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Imaging of Complications and Toxicity following Tumor Therapy

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Part I

Basics of Toxicity of Tumor Therapies

Chemotherapy and Targeted Therapy

Florian Lordick and Ulrich Hacker

Contents

Abstract

A precise knowledge of antineoplastic drugs is an indispensable basis for the care of patients with cancer. The mechanisms of action and resistance, cross-resistance patterns, pharmacodynamics and pharmacokinetics, pharmacological interaction, and last but not least potential adverse effects should be part of this knowledge. As contemporary cancer care requires interdisciplinary and multiprofessional structures, the radiologist is an important and integral part of the oncological treatment team. He has several key roles. Besides the determination of an accurate clinical staging which is the basis for all treatment recommendations, he evaluates the response to anticancer treatment and defines the remission status following treatment. Importantly, he assesses acute and long-term treatment toxicities, both having a tremendous impact on patients' safety and quality of life. This article summarizes the principles of medical anticancer treatment and outlines the major side effects associated with drug classes and specific antineoplastic compounds.

Abbreviations

2-CDA	2-Chlordeoxyadenosine
5-FU	5-Fluorouracil
6-MP	6-Mercaptopurine
6-TG	6-Thioguanine

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ACNU	Nimustine
ADL	Activity of daily living
AE	Adverse event
ALK	Anaplastic lymphoma kinase
AMSA	Amsacrine
AraC	Cytosine arabinoside
ARDS	Acute respiratory distress syndrome
BCNU	Carmustine
bcr/abl	Breakpoint cluster region protein/ Abelson murine leukemia viral oncogene homolog 1
CCDP	Cisplatin
CCNU	Lomustine
CD	Cluster of differentiation
c-KIT	Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DNA	Deoxyribonucleic acid
DTIC	Dacarbazine
EGFR	Epidermal growth factor receptor
EML4	Echinoderm microtubule-associated protein-like 4
HDAC	Histone deacetylase
HER2	Human epidermal growth factor receptor 2
ILD	Interstitial lung disease
mTOR	Mammalian target of rapamycin
MTX	Methotrexate
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
PD-1	Programmed cell death protein 1
PDL-1	Programmed cell death ligand 1
PET	Positron emission tomography
PlGF	Placental growth factor
PRES	Progressive reversible encephalopathy syndrome
RAF	Rapidly accelerated fibrosarcoma
SOC	System Organ Class
TKI	Tyrosine kinase inhibitor
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
VP-16	Etoposide
WHO	World Health Organization

1 Basic Principles of Medical Anticancer Therapy

Besides the locally active treatment modalities (surgery and radiation therapy), drug therapy is the third important column of anticancer treatment. Applied via the bloodstream, medical therapy can hit not only the primary tumor but also lymphatic and hematogenous disseminated tumor cells and metastases.

"Cytotoxic drug" denominates a compound that inhibits cell division and kills cells. By its effects on nucleic acid formation, DNA synthesis and repair, and protein synthesis and by the inhibition of particular protein functions that are associated with survival, proliferation, and migration, these drugs exert antiproliferative cytostatic effects or cytotoxic effects as programmed cell death (apoptosis), cell destruction (necrosis), and induction of senescence. Of note, all these effects do not only occur in neoplastic tumor cells but can alter also cells of the healthy tissue, depending on the susceptibility of particular organs to the cytotoxic drug effects. Therefore, cancer chemotherapy has transitioned from the use of cytotoxic drugs to the era of agents with an apparent selectivity for a cancer-specific target (Phelps and Sparreboom 2014). However, targets which are completely specific for cancer cells seem to be rare. And even if such characteristics exist, like the Philadelphia chromosome translocation in chronic myeloid leukemia coding for the cancer-specific bcr/abl tyrosine kinase (Heisterkamp et al. 1985), drugs hitting that target do not work absolutely target specific and do have an impact on functional structures of healthy tissue cells as well.

A classification of anticancer treatment into classical cytostatic or cytotoxic chemotherapy, antihormonal therapy, monoclonal antibody treatment, or treatment with tyrosine kinase inhibitors has historic reasons and appears arbitrary as the cell biological effects of those therapies are pleiotropic and have a great overlap. A certain relevance lies in the discrimination of the mostly non-cancer selective classical cytotoxic treatment ("chemotherapy") and the so-called selective targeted treatment forms like antihormonal therapy, therapeutic

antibodies, and kinase inhibitors. The therapeutic index of classical cytotoxic drugs like alkylating agents is often smaller than that of biologically targeted forms of therapy (Fig. 1).

Classical cytotoxic drugs have different mechanisms of action which are outlined in Fig. 2.

Hanahan and Weinberg described the hallmarks of cancer in a previous landmark article that was updated in 2011. These hallmarks include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Conceptual progress in the last decade has added two emerging hallmarks of potential generality to this list – reprogramming of energy metabolism and evading immune destruction. The "tumor microenvironment" that consists of apparently normal cells adds to the complexity of current tumor characteristics which forms the basis for contemporary drug development and targeted treatment of cancer (Fig. 3) (Hanahan and Weinberg 2011).

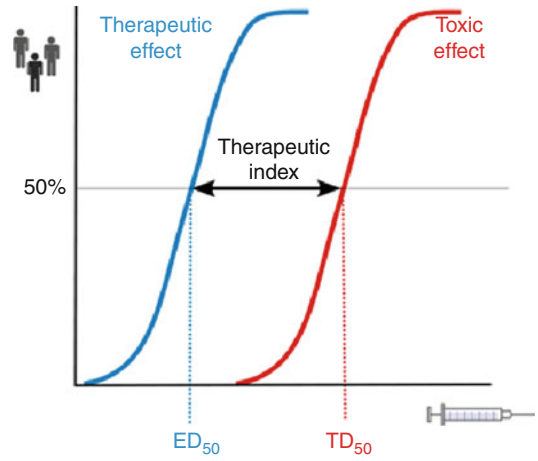

Fig. 1 The concept of therapeutic index refers to the relationship between toxic and therapeutic doses. This pharmacodynamic parameter is relevant to clinical practice because it determines how safe or toxic a drug is. Both ED50 and TD50 are calculated from dose-response curves, which represent the frequency with which each dose of drug elicits the desired response or toxic effect in the population. The dose required to cause a therapeutic effect (positive response) in 50 % of a population is the ED50. The dose required to produce a toxic effect in 50 % of the studied population is the TD50 (Redrawn from Craig and Stitzel (2003))

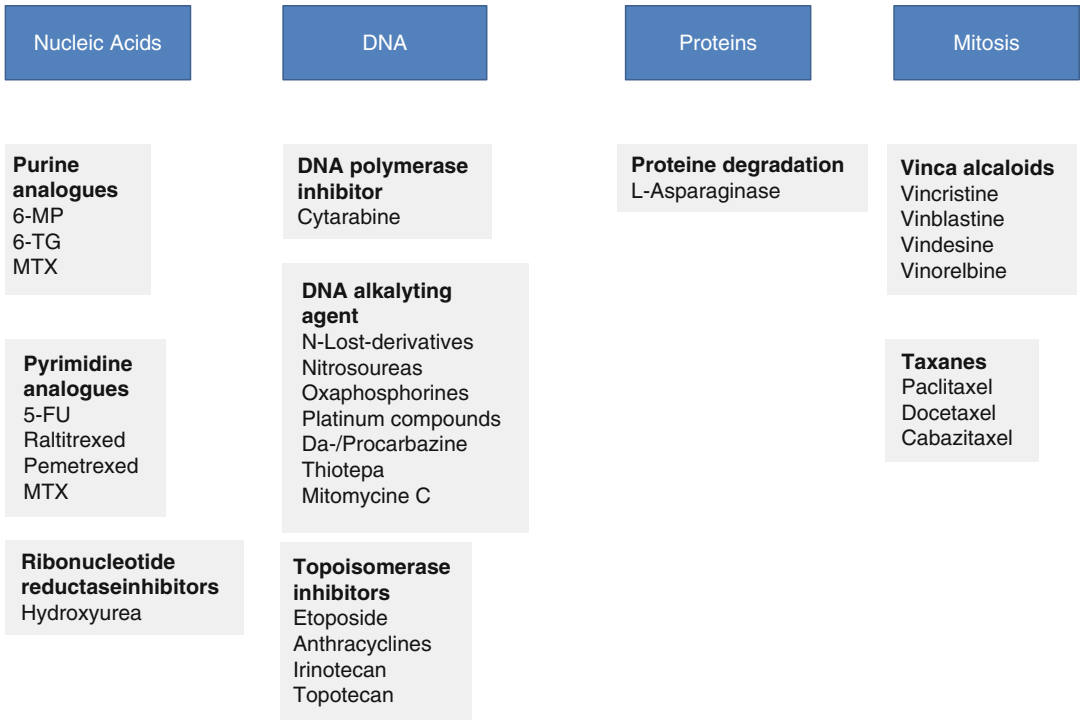

Fig. 2 Target structures of classical cytotoxic drugs: *DNA* deoxyribonucleic acid, *MTX* methotrexate, *5-FU* 5-fluorouracil, *6-MP* 6-mercaptopurine, *6-TG* 6-thioguanine

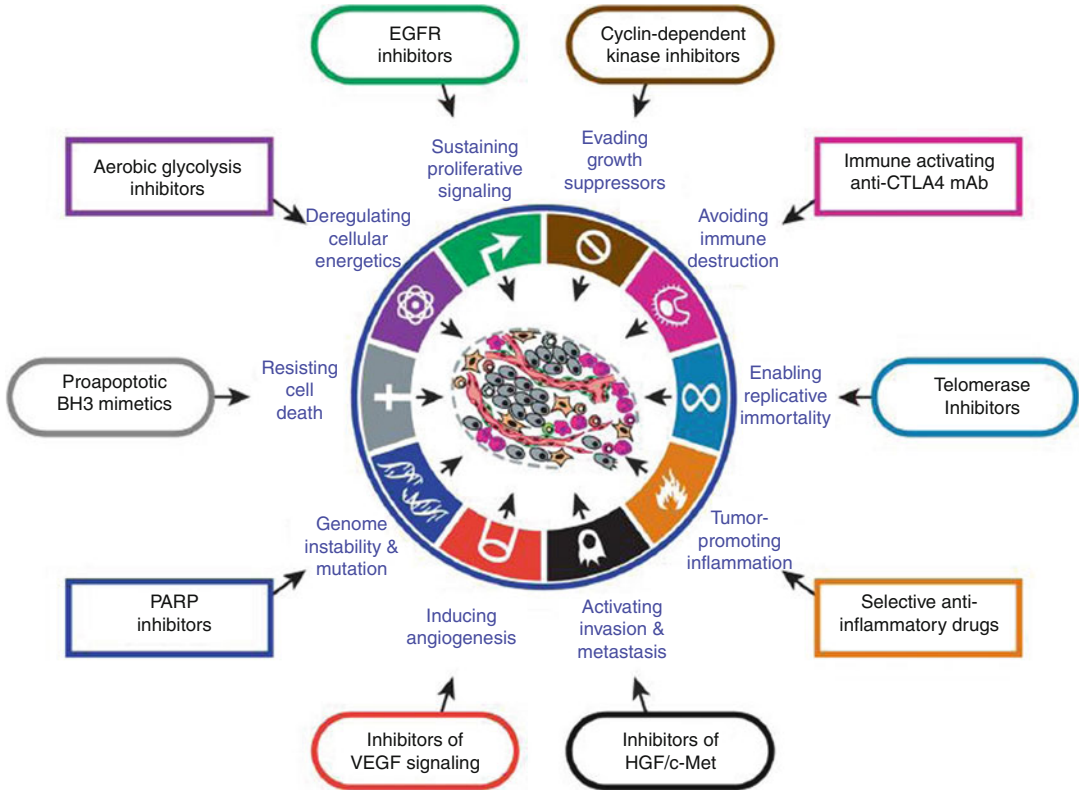

Fig. 3 The hallmarks of cancer (Redrawn from Hanahan and Weinberg (2011)) are the basis for contemporary drug development and targeted anticancer treatment

2 Definitions of Anticancer Drug Therapy

2.1 Mono- Versus Combination Therapy

In principle, combination chemotherapy has advantages over monotherapy due to additive or multiplicative effects of tumor cell kill. Primary or secondary resistant tumor cell clones can be eradicated or suppressed by different mechanisms of action. Ideally, combinations have the following features:

- The combined agents are equally effective.
- Lack of cross-resistance.
- Different mechanisms of action.
- Additive or synergistic mechanisms of action.
- No overlapping toxicities.

For most combinations, this ideal situation does not exist. Especially with regard to side effects, some addition of toxicity must always be accepted when combinations are used.

2.2 Induction Chemotherapy

Induction chemotherapy is used when at the time of diagnosis no acceptable therapeutic alternative exists. Induction chemotherapy shall bring the cancer into a state of better therapeutic options. The goal is "the induction" of an optimal remission, which is at best a "complete remission." High treatment intensities are usually necessary for an optimal induction. Therefore, the probability of inducing adverse effects is usually high.

2.3 Consolidation Therapy

The consolidation therapy shall provide the eradication of clinically occult residual tumor. It shall improve the rate of true complete remissions. Thereby, consolidation shall increase the chances of cure or increase the duration of response.

2.4 Maintenance Therapy

Maintenance therapy, in its classical sense used in the treatment of hematological malignancies like acute leukemia, follows consolidation and shall eradicate or control further residual tumor cells, e.g., those that – due to kinetic resistance – were not yet eradicated by the previous treatment. Maintenance therapy can increase the chance of cure or prolong the time interval until further tumor progression. The latter goal is nowadays often chosen in the palliative treatment of solid tumors when a remission has been achieved by a more intensive treatment period preceding maintenance.

2.5 Perioperative (Neoadjuvant and/or Adjuvant) Chemotherapy

Neoadjuvant (also primary or preoperative) therapy is a treatment in patients with localized or locoregional tumor extension in which the application of local treatment alone (operation or radiation therapy) may lead to an unsatisfactory outcome. Neoadjuvant chemotherapy is applied to reduce the extent of surgery (e.g., in breast cancer, where size reduction of large tumors allows for more breast-conserving surgery following neoadjuvant chemotherapy) and to increase the chances of cure (like in gastric or muscle invasive bladder cancer). In some cancers (e.g., osteosarcoma and Ewing sarcoma), postoperative treatment is tailored on the basis of the achieved response during neoadjuvant therapy.

The goal of adjuvant chemotherapy is the eradication of subclinical metastases ("micrometastases") following primary local treatment (operation or radiation therapy). The clinical goal of treatment is to increase the cure rate.

Accepted indications for perioperative chemotherapy are shown in Table 1. As increased cure rates are the goal of neo-/adjuvant chemotherapy, optimal dose intensity is necessary and some toxicity must be accepted. On the other hand, treatment safety is of utmost importance as patients may survive with the operation alone. In addition, long-term side effects should be avoided as they may lead to a significant impairment of quality of life of cancer survivors; alter physical, cognitive, and social functioning; and may even induce secondary diseases (cancers, leukemia, organ dysfunctions, cardiovascular diseases, etc.) leading to a negative impact on life expectancy.

Table 1 Examples for tumors with an established indication for perioperative (neoadjuvant or adjuvant) therapy

Breast cancer
Ovarian cancer
Esophageal cancer
Gastric cancer
Pancreatic cancer
Colon cancer
Rectal cancer
Lung cancer
Testicular cancer
Urothelial cancer
Ewing sarcoma
Osteosarcoma
Rhabdomyosarcoma

2.6 Palliative Therapy

Palliative chemotherapy is a treatment intended to prolong life, to control symptoms, and to augment quality of life. In case of symptomatic disease, more intensive induction treatment regimens are often applied. For a further stabilization of the tumor, most often less intensive monotherapies are regarded as standard of care. Treatment-emergent side effects must be carefully weighed against potential treatment benefits.

3 Classification of Anticancer Drugs

The classification of anticancer drugs can follow different criteria. Traditionally, the World Health Organization (WHO) chose the mechanisms of action (e.g., alkylating agent) and the origin of compounds (e.g., antitumor antibiotics) as their leading criteria for classification. Table 2 groups the compounds predominantly according to their mechanisms of action.

4 Classification of Treatment Toxicity

Side effects of medical treatment have been classified according to uniform criteria as long as the drug is applied within a clinical study. Internationally, the so-called Common Toxicity Criteria (CTC) or the newer Common Terminology Criteria for Adverse Events (CTCAE) as developed and published by the National Cancer Institute (NCI, Bethesda, USA) are most commonly used. Meanwhile, these criteria have been well implemented into clinical practice and proved useful. Therefore, thorough oncologists and multidisciplinary teams use it outside of clinical studies in routine cancer care. The current version of CTCAE V4.03 can be downloaded from the Internet (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

Table 2 Classification of anticancer drugs according to their mechanisms of action and biochemical properties

Drug class	Group	Compound
Alkylating agent	N-lost-derivatives	Bendamustine
		Busulfan
		Chlorambucil
	Nitrosourea derivatives	Nimustine (ACNU)
		Carmustine (BCNU)
		Lomustine (CCNU)
	Oxaphosphorines	Cyclophosphamide
		Ifosfamide
		Trofosfamide
	Platinum derivatives	Cisplatin (CDDP, DDP)
		Carboplatin
		Oxaliplatin
	Tetrazines	Dacarbazine (DTIC)
		Temozolomide
	Aziridines	Thiotepa
	Others	Amsacrine (AMSA)
		Estramustinphosphate
		Procarbazine
		Treosulfan
Antibiotics	Anthracyclines	Daunorubicin
		Doxorubicin
		Epirubicin
		Idarubicin
	Anthracenedione	Mitoxantrone
	Others	Actinomycin-D
		Bleomycin
		Mitomycin C
Alkaloids	Podophyllotoxin derivative	Etoposide (VP-16)
	Vinca alkaloids	Vinblastine
		Vincristine
		Vindesine
		Vinorelbine
	Taxanes	Cabazitaxel
		Docetaxel
		Paclitaxel
	Camptothecin derivatives	Irinotecan
		Topotecan

Table 2 (continued)

Drug class	Group	Compound
Antimetabolite	Antifolates	Methotrexate (MTX)
		Pemetrexed
	Purine analogues	6-Mercaptopurine (6-MP)
		6-Thioguanine (6-TG)
		Fludarabine
		2-Chlordeoxyadenosine (2-CDA)
	Pyrimidine analogues	5-Fluorouracil (5-FU)
		Capecitabine
		Clofarabine
		Cytosine arabinoside (AraC)
		Gemcitabine
	RNR inhibitor	Hydroxyurea
DNA demethylation	Demethylating agents	Azacytidine
		Decitabine
Protein degradation	Enzyme	L-asparaginase
Aromatase inhibition	Nonsteroidal inhibitors	Anastrozole
		Letrozole
	Steroidal inhibitor	Exemestane
Other hormonal therapies	Antiandrogens	Abiraterone
		Bicalutamide
		Flutamide
		Nilutamide
	Antiestrogen	Fulvestrant
	Gestagens	Medroxyprogesterone acetate
		Megestrol acetate
	Selective estrogen receptor modulators	Raloxifene
		Tamoxifen
Immune modulators	Cytokines	Interferon alpha
		Interleukin 2
	IMIDs	Lenalidomide
		Thalidomide
		Pomalidomide
	Immune checkpoint inhibitors	Ipilimumab
		Lambrolizumab
Monoclonal antibodies	CD20 antibodies	Rituximab
		Ofatumumab
	CD30 antibody-toxin conjugate	Brentuximab vedotin
	CD33 antibody	Gemtuzumab ozogamicin
	CD52 antibody	Alemtuzumab
	EGFR antibodies	Cetuximab
		Panitumumab
	HER2 antibodies	Trastuzumab
		Pertuzumab
	HER2 antibody-toxin conjugate	Trastuzumab emtansine
	VEGF antibody	Bevacizumab
	VEGF recombinant fusion protein	Aflibercept
	VEGFR2 antibody	Ramucirumab

(continued)

Table 2 (continued)

Drug class	Group	Compound
Tyrosine kinase inhibitors	Bcr/abl	Imatinib
		Dasatinib
		Nilotinib
	cKIT	Imatinib
	EGFR	Afatinib
		Erlotinib
		Gefitinib
	HER2	Lapatinib
	Histone deacetylase (HDAC)	Romidepsin
		Vorinostat
	mTOR	Temsirolimus
		Everolimus
	Multiple kinases	Axitinib
		Nintedanib
		Pazopanib
		Regorafenib
		Sorafenib
		Sunitinib
	Proteasome	Bortezomib
		Carfilzomib
	RAF	Vemurafenib
	Smoothened receptor (hedgehog signaling)	Vismodegib
	Somatostatin receptors	Octreotide
		Lanreotide

Compounds are listed with their generic names. Where appropriate, commonly used abbreviations are listed in parentheses

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for *adverse event (AE)* reporting. A grading (severity) scale is provided for each AE term. *System Organ Class (SOC)*, the highest level of the reporting hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). Within each SOC, adverse events are listed and accompanied by descriptions of severity (grade).

An AE is any unfavorable and unintended sign (including an abnormal laboratory or imaging finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

Grade refers to the severity of the AE. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline (Table 3). Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.

5 Specific Toxicities Associated with Anticancer Treatment

All organ systems can be subject to treatment-emergent toxicities.

With classical cytotoxic treatment, myelosuppression (neutropenia, thrombocytopenia, and anemia) is a common side effect. Between 80 and 100 % of all patients undergoing chemotherapy have some grade of myelosuppression leading to

Table 3 Toxicity grades according to the "Common Terminology Criteria for Adverse Events" (CTCAE) reporting system provided by the National Cancer Institute, Bethesda, USA

Grade	Severity
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (ADL)[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to an adverse event

A semicolon indicates "or" within the description of the grade

[a]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b]Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

alterations of the differential blood counts. Severity and duration depend of course on the applied cytotoxic drug and schedule as well as additional risk factors, like age and general health status. In case of neutropenia, patients are at particular risk of acquiring infections. Febrile neutropenia is an emergency situation during antineoplastic treatment. It requires immediate clarification and start of empiric antibiotic treatment. In most cases (except low-risk neutropenia in otherwise unimpaired and compliant patients), this should be done following hospitalization, and intravenous broad-spectrum antibiotics should be given (Klastersky and Paesmans 2013). In more than two thirds of patients, the focus of febrile neutropenia remains unknown, but pulmonary infections, bloodstream infections, urinary infections, infections of the skin and soft tissues, as well as infections of the upper aerodigestive tract should be excluded by appropriate clinical, paraclinical, and radiological diagnostics.

Apart from myelosuppression, non-hematological adverse events are common and need to be well known by the treatment team. Table 4 outlines a selection of substance- and group-specific non-hematological toxicities of anticancer drugs.

Our expectation was that with the introduction of new, more specific and biologically targeted drugs, the efficacy of anticancer treatment would increase, while the side effects would decrease. This hope was desperately disappointed (Niraula et al. 2012). International investigators analyzed all randomized controlled trials evaluating agents approved for the treatment of solid tumors by the US Food and Drug Administration between 2000 and 2010. Odds ratios were computed for three end points of safety and tolerability: treatment-related death, treatment discontinuation related to toxicity, and grade 3 or grade 4 adverse events (AEs). These were then pooled in a meta-analysis. Correlations between these end points and the hazard ratios for overall survival and progression-free survival were also assessed. The investigators came to the conclusion that new anticancer agents that lead to improvements in time-to-event end points also increase morbidity and treatment-related mortality. The balance between efficacy and toxicity may be less favorable in clinical practice because of selection of fewer patients with good performance status and limited comorbidities. Patients' baseline health characteristics should be considered when choosing therapy.

With the use of targeted therapies, novel side effects have emerged that are closely related to the specific mechanisms of action of the respective drug. Targeted therapies in general block certain signaling pathways that play important roles in promoting tumor cell survival and proliferation or interfere with stromal cells like vascular endothelial cells to inhibit tumor angiogenesis or with immune cells to modify antitumor immune responses. Monoclonal antibodies and tyrosine kinase inhibitors (TKI) represent the drug classes that are most commonly used for targeted cancer therapy. Furthermore, specific intracellular signaling checkpoints can be blocked by chemical compounds (i.e., mTOR inhibitors). Another group of drugs targets immune function to improve host anticancer immunity. CTLA-4 antibodies are used to enhance T-cell co-stimulation,

Table 4 Selection of substance and group-specific non-hematological toxicities of anticancer drugs

Substance/group	Typical adverse effect
Alemtuzumab	Opportunistic infection
Anthracyclines/mitoxantrone	Cardiomyopathy, cardiac arrhythmia
Aromatase inhibitors	Bone and joint pain, osteoporosis
Bevacizumab	Arterial hypertension, proteinuria, impaired wound healing, gut perforations, bleeding
Bleomycin	Pulmonary toxicity, lung fibrosis
Bortezomib	Neuropathy
Busulfan	Pulmonary toxicity, veno-occlusive disease
Cetuximab/panitumumab	Acneiform exanthema, allergic reactions
Chlorambucil	Pulmonary toxicity, lung fibrosis
Cytarabine	Central nervous toxicity (especially high-dose AraC leads to cerebellar alterations)
Docetaxel	Finger- and toenail alterations, edema, neuropathy, taste alterations
Erlotinib/gefitinib	Pneumonitis, acute respiratory distress syndrome (ARDS)
Fluoropyrimidines	Diarrhea, stomatitis, hand-foot syndrome, cardiotoxicity (arrhythmias, heart burn, myocardial infarction)
Imatinib	Edema, skin rash
Irinotecan	Diarrhea, cholinergic syndrome
Methotrexate	Central nervous toxicity, hepatic and pulmonary toxicity, nephrotoxicity in case of inadequate renal elimination
Mitomycin C	Hemolytic-uremic syndrome, pulmonary toxicity
Sunitinib/pazopanib/sorafenib/regorafenib	Arterial hypertension, hand-foot syndrome, thyroid disorders
mTOR inhibitors (everolimus, temsirolimus)	Arterial hypertension, pneumonitis, mucositis, erythema, hand-foot syndrome, hyperlipidemia
Nitrosoureas	Pulmonary toxicity, lung fibrosis, renal toxicity
Oxazaphosphorines (cyclophosphamide, ifosfamide)	Urothelial toxicity, renal toxicity, central nervous toxicity (reversible psychosyndrome with high-dose ifosfamide)
Paclitaxel/docetaxel	Neuropathy, allergic reactions, onycholysis
Platinum compounds	Renal impairment (cisplatin), ototoxicity (cisplatin), neuropathy (oxaliplatin > cisplatin >> carboplatin)
Tamoxifen	Thromboembolic events
Trastuzumab/pertuzumab/lapatinib	Cardiac toxicity
Vinca alkaloids	Neuropathy

and drugs targeting the PD-1/PD-L1 pathway have been developed to block inhibitory immune checkpoints.

An overview of key side effects can be found in Table 2. Specific side effects resulting in pathological radiological findings are shortly summarized in the following section.

Agents Targeting the Epidermal Growth Factor Receptor (EGFR): The monoclonal antibodies (cetuximab, panitumumab) are used for the treatment of RAS wild-type metastatic colorectal cancer, while TKI (gefitinib, erlotinib, afatinib) represent a standard of care in the treatment of EGFR-mutated non-small cell lung cancer (NSCLC) patients. Skin toxicities occur with high frequency in both groups of drugs. In contrast, interstitial lung disease (ILD) represents a rare complication, and the mechanism is not fully understood. Disruption of the alveolar epithelial function however may play a role. Based on this, the frequency of ILD is higher in smokers and in patients with preexisting lung disease (Ando et al. 2006).

Agents Targeting Her-2: Chemotherapy combined with monoclonal antibodies (trastuzumab, pertuzumab) represents a treatment standard in

Her2-positive breast cancer and in Her2 gastric cancer (trastuzumab). The TKI lapatinib targeting EGFR and Her2neu is approved for the treatment of breast cancer. An important side effect of this class of drugs is cardiotoxicity that is related to the expression of Her2 on cardiomyocytes. Mechanistically, Her2 signaling results in sarcomere stability and initiates repair processes that are important to counteract toxic stress (Tocchetti et al. 2012).

Agents Targeting Tumor Angiogenesis: The monoclonal antibody bevacizumab binds vascular endothelial growth factor (VEGF), and the fusion construct aflibercept binds VEGF and placental growth factor (PlGF). Both drugs are used in combination with chemotherapy for the treatment of metastatic colorectal cancer. Additionally, a large number of TKI targeting VEGF receptors and other receptors are in clinical use for the treatment of a wide variety of cancer types (Table 2). Hypertension and proteinuria represent common side effects of VEGF-targeting therapy. Furthermore, the rate of thromboembolic complications is increased. Other side effects are related to impaired tissue repair capacity and comprise gastrointestinal pneumatosis perforations and the formation of fistulas (Shinagare et al. 2012). Overall, bleeding is a rare side effect. However, frequent bleeding complications have resulted in the exclusion of the use of bevacizumab in squamous cell carcinoma of the lung. Progressive reversible encephalopathy syndrome (PRES) is a very rare (≤0.1 %) but severe neurological complication that has been reported in patient treatment with bevacizumab or aflibercept (Seet and Rabinstein 2012). The disruption of cerebrovascular endothelial cell signaling is related to the disruption of cerebrovascular autoregulation preferentially in the posterior circulation of the brain. Finally, pancreatitis (sunitinib, sorafenib, pazopanib) and acalculous cholecystitis (sunitinib) have been reported in the literature on a casuistic basis.

Anaplastic Lymphoma Kinase (ALK) Inhibitors: ALK inhibitors are used for the treatment of NSCLC harboring specific genomic rearrangements (EML4-ALK). Pneumonitis has been reported with the use of the ALK inhibitor crizotinib and symptoms started within two months of treatment. The underlying mechanisms are not yet clarified.

RAF-Targeting Agents: RAF-targeting agents include the multi-TKI sorafenib for the treatment of renal cell and hepatocellular cancer as well as vemurafenib and dabrafenib, which are used for the treatment of melanoma harboring the B-Raf mutation V600E and other B-Raf mutations. An increase in the occurrence of cutaneous squamous cell carcinomas has been reported, and nodular panniculitis (Monfort et al. 2012) may result in increased radiotracer uptake during 18F-FDG positron emission tomography (PET).

Agents Targeting Mammalian Target of Rapamycin (mTOR) and Targeted Immune Modulators: These agents (everolimus, temsirolimus) are used for the treatment of breast and renal cancers and pancreatic neuroendocrine tumors. Mucositis and aphthous mucosal lesions are common side effects. Additionally, interstitial pneumonitis is an important side effect of this class of drugs with up to 36 % of patients showing any pulmonary abnormalities during treatment (Duran et al. 2014).

Ipilimumab is a novel targeted immune modulator that interacts with CLTA-4, thus fostering co-stimulatory function to improve host antitumor immune response. Due to immune function deregulation, autoimmune-related side effects like enterocolitis and hypophysitis may occur. Additionally, unspecific lymph node enlargement and soft tissue changes like myositis or fasciitis as well as retroperitoneal fat opacities due to lymphocyte infiltration may interfere with treatment response assessment (Bronstein et al. 2011).

As examples of "new toxicities" emerging from biologically selective targeted drugs, Fig. 4 displays a perforation at the rectosigmoid level that occurred during treatment of metastatic colorectal cancer with the anti-VEGF antibody bevacizumab. Another patient who was also treated for metastatic colorectal cancer received the monoclonal anti-EGFR antibody cetuximab plus chemotherapy and developed a grade 3 skin rash during weeks 4–6 of this combined treatment (Fig. 5).

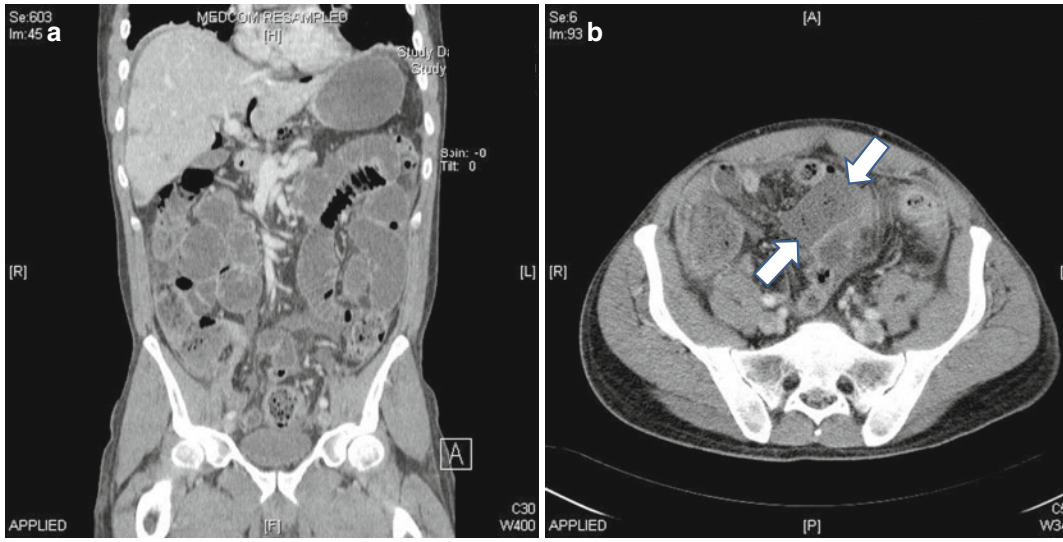

Fig. 4 Gut perforation leading to an ileus and peritonitis, emerging from a pararectal abscess in a patient with colorectal cancer with simultaneous liver and lung metastases. (**a**) Is illustrating the coronary section through the abdomen; (**b**) is illustrating a transversal section through the pelvis. The two *white arrows* in **b** are highlighting the formation of a pararectal abscedation. This patient was treated with the anti-VEGF monoclonal antibody bevacizumab in combination with chemotherapy

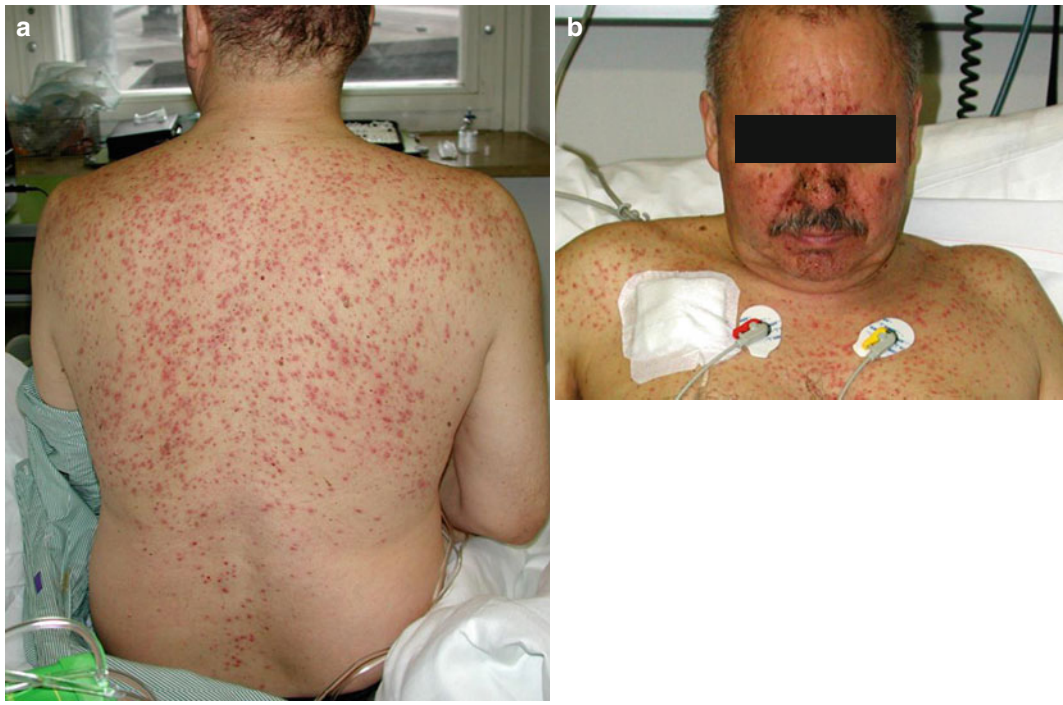

Fig. 5 (**a**, **b**) Patient who developed severe (grade 3 according to CTCAE V4.03) skin rash during weeks 4–6 of chemotherapy combined with the anti-EGFR-directed monoclonal antibody cetuximab

Conclusions

For clinical practice, we have to state that medical anticancer treatment is more demanding than ever, as toxicities are very common, polymorphic and allotropic. They may lead to severe impairment of the patients' safety and quality of life. All members of the treatment team, including the radiologist, need to do their best to support patients during anticancer treatment. Treatment-emergent as well as tumor-related complications may not be missed, and the severity of events must be appropriately classified. In addition, for drug development it has been advocated to move "Toward Patient-Centered Drug Development in Oncology" (Basch 2013).

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Radiotherapy

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Abstract

The focus of this chapter lies on the description of the general basics of early and late radiation effects and the translation of these pathogenetic processes into imaging; furthermore, a few short clinical examples including imaging patterns of those underlying pathogenetic normal tissue reactions are given to provide a better understanding. In addition, the margin concepts used in radiotherapy as well as the important radiation techniques are summarized, as it is very important for diagnostic radiologists to correlate post-therapeutic tissue and organ changes in follow-up examinations with dose characteristics of a certain treatment to achieve a higher degree of reliability in image interpretation. Furthermore, for

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