptoms. Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms associated with these reactions overlap (Table 1) [4].

Signs and symptoms — Infusion reactions may affect any organ system in the body. Most are mild in severity, although severe and even fatal infusion reactions occur [14]. The most common signs and symptoms of infusion reactions are: allergic reaction/hypersensitivity (including drug fever), pruritus/itching, rash/desquamation, urticaria (hives, welts, wheals), rigors/chills, headache, arthralgia/myalgia, tumor pain, fatigue (asthenia, lethargy, malaise), dizziness, sweating, nausea/vomiting, cough, dyspnea, bronchospasm, hypotension/hypertension, tachycardia [14].

Table 1: Grading of HSRs according to the NCI Common Terminology Criteria for Adverse Events v3.0 [4].

	Grade				
	1	2	3	4	5
Hypersensitivity (allergic reaction)	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever -38°C (100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
Acute infusion reaction (cytokine release syndrome)	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medication indicated for 24 hours	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death

Abbreviations: HSRs, hypersensitivity reactions; NCI, National Cancer Institute; NSAIDs, nonsteroidal anti-inflammatory drugs
⁴Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 2007 May;12(5):601–9.

Timing — The time taken by monoclonal antibodies to develop the infusion reactions after the initiation of drug infusion is 30 minutes to two hours. The symptoms might further be delayed for 24 hours. Mostly the reactions occur after the first and second infusion of the drug. Around 10–30% occur during the subsequent treatments [4]. In general, the likelihood of an infusion reaction declines with each subsequent course of therapy. Approximately 90% of severe infusion reactions with cetuximab were observed during the first infusion [20]. For rituximab, the incidence of any-grade infusion reactions during the first, fourth, and eighth infusion was 77%, 30%, and 14%, respectively [27]. This rate of 10–30% of delayed events in subsequent doses indicates the importance of close monitoring following administration of any infusion.

Incidence: The incidence of a mild-to-moderate infusion reaction during the first drug administration varies among individual monoclonal antibodies and is highest for rituximab (77 percent), alemtuzumab (over 50percent), cetuximab (16–19 percent), trastuzumab (up to 40 percent), panitumumab (5 percent)) [15–19].

Most infusion reactions occur rapidly, but not all; in general, the more rapid the onset is, the more severe the reaction [4]. The fatal outcome can occur rapidly. Therefore, realizing the risks and recognizing the early signs and symptoms is crucial in the management of severe infusion reactions.

Infusion Reactions with monoclonal antibodies

Rituximab (RITUXAN)

Rituximab is a chimeric monoclonal antibody that targets CD20, which is a human B-lymphocyte-restricted

differentiation antigen, Bp35. CD20 is hydrophobic transmembrane protein with a molecular weight of approximately 35 kDa located on pre-B and mature B lymphocytes. Rituximab has been indicated for the treatment of patients with: non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukemia (CLL) [15]. CD20 antigen is expressed on greater than 90% of B-cell non-Hodgkin’s lymphomas (NHL), but the antigen is not found on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissues. The possible mechanism of action of rituximab is the binding of the Fab domain of monoclonal antibody to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis in vitro. The mechanism of cell lysis includes complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC) however; complement-mediated cytotoxicity is most likely the dominant mechanism in vivo. The high selectivity of rituximab for B-cells led to further investigations which involve autoimmune B-cell-driven diseases, such as rheumatoid arthritis. Positive outcomes in clinical trials led to FDA approval for rituximab for the treatment of rheumatoid arthritis [15].

Rituximab has been demonstrated to cause severe infusion reactions. Although true anaphylactic or hypersensitivity reactions are reported, most of the reactions from rituximab are considered to be, at least partially, due to increased cytokine release [20, 21]. Most of the 80% severe reactions Grade 3 or 4 typically occurred during the first infusion. The time to onset of infusion reactions is 30–120 minutes. As reported in 2% to 10% of patients, Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory

distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death [22]. Fatal infusion reactions were reported in 0.04% to 0.07% of patients during postmarketing surveillance [15]. This highlights the importance of careful monitoring of patients during infusions, and administration should be discontinued and supportive treatment provided for grade 3 or 4 infusion reactions [15].

Trastuzumab (HERCEPTIN)

Trastuzumab is a humanized monoclonal antibody indicated for the treatment of HER2/neu-positive metastatic breast cancer, HER2-over expressing metastatic gastric or gastroesophageal junction adenocarcinoma [18]. The family of epidermal growth factor receptors comprises HER1, HER2, HER3, and HER4. These tyrosine kinases play a critical role in cellular growth and are frequently up-regulated in numerous cancers, including breast carcinoma. The overexpression of HER2 has been found in about 20–30% of breast cancers, which is classified as the HER2-positive subtype and has the second-poorest prognosis among breast cancer subtypes. Targeting HER2 is an attractive therapeutic approach. Preclinical data, both in vitro and animals showed inhibition of proliferation of human tumor cells that overexpress HER2. In vitro studies demonstrated, trastuzumab mediated antibody dependent cellular cytotoxicity preferentially exerted on HER2 overexpressing cancer cells as compared with cancer cells that do not overexpress HER2. The approval of trastuzumab in 1998 has significantly improved patients' outcomes and paved the way for the beginning of advent of targeted approaches in breast cancer treatment [18].

In clinical trials, approximately 40% of patients experienced the most commonly reported symptoms chills and fever, during the first infusion with the drug [23]. Treatment of symptoms was done with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of trastuzumab infusion). In < 1% of patients, permanent discontinuation of Trastuzumab for infusional toxicity was required. Other signs and/or symptoms included nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. Infusional toxicity occurred in 21% and 35% of patients, and was severe in 1.4% and 9% of patients, on second or subsequent drug infusions administered as monotherapy or in combination with chemotherapy, respectively. In postmarketing reports, serious and fatal infusion reactions have been reported [18]. Severe reactions which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable including progressive worsening; initial improvement followed by clinical deterioration, or delayed post-

infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction.

Alemtuzumab (CAMPATH)

Alemtuzumab is a cytolytic monoclonal antibody directed against CD52, which is an antigen present on the surface of B and T lymphocytes, a majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes [16]. A proportion of bone marrow cells, including some CD34+ cells, express variable levels of CD52. Alemtuzumab binds to CD52 on the leukemic cells which leads to antibody-dependent cell mediated cytotoxicity. Alemtuzumab is indicated as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) [16].

Alemtuzumab is associated with infusion reaction during or shortly after its infusion. The intravenous administration of alemtuzumab is usually accompanied by transient infusion-related side effects manifesting primarily as flu-like symptoms [24]. The infusion reactions include pyrexia, chills/rigors, nausea, hypotension, urticaria, dyspnea, rash, emesis, and bronchospasm. In clinical trials, during the first week of treatment the frequency of infusion reactions was found to be the highest. In post-marketing reports, serious including fatal reactions have been identified. These include syncope, pulmonary infiltrates, acute respiratory distress syndrome (ARDS), respiratory arrest, cardiac arrhythmias, myocardial infarction, acute cardiac insufficiency, cardiac arrest, angioedema, and anaphylactoid shock.

Bevacizumab (AVASTIN)

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody, which binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells [25]. The interaction of VEGF with its receptors Flt-1 and KDR leads to endothelial cell proliferation and new blood vessel formation. Bevacizumab, a vascular endothelial growth factor-specific angiogenesis inhibitor, has been indicated for the treatment of metastatic colorectal cancer, non-squamous non-small cell lung cancer, metastatic breast cancer and glioblastoma.

In less than 3% patients first dose of bevacizumab was associated with infusion reactions. Severe reactions were noted in 0.2% of patients [25]. Infusion reactions include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. The management of severe infusion reaction with bevacizumab involves complete cessation of therapy and administration of appropriate medical therapy.

Cetuximab (ERBITUX)

Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR) [26]. EGFR is expressed in many human cancers including those of the head and neck, colon, and rectum. Cetuximab is indicated in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck and for K-Ras wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC). Cetuximab is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant region. Cetuximab competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as TNF- α by binding specifically to the EGFR on both normal and tumor cells. Binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production.

Severe infusion reactions with cetuximab include rapid onset of airway obstruction leading to bronchospasm, stridor and hoarseness; hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. In these cases medical intervention and immediate, permanent discontinuation of cetuximab was required. In clinical trials, infusion reactions occurred in 15–21% of patients across all clinical studies. Severe infusion reactions (NCI-CTC Grades 3 and 4) were observed in approximately 2–5% of patients with fatal outcomes in one patient. In 90% cases severe infusion reactions occurred within minutes of initiating the first dose of cetuximab despite premedication [26, 27]. All Grade 4 infusion reactions occur within minutes of the first infusion, but less severe reactions appeared with the second or subsequent reactions, indicating a possible difference in mechanisms underlying mild and severe infusion reactions.

Panitumumab (VECTIBIX)

Panitumumab is a fully human IgG2 monoclonal antibody, which is an epidermal growth factor receptor antagonist. It is indicated as a single agent for the treatment of metastatic colorectal carcinoma [28]. Panitumumab improved outcomes when added to best supportive care in patients with chemotherapy-refractory metastatic colorectal cancer. Panitumumab competitively inhibits the binding of ligands EGF and TNF- α to EGFR on both the normal and tumour cells. Binding of panitumumab to the EGFR inhibits ligand-induced receptor autophosphorylation and activation of receptor-associated kinases. This results in cell growth inhibition, apoptosis induction, decreased proinflammatory cytokine, production of vascular growth factors and internalization of the EGFR.

Panitumumab was safe and well tolerated. With panitumumab monotherapy, infusion reactions occurred in 4% of patients of which approximately 1% were severe Grade 3–4. Most of its adverse effects are related to some form of skin toxic effect. Severe infusion reactions included anaphylactic reactions, bronchospasm, and hypotension [29].

Ofatumumab (ARZERRA)

Ofatumumab is a cytolytic monoclonal antibody directed against CD20 molecule. The CD20 molecule is expressed on normal B lymphocytes (pre-B- to mature B-lymphocyte) and on B-cell CLL. Ofatumumab is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab [30]. The Fab domain of ofatumumab binds to the CD20 molecule and the Fc domain mediates immune effector functions to result in B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.

Infusion reactions were more frequent in patients with the first two infusions. In 44% of patients infusion reactions occurred on the day of the first infusion and in 29% of patients on the day of the second infusion [30]. The occurrence of infusion reactions took place less frequently during subsequent infusions. Serious infusion reactions with reported were bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, syncope, cardiac ischemia/infarction, back pain, abdominal pain, pyrexia, rash, urticaria, and angioedema. Infusion reactions were common with early doses but subsided with subsequent infusions [31].

IPILIMUMAB (YERVOY)

Ipilimumab is a recombinant, human monoclonal antibody that specifically binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and blocks the interaction of CTLA-4 with its ligands, CD80/CD86 [32]. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response. Ipilimumab has been indicated for the treatment of unresectable or metastatic melanoma [33].

In clinical studies approximately 1% patients tested positive for binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay [32]. These patients also did not show infusion-related or peri-infusional reactions.

Pertuzumab (PERJETA)

Pertuzumab is a HER2/neu receptor antagonist which targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2) and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4 [34]. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways, mitogen-activated protein (MAP) kinase, and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways results in cell growth arrest and apoptosis, respectively. Pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC). While pertuzumab alone inhibited the proliferation of human tumor cells, the combination of pertuzumab and trastuzumab augmented anti-tumor activity in HER2-overexpressing xenograft models.

Pertuzumab is indicated for use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. It is also used in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer [35].

In all the clinical studies, infusion reactions have occurred with pertuzumab. In one study initial dose of pertuzumab was given the day before trastuzumab and docetaxel. When only pertuzumab was administered on the first day, the overall frequency of infusion reactions was 13.0% in the Pertuzumab-treated group and 9.8% in the placebo-treated group. Infusion reactions of Grade 3 or 4 were less than 1%. The most common infusion reactions were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting. During the second cycle when all drugs were administered on the same day, the most common infusion reactions in the pertuzumab-treated group were fatigue, dysgeusia, hypersensitivity, myalgia, and vomiting [34].

Infusion Reactions with monoclonal antibody-drug conjugates

Brentuximab vedotin (ADCETRIS)

Brentuximab vedotin is a CD30-directed chimeric IgG1 antibody-drug conjugate. Monomethylauristatin E (MMAE) is a small molecule, which disrupts microtubule [36]. It is covalently attached to the brentuximab vedotin via a linker. The anticancer activity of brentuximab vedotin is due to the binding of the antibody-drug conjugate (ADC) to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest

and apoptotic death of the cells. Brentuximab vedotin is indicated for treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates. It is also indicated for systemic anaplastic large cell lymphoma after failure of at least one prior multiagent chemotherapy regimen.

Brentuximab vedotin have been associated with infusion-related reactions, including anaphylaxis. In phase 1 clinical trials two cases of anaphylaxis were reported whereas in phase 2 clinical trials, Grade 1 or 2 infusion-related reactions were reported for 12% patients [36]. The most common adverse reactions associated with infusion-related reactions were chills, nausea, dyspnea, pruritus, pyrexia, and cough.

ado-Trastuzumab emtansine (KADCYLA)

ado-Trastuzumab emtansine is a HER2-targeted monoclonal antibody and microtubule inhibitor conjugate. Trastuzumab is the humanized anti-HER2 IgG1 monoclonal antibody. The small molecule cytotoxin, DM1, is a microtubule inhibitor [37]. Upon binding to sub-domain IV of the HER2 receptor, ado-trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in intracellular release of DM1-containing cytotoxic catabolites. Binding of DM1 to tubulin disrupts microtubule networks in the cell, which causes cell cycle arrest and cell apoptosis. In addition, ado-trastuzumab emtansine inhibits HER2 receptor signaling, mediates antibody-dependent cell-mediated cytotoxicity and inhibits shedding of the HER2 extracellular domain in human breast cancer cells that overexpress HER2 [37].

ado-Trastuzumab emtansine is indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Treatment with ado-Trastuzumab emtansine is not recommended for patients with in patients who had trastuzumab permanently discontinued due to infusion-related reactions and/or hypersensitivity treatment. Infusion-related reactions are characterized by flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia [37]. The overall frequency of infusion-related reactions in patients treated with ado-Trastuzumab emtansine was 1.4%. In most patients, after the infusion was completely stopped, these reactions resolved over the course of several hours to a day. In clinical trials of single-agent ado-Trastuzumab emtansine, one case of a serious, allergic/anaphylactic-like reaction was observed. Across clinical trials 3% of patients experienced infusion reactions of all grades and severe reactions were extremely rare, occurring in 1% approximately.

Prevention and management of infusion reactions

The details of prevention and management of transfusion reactions are outside the scope of this article. Some general pointers about how to prevent and manage infusion reactions are discussed here.

Prevention

Close patient monitoring is essential during and immediately after all monoclonal antibodies infusions, particularly when the risk of hypersensitivity reactions is higher, such as during the first infusion of monoclonal antibodies. Vital signs should be checked at intervals; before, during, and after the infusion [38]. The possibility of a delayed reaction should also be considered. These delayed reactions may occur hours or days after an infusion. Patients should be made aware of and strongly encouraged to notify a clinician immediately if they notice any discomfort during the infusion. Pharmacological prophylaxis with antihistamines, corticosteroids, or both is generally recommended to reduce the frequency and severity of hypersensitivity reactions [39]. Premedication with diphenhydramine is recommended before each infusion of cetuximab [26]. If no hypersensitivity reaction is observed, premedication can be safely discontinued after the first infusion of cetuximab [27]. Diphenhydramine can be replaced by loratadine which is a nonsedating antihistamine, in patients who do not experience an infusion reaction during the first infusion of cetuximab. Hypersensitivity reactions are unpredictable and can occur at any time, despite preventive measures. Therefore, clinicians should be prepared to manage a reaction, should one occur, during each administration [39]. Standing orders should be in place to allow immediate intervention if a reaction occurs, without waiting for a physician [38]. A “crash cart” with the resources needed for resuscitation should be readily available. This includes pharmacological agents such as epinephrine and aerosolized bronchodilators and medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator. Sufficient medical resources should be available to sustain a patient who experiences a severe infusion reaction until they can be admitted [38].

Management

Prompt recognition of infusion reactions and immediate medical attention are essential to reducing the risk of severe symptoms [40] in patients developing infusion reactions. There should be a protocol with physician and nurses which outlines the emergency management of hypersensitivity reactions [38]. These protocols allow for immediate intervention by the medical staff if a reaction occurs, without even waiting for a physician. When an infusion reaction occurs, the infusion should be interrupted and supportive care

should be administered until the symptoms resolve. In most cases, mild-to-moderate reactions will resolve after a brief infusion interruption and the administration of supportive care.

Most patients who experience a mild-to-moderate reaction (Grade 1 or 2) during the first exposure with monoclonal antibodies, will tolerate readministration of the agent using a slower infusion rate and premedication. Readministration should be done after all symptoms have resolved [39]. Re-challenge is discouraged in patients who have a severe initial reaction (Grade 3 or 4), underscoring the need for accurate grading of hypersensitivity reactions and infusion reactions. Premedication for re-challenge typically includes antihistamines and corticosteroids [41]. For monoclonal antibodies, reducing the infusion rate by half is recommended. The decision to re-challenge with any agent should be based on multiple factors, including the risk for a serious recurrent reaction and the potential clinical benefit of further treatment. Continuing active treatment should be a priority for patients who have mild-to-moderate reactions and strategies that safely allow continuation should be considered. If a drug is given as salvage therapy or as palliative care, the long-term clinical benefits of continued treatment are likely to be small and may not warrant the risk for severe toxicity. In this case, switching to an alternative agent, if available, may be appropriate. Accurate grading of hypersensitivity and infusion reactions, including distinguishing between moderate and more severe reactions, may be critical to determine the best treatment plan following resolution of symptoms.

CONCLUSIONS

Monoclonal antibodies have been successfully used for treatment of wide array of diseases including the life threatening conditions such as cancer. Infusion reactions to monoclonal antibodies are immediate, often occurring within the first few minutes of the first infusion. Severe infusion reactions are not very common, but mild-to-moderate reactions takes place with some of the cancer therapies. The time of onset of symptoms varies with each of these drugs. The clinical signs and symptoms of these infusion reactions are significantly similar, irrespective of the class of agent used or the mechanism of actions associated with these drugs. The treatment goal requires the lowering of risk associated with these agents. For this an initial careful assessment of patient history such as drug allergies or other immune status is important. During the course of treatment premedication and careful patient monitoring is utmost important. Precise grading of toxicity and adverse reactions is useful while taking the decision about continuation of treatment. Treatment decisions when signs of infusion reactions develop, re-challenging with the drug after resolution of symptoms or complete termination of treatment is needed. Most of the infusion reaction symptoms

are alleviated after administering supportive care for symptoms using a reduced infusion rate, premedication, and/or a desensitization protocol. For severe reactions, the infusion should be stopped, supportive care should be provided, and, in most cases, treatment should be discontinued.

Author Contributions

Anubha Singh – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Deepak Kumar Singh – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Usha Bhoria – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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