REVIEW

Immediate Reactions To Monoclonal Antibodies In Clinical Hematology

Dr Vasiliki Kyriazi, MD.
Bristol Haematology Oncology Centre, NHS Foundation Trust, Bristol, United Kingdom.

ABSTRACT

Monoclonal antibodies (MoAbs) have been widely used in clinical hematology. As foreign macro-molecules, they can cause infusional reactions during the administration or within 24 hours after the infusion, which encompass a spectrum of mechanisms. Although most of these reactions are non-allergic, are often indistinguishable from true allergic reactions mediated by IgE immunoglobulins. The diagnosis is often challenging and relies mainly on clinical criteria. They occur during the first doses, soon after the initiation of treatment. The symptoms are usually well controlled by the immediate drug discontinuation or reduction of the infusion rate. The management remains largely supportive, consisting of oxygen, intravenous fluids, bronchodilators, antihistamines and steroids. Most of MoAb protocols recommend premedication with steroids and antihistamines and gradually escalating infusion rates. Increased medical and nursing vigilance is required and resuscitative equipment should always be readily available. These events affect patients' quality of life, leading to treatment delay or discontinuation and series of tests. The decision to rechallenge the treatment depends on severity grading, clinical parameters and treatment goals. This article provides an update of MoAbs used in clinical hematology. It summarizes the pathophysiology, the diagnostic approach, the preventive measures and treatment of MoAb-related reactions.

KEY WORDS: Drug Allergy, Hematology, Hypersensitivity, Infusion Reactions, Monoclonal Antibodies.

Corresponding author:

Dr Vasiliki Kyriazi, Bristol Haematology Oncology Centre, NHS Foundation Trust, Bristol, BS2 8ED, United Kingdom.
E-mail: kyriazivasiliki@yahoo.com

INTRODUCTION

The introduction of MoAbs has significantly changed the treatment of many hematologic disorders. MoAbs are immunoglobulins targeting cells expressing a specific antigen on their surface, reducing significantly the toxicity compared to conventional chemotherapy. Nevertheless as foreign molecules, they may cause immediate reactions which are widely characterized as infusional reactions. The term includes symptoms and signs observed during the drug infusion or within 24 hours after the infusion [1]. In daily practice the terms allergy, hypersensitivity and reaction are often used interchangeably, overlooking the underlying pathophysiology. Drug reaction encompasses all adverse events related to drug administration, regardless of etiology, while the term hypersensitivity refers to immune-mediated response to a drug in a sensitized patient [2].

Generally, the infusion-related reactions can be divided into allergic and non-allergic. Clinical presentation widely varies between mild mucocutaneus manifestations and cardiopulmonary failure and death. Interestingly, the symptoms are often identical regardless the pathophysiological mechanism, which leads to problematic recording, difficulty in understanding the risk factors and establishing preventive measures. The management is similar and requires patient's awareness and a high degree of medical and nursing vigilance.

This study will describe the types of infusional reactions and implicated biologic pathways. The available data about the frequency and severity of reactions in relation to different types of MoAbs commonly used in clinical practice will be presented. It also summarizes the known risk factors, potential ways of prevention and treatment approach.

METHODS

For the scope of this review the literature search was conducted through PubMed using as keywords: drug allergy, hematology, hypersensitivity, infusion reactions, and monoclonal antibodies. Searching limits included: research and review articles in adult humans, published in the last decade in English language. References of retrieved articles were reviewed with emphasis on practical information. Prescribing information was used to elicit data about the incidence of infusional reactions and suggested precautions for each MoAb.

PATHOPHYSIOLOGICAL PATHWAYS

The immune system, which can be activated by any foreign molecule, consists of innate and adaptive immune response.

The innate immune response is non-specific and pre-exists to antigen exposure. It incudes a number of cells such as natural killer (NK) cells, mast cell, dendritic cells, eosinophils, neutrophils, macrophages, monocytes; and molecules such as cytokines and acute phase proteins [3]. The complement system is a part of innate immune response and enhances the action of antibodies and phagocytic cells. It consists of liver-produced proteins which circulate as inactive precursors. Trigger factors, such as antigen-antibody complexes, lectin and endotoxins, induce a serial cleavage and activation of these proteins, leading to cytokine release and formation of the cell-killing membrane attack complex [4].

The adaptive immune response is specific against particular antigens, and encompasses the activation of B and T lymphocytes. B lymphocytes produce antibodies that recognize specific antigens on the surface of foreign cells. The intact antibody is Y-shaped and consists of a pair of light chains and a pair of heavy chains. Light chains are composed of one variable region and one constant region. Heavy chains are usually composed of one variable and three constant regions. The upper portion is called Fab (Fragment antigen binding) and has the antigen binding sites, while the lower portion Fc (Fragment crystallizable) is responsible for the reaction against the antigen. The complementarity-determining regions (CDRs) are found in the variable fragment (Fv) portion of Fab. Antigen binding to antibody triggers phagocytosis, cytolysis, activation of NK cells, and modification of the receptors on the host cell surface, leading to cell destruction or inhibition of cell proliferation [3].

Cytokines is a broad category of small proteins which includes interleukins (ILs), interferons (IFNs) and tumor necrosis factor (TNF). Macrophages, B lymphocytes, T lymphocytes, NK cells, mast cells are cellular resources of cytokines. Additionally, they can be produced by and influence the behaviour of a variety of non-immune cells, such as cancer cells. Cytokines influence cellular growth, motility and differentiation. In inflammatory and infective conditions, cytokines cause fever, chills, fatigue, nausea and hypotension [5], [6].

Immediate allergic reactions and anaphylaxis

Gell and Coombs' system classify the immediate allergic reaction as type I hypersensitivity response, which is a direct, systemic hypersensitivity reaction mediated by IgE antibodies [7]. Anaphylaxis is a serious systemic allergic reaction that is rapid in onset with potential fatal consequences [8].

Following to first exposure to an allergen, naïve B lymphocytes produce IgM antibodies, which are increased logarithmically within 4-10 days via the clonal proliferation of B cells [9]. Upon re-exposure to the allergen, memory B cells are activated and antibody production is switched from IgM to IgE usually by somatic hypermutations [10]. The half-life of circulating IgE is 2 days, but they can also bind to the surface of mast cells and basophils, remaining there for weeks [11]. In a subsequent exposure to the allergen, the bound IgE antibodies react with the production of histamine, leukotrienes and prostaglandines from mast cells in tissues and basophils in peripheral blood. These factors can cause muscle contraction, vasodilation, fluid extravasation and increase of mucosal secretions [12].

Non- allergic reactions and cytokine release syndrome

Non-allergic reactions are also known as pseudo-allergic or anaphylactoid reactions and are not mediated by IgE antibodies. The pathophysiology involves cytokine release and activation of complement cascade.

Drug binding to the surface of a target cell activates the innate immunity, such as monocytes, macrophages, cytotoxic T lymphocytes and NK cells. These cells in turn release cytokines, such as TNF and IFN-gamma, 1-2 hours after exposure, followed by release of IL-6, IL-10, and in some cases IL-2 and IL-8 [13].

Activated immune cells by MoAbs bind to the Fc portion of the antibody and destroy the target cell either by phagocytosis or cytolysis, leading to cytokine release [14]. The complement activation results in C3a, C5a and C5b-9 release, which activate mast cells, basophils and other phagocytes and lead to secretion of vasoactive mediators [15].

DIAGNOSIS AND GRADING OF INFUSIONAL REACTIONS

Most MoAb-related reactions are derived by cytokine release without the mediation of IgE antibodies [1], [14]. They are usually mild to moderate and allow the drug administration. Both allergic and non-allergic reactions manifest with identical clinical symptoms, making the diagnosis challenging. Based on Common Terminology Criteria for Adverse Events, published by the National Cancer Institute, grade 1 comprises mild transient reactions, not requiring any intervention; and grade 2 comprises those responding promptly to symptomatic treatment. Grade 3 reactions are prolonged and symptoms re-occur following the initial improvement. Grade 4 reactions can have life threatening consequences and urgent intervention is indicated, whereas grade 5 results to patient's death [16].

Allergic reactions typically occur after several exposures to the drug [7]. They occur within minutes upon re-exposure, although delayed reactions, 10-12 hours post injection, have been observed. Generally, the faster the reaction is the more serious clinical complications [3]. Allergy or even anaphylaxis during the first administration of MoAbs are rare and can be attributed to cross reactivity mechanisms [15]. In IgE-mediated events, the increased vascular permeability can cause a transfer of up to 50% of intravascular fluid into the extravascular space in 10 minutes and life threatening events may occur due to shock and hypoxia [12], [17]. Prophylaxis with antihistamines is not usually effective [18].

In pseudo-allergic reactions, symptoms are mild to moderate and occur during the first 2 hours of the first drug infusion. Nevertheless, delayed reactions have been reported, especially in premedicated patients. Symptoms usually resolve with the drug re-exposure likely due to the smaller tumor burden, and therefore lower cytokine release by the malignant cells [19]. Symptoms can be derived from

several organs, such as nasopharynx (rhinitis), eyes (conjunctivitis), mucosa (angioedema), respiratory tissue (asthma), gastrointestinal tract (gastroenteritis) and skin (eczema) [20]. Systemic symptoms like fever, chills, flushing, rash, pruritus, dyspnea, back pain, headache, and distress have also been reported [15]. Hypotension, cardiac arrest, bronchospasm and exfoliative dermatitis are rarely reported, making difficult the differential diagnosis from true allergic and anaphylactic events [21]. Table 1 summarizes the main differences between allergic and anaphylactoid reactions.

Allergic Reactions	Non-allergic Reactions
IgE-mediated	Complement or cytokine-mediated
Re-exposure increases the risk; reaction occurs within seconds to minutes to antigen exposure	Occur during the first exposure and become milder upon repeated administration
Life threatening systemic reaction; anaphylaxis	Usually mild to moderate symptoms
Antihistamines and steroids do not prevent the reaction	Response to prophylaxis with antihistamines and steroids
Infusion interruption and urgent intervention are usually required	Response to temporal infusion interruption/ slower infusion rate
Positive skin tests confirm the diagnosis	Unpredictable by standard allergy tests
Rechallenging is contraindicated	Rechallenging can be attempted

Table 1. Differences between allergic and non-allergic reactions

Laboratory investigation of infusional reactions is not routinely performed. The measurement of urinary histamine and serum tryptase can confirm the diagnosis of anaphylaxis [22]. Tryptase is produced by basophils and mast cells and peak levels are noted 30 minutes to 2 hours from symptoms' onset and come back to baseline 48-72 hours after the anaphylactic episode. The disparity between baseline and peak values is indicative of mast cells and basophils activation. However, the serum tryptase levels have been found unchanged in 36.6% of clinically proven anaphylactic episodes and increased in complement-mediated reactions [23], [24]. Testing for specific IgE antibodies is not useful in confirming the diagnosis of anaphylaxis at the time of presentation, but it can be used in identifying sensitized patients to specific allergens [25]. A retrospective study by Chung et al. showed that the presence of serum Cetuximab-IgE antibodies in patients with colorectal cancer was a highly predictive factor for a serious reaction during the infusion [26]. Skin prick and intradermal tests, which involve the allergen injection into the skin dermis, have high predictive value in penicillin-induced reactions. However, in other cases, a negative test does not effectively rule out the presence of specific IgE antibodies [8], [20]. Quantification of cytokines such as IL-2, IL-6, IL-8, IFN, TNFa and complement factors, such as CH50, C3a, C5a, SC5b-9, could be experimentally used in understanding the underlying pathophysiological process [15]

MONOCLONAL ANTIBODIES IN HEMATOLOGY PRACTICE
MoAbs are immunoglobulins produced by a specific clone of B lymphocytes, which selectively bind to molecular target on cellular surface and inhibit or destroy the cancer cells. Some of them are conjugated with radioisotopes, cytostatics or toxins [14].

Although murine MoAbs were structurally similar to human ones, the differences between them were sufficient to evoke an immune response when they were injected into humans. Advances in genetic engineering led to the development of humanized MoAbs. Chimeric MoAbs, such as Rituximab, contain variable regions from a murine source and human constant regions and more than 50% of the molecule is human. Humanized MoAbs are predominantly derived from a human source except for the CDRs domains, which are murine. Humanized MoAbs consist of more than 90% of human sequences, wherein the part determining the antibody specificity derived from highly variable mice regions [27].

Over the past two decades numerous antibodies have been approved for the treatment of malignant and non-malignant disorders. MoAbs either as monotherapy or in combination with conventional chemotherapy have brought significant changes in hematology. Due to targeted action they are better tolerated compared to chemotherapeutics. However, as foreign proteins they can trigger reactions, which are usually mild and transient, responding to infusion cessation or flow rate reduction [table 2].

Rituximab
Rituximab was introduced in clinical practice in 1997 and is the best studied antibody. It is a chimeric antibody (human/ murine) that targets B cells expressing the CD20 antigen. CD20 is a transmembrane phosphoprotein expressed from pre-B to mature B lymphocytes. CD20 is present in 90% of B-cell non-Hodgkin's lymphoma (B-NHL), B-cell chronic lymphocytic leukemia (B-CLL) and hairy cell leukemia [28]. Direct binding of Rituximab to C1q triggers a cascade of reactions leading to destruction of B cells [28]. Moreover, receptors on NK cells and macrophages recognize and bind the Fc portion of Rituximab, causing the destruction of malignant B cells. Rituximab also affects the cell proliferation, differentiation and apoptosis [29], [30].

The standard intravenous dose for B-NHL is 375 mg/m2 body surface and the frequency depends on the indication. The first Rituximab dose is administered slowly, starting at 50 mg/h and increasing by 50 mg/h every 30 minutes up to maximum 400 mg/h. Fractionated dosing regimens, i.e. administration of 100 mg of the total dose on day 1 and the remaining dose on day 2, are used for high risk patients [19]. According to package insert, premedication with antihistamines and acetaminophen (or equivalent) prior to each dosing. Patients with pre-existing cardiac or pulmonary disorders, previous infusional reaction, and circulating lymphocytes count equal to or higher than 25,000/mm3 should be closely monitored [31].

In standard intravenous administration, mild reactions such as fever, rigors and chills have been reported in 85% of cases. Serious manifestations, such as bronchospasm, angioedema, and arrhythmia occur in 2%-10% of patients [32]. The incidence of fatal reactions is 0.04%-0.07%. Most of infusional events are considered to be cytokine-mediated, although true allergic reactions have been reported [32]. They usually emerge 30-120 minutes after starting the infusion and are more severe during the first infusion. In patients with indolent B-NHL the incidence of infusional reactions during the first, fourth and eighth dose of Rituximab was 77%, 30% and 14% respectively; and 7% of reactions in the first cycle was grade 3-4 [31], [32]. Reactions grade 3-4 occurred in 9% of patients with

diffuse large B-cell NHL (DLBCL) and the incidence decreased to 1% in the eighth cycle [33].

Adult patients with previously untreated DLBCL and follicular NHL, with uneventful first standard intravenous infusion, without any significant cardiovascular disease or circulating lymphocyte count more than 5,000/mm3 can have a 90-minute Rituximab infusion in cycles 2-8. In this case, 20% of the total dose is given over the first 30 minutes and the remaining 80% over the following 60 minutes. The incidence of grade 3-4 infusion reactions in days 1-2 of cycle 2 was 1.1% and the cumulative incidence in cycles 2-8 was 2.8%. No fatal events reported on days 1 and 2 of any cycle [31].

In 2014, subcutaneous Rituximab was licensed for patients with previously untreated stage III−IV follicular NHL in combination with chemotherapy, follicular NHL responding to induction therapy, and CD20-positive DLBCL in combination with CHOP chemotherapy. In SABRINA study, infusional reactions were more common with subcutaneous Rituximab compared with intravenous Rituximab (50% [31/62] and 32% [21/65] respectively), possibly due to local injection site reactions [29]. Most reactions, i.e. 98% in the intravenous group and 95% in the subcutaneous group, were grade 1 or 2 [34]. Before starting subcutaneous injections, patients must receive a full dose of intravenous Rituximab so as potential reactions to be managed by slowing or stopping the infusion [31].

Moab	Target (Indication)	Overall incidence	Grade 3-4 reactions	Prophylaxis
RITUXIMAB Chimeric (human / murine)	CD20 (NHL)	Standard IV 85% 90-min IV N/a Subc 50%	Standard IV 2-10% 90-min IV 1.1-2.8% Subc 1-2%	Premedication: antihistamines, acetaminophen (or equivalent) ± steroids. Split dosage regimes in high risk patients (i.e. lymphocyte count ≥25,000/mm^3). Escalating infusion rate. Rapid and subc infusion is allowed in patients who tolerated prior slow iv infusion
OFATUMOMAB Human	CD20 (NHL)	28-68%	4-8%	Premedication: antihistamines, acetaminophen (or equivalent) ± steroids Split dosage regime for the 1st cycle Escalating infusion rate
90Y-IBRITUMOMAB TIUXETAN Radio-labelled, recombinant murine	CD20 (NHL)	N/a	<2%	Slow IV infusion over 10 minutes; bolus infusion is contraindicated
OBINUTUZUMAB Humanized	CD20 (NHL)	66%	21%	Premedication: antihistamines, acetaminophen (or equivalent) ± steroids.Split dosage regime for the 1st cycle. Escalating infusion rate
ALEMTUZUMAB Humanized	CD52 (B-CLL/SLL, T-PLL)	N/a	10-35%	Premedication: antihistamines, acetaminophen (or equivalent) ± steroids in 1st cycle and prior to each dose escalation Weekly escalated dosage if tolerated
BRENTUXIMAB VEDOTIN Chimeric (human/ murine), conjugated to MMAE	CD30 (HL, sALCL)	N/a	N/a	Premedication is recommended in patients with prior history of infusional reaction
GEMTUZUMAB OZOGAMICIN Recombinant humanized, conjugated to calicheamicin	CD33 (AML)	82%	6%	Leukoreduction prior to infusion (aim: leucocyte count<30,000/m^3) Premedication: antihistamines, acetaminophen (or equivalent) ± steroids
ECULIZUMAB Recombinant humanized	C5 (PNH)	36%	N/a	Premedication is not routinely indicated Push or bolus infusion is contraindicated

Table 2. Infusion-related reactions and MoAbs in clinical hematology

Ofatumumab

Ofatumumab is a human IgG1 antibody that targets a distinct epitope of CD20, leading to complement-dependent cytotoxicity and lysis of tumor cells. Binding to CD20 induces the recruitment of NK cells and the subsequent cell death through antibody-dependent cell-mediated cytotoxicity [35], [36].

The usual first dose is 300 mg, which is subsequently increased to 1,000 mg or 2,000 mg [36]. The initial rate of the first infusion is 12 ml/h and it can be increased every 30 minutes to a maximum of 400 ml/h. In good tolerence, the subsequent infusions can start at a rate of 25 ml/h which can be increased every 30 minutes up to 400 ml/h. Patients should always be premedicated 30 minutes to 2 hours prior to infusion [36].

According to product characteristics, the reported incidence of infusional reactions was 68% at any time during treatment. The majority of reactions was grade 1 or 2; and 8% was grade 3 at any time during the treatment. Two percent of infusional reactions led to treatment discontinuation, but no fatal events have been reported [36]. In a retrospective observational study of 103 heavily pre-treated patients with B-CLL, infusional reactions to Ofatumumab occurred in 19 subjects (28%), and were grade 3-4 in 4 patients [37]. The incidence of infusional reactions was 46% during the first infusion in a cohort of 59 B-CLL patients and 38% in 79 patients with bulky Fludarabine-refractory disease [38].

Yttrium-90 Ibritumomab tiuxetan

In radioimmunotherapy, the anti-CD20 MoAbs lead to direct cell apoptosis through the radioactive portion of their molecule [39]. Activation of complement pathway, antibody-dependent cytotoxity and cell apoptosis are other potential mechanisms of action, already known from other anti-CD20 MoAbs [39]. Infusional reactions are similar to those seen with naked MoAbs. Grade 3-4 reactions are less than or equal to 2% and partially preventable with premedication with steroids and antihistamines [40].

Yttrium-90 Ibritumomab tiuxetan is a radio-labelled recombinant murine IgG1 kappa antibody, specific for CD20 antigen, which is conjugated to a pure beta-emitter, Yttrium-90 (90Y) [41], [42]. It is recommended for relapsed and refractory CD20- positive low grade B-NHL or for those achieving partial remission after initial therapy. 90Y Ibritumomab is given following pretreatment with Rituximab, over 10-minute intravenous infusion. Administration-related reactions are commonly observed. However, severe grade 3-4 reactions including anaphylaxis occur in less than 1% of patients [42].

Obinutuzumab

Obinutuzumab is a glycoengineered IgG1 anti-CD20 MoAb, which induces direct cell death and enhanced

antibody-dependent cellular cytotoxicity with less complement-dependent cytotoxicity compared to Rituximab [43], [44]. Based on prescribing information, two thirds of patients experienced reactions to the first 1000 mg of the antibody. Therefore, the first Obinituzumab dose is split between day 1 (100 mg over 4 hours) and day 2 (900 mg, starting at 50 mg/h and escalating the rate in increments of 50 mg/h every 30 minutes to a maximum rate of 400 mg/h) [45]. Premedication with acetaminophen (or equivalent), antihistamines, and steroids is recommended by the manufacturer [45].

Goede et al. randomly assigned 781 patients with previously untreated B-CLL to receive Chlorambucil, Obinutuzumab plus Chlorambucil, or Rituximab plus Chlorambucil. Infusional reactions were more frequent (all grades: 66%, grade 3-4: 21%) in Obinutuzumab–Chlorambucil arm than in Rituximab–Chlorambucil arm (all grades: 38%, grade 3-4: 4%) during the first infusion [46]. There were no grade 3 or 4 reactions in subsequent infusions. No deaths were associated with infusion-related reactions. Neither the lymphocyte count nor the tumor burden at baseline was a strong predictor of infusional reactions. Prophylactic measures had only a moderate effect on the frequency of reactions [46].

Alemtuzumab

Alemtuzumab is a humanized anti-CD52, derived from the original rat antibody Camppath-1G and binds to CD52, an antigen present on the surface of B and T lymphocytes, majority of monocytes, macrophages, NK cells, some granulocytes and a proportion of bone marrow cells. Binding to leukemic cells leads to antibody-dependent cellular-mediated lysis [47], [48]. It is licensed for TP53 deleted/ mutated B-CLL, purine-analogue refractory B-CLL and T-prolymphocytic leukemia (T-PLL) [49]. It is given intravenously over 2 hours. Subcutaneous administration is recommended for B-CLL but not in T-PLL. The dose is gradually escalated to maximum recommended single dose of 30 mg.

Infusional reactions are common. Grade 3-4 pyrexia occurs in approximately 10% of previously untreated patients and in approximately 35% of previously treated patients. The frequency is higher during the initial week of treatment and decreases in subsequent doses. Manufacturer recommends antihistamines and acetaminophen (or equivalent) 30 minutes prior to first infusion and each dose escalation [48].

Brentuximab vedotin

Brentuximab vedotin is a chimeric IgG1 anti-CD30 antibody which is covalently linked to anti-mitotic molecule monomethylauristatin E (MMAE). CD30 is a membrane molecule, expressed by activated T and B lymphocytes. MoAb binds to CD30 and internalisation of the MoAb-CD30 complex initiates. Within the cell, MMAE is released and binds to tubulin. Disruption of microtubule network induces cell cycle arrest and apoptosis of CD30-expressing tumor cell [39], [50]. Brentuximab is licensed for the treatment of adult patients with relapsed or refractory CD30-positive Hodgkin's lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL) [51].

Brentuximab is administered intravenously over 30 minutes and is well tolerated. As with other chimeric MoAbs, infusion-related reactions can occur. Approximately 35% of patients develop antibodies to Brentuximab. Infusional reactions are observed in patients with persistently positive antibodies to Brentuximab (30%) relative to those with transiently positive antibodies

(12%) and never positive antibodies (7%) [51]. Premedication is usually necessary for those with a history of reactions [52].

Gemtuzumab ozogamicin

Gemtuzumab ozogamicin is composed of a recombinant humanized IgG4 kappa antibody conjugated with a cytotoxic antitumor antibiotic, calicheamicin. The antibody portion binds to CD33 antigen, which is present on the surface of 80% of leukemic blasts [53]. The complex MoAb-CD33 antigen is internalized and upon internalization, the calicheamicin is released inside the lysosomes of myeloid cells and binds to DNA, resulting in DNA double strand breaks and cell death [53].

Gemtuzumab can cause post-infusion symptoms, such as fever and chills, and less commonly hypotension and dyspnea. They usually occur during the first 24 hours after administration. All grades of infusion reactions occur in 82% of patients and grade 3-4 in 6% [53]. In a prospective post-marketing registry study, the incidence of infusional reactions was 8.0% [53]. In a study of 277 patients with relapsed CD33-positive acute myeloid leukemia (AML), Gemtuzumab, at a dose of 9 mg/m2, commonly caused acute infusional reactions, with approximately 30% and 10% of patients experiencing grade 3-4 events after the first and second dose, respectively. In the registration trials, such toxicities included chills (8%), fever (6%), hypotension(4%),nausea (3%),and hypertension(2%) [54]. The risk can be reduced with prior leukoreduction with hydroxyurea or leukapheresis, so as the peripheral white blood count to be lower to 30,000/mm3. Premedication with acetaminophen (or equivalent) and antihistamines is recommended. Methylprednisolone prior to drug infusion seems to ameliorate the symptoms [53].

Eculizumab

Eculizumab is a humanized anti-C5 MoAb that inhibits complement at C5 and prevents the generation of the terminal complement complex C5b-9. It is the first effective therapy for paroxysmal nocturnal hemoglobinuria (PNH), where the uncontrolled terminal complement activation and the resulting complement-mediated intravascular hemolysis are blocked by the antibody [55]. The dose depends on the indication and treatment phase; and in adults it is given intravenously over 25-45 minutes [56].

Eculizumab can provoke infusional reactions or immunogenicity, causing allergic or hypersensitivity reactions. However, the incidence of reactions within 48 hours from administration did not differ from placebo in PNH or atypical hemolytic uremic syndrome (aHUS). In clinical trials, no PNH or aHUS patients experienced an infusion reaction requiring the drug discontinuation [56]. In SEPHERED study, Eculizumab was well tolerated throughout the 52-week treatment period with a majority of adverse events reported as mild to moderate and unrelated to the drug [53]. No serious adverse events were considered probably or definitely related to treatment. The incidence of serious adverse events was similar to that reported in placebo arm of TRIUMPH study [57]. Hillmen et al. studied the long-term safety and efficacy of Eculizumab in 195 patients over 66 months. Adverse events related to MoAb infusion were reported in 71 patients (36.4%). Peripheral edema, pruritus and rash were the most common and none of these led to drug discontinuation [58].

MANAGEMENT OF INFUSIONAL REACTIONS

Medical and nursing staff involved in prescribing, dispensing and administering the MoAbs should be trained

to promptly recognise and treat infusional reactions. Immediate reactions to drugs constitute a medical emergency and therefore emergency protocols and equipment should be readily available. The initial management involves the immediate discontinuation of the infusion, checking of patient's vital signs and implementation of supportive measures, such as intravenous fluids and oxygen as required. Patients should be monitored for life threatening signs and symptoms throughout the reaction. Warning signs of impending cardiovascular collapse include hypotension, upper airway edema, wheezing or stridor and urticaria. Moreover, fever, mucous membrane lesions, abnormal pulmonary examination, joint tenderness and swelling indicate a serious reaction [4].

Epinephrine is the drug of choice for serious allergic reactions, especially in case of hypotension and airway compromise. The recommended dose is 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution intramuscularly in the mid-anterolateral aspect of the thigh; maximum doses are 0.5 mg in adults or 0.3 mg in children. The dose can be repeated every 5-15 minutes if needed. Intravenous epinephrine can be given by experienced specialists [59, 60].

Recumbent position and rapid administration of intravenous fluids (Hartman's or normal saline 0.9%) at initial dose of 500-1000 mls in adults or 20 ml/kg in children are used in hypotensive episodes and the dose is repeated as necessary. Intraosseus access for fluids can be used if intravenous route is not available. In a specilist setting glucagon can reverse beta-blockade and dopamine can be used in hypotension resistant to epinephrine and intravenous fluids [59].

Antihistamines have a slower onset of action than epinephrine. Therefore, their use as a single agent in a true anaphylactic reaction is unsafe. However, antihistamines are effective in mild non-allergic reactions [12]. Steroids are not effective in the acute phase of the reaction, but they can reduce the duration of the reaction, alleviate the symptoms in patients with pre-existing immunological disorders; and prevent recurrences. Hydrocortisone (100-200 mg) or its equivalent can be administered every 6-8 hours for the first 24 hours [12], [17]. Inhaled beta-agonists including epinephrine, are indicated in bronchospasm.

The vital signs should be checked every 2-5 minutes until resolution of symptoms and every 15-30 minutes thereafter. Notably, biphasic reactions have been observed in 1%-20% of patients with anaphylaxis [61]. The interval between the initial reaction and recurrence can be up to 72 hours [62]. Patients should be monitored for at least 4 hours after symptoms' subsidence, while in the most serious cases, monitoring for late reactions is recommended for 24 hours [12], [17]. MoAb reinfusion can be attempted at 50% of the previous infusion rate, with gradual increase according to prescribing information [14].

PREVENTION OF INFUSIONAL REACTIONS AND RECHALLENGING

The risk of immediate reactions to drugs is higher in young and middle aged adults, in individuals carrying genetic polymorphisms of human leukocytes antigens and drug metabolism pathways; and in those infected by human immunodeficiency virus (HIV) and Epstein Barr Virus (EBV) [63]. Repeated administration of the drug increases the risk of allergic reaction [64]. Lymphocyte count greater than 25,000/mm3, first drug exposure, diagnosis of

B-CLL and mantle cell lymphoma are known risk factors based on Rituximab experience. Severe reactions to Rituximab were more common in females, elderly patients, and in those with pulmonary infiltrates. Personal history of allergy and autoimmune disease seem to increase the risk of reaction [32]. O'Neil et al. showed that in middle south areas of United States, reaction rates to Cetuximab, an antibody used in colorectal and squamous cell carcinoma of head and neck, was much higher than reported nationwide [65]. Therefore, awareness of potential geographical distribution of infusional reactions to MoAbs could improve the prophylactic care.

Prophylaxis with antihistamines and acetaminophen (or equivalent) with or without steroids prior to administration is recommended for almost all MoAbs, although the benefit from the routine use is not clear [3]. Fractionated dosing regimens, as those applied for many anti-CD20 antibodies and Alemtuzumab, aim to minimize the risk of cytokine release syndrome [48]. Generally, premedication, escalated infusion rates and avoidance of antihypertensives on the day of infusion seem to be effective in preventing anaphylactoid reactions, but do not affect the manifestation of IgE-mediated reactions [21]. The desensitization protocols involve the administration of gradually increasing doses of the drug starting from small doses. So far, they have been successfully used in patients with reactions to Rituximab, including anaphylaxis [1], [3]. Tocilizumab is a humanized MoAb against IL-6 receptor and has been used in the treatment of severe cytokine release syndrome with or without steroids, since IL-6 is regarded a major mediator in cytokine-mediated response [66].

The type and severity grading of the reaction, the therapeutic goals and comorbidities should be taken into account before rechallenging the offending MoAb [3]. Repeated exposures to the drug typically pose a risk of allergic reactions [2]. Therefore, in case of IgE-mediated and grade 4 reactions of any type, rechallenging the same MoAb is not recommended [15]. Non-immune reactions tend to be less severe and reproducible. Patients with grade 1-2 reactions usually tolerate a slower infusion rate and respond to prophylaxis with antihistamines and steroids. The use of alternative antibody is not excluded in clinical practice. For example 131I-Tositumomab was used in patients with repeated reactions to Rituximab [67].

CONCLUSION

Immediate infusional reactions to MoAbs are common in clinical hematology and can be divided into true allergic reactions, mediated by IgE antibodies; and non-allergic or anaphylactoid reactions, mediated by cytokines or complement factors. However, in the absence of objective drug-specific tests, the reactions are clinically indistinguishable. The diagnosis is based on the history of drug infusion, such as time of administration, cycle number, dosage; and the assessment of clinical symptoms. The likelihood of allergic reaction increases with repeated exposures to the drug, while the anaphylactoid ones occur at initial exposure to the factor. Most MoAb-related reactions are anaphylactoid and are usually graded as mild to moderate, presented with urticaria or hives without cardiorespiratory compromise. Rapid and profound B lymphocyte depletion caused by treatment could explain the higher frequency and intensity of reactions during the first dose.

The data regarding potential risk factors are limited and mainly based on Rituximab experience. At present the prophylaxis is empirical and encompasses the gradually

escalated infusion rates and premedication with acetaminophen (or equivalent), antihistamines with or without steroids. The management involves the immediate cessation of the infusion and implementation of measures to support the airways and circulation. Medical and nursing staff should be able to recognize early symptoms and signs of infusional reaction and be familiar with the emergency protocols and equipment. Most of MoAb-related reactions respond to symptomatic measures, allowing the drug reinfusion. Rechallenging the offending MoAb is based on the type and severity of reaction, therapeutic goals, and physician's aspects.

The inconsistent terminology and grading system used in clinical practice lead to inaccurate reporting of the infusional events. The documentation should include the offending agent, cycle number, timing from infusion initiation, symptoms, severity grading, preventive and therapeutic measures undertaken; and patient's response. Detailed recording can facilitate the understanding of the underlying pathophysiology. It can also allow the design and implementation of studies to identify potential risk factors, individualize the prophylactic measures; and optimize the rechallenging process.

ACKNOWLEDGEMENT
Declared none.

COMPETING INTERESTS
The authors declare no competing interests.

REFERENCES

[1] Kang SP, Saif MW. Infusion-related and hypersensitivity reactions of monoclonal antibodies used to treat colorectal cancer–identification, prevention, and management. J Support Oncol. 2007;5(9):451–7.

[2] Riedl MA, Casillas AM. Adverse drug reactions:Types and treatment options. Am Fam Physician. 2003;68(9):1781-90.

[3] Vogel WH. Infusion reactions: Diagnosis, assessment and management. Clin J Onc Nurs. 2010;14(2):E10-21.

[4] Pio R, Corrales L, Lambris JD. The role of complement in tumor growth. Adv Exp Med Bio. 2014;772(3):229–62.

[5] Burska A, Boissinot M, Ponchel F. Cytokines as biomarkers in rheumatoid arthritis. Mediators Inflamm. 2014 March 9;2014:545493. doi: 10.1155/2014/545493.PubMed PMID: 24733962

[6] Dinarello CA. Proinflammatory cytokines. Chest 2000;18(2):503–8.

[7] Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. Oncologist. 2007;12(5):601–9.

[8] Warrington R, Silviu-Dan F. Drug allergy. Allergy Asthma Clin Immunol. 2011;7 Suppl 1:S10.

[9] Abbas AK, Lichtman AH , Pillai S. Humoral immune responses. In Abbas AK, Lichtman AH , Pillai S (editors). Basic Immunology: Functions and Disorders of the Immune System. 4th edition. Philadelphia: Saunders-Elsevier;2014. p.131–150.

[10] Sudowe S, Rademaekers A, Kolsch E. Antigen dose-dependent predominance of either direct or sequential switch in IgE antibody responses. Immunology. 1997;91(3):464–72.

[11] Xiong H, Dolpady J, Wabl M, Curotto de Lafaille MA, Lafaille JJ. Sequential class switching is required for the generation of high affinity IgE antibodies. J Exp Med. 2012;209(2):353–64.

[12] Lieberman P, Kemp SF, Oppenheimer J, Lang DM, Bernstein IL, Nicklas RA, et al. The diagnosis and management of anaphylaxis: An updated practice parameter. J Allergy Clin Immunol. 2005;115(3 Suppl 2):S483–523.

[13] Walker M, Makropoulos D, Achuthanandam R, Bugelski PJ. Recent advances in the understanding of drug-mediated infusion reactions and cytokine release syndrome. Curr Opin Drug Discov Devel. 2010;13(1):124–35.

[14] Breslin S. Cytokine-release syndrome: Overview and nursing implications. Clin J Onc Nurs. 2007;11(1):37–42.

[15] Doessegger L, Banholzer ML. Clinical development methodology for infusion-related reactions with monoclonal antibodies. Clin Trans Immunol. 2015 Jul 17;4:e39. doi:10.1038/cti.2015.14. PubMed PMID: 26246897.

[16] ctep.cancer.gov (home page on the Internet). US National Institute of Health. National Cancer Insitute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [updated 2009 May 28; cited 2010 June 14]. Available from: www.ctep.cancer.gov

[17] Brown SG, Mullins RJ, Gold MS. Anaphylaxis: Diagnosis and management. Med J Aust. 2006;185(5):283–9.

[18] Saif MW. Hypersensitivity reactions associated with oxaliplatin. Expert Opin Drug Saf. 2006;5(5):687–94.

[19] Byrd JC, Waselenko JK, Maneatis TJ, Murphy T, Ward FT, Monahan BP, et al. Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: Association with increased infusion-related side effects and rapid blood tumor clearance. J Clin Oncol. 1999;17(3):791–5.

[20] Baldo BA, Pham NH. Drug Allergy. Clinical Aspects, Diagnosis, Mechanisms, Structure-Activity Relationships. 1st edition. New York: Springer; 2013.

[21] Chung CH. Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. Oncologist. 2008;13(6):725-32.

[22] Scarlet C. Anaphylaxis. J Infus Nurs. 2006;29(1):39–44.

[23] Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Esteso O, Garriga T, et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. Int Arch Allergy Immunol. 2013;160(2):192–9.

[24] Szebeni J. Hemocompatibility testing for nanomedicines and biologicals: Predictive assays for complement mediated infusion reactions. Eur J Nanomed. 2012;4(1):33–53.

[25] Simons FE, Ardusso LR, Dimov V, Ebisawa M, El-Gamal YM, Lockey RF, et al. World Allergy Organization Anaphylaxis Guidelines: 2013 update of the evidence base. Int Arch Allergy Immunol. 2013;162(3):193-204.

[26] Chung CH, Chan E, Berlin J, Gilbert J, Yarbrough W, Satinover S, et al. Cetuximab-related hypersensitivity reactions associated with pre-existing cetuximab-specific IgE antibody. J Clin Oncol. 2007;25(18S ASCO Meeting Abstracts): 9097.

[27] Imai K,Takaoka A. Comparing antibody and small-molecule therapies for cancer. Nat Rev Cancer. 2006;6(9):714-27.

[28] Shim H. One target, different effects: a comparison of distinct therapeutic antibodies against the same targets. Exp Mol Med. 2011;43(10):539-49.

[29] Shan D, Ledbetter JA, Press OW. Signaling events involved in anti-CD20 induced apoptosis of malignant human B cells. Cancer Immunol Immunoth. 2002;48(12):673–83.

[30] Mathas S, Rickers A, Bommert K, Dorken B, Mapara MY. Anti-CD20- and B-cell receptor-mediated apoptosis: Evidence for shared intracellular signalling pathways. Cancer Res. 2000;60(24):7170–6.

[31] Rituxan.com [Internet]. USA. RITUXAN® (Rituximab) Full Prescribing Information, Genentech, Inc. [updated 2014 Aug).Available from : http://www.gene.com/download/pdf/rituxan_prescribing.pdf

[32] Kimby E. Tolerability and safety of rituximab (MabThera). Cancer Treat Rev. 2005;31(6):456-73.

[33] Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus Rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. N Engl J Med. 2002;346(4):235–42.

[34] Davies A, Merli F, Mihaljevic B, Siritanaratkul N, Solal-Céligny P, Barrett M, et al. Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): stage 1 analysis of a randomised phase 3 study. Lancet Oncol. 2014;15(3):343-52.

[35] Cang S, Mukhi N, Wang K, Liu D. Novel CD20 monoclonal antibodies for lymphoma therapy. J Hematol Oncol. 2012 Oct 11;5:64. doi: 10.1186/1756-8722-5-64.

[36] Electronic Medicines Compendium (eMC) [Internet]. UK. SPC Arzerra 100mg & 1000mg concentrate for solution for infusion.[updated 2015 May 26]. Available from: https://www.medicines.org.uk/emc/medicine/23022

[37] Moreno C, Montillo M, Panayiotidis P, Dimou M, Bloor A, Dupuis J, et al. Ofatumumab in poor-prognosis chronic lymphocytic leukemia: a Phase IV, non-interventional, observational study from the European Research Initiative on Chronic Lymphocytic Leukemia. Haematologica. 2015;100(4):511-6.

[38] Osterborg A, Kipps TJ, Mayer J, Stilgenbauer S, Williams CD, Hellmen A, et al. Ofatumumab (HuMax-CD20), a novel CD20 monoclonal antibody, is an active treatment for patients with CLL refractory to both fludarabine and alemtuzumab or bulky fludarabine-refractory disease: Results from the planned interim analysis of an international pivotal trial [abstract]. Blood. 2008;112(11):328-8.

[39] Baldo BA. Adverse events to monoclonal antibodies used for cancer therapy: Focus on hypersensitivity responses .Oncoimmunology. 2013 Oct 17;2(10):e26333.

[40] Stevens PL, Oluwole O, Reddy N. Advances and application of radioimmunotherapy in non-Hodgkin's lymphoma. Am J Blood Res. 2012;2(2):86-97.

[41] Tomblyn M. Radioimmunotherapy for B-cell non-Hodgkin's lymphomas. Cancer Control. 2012;19(3):196–203.

[42] Drugs.com [Internet]. USA. Zevalin FDA Prescribing Information; c2000-2016 [updated 2013 Aug]. Available from: http://www.drugs.com/pro/zevalin.html

[43] Podhorecka M, Markowicz J, Szymczyk A, Pawlowski J. Target therapy in hematological malignances: new monoclonal antibodies. Int Sch Res Notices. 2014 Oct 30;2014:article ID701493. Available from: http://dx.doi.org/10.1155/2014/701493

[44] Mössner E, Brünker P, Moser S, Püntener U, Schmidt C, Herter S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood. 2010;115(22):4393-402.

[45] Gene.com [Internet]. USA: GAZYVA® (obinutuzumab) Full prescribing information, Genentech, Inc. [updated 2016 Feb]. Available from: http://www.gene.com/download/pdf/gazyva_prescribing.pdf

[46] Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, et al. Obinutuzumab plus Chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014;370(11):1101-10.

[47] Alinari L, Lapalombella R, Andritsos L, Baiocchi RA, Lin TS, Byrd JC. Alemtuzumab (Campath-1H) in the treatment of chronic lymphocytic leukemia. Oncogene. 2007;26(25):3644-53.

[48] Campath.com [Internet]. USA: CAMPATH® (alemtuzumab) Prescribing Information, Genzyme, Com. [udated 2014 Sept]. Available from:http://www.campath.com/pdfs/2014-09-Campath_US_PI.pdf

[49] Keating M, Coutré S, Rai K, Osterborg A, Faderl S, Kennedy B, et al. Management guidelines for use of alemtuzumab in B-cell chronic lymphocytic leukemia. Clin Lymphoma. 2004;4(4):220-7.

[50] European Medicines Agency [Internet]. London: Assessment report Adcertis-Brentuximab Vedotin; c1995-2016 [updated 2012 Jul 19). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/E

PAR__Public_assessment_report/human/002455/WC500135054.pdf

[51] Electronic Medicines Compendium (eMC) [Internet]. UK. SPC Adcetris® 50 mg powder for concentrate for solution for infusion [updated 2016 Jan 15]. Available from: https://www.medicines.org.uk/emc/medicine/27173

[52] Perini GF, Pro B. Brentuximab Vedotin in CD30+ Lymphomas. Biol Ther. 2013;3(1):15–23.

[53] Drugs.com [Internet]. USA. Mylotarg® Prescribing Information; c2000-2016 [updated 2010 Apr]. Available from: http://www.drugs.com/pro/mylotarg.html

[54] Larson RA, Sievers EL, Stadtmauer EA, Lowenberg B, Estey EH, Dombret H, et al. Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. Cancer. 2005;104(7):1442–52.

[55] Thomas TC, Rollins SA, Rother RP, Giannoni MA, Hartman SL, Elliott EA, et al. Inhibition of complement activity by humanized anti-C5 antibody and single-chain Fv. Mol Immunol. 1996; 33(17-18):1389-401.

[56] Electronic Medicines Compendium (eMC) [Internet]. UK. SPC Soliris® [updated 2015 Sept 30]. Available from: https://www.medicines.org.uk/emc/medicine/19966

[57] Brodsky RA, Young NS, Antonioli E, Risitano MA, Schrezenmeier H, Schubert J, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008;111(4):1840-47.

[58] Hillmen P, Muus P, Röth A, Elebute MO, Risitano AM, Schrezenmeier H, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol. 2013;162(1):62–73.

[59] Working Group of the Resuscitation Council (UK). Emergency treatment of anaphylactic reactions: Guidelines for healthcare providers [updated January 2008]. Available from www.resus.org.uk

[60] Simons FER, Ardusso LRF, Bilò MB, Dimov V, Ebisawa M, El-Gamal YM, et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis.Curr Opin Allergy Clin Immunol 2012;12(4):389–99.

[61] Kemp SF, Lockey RF, Simons FE. Epinephrine: The drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 2008;63(8):1061–70.

[62] Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. Immunol Allergy Clin North Am. 2007;27(2):309–26.

[63] Mirakian R, Ewan PW, Durham SR, Youlten LJ, Dugué P, Friedmann PS, et al. BSACI guidelines for the management of drug allergy. Clin Exp Allergy. 2009;39(1):43-61.

[64] Ream MA, Tunison D. Hypersensitivity reactions. In: Yasko JM, editor. Nursing management of symptoms associated with chemotherapy. Bala Cynwyd, PA: Meniscus Health Care; 2001. p. 213–24.

[65] O'Neil BH, Allen R, Spigel DR, Stinchcombe TE, Moore DT, Berlin JD, et al. High incidence of cetuximab- related infusion reactions in Tennessee and North Carolina and the association with atopic history. J Clin Oncol. 2007;25(24):3644-8.

[66] Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188–95.

[67] Hayslip J, Fenning R. Safe administration of iodine-131 tositumomab after repeated infusionrelated reactions to rituximab. Oncologist. 2007;12(3):338-40.