

CLINICAL PRACTICE GUIDELINES

Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines[†]

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Introduction

Most anticancer treatments carry a risk for infusion reactions (IRs); incidence may increase when different agents are administered concomitantly. IRs are either allergic reactions to foreign proteins [generally immunoglobulin E (IgE)-mediated allergic responses] or non-immune-mediated reactions [1]. Most IRs are mild with symptoms such as chills, fever, nausea, headache, skin rash, pruritus, etc. Severe reactions are less frequent and may be fatal without appropriate intervention.

It is difficult to evaluate these reactions through prospective randomised studies because of the unexpected nature of these events. There is a lack of consensus in the terminology or grading of the severity of an IR in the medical literature [2].

Definitions

There are few published articles addressing IRs in the medical literature, and there is no consensus on the terminology used to describe these reactions [3]. In 1972, the World Health Organization (WHO) defined an ‘adverse reaction to a drug’ as one that is noxious, unintended and occurs at doses normally used in humans [4]. An adverse drug reaction (ADR) is defined by the United States Food and Drug Administration (FDA) as ‘any undesirable experience associated with the use of a medical product in a patient’ [5]. The European Medicines Agency (EMA) defines an ADR as a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function [6]. An ADR may be classified as:

- A, Augmented pharmacological effects;
- B, Bizarre;

- C, Chronic effects;
- D, Delayed effects;
- E, End-of-treatment effects;
- F, Failure of therapy; or
- G, Genetic reactions.

IRs are ‘Type B’ reactions: non-dose related, unpredictable, generally unrelated to the drug’s pharmacological activity and they usually resolve when treatment is terminated [7, 8]. These reactions are divided into true allergic responses (immune-mediated, such as anaphylactic reactions) and non-allergic (non-immune) sensitivities. Gell and Coombs defined a classification of Type B adverse reactions to therapeutic agents as four true hypersensitivity states (Table 1). Type B adverse non-immune reactions include: pseudo-allergic [anaphylactoid reactions which resemble true Type I reactions with direct mast cell degranulation like the cytokine-release syndrome (CRS)], idiosyncratic reactions (uncommon, unpredictable, unrelated to the drug’s pharmacological action) and intolerances.

In 2001, the European Academy of Allergy and Clinical Immunology (EAACI) published a report trying to standardise the nomenclature of allergy. The World Allergy Organization (WAO) created a Nomenclature Review Committee to review the EAACI Nomenclature Position Statement and to present a globally acceptable nomenclature for allergic diseases [9]. The term ‘hypersensitivity’ should be used to describe objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons. ‘Allergy’ is a hypersensitivity reaction (HSR) initiated by specific immunological mechanisms. ‘Anaphylaxis’ is a severe, life-threatening, generalised or systemic HSR. The term ‘allergic anaphylaxis’ should be used when an immunological mechanism mediates the reaction. Anaphylaxis from any non-immunological cause should be referred to as ‘non-allergic anaphylaxis’ or

Table 1. Gell and Coombs classification of hypersensitivity reactions

Type I	IgE antibody-mediated reactions, e.g. anaphylaxis
Type II	Antibody-mediated cytotoxic reactions, e.g. haemolytic anaemia, thrombocytopenia, blood transfusion reactions
Type III	Immune complex-mediated hypersensitivity, e.g. serum sickness, vasculitis
Type IV	Delayed T cell-mediated responses, e.g. allergic contact dermatitis, psoriasis, maculopapular exanthema, erythema multiforme, toxic epidermal necrolysis

IgE, immunoglobulin E.

Table 2. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following three sets of criteria is fulfilled:

- Acute onset of an illness (minutes to hours) with involvement of skin/mucous membranes (e.g. hives, generalised itch/flush, swollen lips/tongue/uvula) and at least one of the following:
 - Respiratory compromise (e.g. dyspnoea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia).
 - Reduced blood pressure or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence].
- Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - Involvement of skin/mucous membranes (e.g. generalised hives, itch/flush, swollen lips/tongue/uvula).
 - Respiratory compromise (e.g. dyspnoea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia).
 - Reduced blood pressure or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence].
 - Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting).
- Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours). Adults: systolic blood pressure of < 90 mmHg or > 30% decrease from that person's baseline.

‘anaphylactoid reaction’. Anaphylaxis diagnosis is based upon clinical signs and symptoms (Table 2) [10].

The European Network for Drug Allergy (ENDA) has categorised HSRs into two types, according to the onset of symptoms after drug exposure [11, 12]:

- Immediate: HSR onset within 1–6 h after the last drug administration; typically IgE-mediated.
- Non-immediate: they may occur at any time, from 1 h after the initial drug administration, commonly after many days. They are often associated with a delayed T cell-dependent type of allergic mechanism.

A CRS is typically observed after initial treatment with monoclonal antibodies (MoAbs) and consists of a non-allergic, cytokine-mediated HSR within the first hours after infusion [13]. According to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, a CRS is a disorder characterised by nausea, headache,

tachycardia, hypotension, rash and shortness of breath, caused by the release of cytokines from the cells [14].

All these definitions may help to standardise the definition of an IR event, allowing accurate documentation and guiding decisions on the safety of rechallenge.

Risk assessment

When delivering anticancer drugs, apart from being aware of the potential risk of an IR of a specific drug, and during which course it is most likely to happen, other risk factors should be considered by the medical staff [V, C] [2]. Known risk factors for developing an anaphylactic reaction are: age-related factors, concomitant diseases such as chronic respiratory diseases, cardiovascular diseases, mastocytosis or clonal mast cell disorders and severe atopic disease [V, C] [15]. Some concurrent medications such as β -adrenergic blockers and angiotensin-converting enzyme inhibitors might also increase the risk.

In malignancies with a high tumour burden and at risk of a rapid tumour lysis or shrinkage at initiation of chemotherapy and/or targeted therapies, the addition of rasburicase, increased hydration [I, A] [16] and delivery of MoAbs in a fractionated way should be considered [III, B] [17].

Signs and symptoms

Signs and symptoms vary from patient to patient. Typical manifestations include mucocutaneous symptoms in up to 90% of patients (flushing, urticaria, pruritus), respiratory in 40% (wheezing), circulatory in 30%–35% (hypotension) and abdominal symptoms (nausea, vomiting, cramps, diarrhoea), minutes to hours after exposure to the drug [18–20]. The more rapidly a reaction develops, the more severe it is likely to be. The CRS has a similar appearance to a type I HSR and may be clinically indistinguishable. Most reactions are mild to moderate, with ‘influenza-like’ symptoms (fever, chills, muscular pain, rash, fatigue, headache, etc.) and appear within the first couple of hours, most often with the first infusion [21]. A characteristic side-effect of oxaliplatin is acute laryngopharyngeal dysaesthesia, a cold-related sensation of dyspnoea, difficulty in swallowing or talking, jaw tightness and odd sensations in the tongue and/or pharynx, during or after oxaliplatin infusion. Irinotecan-related cholinergic syndrome occurs within the first 24 h of its administration and is characterised by diarrhoea, emesis, diaphoresis, abdominal cramping and, less commonly, hyperlacrimation and rhinorrhoea [22].

The CTCAE version 4.03 distinguishes between infusion-related reactions and CRS (Table 3) [14]. Grading adverse reactions in a standardised way is essential to evaluate the severity of an IR [V, C].

Diagnosis

Biochemical mediators released during the degranulation of mast cells and basophils can be measured [19]. Plasma histamine begins to rise within 5 min and remains elevated for 15–

Table 3. Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

	Grade				
	1	2	3	4	5
Infusion-related reaction ^a	Mild-transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment; prophylactic medications indicated for ≤ 24 h	Prolonged (not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Cytokine release syndrome ^b	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment; prophylactic medications indicated for ≤ 24 h	Prolonged (not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae	Life-threatening consequences; pressor or ventilatory support indicated	Death
Allergic reaction ^c	Transient flushing or rash, drug fever <38 °C; intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment; prophylactic medications indicated for ≤ 24 h	Prolonged (not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis ^d			Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related oedema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death

^aInfusion-related reaction definition: a disorder characterised by adverse reaction to the infusion of pharmacological or biological substances.

^bCytokine-release syndrome definition: a disorder characterised by nausea, headache, tachycardia, hypotension, rash and shortness of breath; it is caused by the release of cytokines from the cells.

^cAllergic reaction definition: a disorder characterised by an adverse local or general response from exposure to an allergen.

^dAnaphylaxis definition: a disorder characterised by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.

60 min. Urinary histamine metabolites, including methylhistamine, may be found for up to 24 h after onset of anaphylaxis [23]. Blood samples for measurement of tryptase levels are optimally obtained 15 min to 3 h after symptom onset [21, 24]. A serial measurement of tryptase levels during an anaphylactic episode followed by a baseline tryptase level after recovery of the event is more useful than a single measurement. However, normal levels of either tryptase or histamine do not rule out the clinical diagnosis of anaphylaxis [15]. Besides, these tests are not universally available, not carried out on an emergency basis and not specific for anaphylaxis [V, C].

Management

Preparation:

- Before the administration of any drug, the patient should be asked about medical history, previous allergic disorders, atopic status and concomitant treatments [V, C] [24].
- If premedications are to be taken orally, oncology nurses should check that the patient has actually taken them [V, C].
- An updated protocol for the management of IRs should be at hand as well as the medical equipment needed for resuscitation (see Figure 1) [V, C].

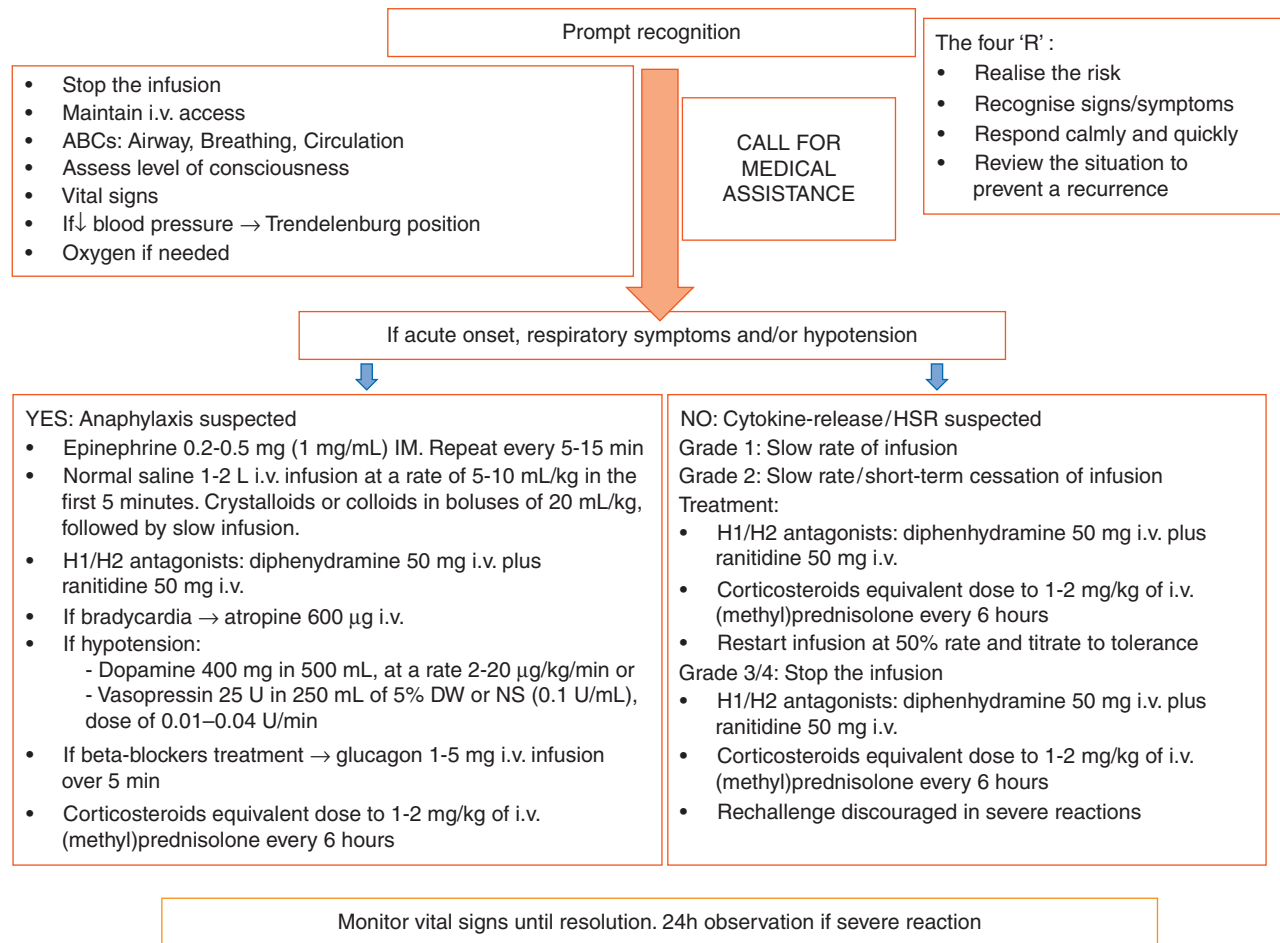


Figure 1. Management of infusion reactions.

DW, dextrose water; HSR, hypersensitivity reaction; IM, intramuscular; i.v., intravenous; NS, normal saline; U, units.

Observation:

- Prompt recognition and immediate medical attention are essential.
- Before an IR, some patients feel odd or uncomfortable or express a need to urinate or defecate [19]. Those symptoms should be taken seriously and the patient should be evaluated by measuring blood pressure and pulse rate [V, C].

Management:

- Stop the administration of medication [V, C].
- Maintain the intravenous (i.v.) access [V, C]. Assess the 'ABCs' (Airway, Breathing and Circulation) and the patient's level of consciousness [V, C] [25].
- Position: in the case of hypotension, the patient should be placed in the Trendelenburg position; in the case of respiratory distress, the patient should be sitting up; and, if unconscious, the patient should be placed in a recovery position [V, C].
- Administrate oxygen, if needed [V, C].
- Call for medical assistance as soon as possible [V, C].
- When a patient fulfils any of the three criteria of anaphylaxis (see Table 2), epinephrine (adrenaline) must be delivered immediately at a dose of 0.01 mg/kg (1 mg/mL dilution, to a maximum total dose of 0.5 mL) intramuscularly into the lateral thigh muscle [IV, B] [26]. This can be

repeated every 5–15 min [V, C] [10, 19, 25, 26]. Failure of a prompt response with severe hypotension or cardiac arrest should be followed by administration of i.v. epinephrine [IV, B].

- Fluid resuscitation: a rapid infusion of 1–2 litres of normal saline at a rate of 5–10 mL/kg in the first 5 min is recommended [IV, B] [25]. Crystalloids or colloids should be given in boluses of 20 mL/kg, followed by slow infusion [IV, B] [10, 26, 27].
- Antihistamines: the combined use of H1 and H2 antagonists is superior to the use of H1 (diphenhydramine) or H2 antagonists (ranitidine, cimetidine) alone [I, B] [28]. Diphenhydramine (1–2 mg/kg or 25–50 mg) may be given slowly via i.v. in combination with ranitidine (50 mg diluted in 5% dextrose water to a total volume of 20 mL) injected i.v. over 5 min [V, C] [2, 25].
- Bradycardia must be treated with atropine 600 µg i.v. [V, C] [19].
- Glucagon 1–5 mg i.v. infusion over 5 min and followed by an infusion (5–15 µg/min) titrated to clinical response may be useful for treating refractory cardiovascular effects in patients receiving β-blockers [V, C] [2, 10, 29].
- Vasopressors: dopamine (400 mg in 500 mL of 5% dextrose water) administered at 2–20 mg/kg/min and titrated to

increase systolic blood pressure might be required if epinephrine and fluid resuscitation have failed to alleviate hypotension [IV, D] [25]. Vasopressin and norepinephrine may also be used in anaphylaxis that is unresponsive to epinephrine, although the only evidence of efficacy in anaphylaxis is based on clinical case reports [IV, D] [30]. Vasopressin usual concentration is 25 units (U) in 250 mL of 5% dextrose water or normal saline (0.1 U/mL), with a dose range of 0.01–0.04 U/min [31].

- Corticosteroids are effective in preventing biphasic reactions, but are not critical in the management of anaphylaxis [V, D]. If given, the dosing of i.v. corticosteroids should be equivalent to 1–2 mg/kg of (methyl)prednisolone every 6 h [V, C] [10].

Post-reaction:

- Vital signs should be monitored and recurrence symptoms should be controlled [V, C].
- After a severe reaction, close observation for 24 h is recommended [V, C].

A CRS differs from other infusion-related reactions and can be managed by:

- Short-term cessation of the infusion and
- Symptomatic treatment:
 - histamine blockers;
 - corticosteroids;
 - antipyretics.
- After resolution of symptoms, the infusion can be restarted at half the rate and titrated to tolerance [IV, B] [2].

How to document an IR

Accurate documentation of the IR episode is critical, and should include pre-infusion assessments, an appropriate description and grading of the IR (according to accepted classifications such as CTCAE) and how it was managed [V, B] [25]. A protocol of management and documentation of IRs was developed at Memorial Sloan Kettering Cancer Center [32]. Those chemotherapy and biological agents with the highest incidence of IRs were identified. A multidisciplinary team established standardised guidelines and treatments to be used in the case of an IR. At the first sign of an IR, the protocol of management was activated and the IR was registered. A checklist was used to document which medications were used for the management of the IR. This initiative increased the reporting of IRs secondary to chemotherapy/biological therapies by 88%. An example of how to document an IR is shown in Table 4.

Rechallenge

The severity and nature of the reaction will determine the decision to restart the treatment based on clinical factors such as the risk of a serious recurrent reaction and the potential clinical benefit of further treatment [V, C] [3]. After all symptoms have resolved, rechallenge with a reduced infusion rate and additional premedication (such as corticosteroids and antihistamines) is usually successful [V, C]. However, rechallenge in IRs with CTCAE severity grade 3 or higher or in true anaphylaxis should not be attempted [V, B].

Table 4. Example of how to document an IR

Pre-infusion assessment	Drug Number of cycles Reintroduction of treatment (Yes/No) Relevant medical history/allergy/atopy Concomitant medication Oral premedication correctly taken
Relevant information of the IR event	Infusion rate Premedication Timing of symptom onset Vital signs Symptoms/signs Standard grading (CTCAE)
Management	Intervention Time to symptom resolution Patient response Reintroduction (Yes/No) Rate reintroduction
CTCAE, Common Terminology Criteria for Adverse Events; IR, infusion reaction.	

For patients who have recurrent IRs despite premedication, desensitisation protocols have been used with certain drugs with varying success in experienced centres. In desensitisation protocols, an initial small diluted dose of the agent with a prolonged infusion time and gradual escalation of the dose is administered. Desensitisation induces tolerance to a drug only temporarily, dependent on continuous exposure [33]. Once the drug is cleared, the state of tolerance is lost. Patients remain allergic to the drug and must be desensitised for every course of treatment. No standard desensitisation protocol exists and they are not widely accepted as they are time consuming.

Drugs which may frequently cause IRs

Chemotherapy

Acute HSRs to chemotherapeutics are infrequent and usually mild, but certain drugs such as platinum, taxanes and others still have a significant incidence of IRs. The pathophysiology, clinical manifestations, onset and management are variable. Chemotherapy schemes combining different drugs are very common in oncology and it is crucial to recognise the features of an IR to determine which drug is most likely to have caused it and act accordingly. Examples of the characteristics and management of IRs in different chemotherapy drugs are summarised in Table 5.

Anthracyclines. Anthracyclines rarely cause IRs and most reactions are mild. The incidence of IRs is higher with PEGylated liposomal doxorubicin and daunorubicin at 7%–11% of patients [34, 35]. Complement activation may play a key role in HSR to PEGylated liposomal doxorubicin [36]. HSRs with IgE mediation are rarely reported.

Table 5. Characteristics and management of IRs with some chemotherapy drugs

Drug	Incidence of IRs	Onset	Signs/symptoms	Prophylaxis	Management of IRs
Anthracyclines [12, 33–35]	7%–11% with PEGylated liposomal doxorubicin and daunorubicin.	The majority of IRs occur on the first infusion.	Chest pain, pruritus, syncope, flushing, chills, fever, urticaria, angioedema, rash, tachycardia, hypotension, dyspnoea, nausea, vomiting, headache, back pain.	Slow infusion rate. Premedication not routinely recommended [IV, B].	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop treatment and aggressive symptomatic therapy. Consider desensitisation. [IV, B]
Asparaginase [3, 42, 64]	60% HSRs. 10% severe reactions.	Usually after several doses, within 1 h of drug administration. Caution in retreatments.	Pruritus, dyspnoea, rash, urticaria, abdominal pain, bronchospasm, hypotension, angioedema, laryngospasm.	Corticosteroids and antihistamines [IV, B].	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop treatment and aggressive symptomatic therapy. [IV, B] Switch to PEGasparaginase, the least immunogenic drug formulation [IV, B].
Bleomycin [65]	1%	Immediate or delayed for several hours, usually after the first or second dose.	Hypotension, mental confusion, fever, chills, wheezing.	Because of the possibility of an anaphylactoid reaction, lymphoma patients should be treated with 2 units or less for the first 2 doses. If no IR occurs, then the regular dosage schedule may be followed [IV, B].	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop treatment and aggressive symptomatic therapy. [IV, B]
Carboplatin [3, 12, 37–39, 42]	HSRs 12%	Highly variable (minutes to hours). The risk increases with cumulative doses. Highest incidence 8th course.	Rash, itching, erythema on palms and soles, abdominal cramps, facial oedema, bronchospasm, hypotension, tachycardia, dyspnoea, chest pain.	Corticosteroids and H1/H2 antagonists not routinely recommended. Consider in high-risk patients. Premedication may not prevent an IR. [IV, B]	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop treatment and aggressive symptomatic therapy. Consider desensitisation. [IV, B]
Docetaxel [3, 12, 33, 34, 42, 51]	30% IRs without premedication. 2% severe reactions with premedication.	First or second dose, within the first 10 min of infusion.	Hypotension, dyspnoea, bronchospasm, urticaria, skin reactions, angioedema, flushing, pruritus, tachycardia, chest or back pain.	Breast, NSCLC, HNC, gastric cancer: oral dexamethasone 8 mg bid for 3 days (starting 1 day before docetaxel administration). Prostate cancer: oral dexamethasone 8 mg, 12, 3 and 1 h before the infusion. [IV, B]	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop treatment and aggressive symptomatic therapy. Consider desensitisation. [IV, B]
Etoposide [12, 34, 42, 66]	Anaphylactic reactions 1%–3%.	Usually after first doses.	Hypotension, fever, chills, urticaria, bronchospasm, angioedema, chest discomfort.	Slow infusion over 30–60 min. Corticosteroids and antihistamines. [IV, B].	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop treatment and aggressive symptomatic therapy. Consider desensitisation. [IV, B]

Continued

Table 5. Continued

Drug	Incidence of IRs	Onset	Signs/symptoms	Prophylaxis	Management of IRs
Oxaliplatin [3, 12, 41, 42, 67]	HSR 0.5%–25%. Severe reactions <1%.	Within 60 min after the start of infusion (typically 5–10 min). Highest incidence seventh to eighth course.	Sweating, watering, pruritus, rash, back or chest pain, laryngospasm, dyspnoea, fever, urticaria, bronchospasm, hypotension.	Corticosteroids and H1/H2 antagonists not routinely recommended. Consider in high-risk patients. Premedication may not prevent an IR. [IV, B]	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop treatment and aggressive symptomatic therapy. Consider desensitisation. [IV, B] If acute laryngopharyngeal dysaesthesia, warm up the air the patient is breathing; does not require i.v. treatments; oxaliplatin should be administered over 6 h [IV, B].
Paclitaxel [3, 12, 34, 42–46]	30% IRs without premedication. Severe anaphylactic reactions in 2%–4%.	First or second dose, within the first 10 min of infusion.	Flushing, skin reactions, dyspnoea, Hypotension, tachycardia, bronchospasm, angioedema, urticaria.	One dose of i.v. dexamethasone plus diphenhydramine (50 mg i.v.) and a H2 receptor antagonist (ranitidine 50 mg or cimetidine 300 mg i.v.) 30 min before paclitaxel infusion [II, A].	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop treatment and aggressive symptomatic therapy. After an IR, despite adequate premedication, about 1%–2% will experience severe an HSR. Consider desensitisation. [IV, B]
Procarbazine [12, 34, 42, 68]	6%–18%. Higher with concomitant use of anticonvulsant.	The majority occur in the first courses of treatment.	Fever, maculopapular rash, urticaria, angioedema, fever, toxic epidermal necrolysis.	Once HSR occurs, premedication with oral corticosteroids is usually not successful [IV, B].	Grade 1/2: symptomatic treatment. Grade 3/4: stop treatment and aggressive symptomatic therapy. [IV, B]

bid, twice a day; HNC, head and neck cancer; HSR, hypersensitivity reaction; IR, infusion reaction; i.v., intravenous; NSCLC, non-small cell lung cancer.

Platinum derivatives. IRs to platinum compounds are generally consistent with Type I IgE-mediated HSRs associated with repeated exposure to the agent [3]. A high frequency of anaphylactic-like reactions has been reported (10%–27%) [34, 37]. Type IV reactions have also been described with platinum drugs [38]. The incidence of an HSR with carboplatin is about 12%, and it develops mainly in patients who have been extensively pretreated with this agent (e.g. ovarian cancer patients) [38, 39]. A retreatment interval > 2 years increases the risk of developing an HSR. In patients receiving their eighth course of carboplatin, or the second dose after reintroduction of the agent, particular caution is advised [39]. Oxaliplatin causes acute HSRs in 0.5%–25% of cases and maximum incidence happens at the seventh to eighth administration [12]. Skin tests may predict

reactions to carboplatin. A negative skin test seems to predict, with reasonable reliability, for the absence of a severe HSR with the subsequent drug infusion [40]. The first IR with oxaliplatin is usually mild but it may become more severe at rechallenge [12]. Approximately 50% of patients rechallenged with platinum compounds experience recurrent HSRs despite premedication [3, 41]. Desensitisation protocols are an option [42].

For patients who develop acute laryngopharyngeal dysaesthesia during or after oxaliplatin infusion, management by warming up the air the patient is breathing is sufficient to improve the symptoms and no other measures are needed [IV, C] [41].

Taxanes. IRs with paclitaxel occur in up to 30% of patients but a prolonged drug infusion and premedication has reduced the rate

of severe reactions to 2%–4% [42, 43]. Reactions to taxanes are believed to be anaphylactoid, not mediated by IgE, probably due to a direct release of mast cell mediators such as histamine and tryptase [2, 3]. It is unclear whether paclitaxel reactions result from a non-immune effect of the drug or from the excipient kolliphor EL (formerly known as cremophor EL) added to solubilise the drug. The incomplete mixing of paclitaxel and kolliphor EL before administration may lead to complement activation and account for the variable and characteristically rapid first exposure reactivity [44]. For docetaxel, it has been suggested that this may be caused by the drug vehicle polysorbate-80.

All patients should receive premedication with corticosteroids plus antihistamines before taxane administration [IV, A] [34]. A randomised trial compared the efficacy and side effects of premedication with oral versus i.v. dexamethasone prior to a first cycle of paclitaxel [45]. There was no difference in paclitaxel-associated HSR rate between groups, nor in the incidence of a severe IR. However, short-term i.v. dexamethasone was associated with fewer side-effects than oral dexamethasone [II, A]. After an IR, despite adequate premedication with antihistamines and corticosteroids, about 40% of patients suffer from mild HSRs and about 1%–2% of patients develop severe potentially life-threatening HSRs [46]. Research in the database of the US project Medical Research on Adverse Drug Events and Reports showed six cases of severe anaphylactic reactions under treatment of adjuvant breast cancer with paclitaxel solubilised in kolliphor EL [47]. Reasons are the presence of oxethylated oleic acid in kolliphor EL, which leads to the release of histamines, and a kolliphor EL-mediated complement activation, which has been described as concentration-dependent [48, 49]. Because of this aspect kolliphor EL nests in the infusion solution are to be avoided, which might be caused by an insufficient mixing of the strongly viscous formulation of paclitaxel in kolliphor EL [50].

Patients who experience severe HSR to taxanes should not be rechallenged with these drugs [43, 51]. Successful desensitisation protocols have been developed [33, 42].

Monoclonal antibodies

MoAbs are non-endogenous proteins which can provoke all four types of HSRs. Chimeric MoAbs are structural chimeras containing murine variable regions, which target the antigen of interest, and human Fc Ig components, which reduce the immunogenicity of the antibody. In humanised antibodies, the human portion represents more than 90% of the antibody. Fully human antibodies are 100% human [52]. Although the development of humanised MoAb has reduced the occurrence of human anti-mouse antibodies in patients, human anti-human antibodies (HAHAs) can develop and IRs can still occur. However, a correlation between IRs and human anti-chimeric antibodies or HAHAs has not been demonstrated [3]. The potential immunogenicity of MoAb persists at least to some degree.

The incidence of an IR during the first drug administration of a MoAb varies from 77% with rituximab, 40% with trastuzumab to 15% with cetuximab [8]. The likelihood of an IR declines with each subsequent course of therapy. A distinctive side-effect of MoAbs is the potential for non-allergic IRs caused by cytokine release within the first hours after infusion [2]. It is thought that the MoAbs target interaction may lead to release of cytokines that

produce a range of symptoms similar to those seen in Type I allergic responses [8]. Unlike Type I reactions, symptoms appear to subside with each subsequent dose [12]. Less frequently, MoAbs can cause allergic IRs. Examples of characteristics and management of IRs in different MoAbs are summarised in Table 6.

Cetuximab. Cetuximab is a chimeric MoAb IgG1 targeting the epidermal growth factor receptor (EGFR). Reactions may be anaphylactic or anaphylactoid in nature or represent a CRS [53]. The incidence of anaphylactic reactions is quite small. Cetuximab-reactive IgE antibodies found in the serum of patients with anaphylaxis are specific for the disaccharide α -1-3-galactose present on the heavy chain of the Fab fragment of recombinant cetuximab [54]. Most patients who reacted already had the antibodies in their serum before receiving the drug.

The first dose should be administered slowly while all vital signs are closely monitored for at least 2 h [IV, A] [53]. Premedication with corticosteroids plus antihistamines reduce grade 3 or 4 reactions to only 1%, compared with an incidence of 4.7% for those receiving antihistamines alone [55].

Rituximab. Rituximab is a chimeric MoAb IgG1 that specifically targets B lymphocytes by recognising the antigen CD20 on their surface. Rituximab is associated with infusion-related reactions, which may be related to cytokine release from the lymphocytes, tumour lysis syndrome and anaphylactic HSRs [17]. The incidence of IRs in the first administration of rituximab is 77% and decreases in subsequent infusions [12]. Severe reactions happen in 10% of patients (80% in the first rituximab infusion), and typically occur in patients with high numbers of circulating lymphocytes; they are usually reversible with appropriate interventions [1].

A slow initial rate of infusion is recommended to reduce the risk of IRs [2]. Premedication consisting of an antipyretic and an antihistamine should always be given [IV, A]. Patients with a high tumour burden may be at higher risk of severe CRS. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or split dosing over 2 days during the first cycle and any subsequent cycles if the lymphocyte count is still $> 25 \times 10^9/L$ [IV, A] [13, 17].

Trastuzumab. Trastuzumab is a humanised MoAb IgG1 targeting the human EGFR2 (HER2) [8, 56]. Most IRs are mild and occur on the first infusion. IR incidence decreases in subsequent infusions. Severe IRs, including anaphylaxis, are rare [1]. In grade 1 or 2 reactions, after resolution of symptoms, further infusions of trastuzumab can be given.

Immunotherapy

Immunotherapy has emerged recently as a new anti-cancer treatment alternative. These drugs have a low incidence of IRs, and most of them are mild to moderate. IRs with agents that target the programmed death protein 1 and its ligand (PD-1/PD-L1 pathway) comprise $< 1\%$ of adverse events (AEs) in phase III studies [57], but when a peptide vaccine was added to nivolumab, the rate of IRs increased to more than 20% [58, 59]. A cytokine release and non-specific activation of an immune response are thought to be the cause of these reactions. There are very few publications available (in the form of case reports) regarding these AEs. A

Table 6. Characteristics and management of IRs with some monoclonal antibodies

Drug	Type of antibody	Mechanism of action	Incidence of IRs	Signs/symptoms	Prophylaxis	Management of IRs
Alemtuzumab [12, 69, 70]	Humanised	Anti-CD52	Serious reactions in 3%.	Headache, rash, pyrexia, nausea, urticaria, pruritus, insomnia, chills, flushing, fatigue, dyspnoea, dysgeusia, chest discomfort, tachycardia, dizziness, pain.	Alemtuzumab may be administered in a fractionated way to avoid CRS. Premedication: corticosteroids [(methyl)prednisolone 1 g] on the first 3 days. Consider use of antihistamines and/or antipyretics. [IV, B]	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop the infusion. Aggressive symptomatic treatment. After resolution of all symptoms, treatment can be resumed at slower rate, unless severe reaction. [IV, B]
Atezolizumab [71]	Humanised	Anti-PD-L1	1%–2%.	Chills, itching, flushing, shortness of breath, swelling, dizziness, fever, pain.	Premedication is not recommended [IV, B].	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop the infusion. Aggressive symptomatic treatment. Permanently discontinue. [IV, B]
Bevacizumab [72]	Humanised	Anti-VEGF	IRs < 3% during the first infusion. Severe in < 1%.	Dyspnoea, flushing, rash, blood pressure changes, chest pain, rigours, nausea, vomiting.	First dose in 90 min. Subsequent doses in 30–60 min. Premedication is not recommended. [IV, B]	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop the infusion. Aggressive symptomatic treatment. After resolution of all symptoms, treatment can be resumed at slower rate, unless severe reaction. [IV, B]
Blinatumomab [73, 74]	Bispecific T cell-engaging antibody	Anti-CD19/CD3	IRs in 44%–67%. Serious reactions 0.5%. Median time to onset of a CRS event 2 days. A signature composed of three cytokines could accurately predict which patients would develop severe CRS.	Pyrexia, asthenia, headache, hypotension, nausea, disseminated intravascular coagulation, capillary leak syndrome.	Dexamethasone 20 mg i.v. 1 h before infusion. Antipyretic is recommended during the first 48 h of each cycle. [IV, B]	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3: stop the infusion. Aggressive symptomatic treatment. After resolution of all symptoms, treatment can be resumed at 9 µg/day. Escalate to 28 µg/day after 7 days if the toxicity does not recur. Grade 4: Permanently discontinue. [IV, B]
Brentuximab vedotin [75]	Chimeric	Anti-CD30	11%–15%, mostly grade 1/2.	Headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus, cough.	Premedication if prior IR may include: paracetamol, an antihistamine and corticosteroid [IV, B].	Grade 1/2: stop or slow the infusion rate; symptomatic treatment. Grade 3: stop the infusion. Aggressive symptomatic treatment. The infusion may be restarted at a slower rate after symptom resolution. Grade 4: permanently discontinue. [IV, B]

Continued

Table 6. Continued

Drug	Type of antibody	Mechanism of action	Incidence of IRs	Signs/symptoms	Prophylaxis	Management of IRs
Cetuximab [1, 3, 8, 53, 55, 76]	Chimeric	Anti-EGFR	90% on the first infusion. Severe 2%–5%.	Flushing, rash, fever, urticaria, chills, bronchospasm, dyspnoea, nausea, vomiting, blood pressure changes, angina, myocardial infarction.	First dose slow infusion rate. Premedication with corticosteroids plus antihistamines [IV, B]. Premedication can be discontinued after the second infusion if no IR is observed [IV, B].	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop the infusion. Aggressive symptomatic treatment. After resolution of all symptoms, treatment can be resumed at slower rate, unless severe reaction. [IV, B]
Daratumumab [77, 78]	Human	Anti-CD38	IRs 40%–50%, most mild to moderate in severity. 82%–95% on the first infusion.	Nasal congestion, chills, cough, allergic rhinitis, throat irritation, dyspnoea and nausea. Less frequent: bronchospasm, hypertension and hypoxia.	Premedication 1 h before every infusion: i.v. corticosteroid [(methyl)prednisolone 100 mg, or equivalent], oral antipyretics (paracetamol 650–1000 mg) and oral or i.v. antihistamine (diphenhydramine 25–50 mg or equivalent). Following the second infusion, the dose of i.v. corticosteroid may be reduced [(methyl)prednisolone 60 mg]. Post-infusion medication: oral corticosteroid [20 mg (methyl)prednisolone or equivalent] on each of the 2 days following all infusions. [IV, B]	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Once the patient is stable, the infusion should be resumed at half the rate, and titrated to tolerance. Grade 3: stop the infusion. Aggressive symptomatic treatment. If IR improves to \leq grade 2, treatment can be resumed at half the rate and titrated to tolerance. If \geq grade 3 at the subsequent infusion, permanently discontinue. Grade 4: permanently discontinue. [IV, B]
Ipilimumab [60, 79, 80]	Human	Anti-CTLA-4	2%–5%, the majority grade 2 IRs. More common after the first dose.	Pruritus, maculopapular rash, cough, shortness of breath, chills, rigors, facial flushing, chest, abdominal or back pain.	Premedication with antipyretic and antihistamines may be considered. It may be reasonable to observe patients for a short period of time after the infusion because of the risk of IRs. [IV, B]	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Restart infusion with close monitoring. Grade 3/4: stop the infusion. Aggressive symptomatic treatment (including corticosteroids). Permanently discontinue. [IV, B]

Continued

Table 6. *Continued*

Drug	Type of antibody	Mechanism of action	Incidence of IRs	Signs/symptoms	Prophylaxis	Management of IRs
Nivolumab [81, 82]	Human	Anti-PD-1	5%, including grade 3–4 IRs.	Facial flushing, hives, angioedema	In the case of an IR, premedication with antipyretics and antihistamines may be considered [IV, B].	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: aggressive symptomatic treatment. Permanently discontinue. [IV, B]
Ofatumumab [83, 84]	Human	Anti-CD20	61%, the majority grade 1/2. More frequent on the first infusion.	Bronchospasm, cardiac events, chills, rigors, cough, diarrhoea, dyspnoea, fatigue, flushing, hypertension, hypotension, nausea, pain, pulmonary oedema, pruritus, pyrexia, rash.	Premedication 30 min to 2 h before ofatumumab: oral paracetamol 1 g, oral or i.v. antihistamine (e.g. diphenhydramine 50 mg or cetirizine 10 mg), i.v. corticosteroid (prednisolone: in previously untreated or relapsed CLL 50 mg and in refractory CLL 100 mg). If the patient does not experience an IR in the first and second infusion, corticosteroid may be reduced or omitted. Before ninth infusion (first monthly infusion), full dose of premedication agents. If no IR, prednisolone may be reduced to 50 mg. [IV, B]	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Restart at half the infusion rate and titrate to tolerance. Grade 3: stop the infusion. Aggressive symptomatic treatment. Restart at 12 mL/h and titrate to tolerance. Grade 4: permanently discontinue. [IV, B]
Panitumumab [1, 85, 86]	Humanised	Anti-EGFR	IRs in 4% of patients. Severe in < 1%.	Chills, dyspnoea, flushing, blood pressure changes, pyrexia, tachycardia, vomiting, anaphylaxis, angioedema, bronchospasm.	First dose in 60–90 min. Subsequent doses in 30 min. Premedication is not recommended. [IV, B]	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Restart at half the infusion rate. Grade 3/4: permanently discontinue. [IV, B]
Pembrolizumab [57, 87, 88]	Humanised	Anti-PD-1	3% IRs. Grade ≥ 3 < 1%.	Pyrexia, chills	Premedication with antipyretic and antihistamine may be considered [IV, B].	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: permanently discontinue. [IV, B]

Continued

Table 6. Continued

Drug	Type of antibody	Mechanism of action	Incidence of IRs	Signs/symptoms	Prophylaxis	Management of IRs
Rituximab [1, 2, 8, 12, 17]	Chimeric	Anti-CD20	77% on the first infusion. Severe reactions 10%.	Fever, chills, rash, dyspnoea, hypotension, nausea, rhinitis, urticaria, pruritus, asthenia, angioedema, bronchospasm. May be associated with features of tumour lysis syndrome.	A slow initial rate of infusion is recommended. Premedication: antipyretic and antihistaminic (e.g. paracetamol and diphenhydramine). Glucocorticoids should be considered in non-Hodgkin's lymphoma and CLL [IV, B]. If high tumour burden, consider a reduced infusion rate for the first infusion or split dosing over 2 days [IV, B].	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Grade 3/4: stop the infusion. Aggressive symptomatic treatment. After resolution of all symptoms, treatment can be resumed at half the previous rate, unless severe reaction. [IV, B]
Trastuzumab [1, 56, 89, 90]	Humanised	Anti-HER2	20%–40% on the first infusion. Severe reactions <1%.	Chills, fever, blood pressure changes, bronchospasm, itching, dyspnoea, wheezing, arrhythmia, angioedema.	Loading dose in 90 min. Subsequent doses in 30 min. Premedication is not recommended. [IV, B]	Grade 1/2: stop or slow the infusion rate. Symptomatic treatment. Meperidine for chills and rigours. Grade 3/4: stop the infusion. Aggressive symptomatic treatment. After resolution of all symptoms, treatment can be resumed at slower rate, unless severe reaction. [IV, B]

CLL, chronic lymphocytic leukaemia; CRS, cytokine-release syndrome; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IR, infusion reaction; i.v., intravenous; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor.

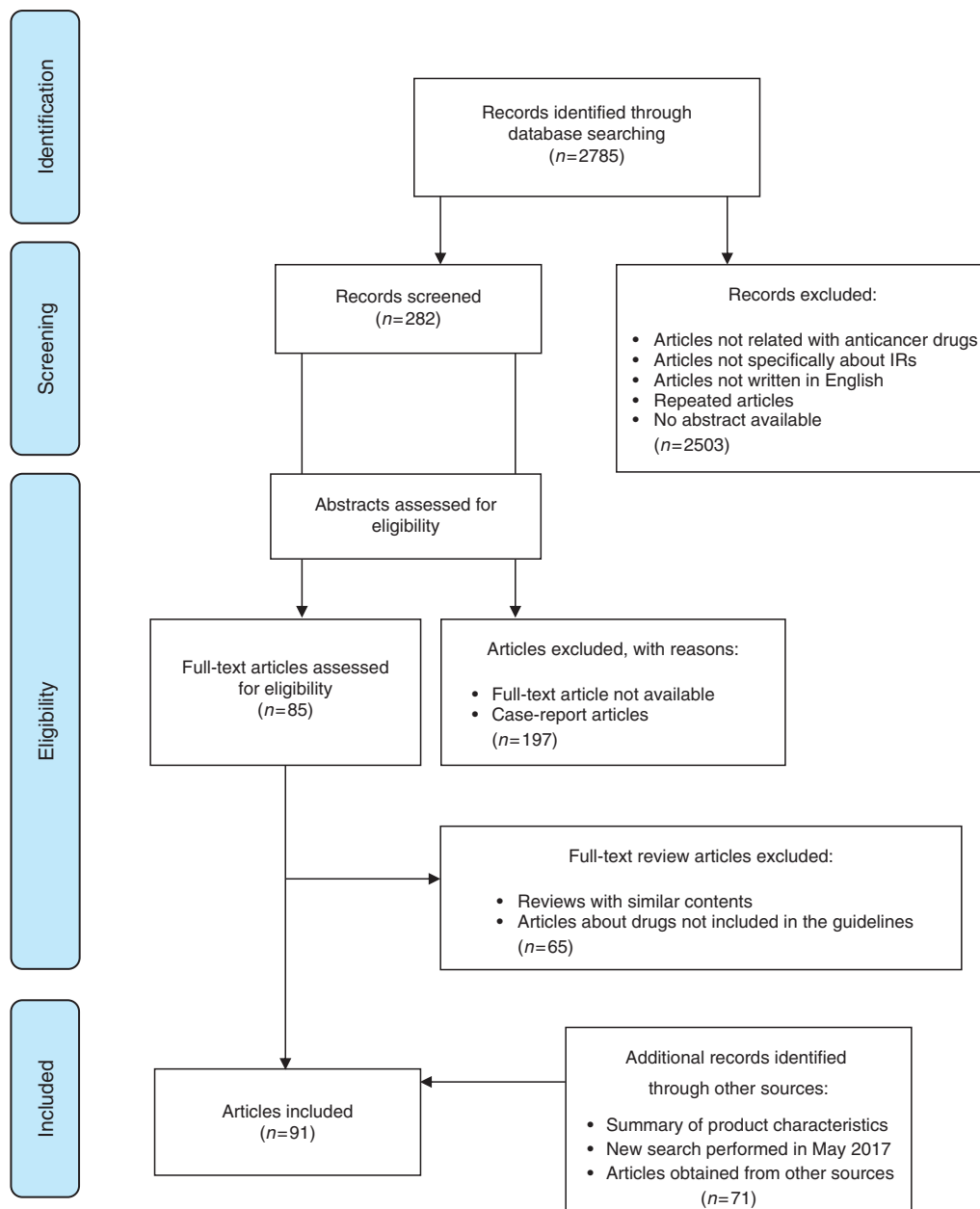


Figure 2. Selection of articles using PRISMA statement [63].

IRs, infusion reactions; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

retrospective study comparing the incidence of infusion-related reactions to CTLA-4-blocking antibody ipilimumab in patients receiving doses of either 3 or 10 mg/kg infused over 90 or 30 min, showed that IRs to ipilimumab happen more frequently after the first dose, suggesting that the first dose is a sensitising one [60]. Table 6 shows examples of some of immunotherapy drug characteristics and recommendations for management of IRs.

Follow-up

Following any IR episode, the clinician should attempt to establish, based on the precipitating drug and the characteristics of the event, the steps that could be taken to prevent future episodes [V,

C]. After the treatment of an anaphylactic reaction, an observation period should be considered for all patients because of the risk of a biphasic reaction [V, B] [10]. There are no reliable predictors of biphasic reactions, but it seems that they are more likely in patients who present initially with severe symptoms [25]. Observation periods should be individualised on the basis of the severity of the initial reaction, reliability of the patient and proximity to an emergency facility, with prolonged observation times or hospital admission for patients with severe or refractory symptoms [V, C]. If the nature of the reaction is highly suspicious of an anaphylactic reaction, consultation with an allergist/immunologist is warranted [V, B]. An IR event often generates psychological distress to the patients and caregivers [26, 61]. Psychological intervention should be provided to alleviate

Table 7. Summary of key information**Definitions**

Adverse drug reaction:

- The WHO defined an ADR as one that is noxious, unintended and occurs at doses normally used in humans.
- The FDA defined an ADR as any undesirable experience associated with the use of a medical product in a patient.
- The EMA defines an ADR as a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.
- ADRs may be classified as:
 - A, Augmented pharmacological effects;
 - B, Bizarre;
 - C, Chronic effects;
 - D, Delayed effects;
 - E, End-of-treatment effects;
 - F, Failure of therapy; and
 - G, Genetic reactions.
- IRs are Type B reactions:
 - Non-dose related, unpredictable, unrelated to the drugs' pharmacological activity and usually resolve when treatment is terminated.
 - Divided into:
 - True allergic responses (immune-mediated) and
 - Non-allergic (non-immune) sensitivities.

World Allergy Organization Nomenclature:

- The WAO created a Committee to review the EAACI nomenclature position statement and presented a globally acceptable nomenclature for allergic diseases.
- Hypersensitivity should be used to describe objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons.
- Allergy is an HSR initiated by specific immunological mechanisms.
- Anaphylaxis is a severe, life-threatening, generalised or systemic HSR.
 - The term allergic anaphylaxis should be used when an immunological mechanism mediates the reaction.
 - Anaphylaxis from any non-immunological cause should be referred to as non-allergic anaphylaxis or anaphylactoid reaction.
 - Anaphylaxis diagnosis is based upon clinical signs and symptoms (see Table 2).

Classification of HSRs by the European Network for Drug Allergy:

- The ENDA has categorised HSRs into two types, according to the onset of symptoms after drug exposure:
 - Immediate: HSR onset within 1–6 h after the last drug administration; typically IgE-mediated.
 - Non-immediate: they may occur at any time, from 1 h after the initial drug administration, commonly after many days. They are often associated with a delayed T-cell-dependent type of allergic mechanism.

Cytokine-release syndrome definition:

- A CRS definition by the CTCAE version 4.03 is a disorder characterised by nausea, headache, tachycardia, hypotension, rash and shortness of breath, caused by the release of cytokines from the cells.

Risk assessment

- It is important to be aware of the potential risk of an IR to a concrete drug, and during which course it is most likely to happen [IV, C].
- Known risk factors for developing an anaphylactic reaction are [V, C]:
 - Age-related factors.
 - Concomitant diseases (e.g. chronic respiratory diseases, cardiovascular diseases, mastocytosis or clonal mast cell disorders).
 - Severe atopic disease.
 - Concurrent medications which increase the risk (e.g. β -adrenergic blockers, angiotensin-converting enzyme inhibitors).
- If there is a high risk of a rapid tumour lysis at initiation of chemotherapy and/or targeted therapies, in malignancies with a high tumour burden, consider:
 - Addition of rasburicase and increased hydration [I, A].
 - Delivering MoAbs in a fractionated way [III, B].

Signs and symptoms

- The National Cancer Institute CTCAE version 4.03 distinguishes between infusion-related reactions and CRS (see Table 3).
- Grading adverse reactions in a standardised way is essential to evaluate the severity of an IR [V, C].

Diagnosis

- Measurement of biochemical mediators released during the degranulation of mast cells and basophils:
 - Histamine:
 - Plasma histamine begins to rise within 5 min and remains elevated for 15–60 min.
 - Urinary histamine metabolites, including methylhistamine, may be found for up to 24 h after onset of anaphylaxis.
 - Tryptase:
 - Blood samples for measurement of tryptase levels are optimally obtained 15 min to 3 h after onset of an IR.
 - A serial measurement of tryptase levels during an anaphylactic episode followed by a baseline tryptase level after recovery of the event is more useful than a single measurement.
 - Normal levels of either tryptase or histamine do not rule out the clinical diagnosis of anaphylaxis. These tests are not universally available, not carried out on an emergency basis and not specific for anaphylaxis [V, C].

Continued

Table 7. *Continued***Management**

Preparation:

- Before the administration of any drug, the patient should be asked about his/her medical background [V, C].
- Medical staff should ensure that the patient has taken oral premedication appropriately, if applicable [V, C].
- An updated protocol of management of IRs should be at hand as well as the medical equipment needed for resuscitation (see Figure 1) [V, C].

Observation:

- Prompt recognition and immediate medical attention are essential.
- During the infusion of an anti-cancer drug, any symptom experienced by the patient should be taken seriously and his/her vital signs should be evaluated [V, C].

Management:

- Stop the administration of medication [V, C].
- Maintain the i.v. access [V, C].
- Assess the ABCs and the patient's level of consciousness [V, C].
- Position [V, C]:
 - In the case of hypotension, the patient should be placed in the Trendelenburg position.
 - In the case of respiratory distress, sitting up.
 - If unconscious, in recovery position.
- Administrate oxygen, if needed [V, C].
- Call for medical assistance as soon as possible [V, C].
- When a patient fulfils any of the three criteria of anaphylaxis (see Table 2):
 - Epinephrine (adrenaline) must be delivered immediately at a dose of 0.01 mg/kg (1 mg/mL dilution, to a maximum total dose of 0.5 mL) intramuscularly into the lateral thigh muscle [IV, B].
 - This can be repeated every 5–15 min [V, C].
 - Failure of a prompt response should be followed by administration of i.v. epinephrine [IV, B].
- Fluid resuscitation:
 - A rapid infusion of 1–2 litres of normal saline at a rate of 5–10 mL/kg in the first 5 min is recommended [IV, B].
 - Crystalloids or colloids should be given in boluses of 20 mL/kg, followed by slow infusion [IV, B].
- Antihistamines:
 - The combined use of H1 and H2 antagonists is superior to the use of H1 (diphenhydramine) or H2 antagonists (ranitidine, cimetidine) alone [I, B].
 - Diphenhydramine (1–2 mg/kg or 25–50 mg) may be given slowly via i.v. in combination with ranitidine (50 mg diluted in 5% dextrose to a total volume of 20 mL) injected i.v. over 5 min [V, C].
- Bradycardia must be treated with atropine 600 µg i.v. [V, C].
- Patients receiving β-blockers: Glucagon 1–5 mg i.v. infusion over 5 min and followed by an infusion (5–15 µg/min) titrated to clinical response may be useful for treating refractory cardiovascular effects [V, C].
- Vasopressors:
 - Dopamine (400 mg in 500 mL of 5% dextrose water) administered at 2–20 mg/kg/min and titrated to increase systolic blood pressure might be required if epinephrine and fluid resuscitation have failed to alleviate hypotension [IV, D].
 - Vasopressin and norepinephrine may also be used in anaphylaxis that is unresponsive to epinephrine [IV, D].
 - Vasopressin usual concentration is 25 U/250 mL of 5% dextrose water or normal saline (0.1 U/mL), with a dose range of 0.01–0.04 U/min.
- Corticosteroids:
 - Effective in preventing biphasic reactions, but are not critical in the management of anaphylaxis [V, D].
 - If given, the dosing of i.v. corticosteroids should be equivalent to 1–2 mg/kg of (methyl)prednisolone every 6 h [V, C].

Post-reaction:

- Vital signs should be monitored and recurrence symptoms should be controlled [V, C].
- After a severe reaction, close observation for 24 h is recommended [V, C].

A CRS differs from other infusion-related reactions and can be managed by:

- Short-term cessation of the infusion and
- Symptomatic treatment:
 - Histamine blockers.
 - Corticosteroids.
 - Antipyretics.
- After resolution of symptoms, the infusion can be restarted at half the rate and titrated to tolerance [IV, B].

How to document an IR

- Accurate documentation of the IR episode including pre-infusion assessments, an appropriate description and grading of the IR and how it was managed is recommended [V, B].
- An example of how to document an IR is shown in Table 4.

Continued

Table 7. Continued**Rechallenge**

- The severity and nature of the reaction will determine the decision to restart the treatment based on clinical factors such as the risk of a serious recurrent reaction and the potential clinical benefit of further treatment [V, C].
- After all symptoms have resolved, rechallenge with a reduced infusion rate and additional premedication (such as corticosteroids and antihistamines) is usually successful [V, C].
- Rechallenge in IRs with CTCAE severity grade 3 or higher or in true anaphylaxis should not be attempted [V, B].
- Desensitisation protocols have been used in experienced centres with certain drugs with varying success.

Follow-up

- Following any IR episode, the clinician should attempt to establish, based on the precipitating drug and the characteristics of the event, the steps that could be taken to prevent future episodes [V, C].
- After the treatment of an anaphylactic reaction, an observation period should be considered because of the risk of a biphasic reaction [V, B].
- Observation periods should be individualised based on the severity of the reaction, reliability of the patient and proximity to an emergency facility, with prolonged observation times or hospital admission for patients with severe or refractory symptoms [V, C].
- If the nature of the reaction is highly suspicious of an anaphylactic reaction, consultation with an allergist/immunologist is warranted [V, B].
- Psychological intervention should be provided to alleviate symptoms of uncertainty related to a potential IR with anti-cancer drugs [V, B].
- It's important to provide psychological support and to have a complete, informative discussion with the patient about the potential benefits of continuing with the drug and the risk of IR recurrence [V, B].

ABCs, Airway, Breathing and Circulation; ADR, adverse drug reaction; CRS, cytokine-release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; ENDA, European Network for Drug Allergy; FDA, United States Food and Drug Administration; HSR, hypersensitivity reaction; IgE, immunoglobulin E; IR, infusion reaction; i.v., intravenous; MoAb, monoclonal antibody; U, units; WAO, World Allergy Organization; WHO, World Health Organization.

Table 8. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System^a)**Levels of evidence**

- | | |
|-----|--|
| I | Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity |
| II | Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity |
| III | Prospective cohort studies |
| IV | Retrospective cohort studies or case-control studies |
| V | Studies without control group, case reports, expert opinions |

Grades of recommendation

- | | |
|---|--|
| A | Strong evidence for efficacy with a substantial clinical benefit, strongly recommended |
| B | Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended |
| C | Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional |
| D | Moderate evidence against efficacy or for adverse outcome, generally not recommended |
| E | Strong evidence against efficacy or for adverse outcome, never recommended |

^aBy permission of the Infectious Diseases Society of America [91].

symptoms of uncertainty related to a potential IR with anti-cancer drugs [V, B]. A study investigated the effects of structured

patient education intervention on knowledge, emergency management skills and psychological parameters in patients with previous episodes of anaphylaxis and caregivers of affected children [62]. In comparison with the control group who received standard auto-injector training only, the educational intervention led to a significant improvement of knowledge from baseline to 3-month follow-up, and to a significant reduction of caregiver anxiety. This underlines the importance of providing psychological support and having a complete, informative discussion with the patient about the potential benefits of continuing with the drug and the risk of IR recurrence [V, B].

Methodology

After a systematic search on December 2014, in several medical search engines (PubMed and ISI Web of Knowledge) of the terms: 'allergic reaction chemotherapy', 'allergic reaction monoclonal antibody', 'infusion related reaction chemotherapy', 'infusion related reaction monoclonal antibody', 'allergy reaction cancer', and 'infusion related reaction', 2785 publications were found related to these terms. Figure 2 shows a PRISMA statement Flow Diagram to explain the articles selection. A total of 2503 articles were eliminated for the following reasons: no anticancer drugs, articles not specifically about IRs, articles not written in English, repeated articles or with no abstract available. Eighty-five full-text articles were reviewed, selecting 20 of them, and excluding 65 articles because they were review articles with very similar contents or articles related to drugs not included in the guidelines. The 20 articles were reviewed adding from their references some more articles, plus other articles obtained from other sources and the summary of product characteristics of the different

drugs included in these guidelines. A new search on PubMed of the same terms was performed in May 2017 to obtain more recent articles related to IRs. Only articles from December 2014 to present, about clinical trials performed on humans, and with abstract available, were selected. Review articles were excluded. A total of 67 articles were identified. Most of them were not related to anti-cancer drugs, and others were not specifically about IRs. Following this search, only five articles were identified, and only two of them were added to these guidelines. These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development <http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>. A summary of key information is shown in Table 7. Levels of evidence and grades of recommendation have been applied using the system shown in Table 8. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

Disclosure

AC has reported advisory boards from Merck Serono, Amgen, Roche, Servier, Lilly, Novartis, Takeda and research support from Merck Serono, Roche and Servier; KJ has reported honoraria from Amgen, Merck, MSD, Helsinn, Tesaro, and Hexal and being a member of the advisory board of Merck, MSD, Helsinn, and Tesaro; SR, IB and LGF have declared no conflicts of interest.

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