Antineoplastic Therapy Involved in Hypersensitivity Reactions

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As widely accepted at present, in addition to their benefits, medicines can also be accompanied by side effects and adverse reactions, of which some can be detrimental to therapies or even life-threatening. In some cases, these effects are enabled or enhanced by certain individual-specific hypersensitivity. Among other manifestations, adverse reactions to drugs resulting from excessive sensitivity may include anaphylaxis. Given that regular toxicity studies are not relevant to point to possible delayed hypersensitivity reactions triggered by systemic products and from the perspective of mechanisms involved in the early and late stages phases of hypersensitivity events, in vitro and in vivo tests remain the means to reveal the cells activated and the mediators released in this process.

Keywords: oncology ; infusion reaction ; antineoplastic therapy ; chemotherapy ; allergy ; cancer

1. Platinum Compounds

Used for a broad range of malignancies, platinum analogs have made a major contribution to systemic treatments. With a similar platinum core, cisplatin, carboplatin, and oxaliplatin are the main representatives of this class. Nedaplatin (Japan), heptaplatin (Korea) and lobaplatin (China) are three other therapeutic agents from this category, marketed in single countries. The different complexities of the leaving group and carrier ligand offer distinctive pharmacological proprieties and anticancer activity profiles to each agent. Their mechanism of action involves covalently binding to purinic DNA bases, creating cross-link strands, and inhibiting the normal function of nucleic acids with consecutive apoptosis [1].

In terms of HSR, platinum compounds are a class associated with the high potentiality to cause such events, carboplatin being the main one responsible, followed by oxaliplatin and cisplatin. A true allergic mechanism consistent with type I IgE-mediated HSRs can be established for most of the platinum analogs reactions [2][3]. Different variables have been investigated in various studies with different designs as risk factors for developing hypersensitivity events to these analogs. The most consistent risk factor seems to be prior exposure to these therapies, with the rate of HSR increasing after the administration of several cycles [3].

1.1. Cisplatin

The first member of its class, cisplatin, also known as cisplatinum or cis-diamminedichloroplatinum (II) (CDDP) is used in different combination regimens for the management of various types of solid carcinomas (such as ovarian, lung, bladder, head and neck, upper-GI tumors), as well as sarcomas, lymphomas, and germ cell neoplasias. Its toxic profile makes it more cautiously prescribed, being associated with nephrotoxicity, ototoxicity, neurotoxicity, and high emetogenic potential [1]. In early studies, the incidence of reported HSR to cisplatin was between 5 and 14%; however, premedication with glucocorticoids as part of the antiemetic regimen may have lowered over time the percentage of people who experienced infusion reactions [4]. However, the incidence may be further influenced by concomitant radiation, due to associated increased tumor necrosis and cytokine release [5]. The clinical picture of an HSR to cisplatin can vary from mild reactions to anaphylaxis, with pruritus, urticaria, dyspnea, and hypotension [3][5]. The symptoms frequently appear shortly (10–30 min) after the beginning of the intravenous infusion. The chance of HSR occurrence increases with the number of cycles, and is higher after the 6th cycle. Although there are not so many studies investigating the exact immunological mechanism behind cisplatin HSR, an IgE-mediated process is suggested by the presence of positive skin tests, described especially in studies of cross-reactivity with carboplatin and oxaliplatin and identification of patients who can be safely rechallenged with platinum salts [5][6][7].

1.2. Carboplatin

With a better toxicity profile than its parent compound cisplatin, carboplatin (cis-diamminecyclobutanedicarboxylato platinum II) proved to be effective, especially in advanced or metastatic ovarian carcinoma, as well as other tumors such as cervix, lung, testicular, progressive diffuse large B-cell lymphoma, but with a lower efficacy on the germ cells malignancies [1]. Of all the platinum agents, carboplatin has the highest rate of associated HSRs. The incidence of all types of infusion reactions to carboplatin rises with repeated courses of administration, being up to 40% after at least seven doses [2]. One study reported a risk of up to 100% of developing an HSR to carboplatin in the third-line setting, after multiple exposures [8]. Re-treatment with carboplatin is consistently reported in the literature as the main risk factor for developing HSR [2][3][9]. The clinical features of HSR to carboplatin are highly variable, from mild to severe, but most of them resemble anaphylaxis, with symptoms such as pruritus, flushing, urticaria, facial swelling, chest tightness, dyspnea, cough, abdominal cramping, and hypotension [9][10][11][12][13]. Chest pain, followed by unresponsive cardiac arrest was also reported [11]. Reactions to carboplatin are usually acute, during infusion or shortly after, but can also be delayed, occurring hours or days after infusion [12]. The presence of maculopapular rashes approximately six days after exposure can be classified as a delayed reaction, associated with a higher risk of developing severe clinical phenomena in subsequent cycles [14]. Since a common carboplatin regimen also includes paclitaxel, which is usually infused before the platinum agent, some HSRs to carboplatin may be in fact due to the taxane. However, in contrast to platinum agents, taxanes-associated HSRs do not come in the context of previous exposures and occur typically during the first or second cycle of administration, with more atypical symptoms. These features can help in the accuracy of differential diagnosis [3]. Regarding the immunological basis, there is a large amount of evidence supporting a type I, Ig E mediated, allergic reaction to carboplatin, with positive skin tests as well as the presence of IgE in peripheral blood of patients with such events [9][15].

1.3. Oxaliplatin

Among newer platinum compounds, oxaliplatin is particularly effective in the management of colorectal cancers, in combination with 5-fluorouracil (5FU), both in adjuvant and metastatic settings. The therapeutic action of this analog also extends to other gastrointestinal malignancies such as esophageal, gastric, and pancreatic cancers [1]. Parallel to the increased incidence of colorectal cancer cases, especially in young adults, the expanded usage of oxaliplatin in the clinical setting results in higher reported HSR to this platinum compound, up to 25% [2][16]. The HSRs appear usually during or shortly after administration and include a broad spectrum of manifestations, from cutaneous symptoms (rash, flushing, pruritus) to respiratory (bronchospasm, dyspnea), gastrointestinal (nausea, vomiting), and even cardiovascular (hypo, hypertension) phenomena [9]. Abdominal pain, chill, fever, diaphoresis, and other unspecific symptoms can also be present. Delayed reactions are rare, with few cases presented in the literature [17]. According to a large report, most of the reactions appeared after five cycles of administration, with the majority of the patients having only mild symptoms such as local erythema or pruritus. However, an elevated percentage (37%) of patients experienced severe reactions compatible with anaphylaxis, characterized by alterations in blood pressure, bronchospasm, chest tightness, diffuse erythroderma, or facial swelling [18]. Anaphylactic reactions to oxaliplatin are also described in various other case reports and series [19][20][21][22]. The immunologic mechanism involved in oxaliplatin-related HSR has been extensively studied. Rapid onset of manifestations during or after infusion, usually after multiple exposures along with positive prick tests and IgE detection in patients with reactions to oxaliplatin argues in favor of type I HSR, which should respond to desensitization [19][23][24][25]. Other immune-mediated reactions, which resemble a type II HSR, including immunologic thrombocytopenia, immune hemolytic anemia, Evans syndrome, and drug-induced thrombotic microangiopathy have also been reported for oxaliplatin [18][19][22][26][27][28][29]. Some of these cases resulted in exitus [28][29]. Moreover, based on clinical presentation and biomarkers, a group recently proposed a classification of oxaliplatin hypersensitivity reactions in four different endotypes, respectively: type 1, cytokine release, mixed, and either. Therefore, a cytokine release, a mast cell independent mechanism was suggested for the atypical clinical presentations that include fever, chills, rigors, headaches, and chest pain, in patients who also associated high levels of serum TNF and IL1 [30]. Notably, the HSR to oxaliplatin can be induced by concomitant administration of other drugs, such as leucovorin (within the FOLFOX regimen). Although there are fewer cases reported in the literature, leucovorin can also be responsible for HSR, therefore presumed oxaliplatin reactions can be an infusion reaction to racemic calcium folinate [31][32]. With the help of skin prick tests or drug provocation tests, allergy experts can establish the nature of the problematic drug and propose solutions such as the replacement of infusional 5FU and leucovorin with capecitabine.

1.4. Cross-Reactivity among Platinum Agents

Cross-reactivity between platinum agents has been reported in different studies, with a percentage of up to 45% for oxaliplatin and carboplatin, based on clinical symptomatology as well as skin testing [6][7][23]. It is suggested that patients

exposed to oxaliplatin can also be unable to tolerate the other platinum salts, so further testing should be done before switching to another analog [23].

2. Taxanes

Taxanes are complex alkaloid esters that provide antitumor activity in a broad spectrum of solid malignancies, having as main representatives: paclitaxel, docetaxel, and the more recent addition cabazitaxel. Their mechanism of action consists of interfering in the dynamics and thread milling of the mitotic spindle, and stabilizing the microtubules, with subsequent activation of the pathways related to apoptosis [1]. Taxanes are highly susceptible to causing HSRs. However, in contrast to platinum agents, taxanes-induced HSR have usually different features and occurs during first or second exposure, with more atypical clinical symptoms thought to be anaphylactoid rather than IgE-mediated [33]. This reaction is probably due to a direct release of mast cell mediators such as histamine and tryptase, in the context of the non-immune effects of the drugs or their excipients (cremophor and polysorbate). Nevertheless, new data have emerged and currently more theories are being explored, including an IgE-mediated mechanism [3][33]. Details concerning HSRs induced by each member of the taxane class are discussed in the following paragraphs.

2.1. Paclitaxel

The main indications of paclitaxel include management of advanced ovarian cancer, advanced breast cancer in the neoadjuvant as well as adjuvant setting, first-line treatment of small-cell lung cancer as well as subsequent therapy for AIDS-related Kaposi sarcoma. However, its usage expands to other malignancies, such as gastric, head and neck, bladder, cervical and esophagus cancers [1]. Before the extensive implementation of preventive methods, almost 30% of patients receiving paclitaxel were with HSR. This percentage diminished to less than 5% with the help of appropriate premedication and prolongation of the drug infusion time [2][33]. Paclitaxel is known to cause both standard infusion reactions as well as pseudo-anaphylaxis, either due to the chemotherapeutic component or the solvent used. When present, the clinical symptoms of a paclitaxel HSR outline a picture that includes erythematous rash, urticaria, dyspnea, bronchospasm, and hypotension, although some cases with hypertension have been described. Patients can also complain of gastrointestinal symptoms, back and chest pain [3][4]. Symptoms usually occur within a maximum of 15 min from the beginning of the infusion and in more than 90% of the cases during the first two cycles [3][4][33]. This pattern of immediate reaction has been considered to be more suggestive of a direct mast cell degranulation process, a mechanism that has been explored by several studies. The solvent and emulsifying agent CremophorEl, formulated with paclitaxel, have been proven to induce direct complement activation with consecutive mastocyte and basophils anaphylatoxins induced activation. Direct chemotherapy-induced degranulation with histamine release has also been proposed [33][34]. However, recent studies also raised the possibility of some HSR being IgE-mediated [4][33]. Although less frequently reported in the literature, delayed paclitaxel HSR have also been described, the majority of them presenting as cutaneous modifications such as rash, urticaria, and even angioedema [4][33]. They are considered to be an indicator of an immediate HSR to the next exposure. One case report described a female patient who died of anaphylactic shock following paclitaxel infusion, after presenting lip swelling and urticaria 10 days after the previous cycle [35]. Another potential delayed reaction to paclitaxel includes interstitial pneumonitis, which is associated with the need for mechanical ventilation and high mortality rates [36]. A form of subcutaneous lupus erythematosus, characterized by the presence of specific antibodies and skin eruption has also been described in conjunction with paclitaxel administration [37]. More, there is described in the literature at least one case of paclitaxel-induced Steven Jonson syndrome [38].

2.2. Docetaxel

Docetaxel proved its efficacy in locally advanced or metastatic breast cancer, locally advanced or metastatic NSCLC, metastatic castration sensitive or resistant prostate cancer, advanced gastric adenocarcinoma including esophagogastric junction tumors, and inoperable locally advanced squamous cell of head and neck cancers [1]. In early phase II studies of Docetaxel, up to 30% of the patients experienced acute HSR, but later with the use of appropriate premedication with antihistamines and corticosteroids, the percentage remained under 2% [36][39][40]. Same as with paclitaxel, the reactions appear fast, in the first 10–15 min after infusion and usually in the first or second cycle of administration. The clinical picture of this event, as described by a study presenting 102 NSCLC patients with HSR to docetaxel, includes facial flushing, chest discomfort, back pain, increased heart rate, erythematous rash, cardiovascular alterations such as important hypotension and urticarial [36]. Similar to paclitaxel, non-immediate hypersensitivity reactions, such as immunological interstitial pneumonitis and a particular form of subcutaneous lupus erythematosus have also been described [41][42]. Concerning the immediate docetaxel-induced HSR, most of the works indicate a non-allergic nature of these events [43]. It has been demonstrated in vitro that both docetaxel and its solvent and emulsifying agent polysorbate 80 and polysorbate alone can be responsible for complement activation and subsequent mast cell activation as well as

peroxide-induced degranulation [3][33][44][45]. This theory does not apply to delayed reactions, the non-immediate hypersensitivity events being mediated by a cellular immunological response [46].

2.3. Cabazitaxel

Cabazitaxel is one of the newest additions to the taxane class, being used for the management of castration-resistant metastatic prostate cancer. Opposed to the other taxanes, cabazitaxel has a low affinity for P glycoprotein, a drug exporter, supporting its use for docetaxel-resistant prostate tumors [33]. HSRs to cabazitaxel were reported in phase I and II studies [47][48]. Clinical manifestations have the same pattern of developing as the other taxanes, a few minutes after infusion, in the first two cycles. Given the rapid occurrence of the reactions, they are most likely caused by the non-immune-mediated effects of the emulsifier Polysorbate 80 [47][48][49]. The symptomatology might include rash, erythema, bronchospasm, and sometimes hypotension. As with docetaxel, the main cause for the reactions is thought to be the emulsifier Polysorbate 80 [49]. Nevertheless, in a phase III study where 378 patients were assigned to receive cabazitaxel after docetaxel progression, none experienced HSR to the drug, so overall a clear incidence for these events is still unknown [50].

2.4. Nab-Paclitaxel

With activity in breast cancer, NSCLC, and alongside gemcitabine in pancreatic cancer, Nab-Paclitaxel is a special formulation of paclitaxel contained in particles of human albumin and not Cremophor El. As a result, this chemotherapy drug is associated with fewer HSRs and does not require a special premedication regimen, strengthening the proposed idea that reactions to simple paclitaxel are usually due to the formulation. Severe infusion reactions were rarely described, mainly including dyspnea, desaturation, and back pain [51][52].

2.5. Cross-Reactivity between Taxanes

It appears that it is a high level of cross-reactivity between paclitaxel and docetaxel, which may vary among populations, so caution may be used before substituting one taxane for another [33][53]. A larger study showed that half of the patients who presented an HSR to paclitaxel also developed a reaction when the taxane was switched to docetaxel, for a cross-sensitivity rate of 50% (7 out of 14 patients). Since docetaxel and paclitaxel have different solvents, polysorbate 80 and cremophor L, respectively, the authors suggested that given the high percentage of cross-reactivity, it is more likely that the taxane moiety itself is responsible for the allergic reactions [53]. However, a more successful use was described in several case reports of breast and ovarian cancer for nab-paclitaxel, which was safely administered after docetaxel or paclitaxel HSR [54][55][56].

3. Disruption of Protein Synthesis

Based on the observation that leukemia cells need extracellular asparagine to grow, a hydrolyzing agent for the nonessential amino acid was developed for the treatment of hematological cancers in the form of L-asparaginase. As part of a multidrug scheme for acute lymphoblastic leukemia, asparaginase is known to be associated with HSR, both mild and severe reactions. Currently, there are five formulations of asparaginase available, the non-pegylated forms being considered more immunogenic [57][58][59]. Data shows that approximately 10–30% of subjects receiving *E. coli*-derived asparaginase and 3–37% receiving *Erwinia* asparaginase experience clinical symptoms after infusion [57]. They may occur from the first administration, in this case being unlikely associated with an immune-mediated mechanism. However, the risk increases after multiple cycles, being the highest during the consolidation and reinduction phases [2]. The HSR picture can include dyspnea, pruritus, bronchospasm, skin rash, urticaria, and sometimes hypotension, phenomena that usually appears in the first minutes of infusion, but can also occur later, after a few hours. However, less than 10% of the cases are considered severe [2][4]. Such events can also appear following intramuscular or subcutaneous forms of administration, but with less frequency and include pain, tenderness, swelling, and erythema at the injection site [2][4][57]. Pegylated formulations are more associated with delayed HSR [2][4][57]. The immunological basis of the asparaginase-related HSR has been proven, with antidrug antibodies present in the peripheral blood of patients with such adverse events [57]. Switching to asparaginase with a different immunologic profile might be a solution to HSR, especially for *E. coli*-derived products, with over 90% of the patients being able to complete the treatment [4][57].

4. Bleomycin

Derived from the fungus *Streptomyces verticillus*, bleomycin has strong antitumor activity, especially in germinal cell tumors, gestational trophoblastic disease, and Hodgkin non-Hodgkin lymphoma. Its mechanism of action consists of DNA cleavage [1]. Most of the infusion reactions to bleomycin do not seem to have a clear IgE-mediated background, this agent

is associated with more idiosyncratic reactions such as hyperpyrexia, hypersensitivity pneumonitis, or chest pain [4]. An old study showed no evidence of histamine release, or hypotension after drug administration, supporting the idea of a non-IgE-mediated mechanism [60]. Not related to cancer, another case report described an intraoperative allergic reaction following the injection of bleomycin for sclerotherapy [61]. Nevertheless, it also appears that bleomycin has the potential to aggravate atopic dermatitis and stimulates airway hyperactivity and inflammation in mouse models, therefore more work is needed to elucidate the underlying reaction mechanism [62].

5. Topoisomerase II Inhibitors

5.1. Epipodophyllotoxins

Demethylepipodophyllotoxin derivatives, etoposide (VP 16), and teniposide (VM-26) exert their antitumor activity by inhibiting the activity of the enzymes topoisomerase II. Etoposide is mainly used in the treatment of small-cell lung cancer and testicular tumors, while teniposide is more usually administered in the setting of refractory leukemia [1]. In terms of HSRs to this etoposide, a clinical picture with anaphylaxis can develop following intravenous administration, with hypotension, bronchospasm, chest tightness, and urticaria, usually appearing after multiple exposures [2][63]. However, the incidence seems to be low, around 1–3% [2]. The oral formulation of etoposide is not associated with any HSR, suggesting the fact that intravenous infusion reactions are probably due to polysorbate-80, the same solvent used for docetaxel that causes complement activation and subsequent mast cell direct degranulation [2][63]. Another form of VP16, etoposide phosphate is a water-soluble prodrug with no trace of polysorbate 80 that has successfully proven a good substitute agent after etoposide HSR [63][64]. Despite being extremely rare, more recently, severe anaphylactic-like reactions to this newer formulation have also been described [65]. Regarding teniposide, an older comprehensive analysis showed an incidence of 6.5% of HSR to VM-26, with a higher percentage in children with neuroblastoma and brain tumors, compared to hematologic malignancies [66]. The underlying mechanism seems to be a dose-dependent one, with direct degranulation of basophils following infusion.

5.2. Anthracyclines and Other Related Agents

Originally antibiotics, anthracyclines are currently used in oncological clinical practice, in both solid and hematological malignancies. Their biological mechanism consists of topoisomerase II inhibition and intercalating with the DNA. Doxorubicin and its less cardiotoxic analog epirubicin are mainly used in solid tumors, especially breast cancers, sarcomas, and lymphomas, while daunorubicin and its analog idarubicin are part of chemotherapy protocols in the setting of acute leukemia. With the help of liposomal technology, a newer anthracycline formulation named pegylated liposomal doxorubicin is also used in breast cancer cases with increased cardiological risk and in platinum-resistant ovarian cancers [1]. Anthracyclines (including intravesical-administered doxorubicin) are rarely associated with hypersensitivity reactions. The clinical characteristics of a doxorubicin-related infusion reaction may include rash, dyspnea, headache, back pain, chills, and sometimes hypotension [67]. More frequently, anthracyclines can cause a local flare reaction near the site of drug administration place with erythema or pruritus, but without progressing to a generalized event [4][67]. Nevertheless, with formulations such as pegylated liposomal doxorubicin or liposomal daunorubicin, the incidence of HSRs is around 9–14% [4]. Without premedication, up to 45% of patients can develop such adverse events [68]. However, the pseudo-anaphylaxis seem to be caused by the surface component of the liposome and not the chemotherapy agent itself, generating a direct complement activation [69]. True IgE is not proven to be involved [67][70].

6. Alkylating Agents—Cyclophosphamide/Ifosfamide

Used in the oncology field for the treatment of ovarian cancers, breast carcinomas, lymphomas, leukemia, neuroblastoma, and retinoblastomas, cyclophosphamide acts as an alkylating agent of the nitrogen mustard type, with a potent anticancer and immunosuppressive action. Anaphylaxis is rarely associated with cyclophosphamide infusion, with only a few cases described in the literature [71][72][73]. However, when present, an HSR to this cancer agent tends to develop up to 16 h after infusion, the proposed mechanism is an IgE-mediated reaction to the two main metabolites phosphoramide mustard, and acrolein [72].

A synthetic analog of cyclophosphamide, Ifosfamide is another agent with alkylating activity used in a wide variety of neoplasia such as gynecological and lung cancers, as well as in sarcomas and non-Hodgkin's lymphomas [1]. Ifosfamide is also infrequently associated with HSR. However, when present, most ifosfamide-related reactions are considered to be due to MESNA, an agent used for preventing hemorrhagic cystitis, a very important side effect of both cyclophosphamide and ifosfamide administration [74][75][76].

7. Antimetabolites—Pyrimidine Analogues

The pyrimidine analog, also known as arabinosylcytosine (ARA-C), cytarabine is an antineoplastic antimetabolite agent mainly used to treat hematological malignancies, especially acute non-lymphocytic leukemia, acute lymphocytic leukemia and blast phase of chronic myelocytic leukemia [77]. Anaphylaxis with symptoms such as urticaria, angioedema, or hypotension is rarely reported for cytarabine. Cases of delayed hypersensitivity are also extremely rare, with cutaneous lesions with pruritus, rash, and erythematous maculae being described three days after infusion [78]. Most of the infusion reactions associated with this agent consist of a more flu-like syndrome, with myalgia, arthralgia, conjunctivitis, and skin modifications. This “cytarabine syndrome” appears in one-third of the patients and it is thought to be associated with a cytokine release mechanism and can usually be prevented with appropriate premedication [77].

8. Monoclonal Antibodies

Similar to cytotoxic chemotherapy, monoclonal antibodies used in cancer management can also cause infusion reactions [79][80][81]. Most of them usually appear during the first or second drug infusion, between 30 min and 24 h after initiation of perfusion, with clinical characteristics such as fever, chills, back or abdominal pain, skin rashes, nausea, but also cardiovascular alterations, and dyspnea. A recent study conducted on 104 patients proposed four different pathophysiological backgrounds for Monoclonal induced infusion reactions, including cytokine-mediated, mastocytes and basophils mediated (type I like), T cell and macrophages mediated (type 4 like) and not least mixed reactions [79]. The highest incidence of infusion reactions is reported with the use of avelumab, rituximab, daratumumab, and alemtuzumab, with more than 50% of patients developing clinical symptoms, and in slightly lower percentages with trastuzumab (40%) and cetuximab (20%) [80][81]. While most of the infusion reactions associated with these agents coincide with the cytokine-mediated pattern, Type 1 allergic reactions have also been described with rituximab, trastuzumab, and cetuximab, these agents are known to cause both types of events [80].

8.1. Rituximab

A chimeric monoclonal antibody CD20 targeted, Rituximab is used in cancer care for the management of CD20 positive B-cell Non-Hodgkin’s Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL), but also non-oncological settings for diseases such as pemphigus Vulgaris or rheumatoid arthritis. More than half of the patients have rituximab infusion-related reactions appearing after 30 min of intravenous administration, with symptoms suggestive of a cytokine-mediated pattern such as fever, chills, back pain, sweat, or rhinitis [80][82][83]. The use of subcutaneous rituximab can also induce similar systemic symptoms [80][82]. It is thought that secondary to the interaction of the monoclonal antibody to the T cell surface marker CD20, a variety of cytokines are released by the targeted cell, with even potentially life-threatening manifestations such as pulmonary infiltration or acute respiratory distress syndrome. It seems that fractioning rituximab and using premedication can significantly lower the rates of this kind of reaction [79][81]. However, in less frequent cases, a clinical picture of anaphylaxis with bronchospasm, pruritus, urticaria, and hypotension has also been described, with positive skin tests or IgE specific to rituximab [79][80][81][82]. The information provided in the literature is too thin to establish a relationship between the type of hypersensitivity reactions and the disease for which rituximab is used. However, it might be interesting to investigate whether there is an association between the different doses and schedules of administration of rituximab in oncological and non-oncological settings and the class of HSR. Type IV Gell and Coombs HSRs can also occur in the cancer setting, with Stevens-Johnson syndrome being reported in at least one case of B cell lymphoma [84], while type III HSR is usually reported in non-oncological cases.

8.2. Trastuzumab

Targeting the extracellular domain of the human epidermal growth factor receptor (HER2), trastuzumab is used in different combinations for the treatment of HER2-positive breast cancer, in adjuvant and palliative settings, and also for metastatic gastric and gastroesophageal tumors. This monoclonal antibody is generally associated with infusion reactions during first intravenous administration, most of them being thought to be non-IgE-mediated, with symptoms comprising of chills, fever, nausea, rash, headache, abdominal pain and rhinitis that seems to appear in over 40% of women with HER2 positive disease [85][86]. Moreover, in a retrospective study on 197 breast cancer patients receiving trastuzumab, only three experienced infusion reactions after more than one administration, suggesting a predominant cytokine-dependent mechanism [85]. Although in the summary of product characteristics, it is suggested that the infusion reactions can occur up to 6 h after drug intravenous administration, a more recent paper proved that these events can only occur during the 90 min of infusion [87]. These types of reactions can be managed by temporizing the infusion or slowing the rate of administration, further occurrence of similar symptomatology does not usually appear in subsequent cycles [85][87]. Despite being extremely rare, clinical pictures consisting of anaphylaxis are also described with the use of intravenous

trastuzumab [87]. Urticaria, angioedema, hypotension, and severe dyspnea can signal a type I allergic reaction to the administration of this monoclonal antibody. In such cases, protocols of desensitization can be used to further pursue this type of therapy, when there are no other better therapeutic alternatives [88]. According to a recent research paper regarding grade III hypersensitivity events for the combination trastuzumab pertuzumab, the incidence seems to be very low for the intravenous form and with no reported severe reactions for the subcutaneous formulation [87]. Compared to trastuzumab, other HER2 targeted agents such as Ado-trastuzumab emtansine or fam-trastuzumab deruxtecan are rarely associated with infusion reactions, most of them being mild with classical characteristics such as fever, chills, shortness of breath [89].

8.3. Cetuximab

Causing infusion reactions in up to 25% of patients, cetuximab is a human/mouse chimeric antibody that targets the epidermal growth factor receptor EGFR, used in the management of metastatic KRAS wild-type metastatic colorectal cancer and head and neck tumors [86]. Although being known of causing a cytokine release pattern of reactions, a more clearly defined IgE-mediated mechanism was described for some of the more severe reactions [86][90]. The serum analysis of patients with cetuximab-induced severe infusion reactions showed the presence of IgE antibodies directed to galactose-alpha-1,3-galactose, an oligosaccharide presents on the cetuximab mouse-derived heavy chain, unraveling a type I allergic reaction [90]. Therefore, it can be easily explained that the lack of cross-reactivity between cetuximab and panitumumab, the latest being a fully human-derived monoclonal antibody, lacking galactose-alpha-1,3-galactose [91]. It is also suggested that a history of atopy can act as a risk factor for anaphylaxis in cetuximab-treated patients [92]. In terms of prevention, a more recent Korean nationwide study on 64 patients concluded that the determination of IgE antibodies to cetuximab or galactose-α-1,3-galactose can accurately predict the future development of anaphylaxis in patients that will receive the drug and can be used in clinical practice [93].

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