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Adverse events to monoclonal antibodies used for cancer therapy

Focus on hypersensitivity responses

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Abbreviations: ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; ADR, adverse drug reaction; AGEP, acute generalized exanthematous pustulosis; AIHA, autoimmune hemolytic anemia; ARDS, acute respiratory distress syndrome; BAFF, B-cell activating factor; BAL, bronchoalveolar lavage; BOOP, bronchiolitis obliterans organizing pneumonia; CDC, complement-dependent cytotoxicity; CLA, cutaneous lymphocyte antigen; CLL, chronic lymphoid leukemia; CRS, cytokine release syndrome; CTLA4, cytotoxic T lymphocyte-associated protein 4; CV, cutaneous vasculitis; DILD, drug-induced lung disease; DILI, drug-induced liver injury; DIV, drug-induced vasculitis; DMI, mertansine; DRESS, drug reaction with eosinophilia and systemic symptoms; EGFR, epidermal growth factor receptor; EM, erythema multiforme; EMA, European Medicines Agency; EpCAM, epithelial cell adhesion molecule; ErbB2, human epidermal growth factor receptor 2 or HER2; FDA, Food and Drug Administration; FDE, fixed drug eruption; GCTB, giant cell tumor of the bone; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2 or ErbB2; IR, infusion reaction; KDR, kinase insert domain receptor (VEGFR-2); LON, late-onset neutropenia; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; NHL, non-Hodgkin's lymphoma; NSAID, non-steroidal anti-inflammatory drug; PML, progressive multifocal leukoencephalopathy; RANKL, receptor activator of nuclear factor κB ligand; SDF-1, stromal-derived factor-1; SIRS, systemic inflammatory response syndrome; SJS, Stevens-Johnson syndrome; TCR, T-cell receptor; TEN, toxic epidermal necrolysis; TLS, tumor lysis syndrome; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor

Fifteen monoclonal antibodies (mAbs) are currently registered and approved for the treatment of a range of different cancers. These mAbs are specific for a limited number of targets (9 in all). Four of these molecules are directed against the B-lymphocyte antigen CD20; 3 against human epidermal growth factor receptor 2 (HER2 or ErbB2), 2 against the epidermal growth factor receptor (EGFR), and 1 each against epithelial cell adhesion molecule (EpCAM), CD30, CD52, vascular endothelial growth factor (VEGF), tumor necrosis factor (ligand) superfamily, member 11 (TNFSF11, best known as RANKL), and cytotoxic T lymphocyte-associated protein 4 (CTLA4). Collectively, the mAbs provoke a wide variety of systemic and cutaneous adverse events including the full range of true hypersensitivities: Type I immediate reactions (anaphylaxis, urticaria); Type II reactions (immune thrombocytopenia, neutopenia, hemolytic anemia); Type III responses (vasculitis, serum sickness; some pulmonary adverse events); and Type IV delayed mucocutaneous reactions as well as infusion reactions/cytokine release syndrome (IRs/CRS), tumor lysis syndrome (TLS), progressive multifocal leukoencephalopathy (PML) and cardiac events. Although the term "hypersensitivity" is widely used, no common definition has been adopted within and between disciplines and the requirement of an immunological basis for a true hypersensitivity reaction is sometimes overlooked. Consequently, some drug-induced adverse events are sometimes incorrectly described as "hypersensitivities" while others that should be so described are not.

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Adverse and Hypersensitivity Reactions to Drugs

Over the years a number of different definitions have been advanced to describe an adverse drug reaction (ADR). The most quoted one is that issued by the World Health Organization in 1972, that is, "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function."[1] Disagreements with this definition, for example, with use of the words "noxious" and "drug," have

led to a number of other descriptions. That advanced by Edwards and Aronson[2]—"an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product"—is often referred to, but for many the simplicity of the United States Food and Drug Administration (FDA) definition—"any undesirable experience associated with the use of a medical product in a patient"—is adequate. The FDA states that any serious event induced by a medical product should be reported to the organization and defines "serious" as death, life-threatening, hospitalization, disability or permanent damage, congenital anomaly/birth defect, required intervention to prevent permanent impairment or damage (devices), and other serious important medical events (for example, allergic bronchospasm, serious blood dyscrasias, or seizures or convulsions that do not result in hospitalization).[3]

ADRs have been classified into seven different categories, designated A to G. These categories are: A, Augmented pharmacologic effects; B, Bizarre; C, Chronic (or continuous) effects; D, Delayed effects; E, End-of-treatment (or withdrawal) effects; F, Failure of therapy; and G, Genetic reactions.[2,4] Type A reactions, distinguished primarily on the basis of dose-related reactions, are predictable, can be anticipated from the drug's pharmacological activity, resolve when the dose is reduced or withdrawn and account for ~80% of ADRs. For our purposes, Type B reactions are the main concern. Type B reactions are non-dose-related, unpredictable, generally unrelated to the drug's pharmacological activity, and usually resolve when treatment is terminated. These reactions are divided into true allergic responses (immune-mediated) and non-allergic (non-immune) sensitivities (**Table 1**). The former category is made up of the 4 true hypersensitivity states, as defined by Gell and Coombs: Type I, IgE antibody-mediated reactions; Type II, cytotoxic reactions; Type III, immune-complex-mediated hypersensitivities; and Type IV, delayed, cell-mediated responses.[5] Conversely, pseudoallergy, idiosyncratic reactions and Type B intolerances make up Type B non-immune, non-allergic drug sensitivities (**Table 1**). The term "hypersensitivity" is often misused. Here, it is taken to mean adverse signs and symptoms that are initiated by an antigenic stimulus tolerated by a "normal" person and that have an immune basis or component. Even in the absence of evidence of an immune mechanism, a few drugs show apparent features of a hypersensitivity response. Some reactions to contrast media[6] and non-steroidal anti-inflammatory drugs (NSAIDs)[7] fall into this group, in which mechanisms such as the activation of bradykinin and the drug-induced redirection of the arachidonic acid metabolism from the cyclooxygenase to the lipoxygenase pathway may be involved. Such reactions are described here as non-immune "sensitivities" or "intolerances."[8]

Even though the term "hypersensitivity" is widely used including, for example, in the immunology, allergy, oncology

Table 1. Classification of Type B[a] adverse reactions to therapeutic agents

Hypersensitivity *(Immune; Allergic)*			**Non-allergic sensitivities** *(Non-immune)*	
Hypersensitivity type[b]	Mediated by	Examples	Subtypes	Examples
Type I[c]	IgE antibodies	*Penicillins; cephalosporins; neuromuscular blockers; mAbs; pyrazolones; proton pump inhibitors; L-asparaginase*	Pseudo-Allergy[d]	*Most reactions to NSAIDs;[e] Direct mast cell degranulation (neuromuscular blockers; opioids; contrast media; vancomycin)*
Type II[f]	IgG/IgM cytotoxic reactions	*Penicillins; cephalosporins; quinine; quinidine; sulfonamides; thiouracil; mAbs; gold salts; NSAIDs; procainamide; ticlopidine; oxaliplatin; fludarabine*	Idiosyncratic Reactions[g]	*Halothane hepatitis; malig- nant hypothermia; drug- induced hemolytic anemia in Glu-6-PO_4 dehydrogenase-deficient individuals (anti-malarials, sulfonamides, dapsone)*
Type III[h]	IgG/IgM immune complexes	*Penicillins; cephalosporins; sulfonamides; allopurinol; NSAIDs; carbamazepine; mAbs; tamoxifen; oxaliplatin; anastrozole; gemcitabine; erlotinib; cyclophosphamide*	Intolerances	*? some reactions to contrast media and NSAIDs[i] Tinnitus induced by small doses of aspirin*
Type IV[j,k]	T cells	*NSAIDs; penicillins; local anesthetics; hydroxychloro- quine; anti-convulsants (eg carbamazepine); dapsone; mAbs; tamoxifen; cytarabine; N-mustards*		

Note that mAbs can provoke all 4 types of hypersensitivity reactions. [a]So-called 'Bizarre' reactions that are uncommon unpredictable, rarely dose dependent and unrelated to agent's pharmacologic action. Relative to other categories of adverse reactions, these reactions show high mortality. [b]According to the definition and classification of Gell and Coombs (see ref. 5). [c]Manifest as anaphylaxis, bronchospasm, cardiovascular collapse, urticaria, angioedema. [d]Some reactions closely resemble true Type I reactions and are termed 'anaphylactoid'. [e]NSAIDs, non-steroidal anti-inflammatory drugs. [f]E.g. drug-induced hemolytic anemia, immune thrombocytopenia, immune form of agranulocytosis. [g]May be unrelated or related to dose. Uncommon, unpredictable, unrelated to drug's pharmacologic action. [h]E.g. serum sickness-like reactions, drug-induced vasculitis. [i]Some reactions to NSAIDs and contrast media are clearly not hypersensitivity responses or pseudoallergic or idiosyncratic in nature. [j]E.g. allergic contact dermatitis, psoriasis, maculopapular exanthema, acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, fixed drug eruption, Stevens–Johnson syndrome, toxic epidermal necrolysis. [k]Also known as delayed reactions.

and pharmacology literatures as well as in clinical trial reports, company drug descriptions and drug package inserts, no common definition has been adopted. The word is sometimes mistakenly used to cover reactions that clearly have no immune basis and which are otherwise not easy to classify, or where the mechanism remains to be determined.[9] On the other hand, since the mechanisms accounting for many ADRs are not known or not investigated, and appropriate tests are either not at hand or even developed, some true hypersensitivities remain unrecognized and therefore incorrectly classified. It is not uncommon therefore to see adverse reactions incorrectly described as "hypersensitivities"[10] as well as the use of alternative terms where that of "hypersensitivity" would be justified.

Monoclonal Antibodies Currently Used for Cancer Immunotherapy and Their Mechanisms of Action

As of July 2013, 15 monoclonal antibodies (mAbs) are approved by the FDA and/or European Medicines Agency (EMA) for anticancer immunotherapy (**Table 2**). Catumaxomab, a rat/mouse hybrid bispecific antibody used for malignant ascites, is registered by the EMA, Health Canada and Israeli Ministry of Health, but not the FDA. This mAb binds via its Fc portion to an antigen-presenting cell, one combining site is directed to the transmembrane glycoprotein epithelial cell adhesion molecule (EpCAM), which is expressed on epithelial cancer cells, while the other site binds to CD3, a component of the T-cell receptor (TCR) complex on T lymphocytes.[11,12] The consequent immunological reaction against neoplastic cells reduces the tumor burden from the abdomen of ascites cancer patients. Four of the mAbs nowadays used to treat cancer target the B-lymphocyte antigen CD20,[13,14] which is expressed on 90% of B-cell non-Hodgkin's lymphomas, B-cell chronic lymphocytic leukemia (LCC), hairy cell leukemia and melanoma cancer stem cells but not on plasma blasts or plasma cells. Once the mAb ibritumomab binds its target, the radioactive label complexed by the chelator tiuxetan[15] (**Table 2**) causes cell damage. With tositumomab, the attached ionizing radiation from ^{131}I induces cell death.[14-16] Moreover, for these 2 labeled mAbs as well as for rituximab[14,17,18] and ofatumumab,[14,19] other possible mechanisms of action include the activation of antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and CD20-mediated apoptosis.[20] Cetuximab[14,21,22] and panitumumab[14,22] bind specifically to the epidermal growth factor receptor (EGFR) (also known as HER1, ErbB1) a type I receptor tyrosine kinase expressed by normal cells (e.g., of the skin and hair follicles) and tumor cells (head, neck, colon, rectum), hence competitively inhibiting the binding of ligands including the epidermal growth factor. This results in inhibition of cell growth, decreased production of vascular growth factor and pro-inflammatory cytokines and apoptosis. Pertuzumab, trastuzumab, and ado-trastuzumab emtansine all target HER2 (ErbB2).[23] Trastuzumab inhibits the growth and proliferation of tumor cells that overexpress HER2,[14,24] while ado-trastuzumab emtansine[25] is the same mAb conjugated with the cytotoxic microtubule inhibitor DMI (mertansine), arresting the cell cycle and leading to cell death. Pertuzumab inhibits the heterodimerization of HER2 with other ErbB receptors,[26] blocking the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) signaling pathways and hence resulting in cell growth arrest and apoptosis.[27] ADCC may also be involved in the cytotoxicity of this antibody. The antibody-drug conjugate (ADC) brentuximab vedotin is directed against CD30,[28] a member of the tumor necrosis factor α (TNFα) receptor family and tumor marker expressed by activated T and B cells. Brentuximab vedotin arrests the cell cycle and induces apoptotic death owing to the monomethyl auristatin E (MMAE)-induced disruption of tubulin. By binding to the vascular endothelial growth factor (VEGF), bevacizumab[29] prevents its interaction with fms-related tyrosine kinase 1 (FLT1, also known as VEGFR1) and kinase insert domain receptor (KDR, also known as VEGF2, CD309 and FLK1) on the surface of endothelial cells. This results in the inhibition of microvascular growth and metastatic disease. Alemtuzumab binds to CD52,[30,31] which is present on mature lymphocytes, B cells, most monocytes and a number of other cells. The destruction of leukemic cells by this mAb mainly occurs by ADCC. Denosumab binds to tumor necrosis factor (ligand) superfamily, member 11 (TNFSF11, best known as RANKL),[32] a transmembrane and soluble protein produced by osteoblasts and giant cell tumor of the bone (GCTB) cells that activates osteoclasts, the cells involved in bone resorption. RANKL-stimulated osteoclast activity is a mediator of the metastatic spread of cancer cells to the bone. Denosumab prevents the activation of RANKL on osteoclasts and osteoclast-like giant cells. Ipilimumab binds to cytotoxic T lymphocyte-associated protein 4 (CTLA4) expressed on helper T cells. By interacting with its ligands CD80 (B7–1) and CD86 (B7–2), CTLA4 transmits an inhibitory signal that downregulates immune responses, unlike CD28, which also binds to CD80/CD86 but transmits a stimulatory signal. By blocking the interaction of CTLA4 with its ligands, ipilimumab therefore exerts an indirect T-cell mediated antitumor effect in melanoma patients.[33]

Range of Side Effects of Monoclonal Antibodies

Although mAbs used for cancer immunotherapy are generally better tolerated than widely used 'conventional' chemotherapeutic agents, adverse events following the administration of mAbs can result from a variety of mechanisms and may be quite diverse. **Table 3** summarizes the most frequently occurring/important systemic and cutaneous adverse events of the 15 different mAbs currently used in cancer treatments, summarizing information from published medical/scientific literature; research studies; reports of clinical trials; FDA prescribing information, warnings, precautions, and adverse reactions; data released by drug companies; and prescribing information revisions as a result of post-marketing experience. The wide variety of mAb-associated reactions ranges from, for example, headache, mild gastrointestinal symptoms such as diarrhea, transient rash and itching to severe cytopenias, cardiac toxicity, anaphylaxis,

Table 2. Approved[a] monoclonal antibodies (mAbs) for cancer therapy

Generic name	Type of mAb	Target[b]	Mechanism of action	Approved indication(s)	Trade name
-omabs					
Catumaxomab	Rat IgG2b / Mouse IgG2a bispecfic	EpCAM[c]/CD3[d]	Binds both EpCAM on tumor cell and CD3 on T cell	Malignant ascites	Removab®
Ibritumomab tiuxetan[e]	Murine IgG1κ	CD20	Binds B cells and kills with ADCC,[f] CDC[f] and radiation[e]	Non-Hodgkin lymphoma	Zevalin®
Tositumomab-^{131}I	Murine IgG2aλ	CD20	Binds to and kills B cells with ^{131}I	Non-Hodgkin lymphoma	Bexxar®
-ximabs					
Brentuximab vedotin[g]	Chimeric IgG1κ	CD30[h]	Antimitotic MMAE[g]	Anaplastic large cell lymphoma; Hodgkin lymphoma	Adcetris®
Cetuximab	Chimeric IgG1κ	EGFR[i]	Binds to EGFR and turns off cell division[j]	Colorectal cancer; head and neck cancers	Erbitux®
Rituximab	Chimeric IgG1κ	CD20	Binds to CD20 on B cells leading to cell death	Non-Hodgkin lymphoma	MabThera® Rituxan®
-zumabs					
Alemtuzumab	Humanized IgG1κ	CD52[k]	Eliminates lymphocytes	Chronic lymphocytic leukemia	Campath-1H®
Bevacizumab	Humanized IgG1κ	VEGF[l]	Angiogenesis inhibitor	Colorectal, lung, kidney, brain cancers	Avastin®
Pertuzumab	Humanized IgG1κ	HER2[m]	Inhibits dimerization of HER2 with other HER receptors	Metastatic breast cancer	Perjeta®
Trastuzumab	Humanized IgG1κ	HER2	Prevents overexpression of HER2	Breast cancer	Herceptin®
Trastuzumab emtansine[n]	Humanized IgG1κ	HER2	mAb-drug conjugate. As for trastuzumab plus cytotoxic effect of mertansine (DM1)[o]	Advanced metastatic breast cancer	Kadcyla™
-umabs					
Denosumab	Human IgG2κ	RANKL[p]	Inhibits activation of osteoclasts by RANKL	Bone metastases; Giant cell tumor of the bone (GCTB)	Prolia® Xgeva®
Ipilimumab	Human IgG1κ	CTLA-4[q]	Blocks interaction of CTLA-4 with its ligands[r] and enhances T cell activation	Metastatic melanoma	Yervoy®
Ofatumumab	Human IgG1κ	CD20	Binds to CD20 on B cell causing cell death	Chronic lymphocytic leukemia	Arzerra®
Panitumumab	Human IgG2κ	EGFR[i]	Binds to and prevents activation of EGFR	Colorectal cancer	Vectibix®

International suffixes to distinguish the origins of therapeutic monoclonal antibodies: *-omab*, murine origin, usually IgG1 or IgG2; *-axomab*, bispecific mouse-rat hybrid mAbs (e.g., catumaxomab); *-ximab*, chimeric antibodies, usually IgG1, in which variable region is spliced into human constant region; *-zumab*, humanized antibodies with murine hyperviariable regions (usually IgG1) spliced into human antibody; *-umab*, antibodies from phage display or transgenic mice technology with a complete human sequence (IgG1 or IgG2). [a]Approved by FDA as at June 2013. [b]Specificity of mAb. [c]EpCAM, epithelial cell adhesion molecule. Expressed on epithelial and epithelial-derived neoplasms. [d]CD3, part of the TCR complex on T lymphocytes. [e]With Yttrium-90 or Indium-111. Tiuxetan is a chelator. [f]ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity. [g]Conjugated to the cytotoxic agent monomethyl auristatin E (MMAE). [h]CD30 or TNFRSF8, a cell membrane protein of tumor necrosis receptor family. Expressed on activated T and B lymphocytes. [i]EGFR, epidermal growth factor receptor (HER1, ErbB-1). [j]Not effective in cases with KRAS mutations in cancer cells. [k]Present on the surface of mature lymphocytes and associated with some types of lymphomas. [l]VEGF, vascular endothelial growth factor (a subfamily of growth factors; includes VEGF-A). [m]HER2, human epidermal growth factor receptor 2. Also known as Neu, ErbB2, CD340 or p185. [n]mAb linked to the cytotoxin mertansine (DM1). In the US known as ado-trastuzumab to distinguish from trastuzumab. [o]A maytansinoid tubulin inhibitor. [p]RANKL, receptor activator of nuclear factor kappa-B ligand (CD254), a member of the TNF cytokine family. [q]CTLA-4, cytotoxic T-lymphocyte antigen 4; CD152. [r]Ligands for CTLA-4, CD80/CD86.

Table 3. Hypersensitivity/adverse reactions of monoclonal antibodies used for cancer therapy

mAbs[a]	Hypersensitivity[b]/adverse[c] reactions		Refs
	Systemic	Cutaneous	
Catumaxomab[d]	SIRS; abdominal disorders; CRS; pyrexia; cytopenias[e]; hepatotoxicity; dyspnoea; infections; immunogenicity	Rash; erythema; hyperhidrosis; pruritus; allergic dermatitis	34,35
Ibritumomab tiuxetan	IR; infections; severe cytopenias; immunogenicity; secondary malignancies	EM; SJS; TEN; bullous dermatitis; exfoliative dermatitis	36
Tositumomab-I^{131}	Anaphylaxis; severe cytopenias; IR; fetal harm; hypothyroidism; secondary malignancies; infection; immunization	In clinical trial: Skin reactions, all grades - rash 17%, pruritus 10%, sweating 8%. Grades 3 and 4 - 0 - < 1%; exfol. dermatitis	37,38
Brentuximab vedotin	PN; IR; cytopenias; TLS; immunogenicity; PML; fetal harm; anaphylaxis	SJS; rash; pruritus; alopecia	39,40
Cetuximab	IR; cardiopulmonary arrest; GI; pulmonary toxicity[f]; electrolyte imbalance; infection; anaphylaxis	Acneiform rash; nail changes; pruritus; xeroderma; paronychial inflammation	18,41–44
Rituximab	IR; TLS; PML; renal toxicity; infections; cardiac events; pulmonary events[f]; bowel obstruct. and perforation; neutropenia; RA; anaphylaxis; HBR; SS	Paraneoplastic pemphigus; lichenoid dermatitis; vesiculobullous dermatitis; SJS; TEN	18,44–50
Alemtuzumab[g]	IR; cytopenias; infections[h]; immunogenicity; cardiac events; pulmonary events[f]	Urticaria; rash; erythema; pruritus	44,51–53
Bevacizumab	GI perforation; hemorrhage; wound healing complications; thrombosis; IR; hypertension; necrotizing fasciitis; proteinurea; pulmonary events[f]	Exfoliative dermatitis; alopecia	44,53–57
Pertuzumab	Embryo-fetal toxicity; IR; cytopenias; GI; PN; hypersensitivity/anaphylaxis; LVD	Alopecia; rash; paronychia; pruritus	58,59
Trastuzumab	Cardiomyopathy[i]; embryo-fetal toxicity; IR; LVD; pulmonary events[f]; neutropenia[j]; anaphylaxis/angioedema; anemia; GI	Rash; nail disorders; pruritus	18,44,60,61
Trastuzumab Emtansine[k]	Hepatotoxicity; LVD; fetal harm; pulmonary events; thrombocytopenia; neurotoxicity; hypersensitivity/IR	Rash; pruritus	62
Denosumab	Hypocalcemia; embryo-fetal toxicity; ONJ and osteomyelitis; fatigue/asthenia; dyspnea	Dermatitis; eczema; rash; pruritus	63
Ipilimumab	IMR; diarrhea; fatigue	Dermatitis; pruritus; rash[l]	64–66
Ofatumumab	IR; cytopenias; intestinal obstruction; PML; HBR; pneumonia; pyrexia; infections; cough; dyspnea; diarrhea; fatigue	Rash; urticaria; hyperhidrosis	67,68
Panitumumab[m,o]	IR; pulm. fibrosis[f,n]; pulmonary embolism, electrolyte depletion; GI; fatigue	Rash; dermatitis 'acneiform'; exfoliation; erythema; pruritus; xerosis; paronychia; skin fissures; photosensitivity[o]	18,69

[a]Approved by FDA and/or European Medicines Agency (EMA). [b]Reactions known or suspected of having an immunological basis. [c]Other adverse reactions with no clearly established, or yet to be demonstrated, immune mechanism (eg.nausea, cough, diarrhea, fatigue, sweating etc). [d]Registered by EMA, Health Canada and Ministry of Health, Israel but not FDA. [e]Means one or more of anemia, lymphopenia, neutropenia, thrombocytopenia. [f]See **Table 4**. [g]Withdrawn from US and Europe in 2012 to be re-launched for MS. [h]In particular, Pneumocystis jiroveci, CMV, EBV, herpes virus. [i]Left ventricular dysfunction. Greatest risk when administered with anthracyclines. [j]Highest with myelosuppressive therapy. [k]Called Ado-trastuzumab emtansine in the US [l]SJS/TEN, Sweet's syndrome, DRESS seen rarely. [m]Not indicated for use in combination with chemotherapy due to increased toxicity. [n]Should be discontinued in patients developing interstitial lung disease, pneumonitis, lung infiltrates. [o]Most common adverse reactions are skin toxicities. **Abbreviations:** CRS, cytokine release syndrome; EM, erythema multiforme; GI, gastrointestinal symptoms, e.g., nausea, diarrhea, vomiting, constipation etc; HBR, hepatitis B reactivation; IMR, immune-mediated reactions due to T cell activation and proliferation (enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies); IR, infusion reactions; LVD, left ventricular dysfunction; ONJ, osteonecrosis of the jaw; PML, progressive multifocal leukoencephalopathy; PN, peripheral neuropathy; RA, rheumatoid arthritis; SIRS, systemic inflammatory response syndrome; SJS, Stevens-Johnson syndrome; SS, serum sickness-like reactions; TEN, toxic epidermal necrolysis;, TLS, tumor lysis syndrome

exfoliative dermatitis and rarely life-threatening bullous toxidermias. Being non-endogenous proteins of sufficient size, immunogenicity is always a safety concern and despite progressive efforts in developing chimeric, humanized, and fully human mAbs, the possibility of generating anti-idiotype antibodies means that the potential immunogenicity of mAbs persists, at least to some degree.[70] Although ADRs such as anaphylaxis, serum sickness, autoimmune diseases, urticaria, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are clearly mediated by the immune system,[8] others like some cytopenias

(thrombocytopenia,[71,72] neutropenia[73,74] and anemia[75]) may or may not be so. Some pulmonary[76] and liver[77,78] toxicities, induced infections and cutaneous responses[79-81] are often less well defined and understood and may have at least an indirect connection to immunological processes. This might also be said about IRs/CRS and the systemic inflammatory response syndrome (SIRS),[82-85] but the tumor lysis syndrome (TLS)[86] and some cytopenias,[72,87] as well as heart, pulmonary, hepatic, kidney, embryo-fetal, and neurological toxicities appear to be due to direct cytotoxic actions and/or a number of other non-immune mechanisms.[88,89]

MAb-induced ADRs with an apparent immune basis, those with an indirect immune connection, reactions with a possible—even if minor—immune component and adverse events caused by non-immune toxicities are discussed below.

Hypersensitivity/Adverse Reactions to Monoclonal Antibodies

These are adverse responses that fall into at least one of the 4 categories of hypersensitivity, Types I, II, II and IV, as defined by Gell and Coombs[5] (**Table 1**). MAbs are known to cause all 4 types of hypersensitivities.

Type I (immediate) hypersensitivity

These reactions, mediated by IgE antibodies and sometimes called anaphylactic hypersensitivities, are relatively uncommon upon the administration of mAbs. Immediate hypersensitivity may affect a single organ such as the nasopharynx (allergic rhinitis), eyes (conjunctivitis), mucosa of mouth/throat/tongue (angioedema), bronchopulmonary tissue (asthma), gastrointestinal tract (gastroenteritis), and skin (urticaria, eczema), or multiple organs (anaphylaxis), causing symptoms that range from minor itching and inflammation to death. Anaphylactoid or pseudo-allergic reactions may also provoke flushing, hypotension, mucous secretion, rash, pruritus, and urticaria, making it difficult to distinguish these symptoms from a true, IgE-mediated Type I hypersensitivity reaction, which is generally accompanied by similar, though more severe, symptoms.[8] In particular, cardiovascular collapse and bronchospasm occur more frequently in the course of anaphylaxis while cutaneous manifestations are seen more often during anaphylactoid reactions.[8] Because of the immunogenic potential of the mAbs mentioned above, especially chimeric molecules (brentuximab, cetuximab, rituximab) and those that contain murine or rat sequences (catumaxomab, ibrutumomab, tositumomab), mAbs commonly carry warnings of possible immediate reactions including anaphylaxis, but the actual incidence of such reactions is quite small. Anaphylaxis has been reported for cetuximab, rituximab, trastuzumab, pertuzumab, tositumomab, and ibritumomab, and these latter two mAbs have also been shown to cause bronchospasm and angioedema.[36,37,41,45,58,60,90-94] Cetuximab-reactive IgE antibodies found in the sera of some patients with anaphylaxis to this drug were found to be specific for the disaccharide α-*D*-galactose-(1–3)-β-*D*-galactose present at asparagine 88 of the heavy chain of the Fab fragment.[92] Most patients who reacted already had the antibodies in their serum before receiving the drug. The analysis of patients treated with rituximab at Massachusetts General Hospital in 2006–2010 showed that 79 of 901 patients (9%) experienced an immediate hypersensitivity reaction with most (76%) developing symptoms during their initial infusion.[95] The authors concluded that immediate hypersensitivity to rituximab commonly occurs after the initial infusion and found that Waldenstom's macroglobulinemia patients had a disproportionately higher risk of hypersensitivity. Nonetheless, no evidence of rituximab-specific IgE antibodies or positive skin tests to the mAb were presented.

Infusion reactions or cytokine release syndrome

The infusion of mAbs typically provokes a characteristic infusion syndrome, usually occurring within a few hours from the beginning of the first administration. Most reactions are typically mild to moderate with 'flu'-like symptoms of fever, chills, rigors, nausea, headache, asthenia, rash, pruritus, etc.[96] In a small percentage of patients developing potentially fatal IRs, mostly in the course of the first or second infusion, some signs and symptoms such as hypotension, cardiac arrest, bronchospasm and urticaria may be common to a true Type I, IgE antibody-mediated anaphylactic reaction, making it difficult to discriminate between these two events,[8,97] although IgE-mediated reactions generally have a faster and more severe onset (usually within minutes). IRs, including severe ones, have been reported for all mAbs, the incidence of such reactions (e.g., in response to cetuximab) being similar to the range seen with taxanes (~20–40%) and platinum derivatives (~12–16%).[97] Rituximab and trastuzumab induce the highest incidence of IRs. In general, the incidence of mAb-induced IRs varies from ~15–20% for cetuximab (3% grade 3–4) and 40% for trastuzumab first infusion (< 1% grade 3–4) to 77% for rituximab first infusion (10% grade 3–4). Even after the fourth infusion, 30% of cancer patients react to rituximab, and the incidence of IRs remains 14% after the eighth infusion. Approximately 80% of fatal reactions occurred after the first rituximab infusion. The incidence of IRs to the humanized mAb bevacizumab and the fully humanized agent panitumumab are significantly lower: < 3% (0.2%) for the former and 3% (~1%) for the latter.[97] The mechanisms underlying mAb-induced IRs remain incompletely understood. It is thought that the mAb-target interaction may lead to release of cytokines such as TNFα and interleukins like IL-6 that can produce a range of symptoms seen in infusion reactions, some of which are similar to those seen in Type I allergic responses. Some results indicate that the severity of IRs is related to the number of circulating lymphocytes, for example, a lymphocyte count > 50 x 10^9/L was likely to be associated with a severe reaction,[98] and the regression of IR symptoms in oxaliplatin-treated colorectal cancer patients paralleled a decrease in serum cytokine concentrations.[99] Note that even repeated severe IRs to a particular mAb may not necessarily preclude the administration of another appropriately targeted antibody as demonstrated by the safe use of ^{131}I-tositumomab after repeated IRs to rituximab.[100]

Are some adverse reactions to mAbs true Type II or Type III hypersensitivity responses?

A number of case reports and retrospective analyses suggest that some mAbs, principally rituximab, may cause Type II antibody-mediated cytotoxic hypersensitivity reactions. However, the oncology and some other medical specialty literatures do

not often use this terminology, which is predominantly allergy- and immunology-based. Thrombocytopenia, neutropenia and anemia can occur in some patients treated with mAbs as part of anticancer immunotherapy, but the mechanisms of these potentially serious side effects frequently remain unexplored. Autoimmune forms of thrombocytopenia and hemolytic anemia are Type II hypersensitivities. They are well known complications of lymphoproliferative diseases and occur predominantly in patients with lymphocytic leukemias.[101] For example, late-onset neutropenia, especially after rituximab treatment, has been examined in a growing number of reports but with each of the 3 cytopenias seen during mAb therapy, it is frequently unclear whether or not the depletion of cell numbers is due to an immunological mechanism, i.e., whether it represents a true Type II hypersensitivity response. Likewise, Type III hypersensitivities such as serum sickness-like reactions and vasculitis are also known to occur in response to mAbs, but their frequency and extent during cancer immunotherapy is likely to be underestimated. Some pulmonary events, including mAb-induced lung diseases, are hypersensitivity reactions that result from interaction of the drug with the immune system and involve drug-specific antibodies or T cells. The possible involvement of mAbs in each of these drug-induced Type II and Type III reactions is discussed below.

mAb-induced thrombocytopenia

Compared with the incidence of thrombocytopenia in patients given chemotherapy, grade 3/4 thrombocytopenia to rituximab monotherapy is seen in only 1.7% of patients[102] and this figure is barely increased when the mAb is combined with chemotherapy. Cattaneo et al.[103] reported an incidence of 10.4% in 72 patients affected by non Hodgkin's lymphoma (NHL) and given a total of 317 ritiximab infusions. Transient severe acute thrombocytopenia after rituximab in one patient with hairy cell leukemia and another with mantle cell lymphoma was reversible in a few days following withdrawal of the antibody, but the underlying mechanism remained unclear. While acknowledging that the expression of CD20 (the target of rituximab) on platelets and rituximab-dependent immune-mediated lysis might have contributed to this event, the authors pointed out that in their and other cases, there was a massive bone marrow involvement of neoplastic B lymphocytes.[104] From the study of a case of thrombocytopenia induced by rituximab and a review of the literature, Ram et al.[46] failed to detect the presence of rituximab-dependent antibodies and found that the levels of IL-1 and IL-6 were not increased but those of complement were. They concluded that mAb-induced transient thrombocytopenia might be associated with a CRS and is probably mediated by complement activation. A severe case of potentially life-threatening thrombocytopenia and at least 2 other cases induced by the HER2-targeted mAb trastuzumab have been reported.[61,105,106] About 3% of patients given alemtuzumab for early multiple sclerosis developed potentially fatal thrombocytopenia[107,108] and this mAb was shown to provoke lymphopenia, neutropenia and thrombocytopenia in 5 of 11 patients with peripheral T-cell lymphoproliferative disorders.[109] In this setting, lymphopenia may be due to the direct targeting of CD52 on lymphocytes. Bevacizumab (which targets VEGF) has been associated with arterial thromboembolism[110] and it may facilitate venous thromboembolic events.[111]

mAb-induced neutropenia

Rituximab is associated with both early and late neutropenia and it seems these are caused by different mechanisms. In early studies in the 1990s, grade 3/4 neutropenia was reported in 4.2% of patients given rituximab.[102] It is now known that late onset neutropenia (LON), that is neutropenia occurring at least 4 weeks after administration of the mAb, has a comparatively higher incidence, with 8 different studies revealing figures of from 4% to 27.3%.[112] Some claim the prevalence of this reaction is underestimated.[103] While the mechanisms underlying LON are poorly understood, results suggest that direct cytotoxicity is unlikely[47] (as CD20 is not expressed on granulocytes and progenitor cells) and currently no single explanation has universal support. Immune-mediated mechanisms have been advanced for rituximab-induced LON, including the production of autoantibodies[113] and the expansion of large populations of granular lymphocytes leading to triggering of neutrophil apoptosis upon the activation of Fas and other interactions.[114-116] Dunleavy et al.[112] have proposed an interference with the neutrophil emigration from the bone marrow driven by stromal-derived factor-1 (SDF-1), a chemokine required for the development of early B-cell and granulocyte precursors in the bone marrow, while Terrier et al.[117] believe there is hematopoietic lineage competition due to excessive B-cell activating factor (BAFF)-induced B-cell recovery over granulopoiesis.

mAb-induced hemolytic anemia

Severe anemia has been reported in 1.1% of patients on rituximab monotherapy,[102] but one study showed an incidence of 5.2%.[103] Some notable studies report the development of severe autoimmune hemolytic anemia (AIHA) in a patient with a lymphoproliferative disorder,[118] as well as cases of intravascular hemolysis[119] and multiorgan ischemia due to an autoimmune anti-Pr cold agglutinin.[120] Besides rituximab, alemtuzumab has been shown to provoke pure red cell aplasia and AIHA,[121,122] exacerbate pre-existing AIHA[123] and been involved in the death of a patient due to refractory AIHA.[124] Bevacizumab has been implicated in cases of renal thrombotic microangiopathy.[125,126]

mAb-induced vasculitis

Hypersensitivity vasculitis induced by drugs is a manifestation of a Type III response. Drug-induced vasculitis (DIV) usually occurs in the skin and sometimes in subcutaneous tissue, kidneys, and the lungs. Cutaneous vasculitis (CV), a small vessel systemic vasculitis manifesting as palpable purpura, ranges in severity from benign and self-limiting to life-threatening with multiorgan failure. The mechanisms underlying DIV are still incompletely understood but cellular as well as humoral immune processes appear to be involved. Although CV associated with the TNFα inhibitor infliximab in the treatment of arthritis is well known,[127] this condition is rarely seen following mAb-based cancer therapy. Rituximab-induced vasculitis is the subject of a number of reports[128,129] including a case of CV induced by a first infusion in a patient with B-cell chronic lymphoid leukemia (CLL) confirmed by histological samples that displayed the typical features of small vessel leukocytoclastic vasculitis. No

expression of CD20 was detected on blood vessel walls, making a specific interaction of the mAb with vessel walls unlikely.[49] Although the number of cases is still relatively small, it seems that vasculitis may be associated with cases of CLL.

mAb-induced serum sickness-like reactions

Serum sickness, a classical Type III hypersensitivity reaction due to protein antigen-antibody complexes, occurs as a response to foreign antigens such as antitoxins, antivenins, and vaccines. Although non-protein antigens generally do not provoke the response, some drugs induce a reaction that is clinically similar.[8] Symptoms, which typically appear 6–21 d after drug administration, include lymphadenopathy and fever. Cutaneous symptoms, often urticarial and morbilliform eruptions and sometimes erythema and petechiae, occur in up to 95% of patients. Angioedema, arthritis, arthralgia, and gastrointestinal symptoms are common, joints may be severely affected and splenomegaly, hepatomegaly, peripheral neuropathies, pericarditis, and encephalomyelitis are seen. Chimeric mAbs have the potential to induce serum sickness and this has in fact occurred, the first such example being a reaction to rituximab reported in 2001.[130] Recently, it has been claimed that rituximab-induced serum sickness-like reactions occur in 1–20% of patients,[48] more commonly in patients with autoimmune diseases (particularly autoimmune thrombocytopenia) and marked hypergammaglobulinemia, and it has been proposed that these two conditions are predisposing factors for the development of the reactions.[131,132]

Autoimmune diseases

Autoimmune diseases caused by mAbs are rare but one mAb used for cancer therapy, namely, ipilimumab (targeting CTLA4) has been shown to operate as an immunostimulatory agent by CTLA4 blockade and increased T-cell stimulation[133,134] to produce an autoimmune enterocolitis and/or a range of other adverse reactions including rash and hepatitis.[135]

Pulmonary adverse events caused by mAbs

Pulmonary adverse events caused by mAbs comprise a heterogeneous group of lung diseases often classified under the title drug-induced lung diseases (DILD). Since the mechanisms underlying such lung injuries have generally not been worked out, any classification on the basis of pathogenesis is difficult. Adverse events can be grouped into 4 main categories: interstitial pneumonitis and fibrosis; acute respiratory distress syndrome (ARDS), bronchiolitis obliterans organizing pneumonia (BOOP), and hypersensitivity reactions; although, a range of different classifications may be seen in the literature. Reports of hypersensitivity pneumonitis, a combined Type III and IV hypersensitivity reaction in a T_H1/T_H17 response,[136] are increasing, particularly upon the administration of antineoplastic drugs. **Table 4** lists the mAbs used for cancer therapy that are the main offenders in provoking pulmonary adverse reactions, and shows the different individual adverse reactions induced by each mAb. Once again, rituximab is the most implicated mAb, inducing a heterogeneous spectrum of lung disorders[44,50,137-146] In 2003, the reported rate of possible drug-induced lung injury was < 0.03% from > 540,000 exposed patients.[138,147] BOOP is the most common clinical diagnosis of rituximab-induced lung disease, followed by interstitial pneumonitis, ARDS and hypersensitivity pneumonitis.[137] In a review of 45 cases of lung disease ascribed to this mAb, 3 groups of patients were identified on the basis of the time of onset of the reactions.[50] The most common group exhibited acute/subacute hypoxemic organizing pneumonia starting 2 weeks after the last infusion (i.e., early onset); ARDS occurred within a few hours usually after the first infusion; and organizing pneumonia developed long after rituximab therapy. Based on a number of factors including the recurrence and increasing severity of symptoms with the number of infusions administered, the responsiveness to steroid therapy, rash, eosinophilia, and the occurrence of lymphocytes in bronchoalveolar lavage (BAL) fluid, the authors suggested that early onset organizing pneumonia reflects a hypersensitivity reaction to the chimeric antibody. While late onset organizing pneumonia was thought to be either related to mAb toxicity or to immune system restoration, the commencement of ARDS symptoms within a few hours of infusion suggested either a CRS or a TLS, with no relationship to hypersensitivity. The pathogenesis of rituximab-induced interstitial lung disease remains largely unknown but complement activation and cytokine secretion, particularly of pro-inflammatory TNFα, may be involved.[148] ARDS reported after a single infusion of rituximab has also been associated with release of pro-inflammatory cytokines.[146] A case of fatal intra-alveolar hemorrhage with appearances of hypersensitivity pneumonia (including elevated eosinophil count and serum IgE levels) has been reported upon rituximab administration. The authors of this report suggested

Table 4. Pulmonary adverse events caused by monoclonal antibodies (mAbs) used in the treatment of cancers[a]

mAb	Pulmonary adverse events
Cetuximab	Interstitial pneumonitis
Rituximab	ARDS BOOP Bronchospasm Diffuse alveolar hemorrhage Hypersensitivity pneumonitis Interstitial pneumonitis
Alemtuzumab	Bronchospasm Diffuse alveolar hemorrhage Pulmonary infections (e.g., TB, aspergillosis)
Bevacizumab	Bronchospasm/anaphylaxis Pulmonary hemorrhage from site of tumor
Trastuzumab	ARDS BOOP Dyspnea Interstitial pneumonitis Pleural effusions Pulmonary infiltrates/fibrosis/edema
Panitumumab[b]	Interstitial lung disease[b] Lung infiltrates Pneumonitis Pulmonary fibrosis

[a]Data from ref. 44 [b]Discontinue panitumumab in patients developing interstitial lung disease.[69] ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans organizing pneumonia

that the pathogenesis of such reactions may be due to activation of cytotoxic T lymphocytes, resulting in vascular and alveolar damage, persistent cytokine release and a possible cross-reaction between lung and tumor antigens.[149]

Delayed-type (Type IV) hypersensitivity reactions to mAbs

Unlike Type I, II, and III hypersensitivities that are mediated by antibodies, Type IV reactions depend upon antigen-specific $T_H1/T_H2/T_H17$ lymphocytes and effector mechanisms involving the activation of cytotoxic lymphocytes, macrophages, and eosinophils. Type IV cutaneous reactions to drugs generally become apparent 7–21 d after exposure, with reactions reaching a maximum after 24–72 h. Subsequent reactions may develop only within 1 or 2 d. Sensitivity to the provoking antigen can be transferred by lymphoid cells.[5,8] Examples of drug-induced Type IV cutaneous reactions are allergic contact dermatitis, maculopapular exanthema, psoriasis, acute generalized exanthematous pustulosis (AGEP), fixed drug eruption (FDE), drug reaction with eosinophilia and systemic symptoms (DRESS), SJS, TEN, and erythema multiforme (EM). These different reactions are associated with different T-cell subsets, each of which secrete a particular, yet not mutually exclusive, profile of cytokines and chemokines.[8,150] Type IV cutaneous hypersensitivity reactions induced by mAbs used in cancer therapy are rare, with reports seemingly confined mainly to ibrutumomab, brentuximab, and rituximab (**Table 3**). Cases of dermatitis induced by some of the other mAbs, including catumaxomab, tositumomab, bevacizumab, denosumab, ipilimumab, and panitumumab, may in fact be true Type IV responses as the underlying mechanisms have rarely been investigated (see below). The incidence of serious mucocutaneous reactions in 125,000 patients given rituximab between 1997 and 2001 was estimated to be 0.0008%, which is lower than the expected incidence of such reactions in lymphoma patients.[90] In fact, cutaneous side effects to rituximab that are not usually serious, are fairly often seen, and generally occur 1 to 13 weeks after drug withdrawal. However, SJS, TEN lichenoid dermatitis, vesiculobullous dermatitis, and paraneoplastic pemphigus in response to this agent have been reported.[90,151,152] It has been suggested that the rarely occurring SJS may be associated with cases of follicular NHL.[131]

Target-related mucocutaneous reactions to mAbs

Examples of such reactions which are not genuine hypersensitivities (i.e., not immune-mediated) include adverse reactions provoked by administration of agents that bind EGFR. As with tyrosine kinase inhibitors such as gefitinib and erlotinib, cetuximab and panitumumab commonly cause a moderate to severe, dose-dependent so-called "acneiform" or papulopustular eruption in 50–100% of patients.[153] Such reactions are more severe and widespread with EGFR-targeting mAbs than with small EGFR inhibitors. In the main, the eruption is confined to seborrheic regions, namely, the face, scalp, neck, shoulders, and upper trunk. EGFR is expressed in the epidermis, sebaceous glands, and hair follicles, where it is thought to have an important function in maintaining the health of the epithelium. Although the mechanism of EGFR-targeted mAb-induced skin rash is incompletely understood, it is speculated that inhibition of EGFR causes alterations and rupture of the epithelial barrier, allowing for bacterial access and proliferation, and ultimately the characteristic rash.[153,154] In addition to the papulopustular rash, other less frequent adverse effects include xerosis, palmar-plantar rash, pruritus, talangiectasia, fissures, nail changes (e.g., paronychia), hair changes (e.g., trichomegaly, alopecia), hyperkeratosis, mucositis, pyrogenic granuloma, and hyperpigmentation of the skin.[154,155]

Cardiac adverse events

Cardiac adverse events have occurred with at least 4 of the mAbs approved for cancer therapy. Cardiopulmonary arrest and/or sudden death resulted in ~2% (4) of 208 patients given cetuximab and exposed to radiation therapy. No reactions were seen in 212 patients given radiation alone.[41] Cardiac arrhythmias have been reported for rituximab,[45] cardiomyopathy following trastuzumab,[60] and left ventricular dysfunction (LVD) for pertuzumab, trastuzumab, and trastuzumab emtansine.[58,60,62] Decreases in left ventricular ejection fraction (LVEF) may occur with drugs that block HER2 (ErbB2) activity such as pertuzumab and trastuzumab and it appears that pertuzumab-treated patients given anthracyclines or radiotherapy to the chest may be at higher risk of decreased LVD. Patients receiving trastuzumab alone or in combination therapy show a 4–6-fold increase in the incidence of myocardial dysfunction and again, the incidence is highest when the mAb is administered in combination with an anthracycline. Animal models have been developed to investigate the mechanism of trastuzumab-induced cardiac dysfunction.[18,156] Mice with cardiac-specific deletion of ERBB2 develop cardiomyopathy and sensitivity to anthracyclines with age[157] and trastuzumab has been found to inhibit neuregulin 1 (NRG1), a growth factor necessary for cardiac development and maintenance of heart structure and integrity.[18,158]

Tumor lysis syndrome

TLS occur 48–72 h after the start of anticancer chemotherapy as a result of the rapid, drug-mediated death of large numbers of malignant cells. This results in hyperkalemia, hypercalcemia, hyperphosphatemia, and hyperuricemia, a profound ionic imbalance and a possible progression to acute renal failure, cardiac arrhythmias, seizures, and death.[159] TLS, unlike CRS, is not difficult to distinguish from type I immediate hypersensitivity reactions. TLS is seen most often in patients with leukemias and high-grade lymphomas and, apart from small-cell cancer and neuroblastoma, only rarely in association with solid tumors. The syndrome is well known after brentuximab vedotin and rituximab (incidence ~0.1–0.15%), especially in patients with high tumor load, but the reaction elicited by rituximab is somewhat an atypical TLS and it remains incompletely characterized.[90]

Progressive multifocal leukoencephalopathy

PML is a progressive, usually fatal viral disease that in some respects resembles multiple sclerosis, as the myelin sheath of nerve cells is ultimately destroyed affecting transmission of nerve impulses.[160] It occurs in severely immunodeficient individuals, e.g., in transplant patients on immunosuppressants or AIDS patients, but it is also occasionally seen upon the administration of mAb directed to B cells, in particular, brentuximab, rituximab, and ofatumumab. The infective agent implicated, the so-called JC virus, is a member of *Polyomaviridae* that persists

asymptomatically in about one third of the population. In 2009, 57 cases of PML after rituximab therapy in HIV-negative patients were reported.[161] Earlier, the labeling of the mAb had been amended to indicate the risk of infections, including infections with JC virus.

Need for Systematic Testing to Accurately Identify True Hypersensitivity Reactions to Monoclonal Antibodies

True hypersensitivity reactions have an immunological basis, be it humoral and/or cell-mediated,[5,8] but the mechanisms of an adverse event are not always clearly established before calling it a hypersensitivity response. The scientific literature, clinical trials reports, information provided by drug companies, package inserts, and several other sources of information are replete with examples of such an etymological misuse. There are a number of reasons for this situation. First, a widely accepted definition of a hypersensitivity reaction is lacking and confusion is generated even within its "home" disciplines of immunology and allergy.[162] Moreover, the sheer range and variety of possible drug-induced reactions include cytopenias, vascular disorders, liver injury, lung diseases, and many mucocutaneous reactions, de facto making it difficult to reach a definitive classification. Skin prick and intradermal testing can often, but not always,[8] be used to detect immediate Type I and delayed Type IV reactions to drugs, and results obtained with antigens such as proteinaceous mAbs should be reliable if the tests are properly performed.[8] True Type I reactions are mediated by IgE antibodies and immunoassays to detect IgE specific for individual mAbs are not difficult to devise and develop. Patch testing is both a screening test for hypersensitivity and a provocation test in the skin[8] and can be used to investigate delayed cutaneous reactions.

Systemic reactions

Drug-induced thrombocytopenia, neutropenia, and anemia may be the result of an immune-mediated or cytotoxic mechanism, while liver and lung injuries can show multiple and varied manifestations that appear to be the result of either an immune or non-immune mechanism. This difficulty in assessing and sorting out the signs and symptoms of ADRs is compounded by the absence of well-established clinical and laboratory markers and appropriate tests. Distinguishing between drug-induced thrombocytopenia, neutropenia, and anemia that is either an immune-based suppression of hematopoietic cell lines or a dose-dependent bone marrow cytotoxicity is not always easy, especially in the case of chemotherapeutics, which are often taken as part of combinatorial regimens and for which the marrow suppression of megakaryocytopoiesis is a well-recognized side effect. Although some in vitro tests that detect platelet-reactive serum antibodies are available to aid the diagnosis of drug-induced thrombocytopenia,[163,164] the tests are not standardized and sometimes involve technical difficulties (e.g., related to drug solubility and to metabolic conversion). In addition, the facts that tests are sometimes available only in a few reference laboratories and results are not immediately available in urgent situations are major drawbacks. Likewise, although some anti-neutrophil antibody tests are used to help in the diagnosis of immune-mediated neutropenia and agranulocytosis,[73,74,165] these assays are not widely available, technical difficulties can be limiting (for instance, Fc receptors on neutrophils can lead to false-positive results) and findings may not always be easy to interpret. At first sight, the tests for drug-induced anemias are not as big a problem, but sorting out the different mechanisms involved, including (but not limited to) IgG/IgM to drug-cell membrane complex, complement activation, and the presence of autoantibodies that may be drug-dependent or independent and may react either in the presence or absence of the drug, is often a challenging task.[75] For drug-induced vasculitis there are no markers that can be confidently used to distinguish the condition from other vasculitis,[166] and making a confident diagnosis of immune-mediated drug-induced liver injury (DILI) remains difficult, again due to the absence of reliable specific tests.[77] The situation with DILD is similar: as in vivo drug provocation tests are judged too risky and lymphocyte transformation tests have been applied but appeared to be inadequate,[167] high resolution CT scanning, pulmonary function testing, and bronchoscopy with BAL are often relied upon along with the patient's drug exposure history and cause exclusion.[168,169]

Mucocutaneous reactions

Type IV hypersensitivity reactions of the skin and mucous membranes seen during and after mAb administration such as contact dermatitis, maculopapular rash, AGEP, and lichenoid rash can be investigated by patch testing but this test appears to be less useful for SJS, TEN, and DRESS, for which the timing of the evaluation is important. ELISPOT cytokine assays for the detection of drug-reactive T cells, tests for cutaneous lymphocyte-associated antigen (CLA) as well as the monitoring of the skin-associated chemokine (C-C motif) ligand 27 (CCL27) and its interaction with chemokine (C-C motif) receptor 10 (CCR10) are other promising diagnostic approaches.[8] Methods to identify the mechanisms of some drug-induced site-specific toxicities are not as obvious. This applies to reactions involving the mouth, digestive tract, scalp, hands, feet, nails, and hair, often manifesting as inflammation and ulceration of mucous membranes, rashes, skin fissures, xerosis, some photosensitivities, nail dystrophies, pigmentary changes, pruritus, etc. At least some of these responses are in need of close investigation to establish whether or not any immune processes are involved during any stage of the reaction. This is particularly relevant for targeted therapies such as EGFR inhibitors that are associated with poorly characterized adverse reactions of mucous membranes, skin, nails, and hair.[79-81]

Concluding Remarks: Do Some Hypersensitivity Responses to Monoclonal Antibodies go Unrecognized?

Recently, adverse events with emphasis on hypersensitivity responses to 44 non-targeted and 33 targeted, 'small' anti-neoplastic drugs (i.e., excluding mAbs) have been reviewed.[170] Together with the 'small' targeted chemotherapy drugs, mAbs have revolutionized the treatment of cancers. Besides their

antineoplastic effects, these agents are associated with less adverse reactions than conventional chemotherapy,[8,170] and the mAbs tend to be better tolerated. Nevertheless, a wide spectrum of adverse events to mAbs is observed, necessitating efforts to minimize side effects and to identify, describe and manage the reactions. In any assessment of the side effects of a drug, the possibility of hypersensitivity reactions is always considered and reference to the appearance or absence of such responses is commonly found in clinical trial reports, information released by regulatory agencies and pharmaceutical companies, toxicological investigations and the immunology, pharmacology, and oncology literatures. Although "hypersensitivity" is widely used across a number of disciplines, there appears to be no common agreement on the definition of this term, as demonstrated by the sometimes different features of responses called hypersensitivities. Even though existing testing procedures to precisely identify true drug-induced Type I, II, III, and IV hypersensitivities are frequently inadequate, the systematic and more widespread application of the tests that are available would undoubtedly improve the discrimination of many hematological, vascular, lung, liver, and cutaneous adverse events, leading to an improved analysis of many reactions as well as to an accurate identification of those with an immunological/allergic basis. Further research is needed to refine and standardize existing tests, make them widely accessible and to develop new and improved procedures for the elucidation of mechanisms and accurate diagnosis. This area of chemotherapy has been neglected, especially by immunologists and allergists, such that the true nature of many adverse events remain imprecisely defined. Nowhere is this more apparent than with those drug-induced reactions that are now sometimes incorrectly called hypersensitivities or mistakenly classified as being non-hypersensitivity responses.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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