In this chapter, some of the most important small molecule, non-targeted anticancer drugs in current use, and the adverse/hypersensitivity reactions they elicit, are discussed. A number of these drugs have been used for many years. They generally show little target specificity and display an indiscriminate cytostatic or cytotoxic action on healthy as well as rapidly dividing tumor cells.

At the end of June 2019, the A to Z list of cancer drugs listed by the National Cancer Institute numbered more than 500. In a 2017 analysis based on mechanism of action of 150 anticancer drugs approved by the US Food and Drug Administration (FDA), 61 were classified as cytotoxic and 89 as targeted drugs. In recent years, targeted agents have been increasing at a faster rate although cytotoxic drugs are used to treat more cancer types. For many years, cytotoxic compounds have often been the front line of cancer chemotherapy. Their antineoplastic actions depend on the destruction of rapidly dividing cancer cells via cytotoxic mechanisms or by causing the cells to undergo apoptosis. However, these drugs generally also harm normal rapidly dividing cells such as those in the gastrointestinal tract, bone marrow, and hair follicles causing well-known side effects like mucositis, stomatitis, myelosuppression, and alopecia. This absence of targeted specificity contrasts with the preferred current strategy of selectively killing a particular type of cancer cell.

15.1 Non-targeted Drugs and Their Mechanisms of Action

Cytotoxic drugs used for cancer therapy have a number of different mechanisms of action. They represent a wide range of chemical structures including alkylating agents, antimetabolites, cytoskeletal disruptors, and drugs that directly affect DNA or protein synthesis. These are all agents with relatively broad, rather than targeted and specific, modes of action such as the anticancer agents which are the subject of Chap. 14. Drugs like busulfan, nitrogen mustards, the platinum-based agent cisplatin, gemcitabine, the taxanes and \textit{Vinca} alkaloids, actinomycin D, pyrimidine analogs including 5-fluouracil, and pemetrexed are typical examples of non-targeted drugs that contrast with drugs developed from current strategies based on a more refined understanding of individual cancers and a research focus on selected molecular targets for specific types of cancers. Classification of cytotoxic anticancer drugs is often imprecise and confusing. It may be based on chemical structure (e.g., alkyl sulfonates, anthracyclines, diterpines, organo-platinum agents), mechanisms of action, broad pharmacological categories (e.g., antibiotics, hormones), plant origin (taxanes, \textit{Vinca} alkaloids), or where drugs act in the cell cycle (S, M, G1, or G2 phase). These dissimilar primary classifications may be mixed rather than a division based on a single criterion, for example, a
primary classification based on mechanism of action and chemical structure rather than mechanism alone. Of course, any classification based on a single-shared factor/property will not always be straightforward. For example, many drugs show more than one mechanism of action, and chemical structures, even within one group, can be quite diverse (e.g., alkylating agents). The classification used here for the small molecule non-targeted antineoplastic drugs is based on what is currently known of each drug’s mechanism(s) of action.

Table 15.1 summarizes a large list of non-targeted chemotherapeutic drugs classified on the

| Drug generic and trade names and classification based on mechanism | Cancer indications | Mechanism(s) of action | Hypersensitivity/adverse reactions |
|---------------------------------------------------------------|-------------------|------------------------|----------------------------------|
| **Alkylating agents**                                         |                   |                        |                                  |
| Alkyl sulfonates                                             |                   |                        |                                  |
| Busulfan (Myleran®, Busulfex®)                               | CML. May be given prior to bone marrow/ stem cell transplantation | Alkylation producing guanine-adenine cross-links | Myelosuppression; seizures; hvod; bpd; cd; ct; ef; nausea; stomatitis; vomiting; anorexia; diarrhea; fever |
| Nitrogen mustards                                            |                   |                        |                                  |
| Chlorambucil (Leukeran®)                                     | CLL; NHL; WM      | Alkylation of guanine at N-7 and cross-linking of DNA | Fever; thrombocytopenia; anemia; neutropenia; iha; interstitial pneumonitis; GI; hepatotoxicity |
| Cyclophosphamide (Cytoxan®, Endoxan®, Neosar®)               | Lymphomas; brain; leukemia | Alkylation of guanine at N-7 and cross-linking of DNA | Anaphylaxis; pulmonary toxicity; bms; GI; hemorrhagic cystitis; hvod; ef; cardiac toxicity; utrt |
| Ifosfamide (Ifex®)                                           | Breast; brain; bone; cervical; lung; ovarian; lymphomas | Alkylation and cross-linking of DNA | Bronchospasm; myelosuppression; thrombocytopenia; encephalopathy; nephrotoxicity; GI |
| Mechlorethamine (Mustargen®)                                 | CML; CLL; CTCL; HL; NHL; brain | Alkylation of guanine at N-7 and cross-linking of DNA | Anaphylaxis; lymphocytopenia; GI |
| Melphalan (Alkeran®)                                         | MM; ovarian       | Alkylation of guanine at N-7 and cross-linking of DNA | Anaphylaxis; interstitial pneumonitis; pulm fibrosis; bms |
| Nitrosoureas                                                 |                   |                        |                                  |
| Carmustine (BiCNU®)                                         | Brain; MM; lymphomas | Alkylates DNA and RNA and cross-links DNA | Thrombocytopenia; leukopenia; anemia; pulm fibrosis infiltrates; GI |

Table 15.1 Classification of non-targeted chemotherapeutic drugs used for cancers and their hypersensitivity/adverse reactions
| Drug generic and trade names and classification\(^a\) based on mechanism | Cancer indications | Mechanism(s)\(^a\) of action | Hypersensitivity\(^b\)/adverse\(^c\) reactions |
|---|---|---|---|
| Streptozocine\(^e\) (Zanosar\(^®\)) | Brain; HL; islet cells pancreas\(^f\) | Transported into pancreas β-cells via glucose transporter GLUT2. Damages DNA and activates poly ADP-ribosylation | Renal toxicity; fever; pulmonary fibrosis; bms |
| | | | Urticaria; isr; alopecia; stomatitis |
| Triazines | | | |
| Dacarbazine (DTIC-Dome\(^®\)) | Malignant melanoma\(^g\); HL; sarcoma; islet cells pancreas; neuroblastoma | 3 hypotheses: forms carbonium ions that attack DNA; acts as purine analog and inhibits DNA and RNA synth.; interacts with SH groups | Anaphylaxis\(^h\); fever; hyper eosinophilia; allergic hepatitis\(^i\); bms; GI |
| | | | Rash; photosensitivity; isr; urticaria |
| Temozolomide (Temodal\(®\), Temodal\(®\)) | Brain; melanoma | Alkylates DNA at N-7 or O-6 of guanine | Anaphylaxis; fever; peripheral edema; pneumonitis; GI; thrombocytopenia; neutropenia |
| | | | Rash; pruritus; photosensitivity; acral erythema; urticaria; pigm; mpr; sj; ten; alopecia |
| Ethylenimines | | | |
| Altretamine (Hexalen\(®\)) | Ovarian | N-demethylation gives intermediates (e.g., formaldehyde and iminium species) that react with and damage DNA | Thrombocytopenia; anemia; leukopenia; sensory neuropathy; CNS symptoms |
| | | | Rash and alopecia rare; itching |
| ThioTEPA (Thioplex\(®\)) | Ovarian; breast; CNS; bladder; leukemia; MM | Ethyline cross-links DNA\(^i\) | Fever; anaphylaxis; wheeze; bms; thrombocytopenia; anemia; leukopenia; GI |
| | | | Rash; urticaria; angioedema; pruritus; pigm; isr; alopecia; dermatitis |
| Antimetabolites | Pyrimidine\(^j\) analogs | | |
| Capecitabine (Xeloda\(®\)) | Colorectal; pancreatic; metastatic breast; stomach | Prodrug converted to 5-fluorouracil (see below) | Lymphopenia; thrombocytopenia; neutropenia; anemia; CV symptoms; GI |
| | | | Acral erythema; erythema; exfoliative. Dermatitis; ppk; stomatitis; photosensitivity; hyper pigm; rrr; arak |
| Cytarabine (Cytosar-U\(®, Tarabine PFS\(®, AraC®\)) | AML; NHL; ALL | Cytosine arabinoside similar to deoxycytosine – Competitively incorporated into DNA | Anaphylaxis; thrombocytopenia; leucopenia; fever; dyspnea; ards; GI; hepatotoxicity; bleeding |
| | | | Urticaria; angioedema; acral erythema; pruritus; ten; vascul; agep; neh; mpr\(^k\) |
| 5′-Fluorouracil (Efudex\(®, Adrucil®\)) | Colorectal; breast; pancreatic | Inhibition of thymidylate synthase | Anaphylaxis; myelosuppression; GI; mucositis |
| | | | Acral erythema; mp; pigm; photosensitivity; stomatitis; contact dermatitis; isr; alopecia\(^l\) |

(continued)
| Drug generic and trade names and classification based on mechanism | Cancer indications | Mechanism(s) of action | Hypersensitivity/adverse reactions |
|---------------------------------------------------------------|-------------------|-------------------------|----------------------------------|
| **Gemcitabine** (*Gemzar®*) | NSCL; pancreatic; breast; ovarian; bladder | Nucleoside analog – Replaces cytidine during DNA replication | Fever; hypersens pneumonitis; flu-like symptoms; GI; leukopenia; neutropenia; anemia; thrombocytopenia |
| **Purines** | | | |
| Cladribine (*Litak®, Movectro®*) | HSL; pediatric AML | Inhibits adenosine deaminase and processing of DNA | Fever; DIIHAm; increased risk virus (e.g., herpes) infection; fall in blood count; periph neuropathy; GI; tls; ild |
| Fludarabine (*Fludara®*) | CLL; AML; NHL | Inhibits ribonucleotide reductase and DNA polymerase | Lymphopenia; DIIHAm; thrombocytopenia; neutropenia; aha; GI; ards |
| 6-Mercaptopurine (*Purinethol®*) | ALL; pediatric NHL | Inhibits purine nucleotide synthesis and metabolism | Myelosuppression – toxic to bone marrow; pancreatitis; fever; GI |
| Pentostatin® (*Nipent®*) | HSL; CLL | Inhibits adenosine deaminase and processing of DNA | Anaphylaxis; fever; flushing⁹; GI; leukopenia; thrombocytopenia; anemia |
| **Folate antagonists** | | | |
| Methotrexate® (formerly Amethopterin) (*Trexall®*) | Breast; head; neck; lung; bladder; leukemia; lymphoma | Inhibits dihydrofolate reductase | Anaphylaxis; bronchospasm; pulm infiltrates; hemolytic anemia; Agranulocytosis; myelosuppression; hepatotoxicity; GI⁹ |
| Pemetrexed (*Alimta®*) | NSCL; mesothelioma | Inhibits enzymes in purine and pyrimidine synthesis | Neutropenia; thrombocytopenia; anemia; interstitial pneumonitis; dyspnea; GI; mucositis |
| **Mitotic inhibitors** | | | |
| Taxanes | | | |
| Docetaxel (*Taxotere®*) | Breast; NSCL; ovarian; prostate | Binds to microtubules and inhibits mitotic cell division | Anemia; neutropenia; leukopenia; bronchospasm; dyspnea; back pain; GI |

**Table 15.1** (continued)
| Drug generic and trade names and classificationa based on mechanism | Cancer indications | Mechanism(s)b of action | Hypersensitivity/b/adversec reactions | Systemic | Cutaneous |
|---|---|---|---|---|---|
| Paclitaxel *(Abraxane®, Taxol®)* | Lung; breast; ovarian; head and neck; bladder; testicular; Kaposi's | Binds to β-tubulin subunits; suppresses microtubule function; blocks mitosis | Neutropenia; bms; hypersens pneumonitis; dyspnea; back pain; GI; neurotoxa | | | Acral erythema; isr; erythema multiforme; rrr; agep-like; sjia; alopeciaa |
| Vinca alkaloids | (a) Vinblastine (b) Vincristine (c) Vindesine (d) Vinorelbine *(Velban®, Oncovin®, Eldisine®, Navelbine®)* | (a) HL; NSCL; head and neck; NHL; breast. (b) HL; WT; leukemia. (c) Melanoma; lung; breast; leukemia. (d) Breast; bone; NSCL | Binds to tubulin, prevents spindle formation and cell division | Anaphylaxis; fever; bronchospasm; arf; pulm edema; pleural effusion; interstitial pneumonitisa | | Acral erythema; rash; phlebitis; cellulitis; stomatitis; nail lesions; alopecia; Raynaud’s phenomenon |
| Drugs that interact with or otherwise directly affect DNAa | | | | | |
| Hydroxyurea *(Hydrea®, Droxia®)* | CML; myeloproliferative disorders | Prevents reduction of ribonucleotides to deoxyribonucleotidesa | Fever; hypersens pneumonitis; bms; GI | | | Cutaneous-mucosal oral and leg ulcers; acral erythema; hyper pigm; keratoderma; keratosis; stomatitis; dermatomyositis-like; xerosis; lichen-planus-like; nail alterations; alopeciaa |
| DNA cross-linkers | | | | | |
| Carboplatin *(Paraplatin®, Paraplatin-AQ®)* | Ovarian; lung; breast; head and neck; testicular; brain (children) | Cross-links DNA following formation of an aqua ligand (cl displaced by H2O) which binds to bases, preferably guanine | Anaphylaxis; bms; GI; bronchospasm; dyspnea; periph neuropathy | Rash; pruritus; urticaria; angioedema; erythema; edema |
| Cisplatin *(Platinol®)* | Sarcomas; ovarian; lymphomas; lung; germ cell | As for carboplatin | Anaphylaxis; bronchospasm; dyspnea; hemolytic anemia; Sens neuropathy; GI; renal toxicity | Flushing; rash; urticaria; pruritus |
| Oxaliplatin *(Eloxatin®)* | Colorectala; ovarian; gastric | As for carboplatin | Anaphylaxis; fever; dyspnea; wheezing; Sens neuropathy; GI; types II and III hypersensitivitya | Flushing; erythema; urticaria; angioedema; pruritus; rash; acral erythema; rra |
| Mitomycin C (Mitomycin®, Mitozytrex®) | Oesophageal; bladder; breast; stomach; pancreas | Cross-links DNA by two N-alkylations of guanosine nucleoside. Specific for 5′-CpG-3′. Inhibition of thioredoxin reductase | Bone marrow toxicity; ild; eosinophilic cystitis; hux | Cellulitisa; acd; icd; dermatitis of hands, feet and/or genitals | |
Table 15.1 (continued)

| Drug generic and trade names and classification<sup>a</sup> based on mechanism | Cancer indications | Mechanism(s)<sup>b</sup> of action | Hypersensitivity<sup>h</sup>/adverse<sup>c</sup> reactions |
|---|---|---|---|
| Cross-linkers of opposite DNA strands |
| Pyrrolobenzodiazepine dimers (e.g., SJG-136, NSC 694501)<sup>c</sup> | Ovarian<sup>aa</sup> | In minor groove of DNA, the two imines react with and link N-2 positions on guanines on opposite DNA strands | Thrombocytopenia; vls (edema, dyspnea, hypoalbuminemia, pleural effusion, ascites); dlt |
| Topoisomerase inhibitors |
| Topotecan<sup>(Hycamtin®)</sup> | Ovarian; cervical; SCL. | Stabilizes topo-I complexes inhibiting re-ligation of single strand breaks and leading to lethal double-strand breaks | Alveolar damage; bms; cop; GI |
| Ironotecan<sup>(Camptosar®)</sup> | Colon | Prodrug. Metabolite (SN-38) inhibits topo-I leading to DNA breaks | Anaphylaxis; neutropenia; anemia; dyspnea |
| Topoisomerase II inhibitors |
| Daunorubicin<sup>(Cerubidine®)</sup> | AML; ALL; neuroblastoma | Intercalates between base pairs in DNA helix (see below). Inhibits topo-II and prevents ligation of nucleotide strand after double strand breaks | Anaphylaxis; bms; fever; cardiac tox; GI |
| Doxorubicin<sup>(Doxil®)</sup> | HL; hematological; ovarian; breast; lung; bladder; Kaposi’s | As for daunorubicin | Anaphylaxis; myelosuppression; bronchospasm; hir; cardiotoxicity; GI |
| Etoposide<sup>(Etopophos®)</sup> | SCL; germ cell; Kaposi’s and ES | Inhibits topo-II and ligation of cleaved DNA leading to single and double stranded DNA breaks | Myelosuppression; fever; hypotension; tachycardia; bronchospasm; dyspnea; GI |
| Teniposide<sup>(Vumon®, Vehem®)</sup> | ALL | Complexes with topo-II and DNA causing single and double-stranded breaks in DNA and inhibition of strand re-ligation | Hypotension; bms; fever; bronchospasm; wheeze; intravascular hemolysis<sup>ad</sup>; GI |
| Mitoxantrone<sup>(Novantrone®)</sup> | Breast; AML; NHL; ALL | Intercalates with DNA and inhibits topo-II disrupting DNA repair and synthesis | Anaphylaxis; myelosuppression; GI; CV effects |

<sup>a</sup> Off-label uses (e.g., to lower P53 levels to allow cancer cell proliferation) |
<sup>b</sup> Topoisomerase I inhibitors |
<sup>c</sup> Topoisomerase II inhibitors |
<sup>d</sup> CV effects: cardiovascular effects |
<sup>e</sup> Stomatitis: inflammation of the mouth lining |
<sup>f</sup> Rash: a persistent erythematous eruption on the skin |
<sup>g</sup> Urticaria: an itchy, raised rash often caused by an immune reaction to an allergen |
<sup>h</sup> Angioedema: a swelling of the skin and underlying tissue caused by a reaction to histamine |
<sup>i</sup> Hyperpigment: darkening of the skin |
<sup>j</sup> Myelosuppression: reduction in the numbers of blood cells |
<sup>k</sup> CV: cardiovascular |
<sup>l</sup> GI: gastrointestinal |
<sup>m</sup> Bms: bone marrow suppression |
<sup>n</sup> Dlt: diffuse lung toxicity |
<sup>o</sup> Hid: hypomagnesaemia |
<sup>p</sup> Uror: urinary tract infection |
<sup>q</sup> Acral: affecting the skin of the fingers |
<sup>r</sup> Angio: angiography |
<sup>s</sup> Urtic: urticaria |
<sup>t</sup> Fris: facial swelling |
<sup>u</sup> Hypert: hypertension |
<sup>v</sup> NEF: nephrotic syndrome |
<sup>w</sup> Asma: asthma |
<sup>x</sup> Adema: oedema |
<sup>y</sup> Pruritus: itching |
<sup>z</sup> Rheumat: rheumatoid arthritis |
<sup>aa</sup> Ovarian: ovarian cancer |
<sup>ab</sup> Dlt: diffuse lung toxicity |
| Drug generic and trade names and classification based on mechanism | Cancer indications | Mechanism(s) of action | Hypersensitivity/ adverse reactions |
|---|---|---|---|
| **Intercalation with DNA** | | | |
| Actinomycin D<sup>ae</sup> (*Cosmegen®*) | WT; ES; testicular; trophoblastic | Intercalates between adjacent base pairs of DNA; prevents elongation of RNA by RNA polymerase; stabilizes complexes of topo-I and topo-II with DNA | Leukopenia; anaemia; GI; hepatotox | Rash; isr; stomatitis; rrr; alopecia; photosensitivity |
| **Daunorubicin** | AML; ALL; neuroblastoma | Intercalates between base pairs in DNA helix preventing DNA replication and protein synthesis. See also topoisomerase II inhibitors (above) | Anaphylaxis; bms; fever; cardiac tox; GI | Rash; urticaria; angioedema; hyper pigm |
| **Doxorubicin** | HL; hematological; ovarian; breast; lung; bladder; Kaposi’s | Intercalates between base pairs in DNA helix preventing DNA replication and protein synthesis. See also topoisomerase II inhibitors (above) | Anaphylaxis; myelosuppression; bronchospasm; hir; cardiotoxicity; GI | Rash; acral erythema; isr; pruritus; urticaria; angioedema; neh; rrr |
| **Inducers of DNA breaks** | | | |
| Bleomycin<sup>af</sup> (*Blenoxane®*) | HL; NHL; SCC; testicular; squamous cell | Causes breaks in DNA by unresolved mechanism (? Chelates metal ions producing superoxide and hydroxide radicals; blocks uptake of thymidine by DNA). Mediates oxidative degradation of cellular RNA. | Hypotension; interstitial pneumonitis; pulmonary fibrosis; fever<sup>ag</sup> | Rash; pruritus; angioedema; scleroderma-like; Raynaud’s syndrome; sjs; alopecia; erythema; hyper pigm |
| **Inhibitors of DNA methylation** | | | |
| Azacitidine<sup>a</sup> (*Vidaza®*) | MDS; AML | Inhibition of DNA methyltransferase which prevents DNA synthesis; cytotoxic to abnormal hematopoietic cells in bone marrow via incorporation into DNA and RNA | Thrombocytopenia; bms; anemia; neutropenia; GI; pyrexia; peripheral edema; dyspnea; cough; anaphylaxis | Rash; isr; ecchymoses; xerosis; petechiae; erythema; urticaria; pruritus; Sweet’s syndrome |
Table 15.1 (continued)

| Drug generic and trade names and classification based on mechanism | Cancer indications | Mechanism(s) of action | Hypersensitivity/adverse reactions |
|---|---|---|---|
| **Inhibitors of DNA repair** | | | |
| PARP inhibitors, e.g., Olaparib (Lynparza®) | Breast, ovarian | Block repair of DNA single strand breaks (ssb); trap PARPs 1 and 2 at damaged DNA sites – Trapped DNA-PARP complexes more cytotoxic than unrepaired ssb | MDS/AML; pneumonitis; neutropenia; leukopenia; anemia; fatigue; nausea; resp. tract infections; eft |
| | | | Urticaria; erythematous rash |
| **Disruption of protein synthesis** | | | |
| L-Asparaginase (Elspar®) | ALL; AML | Hydrolyses L-asparagine to L-aspartic acid and NH₃. Some leukemia cells cannot synthesize L-asparagine resulting in inhibition of protein synthesis | Anaphylaxis; laryngospasm; bms (transient); GI; pancreatitis |
| | | | Urticaria; angioedema; rash; pruritus; stomatitis; ten |
| **Miscellaneous group** | | | |
| Lenalidomide (Revlimid®) | MM; MDS | Multiple actions: Inhibits proliferation and apoptosis of tumor cells; activates immune T and NK cells; induces cytokine production; anti-angiogenic properties | Thrombocytopenia; anemia; neutropenia; hypersens pneumonitis; thrombosis; pulm embolism; hepatotoxicity; GI; respiratory effects |
| | | | Rash (morbilliform, urticarial, dermatitic, acniform); pruritus; sjs; xerosis; erythema; ecchymosis; erythema multiforme |

From Baldo BA, Pham NH. Adverse reactions to targeted and non-targeted chemotherapeutic drugs with emphasis on hypersensitivity responses and the invasive metastatic switch. Cancer Metastasis Rev. 2013;32:723–76. Adapted and reproduced with permission from Springer + Business Media

_acd_ allergic contact dermatitis, _agep_ acute generalized exanthematous pustulosis, _ALL_ acute lymphocytic leukemia, _AML_ acute myeloid leukemia, _arak_ inflammatory response in actinic keratosis, _ards_ acute (adult) respiratory distress syndrome, _arf_ acute respiratory failure, _bms_ bone marrow suppression, _bpd_ bronchopulmonary dysplasia, _cd_ cellular dysplasia, _cle_ cutaneous lupus erythematosus, _CLL_ chronic lymphocytic leukemia, _CML_ chronic myeloid leukemia, _cop_ cryptogenic organizing pneumonia, _ct_ cardiac tamponade, _CTCL_ cutaneous T cell lymphoma, _didf_ drug-induced disease flare (tumor flare effect), _DJIIHA_ drug-induced immune hemolytic anemia, _dls_ delayed liver toxicity, _dress_ drug reaction (rash) with eosinophilia and systemic symptoms, _eft_ embryo-fetal toxicity, _eld_ eosinophilic lung disease, _Ewing’s sarcoma, GI_ gastrointestinal symptoms, e.g., one or more of nausea, vomiting, diarrhea, constipation, appetite reduction, dyspepsia etc., _hir_ hypersensitivity infusion reaction, _HL_ Hodgkin’s lymphoma, _HCL_ hairy cell leukemia, _hus_ hemolytic uremic syndrome, _icd_ irritant contact dermatitis, _iba_ immune hemolytic anemia, _ild_ interstitial lung disease, _isr_ injection site reaction, _MDS_ myelodysplastic syndrome, _MM_ multiple myeloma, _mpr_ maculopapular rash, _neh_ neutrophilic eccrine hidradenitis, _NHL_ non-Hodgkin lymphoma, _NSCL_ non-small cell lung cancer, _pigm_ pigmentation, _PARP_ poly ADP-ribose polymerase, _ppk_ palmar-plantar keratoderma, _rpm_ relapsing polychondritis cutaneous symptoms, _rrr_ radiation recall reaction (dermatitis), _SCC_ squamous cell carcinoma, _SCL_ small cell lung cancer, _sjs_ Steven’s-Johnson syndrome, _ten_ toxic epidermal necrolysis, _utr_ urinary tract and renal toxicity, _vls_ vascular leak syndrome, _WT_ Wilms’ tumor

Some drugs exert their action(s) by more than one mechanism and might therefore be classified into more than one category. The classification shown is deemed to be the most appropriate one.

Reactions known or suspected of having an immunological basis

Reactions such as weakness, fatigue, headache, etc. and symptoms like nausea, vomiting, diarrhea, constipation, appetite suppression, etc. are not listed since they are common to so many of the drugs. Where a latter symptom(s) (i.e., nausea, etc.) is important, it is referred to as “GI.”

Allergic reactions ~ 1%
basis of their mechanisms of action. Some of these drugs are still frequently used, while others are used only occasionally and/or to some extent. Alkylating agents that damage DNA such as nitrogen mustards (e.g., chlorambucil and cyclophosphamide), alkyl sulfonates (busulfan), nitrosoureas (carmustine), triazines (dacarbazine), and ethylenimines (altretamine) do so by attaching an alkyl group to the guanine base of DNA. Antimetabolites, still one of the most widely used cytostatic/cytotoxic drugs in cancer therapy, form a large group made up of pyrimidine analogs (e.g., 5-fluorouracil), nucleoside analogs (gemcitabine), and anti-folates (methotrexate). Mitotic inhibitors, the taxanes docetaxel and paclitaxel, inhibit cell division by binding to microtubules. A small number of drugs, in particular, L-asparaginase, affect leukemic cells by disrupting protein synthesis. Some of the earliest antineoplastic drugs were alkylating agents that act by damaging DNA. At least eight different groups of non-targeted antineoplastic agents interact with, inhibit, or damage DNA by different mechanisms. These are made up of a chemically diverse variety of drugs that can be grouped as inhibitors of DNA synthesis such as hydroxyurea; a number of structurally different compounds (organoplatinum agents, the antibiotic mitomycin C, and pyrrolobenzodiazepines) that cross-link DNA; topoisomerase I and topoisomerase II inhibitors (e.g., topotecan and doxorubicin, respectively); drugs such as the antibiotics actinomycin D and daunorubicin that intercalate between DNA base pairs; inhibitors of
DNA methylation (azacitidine); bleomycin which induces breaks in DNA; and inhibitors of the poly ADP ribose polymerase (PARP) family of enzymes that are critical in the maintenance of DNA integrity and repair. PARP inhibitors appear to trap PARP1 and PARP2 enzymes at damaged DNA sites. These trapped enzyme-DNA complexes block DNA replication and are highly toxic to cells. It has been suggested that PARP inhibitors should be assessed on their potency to trap PARP as well as on their capacities to inhibit the enzymes.

As summarized in Table 15.1, some drugs exert their antineoplastic activity by more than one mechanism. Platinum drugs, for example, cross-link DNA and are sometimes classified as “alkylating-like” since they interact with the N-7 position of guanine (like a true alkylating agent) and the anthracycline antibiotics daunorubicin (daunomycin) and doxorubicin (adriamycin) show both topoisomerase II inhibitory activity and also intercalate between base pairs in the DNA helix thus preventing DNA replication and protein synthesis. Lenalidomide (Table 15.1), related to the teratogenic drug thalidomide, has a number of different activities suggesting its application to a range of hematological and solid tumors.

### 15.2 Hypersensitivities and Adverse Events to Non-targeted Antineoplastic Drugs

Drugs used to treat the many different cancers cause a wide variety of adverse events ranging from the relatively minor such as headache; nausea; mild gastrointestinal symptoms; cough; transient rash and itching to severe cytopenias; lung, liver, cardiac, and neural toxicities; a number of reactions of the skin and mucous membranes; and rarely life-threatening anaphylaxis and bullous toxiceremias. From information obtained from the published medical/scientific literature, research studies, and FDA and pharmaceutical company data, Table 15.1 summarizes the most important systemic and cutaneous adverse reactions with these drugs. Hypersensitivities occur with most cancer drugs but are more of a problem with some than others, for example, drugs with high potential to provoke hypersensitivity reactions are platinum compounds, taxane mitotic inhibitors, the epipodophyllotoxins etoposide and teniposide, L-asparaginase, and procarbazine. Those with low potential for causing hypersensitivities include the anthracyclines with their dual mechanism of action, and drugs only occasionally implicated include the nitrogen mustard cyclophosphamide and the folate antagonist, methotrexate (Tables 15.1 and 15.2). Identification of risk factors for the development of hypersensitivity to a drug is important, but, apart from a history of previous exposure in the case of platinum drugs and intravenous administration of L-asparaginase, specific risks for most other cytotoxic anticancer drugs have not been identified.

Some drug reactions that are classified as, or at first sight appear to be, “allergic” do not fit easily into the four Gell and Coombs categories (Chap. 2, Sect. 2.1). Such reactions, sometimes seen with, for example, NSAIDS and contrast media (Chaps. 9 and 10), include alopecia, fol-

| Drugs with high potential | Drugs with low potential | Drugs with occasional potential |
|---------------------------|-------------------------|--------------------------------|
| L-Asparaginase (Escherichia coli-derived, Erwinia-derived, pegasparginase) | Anthracyclines (daunorubicin doxorubicin, epirubicin, mitoxantrone, idarubicin, valrubicin) | Bleomycin |
| Platinum compounds (carboplatin, cisplatin, oxaliplatin) | Mercaptopurine | Cyclophosphamide |
| Taxanes (paclitaxel, docetaxel) | Azathioprine | Vincristine |
| Epipodophyllotoxins (etoposide, teniposide) | | Methotrexate |
| Procarbazine | | Mitomycin C |

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liculitis, and hyperpigmentation. It has been said that so-called idiosyncratic drug reactions most often manifest as cutaneous reactions and hemat- and hepatotoxicities. Antimetabolites such as capecitabine, gemcitabine, and 5-fluorouracil commonly provoke acral erythema (palmar-plantar erythrodysesthesia; hand-foot syndrome) (Fig. 15.1), and, in common with cyclophosphamide and doxorubicin, hyperpigmentation may occur. Mitotic inhibitors, the tax-
anes, and Vinca alkaloids often produce alopecia and nail abnormalities, and radiation recall reactions are seen (Table 15.1, Fig. 15.2). Cytotoxic chemotherapy typically suppresses hematopoiesis causing thrombocytopenia, neutropenia, and anemia, and drug-induced hepatotoxicity is a well-known cause of liver injury. Although these conditions can be instigated by drugs via an immune mechanism (Sects. 15.2.2 and 15.2.3), underlying mechanisms frequently remain unexplored. Incidences of adverse reactions to different cytotoxic drugs are variable, with drugs such as chlorambucil fairly well tolerated; reactions are uncommon with the anthracyclines (daunorubicin 1–2%, doxorubicin 0.6–3%) and relatively high for paclitaxel (10–16%), pemetrexed (14%), L-asparaginase (up to 43%), and the platinum agents (5–27%). For cisplatin and oxaliplatin, onset of adverse symptoms occur after repeated exposure (seven to nine courses for oxaliplatin); for carboplatin, reaction incidences are only ~1% after less than six courses but up to 27% after more than seven courses.

True hypersensitivities are reactions with a humoral and/or cellular immune basis, but many reactions are sometimes incorrectly described as “hypersensitivities,” while other true hypersensitivities go unrecognized (Chap. 1, Sects. 1.2.4 and 1.2.5). Although the term “hypersensitivity” is widely used in immunology and allergy, a common definition of the term is frequently lacking across the disciplines; the word is often applied to reactions which clearly have no immune basis or when the underlying mechanism has not been established. Table 15.3 shows examples of drugs involved in each of the four types of hypersensitivity reactions. Involvement of non-targeted cytotoxic antineoplastic drugs in each of the hypersensitivity states will now be considered.

Table 15.3 Immunopathogenetic mechanisms of hypersensitivity reactions

| Type of HSR | Immunopathogenetic mechanism | Symptoms | Example |
|-------------|------------------------------|----------|---------|
| I           | IgE-mediated                 | Urticaria, angioedema, bronchospasm, anaphylaxis | L-asparaginase platinum salts? |
| II          | Cytolytic antibodies (IgG or IgM) | Hemolytic anemia | Oxaliplatin |
| III         | Antigen-antibody immune complex | Vasculitis | Methotrexate |
| IV          | Cell-mediated sensitized T lymphocytes | Contact dermatitis | Anthracyclines |

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HSR hypersensitivity reaction
15.2.1 Type I Hypersensitivity Responses to Non-targeted Antineoplastic Drugs

Given the number and diversity of cytotoxic drugs used for cancer therapy, good clear-cut demonstrations with diagnostic evidence of immediate type I allergic reactions are few. Among the cytotoxics, L-asparaginase, the platinum salts (Sect. 15.5.2), and methotrexate are well-known to provoke such reactions with positive skin tests and anaphylactic-like reactions, all supporting a type I hypersensitivity mechanism. Positive oxaliplatin and carboplatin skin tests show a sensitivity of 75–100%. L-Asparaginase induces a high incidence of type I allergic reactions including serious anaphylaxis in ~10% of treated patients. Apart from these drugs, however, there have been no clear and unequivocal demonstrations of the existence of drug-specific IgE antibodies to the cytotoxic antineoplastic drugs. Aside from L-asparaginase, the platinum salts, and methotrexate, “anaphylaxis” has also been reported for procarbazine; the alkylating agents cyclophosphamide, melphalan, mechlorethamine, dacarbazine, temozolomide, and thioTEPA; antimetabolites cytarabine and 5-fluorouracil; the Vinca alkaloid mitotic inhibitors; topoisomerase inhibitors irinotecan, daunorubicin, doxorubicin, and mitoxantrone; the purine pentostatin; and azacitidine. Many type I hypersensitivity drug reactions do occur on first exposure (see examples Chaps. 6, 7, and 12), so such reactions that resemble type I responses cannot be immediately dismissed as not true immediate, IgE-mediated responses. The more acute severe reactions probably are mediated by drug-specific IgE antibodies. Anaphylactoid reactions may occur during the first infusion. Examples include some reactions to 5-fluorouracil and the topoisomerase II inhibitors teniposide and etoposide that induce erythema, chills, fever, tachycardia, hypotension, and urticaria/angioedema in up to 10% of patients, often during the first infusion. Most mild reactions seem to be determined by other mechanisms such as direct degranulation of mast cells, direct activation of basophils, or activation of the complement cascade.

15.2.2 Type II Hypersensitivity Responses to Non-targeted Antineoplastic Drugs

Antineoplastic drugs may cause a number of type II antibody-mediated cytotoxic hypersensitivity reactions (Chap. 2, Sect. 2.1 and Chap. 3, Sect. 3.11), but such reactions are often not referred to in these terms in the oncology and other medical specialty literatures. Type II hypersensitivities are antibody (IgG or IgM)-mediated allergic reactions against cellular antigens (or basement membrane) leading to cell damage, lysis, or loss of function via antibody-dependent cell-mediated cytotoxicity, complement activation, or receptor interaction (as in Graves’ disease).

15.2.2.1 Drug-Induced Thrombocytopenia

The normal adult platelet count of ~150–400 × 10^3/μl drops to ~50 × 10^3/μl when patients experience thrombocytopenia. With drug-induced thrombocytopenia (DIT) (Chap. 2, Sect. 2.3.2 and Chap. 3, Sect. 3.11.2), the condition is invariably severe at counts around 20 × 10^3/μl. Many antineoplastic drugs such as alkylating agents, mitotic inhibitors, and antimetabolites cause a dose-dependent bone marrow suppression of platelets and other hematopoietic cell lines, but some cells, including platelets, can be affected by drug-induced type II hypersensitivity reactions. Of the two main categories of DIT, marrow suppression induced by drugs or immune processes, it is the latter that causes the more severe reactions. The time course of each is generally different. Non-immune marrow suppression is usually slow, often developing over weeks. For immune DIT, it is of the order of 1 to 2 weeks, although, depending on the patient, the delay may only be a few hours. An interesting new mechanism involving splenic sequestration of platelets during oxaliplatin-induced liver damage has recently been identified in some cases of oxaliplatin-related thrombocytopenia.

Data on 75,243 chemotherapy regimens of associated anemia and thrombocytopenia contained in medical records of 47,159 US patients undergoing chemotherapy for solid
tumors showed the prevalence of thrombocytopenia ranged from 21.9% in patients treated with taxane-based regimens to 64.2% in the gemcitabine-based treatment groups. During the same time, from 46.4% to 59% of the patients developed anemia. In a similar retrospective hospital-based cohort study of 614 patients receiving 1 of 37 different regimens, the overall frequency of thrombocytopenia was 21.8%. The highest frequencies were seen in patients receiving carboplatin (81.8%) and combination therapies that included carboplatin (58.2%), gemcitabine (64.4%) or paclitaxel (59.3%). The highest relative risks of thrombocytopenia were for combination therapies of carboplatin/gemcitabine and carboplatin/paclitaxel/etoposide.

The capacities of the older antineoplastic drugs to induce dose-dependent thrombocytopenia are well-known – those that do not lead to platelet reduction, or do so only weakly, include L-asparaginase, bleomycin, cisplatin, flutamide, goserelin, luteinid, megestrol, streptozocin, tamoxifen, and vincristine; drugs causing moderate thrombocytopenia include actinomycin D, cyclophosphamide, 5-fluorouracil, 6-mercaptopurine, methotrexate, and procarbazine; and drugs that induce the condition in severe form include busulfan, chlorambucil, cytosine arabinoside, melphalan, nitrogen mustard, nitisoreua compounds, and vinblastine.

Immune-mediated, drug-dependent destruction of platelets may occur via a number of different mechanisms: production of a new antigen after covalent binding of drug to platelet membrane glycoprotein; binding of drug to the platelet GPIIb/IIIa complex inducing a conformational change and a new antigenic determinant; non-covalent binding to platelet membrane glycoprotein forming a drug-glycoprotein complex that reacts with antibody; binding of the Fab fragment of the chimeric human-mouse monoclonal antibody abciximab to the platelet glycoprotein receptor GPIIb/IIIa followed by subsequent recognition by antibody; production of drug-induced autoantibody that reacts with the platelet surface glycoprotein; and heparin-induced thrombocytopenia whereby heparins react with platelet factor 4 producing antibody-reactive antigen immune complexes bound to the platelet Fc receptor and subsequent platelet activation. Besides the mAbs rituximab and trastuzumab (Chap. 14, Sect. 14.2.1) used for cancer therapy, numerous cases of DIT involving oxaliplatin, fludarabine, irinotecan, actinomycin D, cyclophosphamide, pentostatin, and suramin have been shown to occur. Evan’s syndrome (acute thrombocytopenia with hemolysis) to oxaliplatin has also been described. Early onset following previous drug exposure and the detection of antibodies and complement on erythrocytes indicated a type II hypersensitivity reaction.

15.2.2.2 Drug-Induced Neutropenia

Neutropenia is the most common adverse response induced by anticancer drugs. Febrile neutropenia is an important dose-limiting effect of chemotherapy. Mild, moderate, and severe neutropenia are said to be present when the absolute neutrophil counts are 1000–1500, 500–1000, and less than 500 cells/μl, respectively. Drug-induced neutropenia (DIN), probably the most frequent cause of neutropenia, is a potentially serious and life-threatening event and poorly understood. It is caused by decreased production or increased destruction of neutrophils. Chemotherapeutic drugs are a frequent cause of decreased production of neutrophils by suppression of bone marrow myeloid progenitor cells. Two main types of DIN are recognized. One is a dose-related toxicity interfering with cell replication and caused by a number of different drugs including cytotoxic antineoplastic drugs. The other is not dose-related, more often seen in women, older, and allergic patients, thought to be immunologic in origin and mediated by drug-dependent, or drug-independent, antibodies but lacking compelling evidence for the underlying mechanism(s). Within the first of these two groups is a relatively rare (incidence 2.4–15.4 cases/million), potentially fatal disorder, idiosyncratic drug-induced neutropenia, commonly caused by idiosyncratic reactions to nonchemotherapy drugs such as metamizole, clozapine, sulfasalazine, amoxicillin, and cotrimoxazole.

All patients undergoing cancer chemotherapy, but particularly those with hematologic
malignancies, are at risk of neutropenic complications. Antineoplastic drugs well-known for their association with neutropenia include busulfan, carboplatin, cisplatin, cyclophosphamide, doxorubicin, etoposide, melphalan, methotrexate, paclitaxel, and vinorelbine. Some combined treatments tend to be less toxic than others, for example, cyclophosphamide-5-fluorouracil – methotrexate is less toxic than cyclophosphamide or combined cyclophosphamide-5-fluorouracil – doxorubicin. The highest risk of chemotherapy-induced neutropenia is usually associated with the earliest phases of therapy. For example, in patients with advanced breast cancer treated with docetaxel and doxorubicin, approximately 75% of episodes of febrile neutropenia occurred during the first cycle of therapy. Concurrent with the risk of neutropenia is susceptibility to bacterial and fungal infections. These are commonly seen in the oral cavity and on mucous membranes and present as pharyngitis, oral ulcers, and periodontitis, sometimes together with stomatitis and mucositis. Infections of the gastrointestinal tract, lungs, blood stream, and especially the skin also occur.

The pathogenesis of DIN has been ascribed to immunological mechanisms, but there seems to be little convincing evidence that DIN is a true hypersensitivity reaction for most implicated drugs. Three main humoral mechanisms have been suggested – immune complex formation, hapten recognition, and an autoimmune mechanism – but cellular mechanisms have also been suggested. Immune mechanisms do seem to be involved for some drugs such as penicillins which act as haptens, inducing antibody formation against neutrophils. Other drugs such as clozapine are thought to accelerate apoptosis; others cause complement-mediated destruction of neutrophils, while the antineoplastic alkyl sulfonate, busulfan, has a direct toxic effect on myeloid precursor cells.

15.2.2.3 Drug-Induced Hemolytic Anemia

In the analysis of 75,243 chemotherapy regimens of associated anemia and thrombocytopenia mentioned above (Sect. 15.2.2.1), from 46.4% to 59% of treated patients developed anemia. The well-known immune cytotoxic reaction to penicillin resulting from binding of the drug to red cells, reaction of IgM and IgG antibodies with the drug-cell membrane protein complex, and activation of the classical complement pathway causing cell lysis and death is the prototype drug-induced type II hypersensitivity. Another example of a type II cytotoxic antibody-mediated drug reaction, commonly seen with some cephalosporins, is drug-induced immune hemolytic anemia (DIIHA) (Chap. 2, Sect. 2.3.1 and Chap. 3, Sect. 3.11.1) where the drug appears to form an antigenic complex with the red cell surface. DIIHA can also be associated with red cell autoantibodies without the drug participating in the antigen-antibody reaction. The antineoplastic drug fludarabine is an example of such a drug, and other purine analogs, cladribine and pentostatin, have also caused DIIHA. The platinum drugs cisplatin, carboplatin, and oxaliplatin cause immune-mediated hemolysis with or without associated immune thrombocytopenia. It is not fully understood why some drugs sometimes induce antibodies to red cells and what mechanism(s) is involved, but a possible immune basis for any antineoplastic drug that induces anemia should be kept in mind.

15.2.3 Type III Hypersensitivity Responses to Non-targeted Antineoplastic Drugs

Type III hypersensitivity responses result from tissue damage due to the deposition of immune complexes formed from aggregates of antigen and IgG (mostly) and IgM antibodies and the resulting immune response involving activation of the classical complement pathway (Chap. 2, Sect. 2.4 and Chap. 3, Sect. 3.12). Type III hypersensitivity reactions to chemotherapeutic drugs occur less often than types I, II, or IV reactions, but it seems they also go unrecognized more often. Some examples of these reactions are drug-induced vasculitis, serum sickness, immune complex glomerulonephritis, rheumatoid arthritis, and Arthus reaction.
15.2.3.1 Drug-Induced Hypersensitivity Vasculitis

Drug-induced vasculitis (DIV), also known as leukocytoclastic vasculitis (Chap. 2, Sect. 2.4.1 and Chap. 3, Sect. 3.12.2), usually occurs in the skin and sometimes in subcutaneous tissue, kidneys, and the lungs. The most common clinical symptoms at onset include skin rash, arthralgia, and myalgia. For antineoplastic drugs, small-vessel vasculitis is the most frequently seen form of a type III reaction. Cutaneous vasculitis (CV) is a small-vessel systemic vasculitis manifesting as palpable purpura and ranging in severity from being benign and self-limiting to life-threatening with multiple organ failure. CV seen in malignancy may be drug- or infection-induced or paraneoplastic in origin. Approximately 60% of patients with DIV present with CV. Mechanisms underlying DIV are still incompletely understood, but cellular as well as humoral immune processes appear to be involved. A proportion of small-vessel vasculitis patients have anti-neutrophil cytoplasmic antibodies (ANCA) which are used as a diagnostic marker. In ANCA-positive DIV patients with neutrophil damage, antibodies to myeloperoxidase, cathepsin G, human leukocyte elastase, and lactoferrin may be found. These antibodies can be indicative of severe disease. Because of the presence of the many different autoantibodies and low complement C4 levels, DIV may be confused with lupus. Chemotherapy drugs implicated in a growing list of reports of DIV include aromatase inhibitors (e.g., anastrozole), cyclophosphamide, capecitabine, 5-fluorouracil, cytosine arabinoside, docetaxel/filgrastim, gemcitabine, and the platinum salts oxaliplatin and cisplatin. Figure 15.3 shows palpable purpura in the legs of a patient 12 days after a high-dose cisplatin infusion. A skin biopsy revealed positive results for IgM antibodies and complement component C3, confirming the diagnosis of leukocytoclastic vasculitis. Cisplatin and gemcitabine have also been implicated in cases of large vessel vasculitis.

Paraneoplastic vasculitis, an inflammatory reaction of the vessels induced by malignant cells, represents about 5% of cases of CV. Ninety percent of cases occur in hematological malignancies. Occurring during drug therapy, paraneoplastic vasculitis can be difficult to distinguish from DIV. The reactions appear to be the result of paraproteinemia (usually cryoglobulins), but the pathogenesis is unclear. One suggestion is that immune complexes form with tumor antigens

![Fig 15.3 Cisplatin-induced palpable purpura in the legs of a patient, (a) 13 days after cisplatin infusion, (b) 2 days later, and (c) 21 days after cisplatin infusion. A skin biopsy showed leukoclastic vasculitis with a finding of IgM and complement component C3 detected by immunofluorescence. (Reproduced from Quintanilha JCF, Visacri MB, Amaral LS, et al. Leukoclastic vasculitis complicating cisplatin + radiation treatment for laryngeal cancer: a case report. BMC Cancer. 2017;17:831. https://doi.org/10.1186/s12885-017-3848-6)](https://doi.org/10.1186/s12885-017-3848-6)
leading to release of lymphokines and other vasoactive substances that damage vascular endothelium. Other suggested mechanisms include direct antibody-mediated effects on endothelial cells and direct effects of tumor cells on the vascular wall.

15.2.3.2 Drug-Induced Hypersensitivity Liver Injury

Drug-induced liver injury (DILI) can be divided into intrinsic hepatotoxicity and unpredictable and rare liver injury which in turn can be classified into immune-mediated hypersensitivity and idiosyncratic reactions (Sect. 15.2.5.2). Allergic hepatitis is associated with fever and rash, and when caused by drugs, for example, drug reaction (rash) with eosinophilia and systemic symptoms (DRESS; drug-induced hypersensitivity syndrome), the reaction is generally a type IV hypersensitivity response involving CD4+ cells, CD8+ cytotoxic lymphocytes, and NK, Kupffer, and dendritic cells. Type II hypersensitivities may also sometimes occur. There are currently two main hypotheses for the mechanism of immune-mediated DILI. In perhaps the most supported model, the drug or active metabolite(s) as hapten, is said to bind to endogenous proteins forming immunogenic conjugates that generate antibody- and/or T cell-mediated injury. Another view is that most individuals are tolerant to immune injury of the liver, and reactions occur only when tolerance is in some way overcome.

15.2.3.3 Drug-Induced Hypersensitivity Lung Disease

For drug-induced lung disease (DILD) (Chap. 3, Sect. 3.12.3), chemotherapeutic drugs can be grouped into four main divisions: those producing interstitial pneumonitis and fibrosis, hypersensitivity reaction, acute respiratory distress syndrome (ARDS), and bronchiolitis obliterans organizing pneumonia (BOOP) (see below, Sect. 15.2.5.3). DILD hypersensitivity reactions result from interaction of drug with the immune system. Signs of interstitial pneumonia with lymphocytes and plasma cells infiltrating the interstitial space are seen. Immune-mediated damage to the lung in DILD may be due to drug-specific antibodies or, more usually, drug-specific T cells. Eosinophilic pneumonia showing eosinophils in the peripheral blood and bronchoalveolar lavage (BAL) fluid can be caused by almost any medication. Hypersensitivity pneumonitis is a combined type III and type IV hypersensitivity reaction in a Th1/Th17 response. Reports of drug-induced hypersensitivity pneumonitis are increasing, particularly to antineoplastic drugs. Cytotoxic drugs implicated include bleomycin, methotrexate, procarbazine, temozolomide, and the taxanes docetaxel and paclitaxel. No single diagnostic test is sufficient for a diagnosis, rather a combination of careful history, imaging (e.g., high-resolution computed tomography), examination of BAL fluid (positive signs include lymphocytic alveolitis with an increase in CD8+ lymphocytes), serum drug-specific antibody tests, lung biopsy, and perhaps inhalation challenge and the lymphocyte transformation test (LTT). Corticosteroids appear to hasten resolution of symptoms in both drug-induced hypersensitivity and eosinophilic pneumonia.

The lack of definitive diagnostic tests for suspected chemotherapy-associated hypersensitivities makes it difficult to definitively identify some lung reactions thought to have an immune or hypersensitivity basis, but some reactions do appear to be true hypersensitivity responses. One such example is an acute onset form of bleomycin pneumonitis with fever and peripheral blood and BAL eosinophilia reversed by corticosteroids. Other examples include methotrexate-associated pneumonitis, an acute hypersensitivity reaction with bronchospasm to gemcitabine, procarbazine pneumonitis, and pulmonary infiltrates and interstitial pneumonitis following docetaxel and paclitaxel. Some mitomycin C-treated adenocarcinoma patients with an unusual hemolytic-uremic-like syndrome and pulmonary edema develop ARDS. Circulating immune complexes with antibodies to carcinoembryonic antigen, platelets, and gastric carcinoma cell surface antigens detected in a few of the patients suggest that the syndrome may be initiated by tumor cells or cell products released as a result of chemotherapy.
15.2.3.4 Other Drug-Induced Type III Reactions

Oxaliplatin has been associated with type III immune complex-mediated urticaria; joint pain and proteinuria; idiosyncratic reactions including pulmonary fibrosis; and cytokine release syndrome where it is speculated that the drug may act as a superantigen. A reaction consisting of fever, myalgia, bone pain, conjunctivitis, chest pain, and maculopapular rash induced by cytarabine in patients with non-Hodgkin lymphoma or acute lymphoblastic leukemia and termed cytarabine syndrome has been suggested to be a type III hypersensitivity response on the basis of the detection of immune complexes and successful treatment with corticosteroids. Procarbazine has been said to induce a type III reaction with immune complex deposition “manifesting as a toxic epidermal necrolysis,” a reaction normally considered to be a type IV response. Possible type III hypersensitivity reactions were also the tentative conclusions in each of the following studies: procarbazine-induced interstitial pneumonia with eosinophilia improved by corticosteroid administration; patients with diffuse pulmonary infiltrates, alveolar damage and eosinophilia after receiving gemcitabine; hemolytic anemia and a Henoch-Schönlein-type purpura each associated with immune complexes following mitomycin C administration; and pneumonitis with features of a type III response provoked by methotrexate. A further discussion of possible lung hypersensitivities to chemotherapeutic drugs is set out below under drug-induced lung disease lacking a clearly defined hypersensitivity mechanism (Sect. 15.2.5.3). An unusual example of a possible type III hypersensitivity reaction to a chemotherapeutic drug was demonstrated by bronchial challenge tests on an asthmatic nurse occupationally exposed to mitoxantrone in an oncology ward. The patient responded to the drug with a biphasic reaction and an increase in eosinophils, neutrophils, and lymphocytes 6–18 h post challenge.

15.2.4 Type IV Reactions to Non-targeted Antineoplastic Drugs

Less often seen cutaneous reactions to chemotherapeutic drugs include maculopapular exanthemas, allergic contact dermatitis, psoriasis, acute generalized exanthematous pustulosis (AGEP), DRESS, fixed drug eruptions, erythema multiforme, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). These are now generally considered to be immune-based, delayed type IV hypersensitivities mediated by antigen-specific effector T cells (Chap. 3, Sect. 3.8.1). Type IV reactions generally begin from about 7 to 21 days after contact with the drug, and subsequent reactions may appear only 1 or 2 days after re-exposure. Identification and specificity of the culprit drug is established by oral challenge, patch, and intradermal tests (IDT) (not usually for SJS and TEN) read after a delay of at least 48 h. Investigations are proceeding to relate different T cell subsets and cytokine and chemokine profiles with different skin reactions although cytokine overlap occurs.

The main cytotoxic drugs involved in eliciting delayed skin reactions include alkylating agents, particularly the nitrogen mustards; some antimetabolites, e.g., cytarabine, capecitabine, and gemcitabine; some purines; the folate antagonists methotrexate and pemetrexed; and the taxanes. Examples of different cutaneous reactions listed in Table 15.1 show that erythema multiforme and various forms of dermatitis are the delayed cutaneous hypersensitivities most often seen; erythema multiforme has been reported to occur with the alkylating agents busulfan, chlorambucil, cyclophosphamide, and mechloretamine and also with methotrexate, paclitaxel, and lenalidomide. SJS and/or TEN have been reported following the administration of chlorambucil, cyclophosphamide, mechloretamine, temozolomide, cytarabine, gemcitabine, cladribine, methotrexate, pemetrexed, docetaxel, paclitaxel, bleomycin, L-asparaginase, and lenalidomide. AGEP has been induced by cytarabine and paclitaxel.
15.2.5 Drug-Induced Reactions Lacking a Clear Hypersensitivity Mechanism

Some adverse reactions provoked by chemotherapeutic drugs in the skin, liver, vasculature, and lungs show features of antibody and/or cellular involvement that suggest a possible contribution of types I, II, III, and/or IV hypersensitivity mechanisms, but, for a number of reasons, clear and definitive evidence to establish such classifications one way or the other is still often incomplete. In addition to the lack of research so far, at least part of the problem in defining some of these adverse reactions is due to the lack of a generally accepted definition of hypersensitivity, the frequent absence of tests to identify or discount allergic recognition, and the often vague classifications of reactions without any apparent consideration of the possible involvement of any of the four types of hypersensitivity responses. These factors are discussed further below. Some of the more important drug-induced reactions that show at least some features of true hypersensitivity reactions but which are not routinely included in the Gell and Coombs classification of hypersensitivities will now be considered from both immune and allergological perspectives.

15.2.5.1 Some Drug-Induced Cutaneous Reactions Lacking a Clearly Defined Hypersensitivity Mechanism

As already discussed, cutaneous reactions to antineoplastic drugs are common and may range from mild rashes and urticaria to severe type IV cell-mediated toxidermias such as erythema multiforme, SJS, and TEN. Examples of antibody-mediated cutaneous reactions are seen in drug-induced cutaneous vasculitis, a type III hypersensitivity reaction, and some cases of urticaria are true type I IgE antibody-mediated hypersensitivities. Other cutaneous reactions where a hypersensitivity mechanism is less obvious include site-specific toxicities involving the hair, nails, mouth, hands, and feet, all of which are commonly seen. While the aim of chemotherapy is to kill rapidly growing cancer cells, normal rapidly growing cells in the skin, nails, and hair follicles are also inhibited. It is not surprising therefore that adverse reactions such as alopecia, simple macular rash, xerosis cutis, pruritus, pigmentary changes, and nail dystrophies occur often in patients undergoing cancer chemotherapy. Capecitabine, cyclophosphamide, and doxorubicin may induce hyperpigmentation and focal pigmentation, mainly on fingertips. Platinum agents and Vinca alkaloids are known to be associated with alopecia and Vinca alkaloids and taxanes with dermatitis, radiation recall reactions (Fig. 15.4), nail abnormalities, subacute lupus erythematosus, and ulcerations. Precise mechanisms of most of these reactions remain to be determined.

Apart from the well-known type I, II, III, and IV hypersensitivity reactions, major cutaneous and mucocutaneous reactions associated with chemotherapy include stomatitis and mucositis, acral erythema, cutaneous eruption of lymphocyte recovery, neutrophilic eccrine hidradenitis (Fig. 15.5), eccrine squamous syringometaplasia, extravasation reactions (including chemical cellulitis), inflammation of keratosis, photosensitivity, and radiation-associated (recall and enhancement) reactions. As with the abovementioned list of adverse effects, a full understanding of mechanisms underlying these adverse effects is generally lacking. Cytotoxic chemotherapeutic drugs are the most common cause of stomatitis and mucositis. Although these terms are often used synonymously, stomatitis (oral mucositis) is restricted to the oral mucous membranes, while mucositis affects the GI tract from mouth to anus. Approximately 40% of patients receiving chemotherapy experience stomatitis. The most stomatotoxic agents include alkylating agents busulfan, chlorambucil and cyclophosphamide, antimitabolites cytarabine, 5-fluorouracil and methotrexate, antibiotics bleomycin, actinomycin D, doxorubicin and mitomycin C, Vinca alkaloids, and the
taxanes. Cytotoxic antineoplastic drugs destroy the rapidly dividing cells of the oral mucosa at a faster rate than most other normal healthy cells, but the detailed pathogenetic mechanism of stomatitis is still to be worked out. The pathogenesis of acral erythema is not known, but it may be a direct cytotoxic effect. Some suggested mechanisms to explain the palms-soles location (Fig. 15.1) of reactions are based on vascular anatomy, temperature gradi-
ents, rapidly dividing epidermal cells, and high concentration of eccrine glands. 5-Fluorouracil and particularly its prodrug capecitabine (Fig. 15.6) may provoke acral erythema with erythema and swelling in mild cases or blisters, ulceration, and desquamation in severe form. Cutaneous eruptions of lymphocyte recovery is seen as a sharp, transient rise in temperature accompanied by macular and papular eruptions during the earliest recovery in peripheral lymphocyte numbers following chemotherapy for leukemia. The observed rash is thought to indicate the return of immunocompetent lymphocytes to the circulation suggesting an immune pathogenesis.

Neutrophilic eccrine hidradenitis (NEH) (Fig. 15.5), associated with cytarabine, bleomycin, chlorambucil, cyclophosphamide, mitoxantrone, vincristine, and a number of other cytotoxic anticancer drugs, appears as fever, edema, and skin eruptions such as erythematous macules, papules, plaques, and pustules. Necrosis of eccrine epithelial cells together with neutrophils around eccrine sweat glands and ducts and the presence of drug in the sweat of patients suggest direct toxicity of the sweat glands is the cause of NEH.

Eccrine squamous syringometaplasia is a benign skin eruption not associated with any particular cytotoxic chemotherapeutic drug which occurs predominantly in acral or intertriginous areas presenting as erythematous macules, papules, or patches. The reaction is thought to be a direct cytotoxic effect of the drugs.

Extravasation reactions occur when chemotherapeutic drugs are inadvertently allowed to contact the tissues during their IV administration. Reactions may be irritant or vesicant, the former appearing as phlebitis and an erythematous reaction along the vein or at the intravenous site; urticarial flare reactions exhibited by anthracyclines are an example. A well-known drug-eliciting vesicant reaction (called chemical cellulitis) is the antibiotic mitomycin C.

Several drugs, including hydroxyurea, suramin, cytarabine, and 5-fluorouracil, provoke inflammation in pre-existing skin reactions such as actinic keratoses. A suggested mechanism is increased DNA synthesis and uptake of drug by the affected tissues. Lesions that appear after treatment with hydroxyurea (Fig. 15.7) may grow rapidly and aggressively. The pathogenesis is not yet defined but given that hydroxyurea inhibits DNA synthesis and the drug inhibits DNA repair in UV-exposed keratinocytes, a likely mechanism is interference of cell replication in the basal layers of the epidermis.

15.2.5.2 Drug-Induced Liver Injury

DILI mimics all forms of acute and chronic liver disease and is seen predominantly as hepatitis and/or cholestasis. The mechanism of DILI can be divided into direct, sometimes called intrinsic hepatotoxicity (as seen with, e.g., acetaminophen...
(paracetamol)) and unpredictable and rare liver injury which in turn can be classified into immuno-mediated hypersensitivity (Sect. 15.2.3.2) and idiosyncratic reactions. The latter reactions are only seen in susceptible individuals and may be due to idiosyncratic metabolism producing harmful metabolites. Knowledge of mechanisms underlying idiosyncratic DILI remains limited. Direct hepatotoxicity usually manifests as necrotic reactions with little inflammation, while idiosyncratic reactions show injury with clear inflammation. Antineoplastic drugs associated with an acute hepatitis injury pattern include L-asparaginase, azathioprine, carmustine, cyclophosphamide, 6-mercaptopurine, mithramycin, and vincristine.

In considering DILI based on histological patterns and differential diagnoses, Ramachandran and Kakar have distinguished and classified the involvement of a number of different commonly used chemotherapeutic drugs. In chronic hepatitis lacking autoimmune markers, 5-fluorouracil, its prodrug tegafur, and tamoxifen have been implicated. Progression to fibrosing cholestatic hepatitis was reported in a hepatitis C patient given cyclophosphamide and corticosteroids. In autoimmune hepatitis accompanied by hypersensitivity, rash, eosinophilia, and arthralgia, long-term use of the tetracycline minocycline may lead to autoimmune hepatitis or hepatitis that mimics lupus-related hepatitis. The risk of methotrexate-induced liver toxicity is exacerbated by high dosage, existing liver disease, and heavy alcohol use. The alkylating agent procarbazine, metabolized and activated in the liver, may cause granulomatous hepatitis. Methotrexate, 5-fluorouracil, cisplatin, and tamoxifen have been associated with macrovesicular steatosis, while the topoisomerase I inhibitor irinotecan has a direct effect in steatohepatitis. Such an effect, sometimes referred to as chemotherapy-associated steatohepatitis, has also been reported for oxaliplatin. Oxaliplatin may injure sinusoidal endothelial and hepatic stellate cells; thiopurine chemotherapeutic drugs have been implicated in peliosis hepatitis and dacarbazine in hepatic vein thrombosis presenting clinically as Budd-Chiari syndrome.

### 15.2.5.3 Drug-Induced Lung Diseases

The term drug-induced lung disease covers a heterogeneous group of lung diseases. Patients most likely to develop DILD are those receiving chemotherapy with up to about 10% of such patients experiencing injury although the incidence for individual drugs is different. The antineoplastic drugs most commonly involved in DILD are bleomycin, methotrexate, cyclophosphamide, and busulfan, but many chemically and mechanistically different anticancer agents demonstrate pulmonary toxicity including mitomycin C, chlorambucil, melphalan, 6-mercaptopurine, cytarabine, gemcitabine, fludarabine, carmustine, lomustine, etoposide, the taxanes, irinotecan, procarbazine, vinblastine, zinostatin, and the tyrosine kinase inhibitors imatinib and gefitinib. In general, mechanisms involved in drug-induced lung injuries have not been elucidated making it difficult to effect classifications on the basis of pathogenesis. Chemotherapeutic drugs can be grouped into four main divisions: those producing interstitial pneumonitis and fibrosis, hypersensitivity reactions (see Sect. 15.2.3.3), ARDS, and BOOP. Interstitial pneumonia and fibrosis, often provoked by bleomycin, is an inflammation of the lung interstitium and the most commonly occurring DILD. Other drugs involved include busulfan, chlorambucil, cyclophosphamide, melphalan, methotrex-
ate, and paclitaxel. In ARDS, inflammation of the lungs leads to impaired gas exchange and release of mediators causing further inflammation, hypoxia, and ultimately organ failure. All-trans retinoic acid (ATRA) and mitomycin C are examples of chemotherapeutic drugs causing ARDS. In BOOP, organized polypoid granulation inflammatory tissue is seen in the distal bronchiolar airways, respiratory bronchioles, alveoli, and alveolar ducts. Bleomycin, cyclophosphamide, and methotrexate are common causes.

15.3 Diagnosis of Hypersensitivities to Non-targeted Antineoplastic Drugs

In general, diagnosis of type I hypersensitivities to chemotherapeutic drugs is based on clinical assessment and only sometimes with the aid of skin testing and rarely challenge testing. Specific assays for the detection of chemotherapeutic drug-specific IgE antibodies are usually not available, and, when occasionally used, they are generally not validated. The basophil activation test (BAT) is yet to be systematically investigated, validated, and widely applied for mechanistic studies or diagnosis of many small molecule chemotherapeutic drugs, but it has been applied as a biomarker to assess the safety and effectiveness of rapid drug desensitization in allergic patients sensitive to platinum agents. Increased expression of CD203c and CD63 was seen in 11 of 15 (73%) and 6 of 15 (40%) patients allergic to platinum compounds, respectively. High CD63 expression was associated with severe reactions. Reactions seen during rapid drug desensitization were associated with BAT-positive patients and elevated tryptase levels demonstrating that BAT was identifying patients with an increased risk of reactions during desensitization.

The skin prick test (SPT) and IDT may be used to detect both immediate and delayed reactions to drugs, but these tests have not been widely and routinely applied, being used to diagnose hypersensitivities to only a relatively few drugs including platins (Sect. 15.5.2.), taxanes (Sect. 15.5.1), cyclophosphamide, ifosfamide, cytarabine, 5-fluorouracil, methotrexate, mitomycin C, procarbazine, etoposide, epirubicin, and L-asparaginase. Note, however, apart from the taxanes and platins, the diagnostic and predictive value of results with these drugs remains uncertain. Given the many non-targeted anticancer agents, let alone the ever-expanding range and variety of new targeted drugs, it is obvious that skin testing remains under investigated and under-utilized for diagnosis of drug hypersensitivities in oncology. Patch testing is said to be rarely, if ever, positive and not considered useful (see, however, Sect. 15.3.3).

15.3.1 Testing for Type I Hypersensitivities

Skin testing has been employed more often with the taxanes and platins than any other antineoplastic agent, but, even with these drugs, the procedure is only now becoming more widely used as a routine diagnostic test. Hypersensitivity reactions to the taxanes paclitaxel and docetaxel (Sect. 15.5.1) usually develop during the first and second infusion, suggesting the need for desensitization. For the platinum drugs, hypersensitivity responses take longer, usually after five to seven infusions. Drug-specific IgE antibodies are known for the platinum salts, especially carboplatin and oxaliplatin, so the finding of positive skin tests to these drugs indicates true type I immediate hypersensitivities (Sect. 15.5.2.3). For recommended skin test concentrations of the taxanes and platinum agents and for an expanded discussion of these agents see Sects. 15.5.1 and 15.5.2.3).

15.3.2 Testing for Type II and Type III Hypersensitivities

As discussed above, some skin, liver, vasculature, and lung adverse reactions provoked by chemotherapeutic drugs show features of antibody and/or cellular involvement, suggesting a possible contribution of types I, II, III, and/or IV hypersensitivity mechanisms. However, for a heterogeneous
group of diseases and combination of different, often complex, mechanisms as seen, for example, in drug-induced lung and liver diseases, clear and definitive indications to distinguish reactions with an allergic basis are often difficult to establish for a number of reasons. These include the absence of definitive diagnostic tests for suspected chemotherapy-associated hypersensitivities, the lack of a generally accepted definition of hypersensitivity, and the interpretation of mechanistic data without any apparent consideration of the possible involvement of any of the four types of hypersensitivity responses.

15.3.2.1 Tests for Drug-Induced Thrombocytopenia

As mentioned above in relation to drug-induced thrombocytopenia, anemia, and neutropenia, it is important to distinguish immune-based suppression of hematopoietic cell lines from the dose-dependent bone marrow cytotoxicities shown by many antineoplastic drugs, but this is not always easily done. Since thrombocytopenia in response to chemotherapy is commonly the result of marrow suppression of megakaryocytopoiesis, a well-recognized side effect of antineoplastic drugs, immune-mediated DIT is not always considered in the diagnosis. Diagnosis, even harder if the patient is taking multiple medications, often tends to be based on the temporal relationship between drug administration and symptoms and/or on one-at-a-time drug withdrawal along with examination for a possible rebound in the platelet count. In vitro tests in the form of immunoassays that detect platelet-reactive serum antibodies are available, but while these are an aid in the diagnosis of idiopathic thrombocytopenic purpura and autoimmune DIT, the tests are not standardized, often present technical difficulties (such as poor aqueous solubility of the drug and questions of the involvement of metabolites), and do not generally detect the drug-dependent antibodies. Specific tests in the form of enzyme-linked immunoassays (ELISAs) and cytometric procedures for drug-dependent antibodies in individual patients’ sera are available at a few reference laboratories, but limited access to them and the time taken to obtain the result in an urgent situation are major drawbacks. Also, in some cases, a false-negative finding may result if the patient’s own platelets are not employed in the test. Recommendations for the implementation of platelet autoantibody testing for immune thrombocytopenia have been published.

15.3.2.2 Tests for Drug-Induced Neutropenia and Agranulocytosis

In addition to a complete blood count and differential and manual examinations of peripheral blood smears, anti-neutrophil antibody tests may be utilized to help diagnose immune-mediated neutropenia and agranulocytosis. Anti-neutrophil antibodies to neutrophil glycoproteins are detected by several different immunoassays. The neutrophil antigens involved in immune neutropenia have been given the nomenclature HNA-1a, HNA-1b, and HNA-1c (glycoprotein FcγIIB; CD16), HNA-2a (gp50-64; CD177), HNA-3a (gp70-95), HNA-4a (CD11a), and HNA-5a (CD11b). Immunoassays employed include a granulocyte agglutination test, direct and indirect granulocyte immunofluorescence tests, ELISAs, and, perhaps the most specific of the tests, the monoclonal antibody immobilization of granulocyte antigens (MAIGA) assay. Unfortunately, tests for neutrophil antibodies are not widely performed and available; there are a number of technical difficulties including the detection and distinguishing of autoantibodies and drug-dependent antibodies, Fc receptors on neutrophils can produce false positive results, cells show fragility, aggregate, and lyse, and test results are not always easy to interpret. Taken together, these factors help to explain why ready detection of antibodies to neutrophils, and hence easy diagnosis of cases of immune-mediated drug-induced neutropenia/agranulocytosis, is not necessarily easy and sometimes not achievable.

15.3.2.3 Testing for Drug-Induced Anemia

Tests for drug-induced anemias are not as problematic as those for platelets and neutrophils, but the situation can be more complicated than it appears at first sight. Hemolytic anemia result-
ing from high doses of penicillin is the classical cytotoxic type II hypersensitivity. Binding of drug to erythrocytes causes the cells to be recognized as foreign, resulting in IgM and IgG antibodies reacting with the drug-cell membrane protein complex, activation of the classical complement pathway, cell lysis, and death. DIIHA is another example of a type II cytotoxic antibody-mediated drug reaction. It can be associated with red cell autoantibodies that are drug-independent, that is, detected in vitro without adding drug or with drug-dependent antibodies that only react in vitro in the presence of drug. Some drugs bind covalently to the erythrocyte membrane proteins, antibodies bind to the surface-bound drug and following interaction with macrophages, Fc-mediated destruction of red cells occurs. The mechanism with other drugs remains controversial. Fludarabine is the most common drug causing drug-independent red cell autoantibodies, but other antineoplastic purine analogs, cladribine and pentostatin, and the platinum-based chemotherapeutics have also caused DIIHA. Drugs already in use or newly introduced and not yet known to cause anemia will be implicated in the future. Detailed mechanistic studies of most cases of antineoplastic drug-induced HA are generally not routinely undertaken, so it is possible that interesting and surprising findings may be revealed with some of the many drugs now employed, as the following example serves to illustrate. In a study of 300 chronic lymphocytic leukemia (CLL) patients given fludarabine, cyclophosphamide, and rituximab, 5.8% of patients developed HA, but 82.4% of these patients showed a negative direct antiglobulin test suggesting that the drug combination treatment led to antiglobulin test-negative autoimmune HA.

15.3.2.4 Testing for Drug-Induced Vasculitis

Diagnosis of the type III hypersensitivity DIV can be difficult since there are no clearly well-established clinical or laboratory markers that can distinguish the condition from other vasculitidis. Anemia is common in patients with DIV, pulmonary symptoms may correlate poorly with the disease, and CT scanning of the chest, an ANCA screen (Sect. 15.2.3.1), and tissue biopsy may be necessary to reach a definitive diagnosis. Some patients may also have antibodies to phospholipids and/or histones.

15.3.2.5 Testing for Drug-Induced Liver Injury

As mentioned earlier, most cases of DILI fall into three main patterns which may be used along with histological patterns for differential diagnoses. Individual drugs often tend to have their own pattern signature, that is, characteristic of the drug. Injury features such as rash, eosinophilia, and a rapid response on re-challenge suggest that so-called idiosyncratic cholestatic liver injury is allergic in nature. Accurate diagnosis of DILI, especially immune-mediated DILI, together with identification of the causative drug, remains difficult. Specific tests are not available, and there are no relevant experimental models to confidently establish mechanisms and devise potential diagnostic procedures. Current assessment of DILI is therefore largely dependent on serum concentration of total bilirubin and tests for liver damage, namely, measurements of serum alkaline phosphatase and liver transaminases, alanine transaminase, and aspartate transaminase. For immunological tests, LTT has been used for the detection of T cell proliferation, but the test is not always reliable and not always regarded with confidence if only because of doubts about antigen presentation of different drugs.

15.3.2.6 Testing for Drug-Induced Lung Diseases

Diagnosis of immune-mediated DILD provoked by chemotherapeutic drugs is similar to the situation with DILI. Although both an in vivo and in vitro approach would seem to be applicable, neither is totally satisfactory in practice. As discussed earlier, chemotherapeutic drugs can elicit four main types of lung reactions. High-resolution CT scanning, pulmonary function testing, and bronchoscopy with BAL can be used along with the patient’s history of drug exposure, histological evidence of lung damage, and exclusion of other causes. In CT scans, inter-
stitial pneumonitis and fibrosis (e.g., caused by bleomycin) tend to involve the lower lung zones; hypersensitivity reactions may be seen as ground-glass opacities with centrilobular nodules; bilateral ground-glass opacities involving dependent lung regions may be seen in ARDS; and peribronchial or subpleural areas of consolidation are seen in BOOP. In vitro, the LTT has been quite widely used in the attempted diagnosis of DILD in Japan where it has been said that “compelling data as to the sensitivity and specificity of the (test) is currently lacking.” For methotrexate, the LTT has been shown to be inadequate for confirming DILD. Positive results have been claimed for a leukocyte migration test designed to identify cytokines or chemokines produced by drug-stimulated lymphocytes from patients with methotrexate- or paclitaxel-induced pneumonitis. However, the sample numbers are so far small. In vivo drug provocation testing is generally considered too risky since pulmonary damage may be irreversible and the utility of skin testing with drugs in DILD does not appear to have been carefully and systematically investigated.

### 15.3.3 Testing Cutaneous Reactions

Anticancer drug therapies are associated with multiple and various dermatological effects some of which are clearly immune-mediated, usually type IV hypersensitivities, and others which are less well understood mechanistically. Patch testing with drugs (Chap. 4, Sect. 4.2.4), in either pure or commercial form, is used to determine the cause of drug-induced cutaneous drug reactions and for studying the underlying pathophysiological mechanisms. The test is both a screening test for hypersensitivity and a provocation test in the target organ, the skin, where it can be seen as reproducing the disease. Patch testing is valuable for investigating a number of skin reactions including eczema, contact dermatitis, maculopapular rash, photosensitivity, fixed drug eruption, lichenoid rash, and AGEP. It seems to be less useful for investigating urticaria, SJS, and TEN, but, in any case, it should be used with caution for the bullous toxicidermias. Patch testing with antineoplastic drugs is generally considered to be of no value in diagnosing systemic reactions, and it remains unclear how useful the test is for helping in the diagnosis of chemotherapeutic drug-induced cutaneous reactions. The LTT measures a memory T cell response and may identify a causative drug in cases of drug eruptions, but it is important to perform the test at the right time. The time varies and depends on the reaction – for example, with DRESS, patients should be tested 5–8 weeks after the onset of reactions, while for maculopapular drug eruptions, SJS and TEN, testing should take place within 1 week of skin rashes. Other promising in vitro approaches for diagnosing and studying immune-mediated, in particular type IV, cutaneous reactions to drugs include application of the local lymph node assay for identifying contact allergens; ELISPOT cytokine assays for the detection of drug-reactive T cells; and monitoring cutaneous lymphocyte-associated antigen (CLA) (Chap. 4, Sect. 4.7.3.5) and levels of the skin-associated chemokine CCL27 and its interaction with its receptor CCR10 (Chap. 4, Sect. 4.7.3.4).

### 15.4 Prevention and Management of Hypersensitivity Reactions to Non-targeted Cytotoxic/Cytostatic Drugs

For the prevention of allergic reactions to the cytotoxic/cytostatic drugs used in chemotherapy, three strategies are generally employed: premedication, skin testing, and desensitization (Box 15.1). For premedication, steroids and antihistamines are usually used. With the taxanes (Sect. 15.5.1.1), for example, premedication has reduced the incidence of hypersensitivity reactions to 2–4% of cases. Premedication has been recommended for patients hypersensitive to pegasparaginase but appears to be ineffective in preventing IgE antibody-mediated reactions to the platinum drugs.
Skin tests may be useful to predict reactions between courses of chemotherapy. For example, intradermal testing with carboplatin 30 min before chemotherapy with the drug was about to begin, identified patients who could receive carboplatin safely with a negative predictive value of 98.5%. Skin testing with oxaliplatin has produced the same successful outcome in some patients allergic to the drug (see also Sect. 15.5.2.3).

For cancer patients who experience severe adverse reactions despite premedication, when it is not possible or desirable to replace the preferred drug for treatment, or in patients with a positive skin test to platinum drugs, desensitization usually remains as a potentially successful outcome. Although the mechanism(s) underlying successful drug desensitizations are not well understood, procedures are generally effective for both IgE antibody- and non-antibody-mediated immediate hypersensitivities. Desensitizations are mostly undertaken with the taxanes and platinum drugs (Sects. 15.5.1.2 and 15.5.2.4), and most published protocols involve these agents, but it seems likely that the procedure will also be successful with other cytotoxic/cytostatic drugs used in chemotherapy.

Table 15.4 summarizes the main management procedures after reactions to some of the more commonly used non-targeted chemotherapy drugs. For the alkylating agents, cyclophosphamide, ifosfamide, and procarbazine, and the antimetabolite cytarabine, discontinuation of therapy with the drug is really the only feasible option.

| Drug                  | Management after reactions                          |
|-----------------------|-----------------------------------------------------|
| Platinum compounds    | Desensitization                                     |
| Taxanes               | Premedication with steroids and antihistamines      |
| L-Asparaginase        | Substitution with different preparation. Premedication with steroids or antihistamines. Desensitization |
| Procarbazine          | Discontinue                                         |
| Epipodophyllotoxins   | Premedication with antihistamines                   |
| Anthracyclines        | Slow infusion rate                                  |
| Mercaptopurine, azathioprine | Desensitization                           |
| Methotrexate          | Premedication with steroids or antihistamines. Desensitization |
| Cytarabine            | Discontinue                                         |
| Cyclophosphamide and ifosfamide | Discontinue                           |

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A slow infusion rate may help counter reactions to anthracyclines and epipodophyllotoxins; premedication with steroids and/or antihistamines often allows therapy with taxanes, epipodophyllotoxins, and methotrexate to proceed; and desensitization has proved successful for platinum drugs, anthracyclines, mercaptopurine, azathioprine, and methotrexate. Substitution with a different drug is possible with L-asparaginase although premedication with steroids and antihistamines for sensitivity to this drug has been successful, as has desensitization.

15.5 Taxanes and Platinum Drugs: A Closer Look

Hypersensitivity reactions represent a significant problem with certain non-targeted drugs used for chemotherapy, in particular, the platinum compounds, taxanes, L-asparaginase, epipodophyllotoxins, and procarbazine. Other non-targeted cytostatic/cytotoxic antineoplastic drugs also provoke adverse reactions, some of them hypersensitivities, but they are generally less problematic. The important and much used taxanes and platinum drugs show a high potential to cause hypersensitivity reactions and will be further examined.

15.5.1 Taxanes

Taxanes are diterpenes, and the name taxane is derived from the fact that these compounds were found to be produced by plants of the yew genus Taxus. Two taxanes are used as antineoplastic drugs, paclitaxel, and docetaxel. Paclitaxel is so named because it was originally identified in the bark of the Pacific yew tree. Because of the difficulties involved in their synthesis (paclitaxel, e.g., has 11 chiral centers), natural products remain a source for some taxanes. Docetaxel is a semisynthetic analog of paclitaxel produced from a precursor found in the needles of the European yew tree. It differs from paclitaxel at C-10 and in the phenylpropionate side chain (Fig. 15.8a, b). The taxanes are mitotic inhibitors, disrupting microtubule function, so adverse reactions, including hypersensitivity responses, to these drugs when given as anticancer agents might be expected. In a women’s cancer program retrospective study covering the period 1999–2004, severe hypersensitivity reactions occurred in 16 of 718 patients (2.2%) given paclitaxel and in 9 of 93 patients (9.7%) who received docetaxel. Up to 30% of patients have been found to develop acute infusion reactions to taxanes. Acute hypersensitivity reactions are marked by urticaria, flushing, rashes, dyspnea, gastrointestinal symptoms, hypo- and hypertension, and back pain, the latter not yet well understood. Being mitotic inhibitors,
taxanes also may induce radiation recall reactions, alopecia, and nail abnormalities such as fingertip fissures (Fig. 15.9). Docetaxel and paclitaxel may induce inflammation of actinic keratosis and seborrheic keratosis (Fig. 15.10) thought to result from a direct cytotoxic effect of the drug on abnormal DNA synthesis in actinic keratosis. Taxanes present difficulties in their formulation since they are poorly soluble in aqueous media and their consequent presentation in vehicles such as Cremophor also contribute to adverse reactions. Multiple mechanisms may underlie infusion reactions to taxanes. Reactions may be IgE antibody-mediated or due to direct mast cell/basophil or complement activation. The similarity in structure between docetaxel and paclitaxel suggests cross-reactions and cross-sensitivity. Some early results on small numbers of patients indicated successful substitution of docetaxel for paclitaxel, but this conclusion was not supported in the later women’s cancer study mentioned above where ten patients with severe hypersensitivity to paclitaxel also reacted to docetaxel, giving a cross-sensitivity rate of 90%. The different vehicles used for the two drugs indicated that the cross-reactions were probably due to the taxanes and not the vehicles.

Recommended skin test concentrations for docetaxel and paclitaxel are, prick testing, 0.4 mg/ml and 1 mg/ml, respectively, and for IDT, 0.04–0.4 mg/ml and 0.001–0.01 mg/ml, respectively.

15.5.1.1 Premedication for Taxanes

There is a significant risk of hypersensitivity reactions following taxane administration, and to minimize this, patients require premedication. Both docetaxel and paclitaxel are usually administered once every 3 weeks with docetaxel being infused over 1 h and paclitaxel over periods of from 1 to 96 h. The premedication regimen for patients receiving docetaxel consists of oral dexamethasone 8 mg twice daily for 3 days starting 24 h prior to the commencement of infusion. For paclitaxel infused over 1, 3, and 24 h, antihistamines are administered as well as the steroid. The H1 antagonist diphenhydramine (50 mg) and an H2 antagonist (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) are given intravenously prior to infusion beginning, while oral dexamethasone 20 mg is administered 12 and 6 h prior. There is some evidence that premedication is not required for infusions extending over 96 or more hours. The corticosteroid is used to prevent hypersensitivity reactions, decrease fluid retention, and decrease skin and nail adverse effects.
Note that the dose-limiting toxicity of docetaxel and paclitaxel is febrile neutropenia; docetaxel 100 mg m$^{-2}$ administered over 1 h every 3 weeks is associated with neutropenia in ~75% of patients; for paclitaxel 135–300 mg m$^{-2}$ over 24 h, the figure is 52%. Another published premedication protocol that claimed to limit the development of acute hypersensitivity to docetaxel consists of oral methylprednisolone 32 mg, cetirizine 10 mg, and ketotifen 1 mg, 12 and 3 h before infusion. For taxanes given weekly, the efficacy and safety of premedication were assessed in the treatment of non-small cell lung cancer. Weekly administrations of docetaxel and paclitaxel were assessed as safe and active protocols. For docetaxel, oral dexamethasone 4.5–7.5 mg twice daily for the day before, the day of, and the day after, together with intramuscular promethazine 25 mg and intravenous cimetidine 600 mg 30 min before docetaxel, are recommended. For paclitaxel the recommended protocol is dexamethasone 2.25–7.5 mg orally 12 and 2 h before and promethazine 25 mg IM and cimetidine 600 mg IV 30 min before the taxane. For weekly taxane dosage, the question of whether doses of dexamethasone can be reduced is important for patients experiencing, or at high risk of, steroid-induced side effects. Some have claimed that the optimal schedules remain to be determined and larger prospective clinical trials are needed.

A recent multi-institution survey in Japan drew attention to an important effect of histamine H$_2$ antagonists on docetaxel-induced skin toxicity. Analyses revealed that administration of H$_2$ blockers was associated with a significantly higher incidence of acral erythema (Fig. 15.1) and facial erythema. Steroids and H$_2$ blockers affect the metabolism of docetaxel by cytochrome P4503A4 (CYP3A4), but dexamethasone dosage did not change the incidence of hand-foot syndrome or facial edema.

### 15.5.1.2 Desensitization for Hypersensitivity Reactions to Taxanes

In the rapid desensitization protocol for paclitaxel published by Sullivan (Sullivan TJ. Protocols for rapid and slow drug allergy desensitization, Atlanta, Georgia, 2009), three concentrations of drug are employed – full-strength solution, that is, 300 mg paclitaxel in 500 ml in physiological saline (0.6 mg/ml); a 1 in 10 dilution (0.06 mg/ml); and a 1 in 100 dilution (0.006 mg/ml). Except for the last dosage step, each of the 11 preceding steps is infused for 15 min before changing to the next dose. Beginning with the 1 in 100 dilution (0.006 mg paclitaxel/ml) and an infusion rate of 2 ml/h, the solution is infused for 15 min followed by infusion rates of 5, 10, and 20 ml/h, respectively, for steps 2, 3, and 4. For the next four steps (numbers five to eight, again at 15 min intervals), the one in ten dilution of drug (0.06 mg/ml paclitaxel) is infused at rates of 5, 10, 20, and 40 ml/h, respectively. At steps 9, 10, and 11, full-strength solution (0.6 mg paclitaxel/ml) is infused at 10, 20, and 40 ml/h, respectively. For the last step (step 12), full-strength solution is infused at 80 ml/h until the remaining full-strength solution has been given.

The Castells group treated 17 consecutive patients with hypersensitivity to taxanes using a standard 6–7 h desensitization protocol. The patients underwent a total of 77 rapid desensitizations to docetaxel or paclitaxel. Seventy-two of the procedures were tolerated without reactions, four patients responded with hypersensitivity reactions that were milder than their initial reactions, and these patients tolerated re-administration of infusions. Five patients re-challenged before desensitization experienced recurrent reactions even though they were given additional premedication, and the infusion rate was reduced.

### 15.5.2 Platinum Chemotherapeutic Drugs

Platinum-based cytotoxic compounds that cross-link DNA are some of the most active and effective cytotoxic drugs for the treatment of ovarian and almost all the common tumors except breast and prostate tumors. Treatments with platinum drugs are often effected in combination with other anticancer agents, and, overall, it is estimated that up to 50–70% of cancer patients are
treated with platinum drugs. Cisplatin, the first of the so-called organoplatinum drugs, contains no organic component and is, in fact, a metal coordination compound with a square-planar platinum (II) center coordinated to two ammonia and two chlorine ligands in a *cis*-ligand conformation (Fig. 15.11). The success of cisplatin in the clinic focused research interest on other possible platinum chemotherapeutic drugs and led to the general rule that a neutral square-planar platinum (II) center containing two *cis*-amines and two leaving groups are required for good anticancer activity. The first follow-up drug to gain worldwide clinical acceptance was carboplatin that contains the *cis*-Pt(NH$_3$)$_2$ active group of cisplatin with the chloride leaving groups replaced by a bidentate dicarboxylate (Fig. 15.11). Carboplatin has a similar anticancer profile as cisplatin, but, although it is just as effective for ovarian cancer, its potencies against head, neck, and testicular cancers are less. On the other hand, carboplatin evokes fewer side effects, and this has generally made it the drug of choice over cisplatin. In 2004, oxaliplatin became the third widely accepted and

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**Fig. 15.11** Two- and three-dimensional structures of platinum-based chemotherapeutic drugs. Cisplatin, the first of the so-called organoplatinum drugs, contains no organic component. It is a metal coordination compound with a square-planar platinum (II) center coordinated to two ammonia and two chlorine ligands in a *cis*-ligand conformation. Carboplatin contains the *cis*-Pt(NH$_3$)$_2$ active group of cisplatin with the chloride leaving groups replaced by a bidentate dicarboxylate. Oxaliplatin also has the square-planar platinum center but, unlike cisplatin and carboplatin, it has the bidentate ligand 1,2-diaminocyclohexane instead of two monodentate ammine ligands as well as a bidentate oxalate group.
used platinum drug. Oxaliplatin, unlike the other two platinum chemotherapeutics, is effective against colorectal cancer, and, in addition, it is active against some cisplatin-resistant cancers. In the structure of oxaliplatin, the amines are part of the 1,2-diaminocyclohexane framework (Fig. 15.11).

15.5.2.1 Symptoms of Hypersensitivity to Platinum Drugs

Exposure to platinum salts, especially in miners of the metal and other industrial workers, has been known to provoke hypersensitivity reactions since, at least, the 1940s, while reactions to platinum therapeutic agents, viz., cisplatin, were first described in the 1970s. Symptoms to the drugs may develop during infusion within minutes or after hours or days with a mild rash being the first manifestation. The clinical features of the reactions are highly variable – in one survey of carboplatin-induced hypersensitivity, 100% of patients had cutaneous symptoms (mainly palmar or facial flushing), 57% had cardiovascular symptoms, 42% gastrointestinal disturbances, and 40% respiratory symptoms. Commonly seen mild reactions are rash, urticaria, flushing, palmar itching, a burning feeling, hand and facial edema, pruritus, back pain, abdominal cramping, and diarrhea. These symptoms usually resolve quickly with antihistamines and steroids. Moderate to severe symptoms include diffuse erythroderma, tachycardia, chest tightness, wheezing, facial swelling, dyspnea, hypertension, or hypotension (Table 15.1). Other more severe symptoms sometimes reported are bronchospasm, chest pain, seizures, and systemic anaphylaxis that may be life-threatening. Reactions to oxaliplatin are similar to those seen in response to cisplatin and carboplatin, but the responses to oxaliplatin tend to be more heterogeneous and unpredictable with fewer cutaneous reactions; idiosyncratic reactions like cytokine release syndrome and pulmonary fibrosis; fewer reports of severe anaphylaxis; and a higher incidence of respiratory symptoms including laryngeal spasms and hypoxemia. A few cases of type II thrombocytopenia and type III immune complex-mediated urticaria, joint pain, and proteinuria associated with oxaliplatin have also been reported.

15.5.2.2 Incidences of, and Risk Factors for, Hypersensitivity Reactions to Platinum Drugs

For cisplatin, the overall incidence of reactions is 5–20%, reactions occur within minutes of the commencement of infusion, most reactions occur between the fourth and eighth course, and reactions increase with concomitant radiation. The overall incidence of reactions to carboplatin has been reported as 1–44% and, in another study, 9–27%. Reactions occur within minutes or days of infusion; less than 1% of hypersensitivity reactions result during cycles 1–5; 6.5% occur during cycle six; 27% are seen in cycle seven or more; and 44% occur in third-line treatment. Approximately half of all reactions to carboplatin are moderate to severe. Reactions to oxaliplatin occur with an incidence of 10–19% and manifest within minutes or hours of infusion. Again, most reactions appear after a number of treatment cycles (usually at least six).

Risk factors for the platinum chemotherapeutic drugs have not yet been thoroughly studied and well defined. Most information so far has been obtained for carboplatin. Apart from the already clearly established risks of the number of prior treatments with platinum drugs and a high rate of drug infusion, other suggested risk factors discerned so far include a history of drug allergy, a carboplatin-free interval of greater than 13 months, patients with ovarian cancer, children receiving weekly carboplatin infusion rather than monthly infusions, and the female gender. An antineoplastic drug used in combination with a platinum drug may also influence the incidence of hypersensitivity reactions to the platinum agent. For example, the CALYPSO study of the Gynecologic Cancer Intergroup showed that carboplatin with pegylated liposomal doxorubicin produced fewer reactions than the combination of the platinum drug with paclitaxel. Risk factors identified so far for oxaliplatin reactions include a young age, female gender, and use of the drug as salvage therapy.
The deleterious germline BRCA 1/2 mutation is claimed to be an independent risk factor for carboplatin hypersensitivity reactions. Patients with the mutations appeared to develop the reactions to carboplatin after a lower cumulative dose. In an assessment of the prevalence and impact of the BRCA 1/2 mutation in carboplatin-allergic patients undergoing desensitization to the drug, BRCA-positive patients reacted more during rapid desensitization than BRCA-negative patients, and immediate hypersensitivity reactions appeared earlier and were more apparent than seen with BRCA-negative patients. In contrast to earlier findings, however, the cumulative dose to develop hypersensitivity, and the severity of reactions were found to be similar for both groups.

15.5.2.3 Mechanisms and Diagnosis of Platinum Drug-Induced Hypersensitivity Reactions

Reactions are thought to be mainly type I or type IV hypersensitivity responses, but, as mentioned above, a few cases of type II and type III hypersensitivities have been reported. Nevertheless, the complexity and unpredictable nature of many responses suggests that a number of mechanisms, both immune and non-immune, may be operative in many reactions. Early findings of IgE antibodies to platinum salts in platinum-exposed workers, the appearance of sensitization only after multiple infusions, positive skin tests to carboplatin, and anaphylactic reactions were all taken as evidence of a type I hypersensitivity mechanism to the platinum salts. Detection of IgE antibodies reactive with carboplatin and oxaliplatin in the sera of patients with hypersensitivity reactions to these drugs was claimed in tests utilizing the platinum salts conjugated to human serum albumin and immobilized in activated cellulose sponge (ImmunoCAP®, Thermo Scientific). Seven of 12 patients sensitized to carboplatin had IgE antibodies to the drug; all were negative to oxaliplatin, but 2 were IgE-positive to cisplatin. Nine of 12 patients sensitized to oxaliplatin had serum IgE antibodies to oxaliplatin, and 8 were also IgE-positive to carboplatin and cisplatin even though they had no previous exposure to these two drugs. The absence of stringent specificity investigations here is a concern especially as 25% (three patients) in the oxaliplatin control group were IgE antibody-positive for carboplatin and one was positive to oxaliplatin. Also, one patient in the oxaliplatin control group was positive to carboplatin, and two had positive skin tests to oxaliplatin. At the least, studies such as this require quantitative inhibition and cross-reactivity studies with all three platinum salts and other selected platinum salt analogs as well as the examination of a much larger control groups of platinum-exposed patients and other non-exposed controls.

Skin testing with the three platinum drugs has been employed to identify at-risk patients and predict platinum hypersensitivity, and the practice is now finding more widespread acceptance and application as a routine diagnostic procedure. In a study of patients with recurrent ovarian or peritoneal carcinoma who had received more than seven courses of carboplatin, intradermal testing with 100–240 μg of carboplatin revealed 13 of 47 patients (28%) with a positive test. A negative skin test correctly predicted the absence of a hypersensitivity reaction in 166 of 168 courses of chemotherapy (98.8%). Two patients experienced a reaction after showing a negative skin test. A follow-up study on 126 patients confirmed the association between a negative carboplatin skin test and no resultant severe hypersensitivity reaction after the next infusion, but the implications of a positive test remained less certain. Patch, prick, and intradermal tests with cisplatin, carboplatin, and oxaliplatin on 21 patients produced negative patch test results in all 21 patients, 5 positive reactions in the prick test, and 12 positives in the intradermal test. Cross-reactions were observed in four cases, and delayed reactions occurred in three patients. It was concluded that the intradermal test was superior to the other two tests, and its good negative predictive value allows safe retreatment by detecting potential cross-reactions. Results from some other studies also support the superiority of the intradermal test. In response to the report of the three delayed reactions, it was pointed out that intradermal tests with platinum drugs have a good negative predictive value in immediate reactions, but the test can induce false
positives with these drugs. Most skin test investigations have been on patients with carboplatin, but results and conclusions have not always been in agreement. Fifty-three of 60 patients referred for carboplatin hypersensitivity were skin test-positive to the drug, 1 patient showed a delayed positive reaction, 2 became positive after further infusions, and the remaining 4 skin test-negative patients experienced hypersensitivity during a subsequent infusion. Skin tests on 54 patients receiving re-treatment with carboplatin predicted hypersensitivity reactions in only 64% of affected patients leaving the authors to conclude that skin testing did not reliably predict carboplatin-induced reactions. Skin test concentrations generally employed for carboplatin are 10 mg/ml in the prick test and 0.02 ml of 0.1 mg/ml in the intradermal test increasing in tenfold concentration steps to a maximum of 10 mg/ml. In some studies, a maximum skin test concentration of 3 mg/ml has been used for carboplatin. For oxaliplatin, a concentration of 1 mg/ml is used in the prick test and a maximum of 0.1 mg/ml in the intradermal test.

In summary, it has been claimed that skin tests are positive in more than 80% of the platinum drug-treated patients tested, and, when the test is negative, the risk of a hypersensitivity reaction is reduced sevenfold or even eliminated. This, in turn, has led to the recommendation that skin testing should be performed on every patient before the eighth drug infusion. Skin testing may also help in ruling out cross-reacting drugs when substituting one platinum drug for another. Nevertheless, it has been argued that it is not practical to employ skin testing as a routine test in everyday clinical practice since prior experience in its execution is required, and hypersensitivity reactions might still occur even in the case of a negative skin test. The first of these objections cannot be sustained – if the simple skills of skin testing are lacking, the situation can, and should, be readily rectified by professionals who are charged with the responsibility of seeking and maintaining the best available diagnostic procedures. The possibility of reactions in skin test-negative patients is indeed likely but that, again, should always be seen as a possibility to be anticipated and managed, and such a possibility is not a sufficient reason to forego the possible advantages that skin testing can provide.

### 15.5.2.4 Desensitization

Attempts to re-administer the same drug or change to a different platinum drug can be dangerous, and desensitization to the drug is sometimes considered to be the best option. Desensitization protocols to the platinum drugs are not standardized, and a number of different protocols are currently employed in different institutions. Table 15.5 sets out a 12 step, ~ 6 h desensitization protocol for carboplatin in skin

| Step | Infusion rate (ml/hr) | Time infused (mins) | Administered dose (mg) | Cumulative dose infused (mg) |
|------|----------------------|---------------------|-----------------------|----------------------------|
| 1    | 2                    | 15                  | 0.010                 | 0.010                      |
| 2    | 5                    | 15                  | 0.025                 | 0.035                      |
| 3    | 10                   | 15                  | 0.050                 | 0.085                      |
| 4    | 20                   | 15                  | 0.100                 | 0.185                      |
| 5    | 5                    | 15                  | 0.250                 | 0.435                      |
| 6    | 10                   | 15                  | 0.500                 | 0.935                      |
| 7    | 20                   | 15                  | 1.000                 | 1.935                      |
| 8    | 40                   | 15                  | 2.000                 | 3.935                      |
| 9    | 10                   | 15                  | 5.000                 | 8.935                      |
| 10   | 20                   | 15                  | 10.000                | 18.935                     |
| 11   | 40                   | 15                  | 20.000                | 38.935                     |
| 12   | 75\(^c\)             | 184.4               | 461.065               | 500.00                     |
| Totals: | 5 h                  | 49.4 min            | 500 mg                |                            |

Data from Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. Gynecol Oncol. 2004;95:370–6

\(^c\)Conducted in intensive care unit, Brigham and Women’s Hospital. \(\beta\)-Blockers withheld 1 day before. Informed consent obtained. All rescue medications on hand. Patients premedicated with diphenhydramine 25 mg, famotidine 20 mg IV 30 min before initiation of infusion

\(^d\)Using appropriate concentrations to deliver the required dose in the required time

\(^e\)A constant rate of infusion maintained to deliver the remainder of the total carboplatin dose
test-positive patients hypersensitive to the drug and receiving desensitization for the first time. Conversion of a positive skin test to carboplatin to a negative response after desensitization supports the existence of a specific IgE antibody-mediated response in patients. Aside from carboplatin, a number of different desensitization protocols for oxaliplatin have been published, but the number of patients treated so far is small. The essential procedures of premedication, escalating dosage, infusion times, and duration of the procedure are similar to those employed for carboplatin. Drugs used for premedication are generally diphenhydramine or hydroxyzine as histamine H₁ inhibitors; famotidine, cimetidine, or ranitidine as H₂ antagonists; and corticosteroids such as dexamethasone, prednisolone, and hydrocortisone. Oxaliplatin dilutions employed cover the range from 1:100,000 to 1:1 in from 5 to 13 steps over a total time range of from 5.8 to 8 h. Some protocols employ continuous fixed rate infusion extending over 24–48 h. In some procedures, magnesium sulfate and calcium carbonate have been added and claimed to increase the success rate of desensitization.

15.6 Summary

- At the end of June 2019, the A to Z list of cancer drugs listed by the National Cancer Institute numbered more than 500. In a 2017 analysis based on mechanism of action of 150 anticancer drugs approved by the FDA, 61 were classified as cytotoxic and 89 as targeted drugs.
- For many years, cytotoxic compounds have been the front line of cancer chemotherapy. Their antineoplastic actions depend on the destruction of rapidly dividing cancer cells via cytotoxic mechanisms or by causing the cells to undergo apoptosis. These drugs generally also harm normal rapidly dividing cells in the gastrointestinal tract, bone marrow, and hair follicles causing well-known side effects like mucositis, stomatitis, myelosuppression, and alopecia.
- Cytotoxic drugs used for cancer therapy have a wide range of chemical structures including alkylating agents, antimetabolites, cytoskeletal disruptors, and drugs that directly affect DNA or protein synthesis.
- Classification of cytotoxic anticancer drugs is often imprecise and confusing. It may be based on chemical structure, mechanisms of action, pharmacological categories, plant origin (taxanes, Vinca alkaloids), or where drugs act in the cell cycle. These dissimilar classifications may be mixed rather than a division based on a single criterion.
- Hypersensitivities occur with most cancer drugs. Drugs with high potential to provoke hypersensitivity are platinum compounds, taxanes, epipodophyllotoxins, L-asparaginase, and procarbazine. Those with low potential include the anthracyclines, and drugs only occasionally implicated include cyclophosphamide and methotrexate.
- Antimetabolites such as capecitabine, gemcitabine, and 5-fluorouracil commonly provoke acral erythema (palmar-plantar erythrodysesthesia; hand-foot syndrome).
- Cytotoxic chemotherapy typically suppresses hematopoiesis causing thrombocytopenia, neutropenia and anemia, and drug-induced hepatotoxicity.
- Clear-cut demonstrations with diagnostic evidence of immediate type I allergic reactions are few. L-Asparaginase, the platinum salts, and methotrexate show positive skin tests and provoke such reactions.
- Antineoplastic drugs may cause type II antibody-mediated cytotoxic hypersensitivity reactions, e.g., drug-induced thrombocytopenia, drug-induced neutropenia, and drug-induced anemia.
- In drug-induced immune hemolytic anemia (DIIHA), the drug can be associated with red cell autoantibodies without the drug (e.g., fludarabine) participating in the antigen-antibody reaction. The platinum drugs cause immune-mediated hemolysis with or without associated immune thrombocytopenia.
- Drug-induced vasculitis (DIV), also known as leukocytoclastic vasculitis, usually occurs in the skin and sometimes in subcutaneous tissue, kidneys, and the lungs. For antineoplastic drugs, small-vessel vasculitis is
the most frequently seen form of a type III reaction. A proportion of small-vessel vasculitis patients have anti-neutrophil cytoplasmic antibodies (ANCA) which are used as a diagnostic marker.

• In drug-induced liver injury (DILI), the drug or active metabolite(s) as hapten is thought to bind to endogenous proteins forming immunogenic conjugates that generate antibody- and/or T cell-mediated injury.

• Immune-mediated damage to the lung in drug-induced lung disease (DILD) may be due to drug-specific antibodies or, more usually, drug-specific T cells. Hypersensitivity pneumonitis is a combined type III and type IV hypersensitivity reaction in a Th1/Th17 response. Reports of drug-induced hypersensitivity pneumonitis are increasing, particularly to antineoplastic drugs.

• Oxaliplatin has been associated with type III immune complex-mediated urticaria. Other possible type III hypersensitivities are procarbazine-induced interstitial pneumonia with eosinophilia; cytarabine syndrome; pulmonary infiltrates, alveolar damage and eosinophilia after gemcitabine; hemolytic anemia and a Henoch-Schönlein-type purpura each associated with immune complexes following mitomycin C; and pneumonitis with features of a type III response provoked by methotrexate.

• The main cytotoxic drugs involved in eliciting delayed skin reactions include alkylating agents, particularly the nitrogen mustards; some antimetabolites e.g., cytarabine, capecitabine, and gemcitabine; some purines; the folate antagonists methotrexate and pemetrexed; and the taxanes. Cutaneous reactions to chemotherapeutic drugs include maculopapular exanthemas, allergic contact dermatitis, psoriasis, AGEP, DRESS, fixed drug eruptions, erythema multiforme, SJS, and TEN.

• Other cutaneous and mucocutaneous reactions associated with chemotherapy include stomatitis and mucositis, acral erythema, cutaneous eruption of lymphocyte recovery, neutrophilic eccrine hidradenitis, eccrine squamous syringometaplasia, extravasation reactions, inflammation of keratosis, photosensitivity, and radiation-associated reactions. Mechanisms underlying these adverse effects are generally not understood.

• Cytotoxic chemotherapeutic drugs are the most common cause of stomatitis and mucositis. Approximately 40% of patients receiving chemotherapy experience stomatitis.

• Knowledge of mechanisms underlying idiosyncratic DILI remains limited. The mechanism can be divided into direct (intrinsic) hepatotoxicity and unpredictable and rare liver injury which in turn can be classified into immune-mediated hypersensitivity and idiosyncratic reactions.

• Mechanisms involved in drug-induced lung injuries have not been elucidated making it difficult to effect classifications based on pathogenesis.

• The skin prick test and intradermal test may be used to detect both immediate and delayed reactions to drugs, but these tests have not been widely and routinely applied, being used to diagnose hypersensitivities to only a relatively few drugs including platins, taxanes, and L-asparaginase.

• Patch testing with antineoplastic drugs is generally considered to be of no value in diagnosing systemic reactions, and it remains unclear how useful the test is for helping in the diagnosis of chemotherapeutic drug-induced cutaneous reactions. The lymphocyte transformation test measures a memory T cell response and may identify a causative drug in cases of drug eruptions.

• For the prevention of allergic reactions to the cytotoxic/cytostatic drugs used in chemotherapy, three strategies are generally employed: premedication, skin testing, and desensitization.

• For premedication, steroids and antihistamines are usually used. With the taxanes, premedication has reduced the incidence of hypersensitivity reactions to 2–4% of cases.

• Skin tests may be useful to predict reactions between courses of platinum chemotherapy. For example, intradermal testing with
carboplatin 30 min before the commencement of chemotherapy.

- For patients who experience severe adverse reactions despite premedication and when it is not possible or desirable to replace the preferred drug for treatment, or in patients with a positive skin test to platinum drugs, desensitization is usually successful. Procedures are generally effective for both IgE antibody-and non-antibody mediated immediate hypersensitivities. Desensitizations are mostly undertaken with the taxanes and platinum drugs.

- Docetaxel is a semisynthetic analog of paclitaxel. It differs from paclitaxel at C-10 and in the phenylpropionate side chain. The taxanes are mitotic inhibitors, disrupting microtubule function, so adverse reactions might be expected.

- Up to 30% of patients have been found to develop acute infusion reactions to taxanes. Acute hypersensitivity reactions are marked by urticaria, flushing, rashes, dyspnea, gastrointestinal symptoms, hypotension, and back pain.

- Patients with severe hypersensitivity to paclitaxel also often react to docetaxel, giving a cross-sensitivity rate of 90%.

- Recommended skin test concentrations for docetaxel and paclitaxel are prick testing, 0.4 mg/ml and 1 mg/ml, respectively, and for intradermal testing, 0.04–0.4 mg/ml and 0.001–0.01 mg/ml, respectively.

- The premedication regimen for patients receiving docetaxel consists of oral dexamethasone 8 mg twice daily for 3 days starting 24 h prior to the commencement of infusion. For paclitaxel infused over 1, 3, and 24 h, antihistamines are administered as well as the steroid. The H₁ antagonist diphenhydramine (50 mg) and an H₂ antagonist (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) are given IV prior to infusion beginning, while oral dexamethasone 20 mg is administered 12 and 6 h prior.

- Rapid desensitization protocols have been developed and published for docetaxel and paclitaxel.

- It is estimated that up to 50–70% of cancer patients are treated with platinum drugs. Three platinum drugs are used: cisplatin, carboplatin, and oxaliplatin.

- Adverse reactions to platinum drugs may develop during infusion within minutes or after hours or days with a mild rash being the first manifestation. In one survey of carboplatin-induced hypersensitivity, 100% of patients had cutaneous symptoms (mainly palmar or facial flushing), 57% had cardiovascular symptoms, 42% gastrointestinal disturbances, and 40% respiratory symptoms. More severe symptoms sometimes reported are bronchospasm, chest pain, seizures, and systemic anaphylaxis that may be life-threatening.

- Risk factors identified so far for oxaliplatin reactions include a young age, female gender, and use of the drug as salvage therapy. The deleterious germline BRCA 1/2 mutation is claimed to be an independent risk factor for carboplatin hypersensitivity reactions. Patients with the mutations appear to develop the reactions to carboplatin after a lower cumulative dose.

- Reactions to platinum agents are thought to be mainly type I or type IV hypersensitivity responses, but a few cases of type II and type III hypersensitivities have been reported.

- IgE antibodies reactive with carboplatin and oxaliplatin have been detected in the sera of patients with hypersensitivity to the platinum agents.

- Skin testing with the three platinum drugs has been employed to identify at-risk patients and predict platinum hypersensitivity and the test is now finding more widespread acceptance and application as a routine diagnostic procedure. Intradermal tests are superior to prick and patch testing, and its good negative predictive value allows safe re-treatment by detecting potential cross-reactions.

- Attempts to re-administer the same drug or change to a different platinum drug can be dangerous, and desensitization to the drug is sometimes considered to be the best option. A number of different desensitization protocols for the platinum drugs are currently employed in different institutions.
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