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REVIEW

Complications and comorbidities associated with antineoplastic chemotherapy: Rethinking drug design and delivery for anticancer therapy

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Abstract Despite the considerable advancements in chemotherapy as a cornerstone modality in cancer treatment, the prevalence of complications and pre-existing diseases is on the rise among cancer patients along with prolonged survival and aging population. The relationships between these disorders and cancer are intricate, bearing significant influence on the survival and quality of life of individuals with cancer and presenting challenges for the prognosis and outcomes of malignancies. Herein, we review the prevailing complications and comorbidities that often accompany chemotherapy and summarize the lessons to learn from inadequate research and management of this scenario, with an emphasis on possible strategies for reducing potential complications and alleviating comorbidities, as well as an overview of current preclinical cancer models and practical advice for establishing bio-faithful preclinical models in such complex context.

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1. Introduction

It is estimated that there were approximately 19.3 million new cases of cancer and roughly 10 million cancer deaths worldwide in 2020, and the global cancer burden is anticipated to keep increasing over the next two decades[1]. Meanwhile, the aging population is a social characteristic of many nations, including most developed countries like the USA and part of undeveloped countries like China. Chronologic age has been widely acknowledged as one essential risk factor in carcinogenesis, cancer biology, clinical response, and therapeutic outcome across most cancers. With an accelerated aging pace, the cancer burden is particularly pronounced in China where the estimated new cases (2.74 million) account for 1.05% of people older than 60 years (260 million) in 2020[2,3]. Chemotherapy is a fundamental modality for cancer treatment, utilized either as a standalone treatment or as part of combination therapy. Its efficacy has been well recognized since the 60s, contributing significantly to positive clinical outcomes. However, it is a sad truism that chemotherapy can also lead to unintended detrimental consequences in non-cancerous areas, giving rise to issues of chemotherapy-induced complications[4]. Concurrently, the prevalence of comorbidities is increasingly observed in individuals just diagnosed with cancer, especially within the elderly demographic[5]. To avoid potential confusion from terminology, comorbidities are defined as existing conditions at the time of diagnosis that are not consequences of cancer in this work. In contrast, complications refer to diseases occurring after the diagnosis of cancer as adverse events resulting from cancer[6]. These two conditions have the potential to lead to discontinuation of cancer therapy, compromised therapeutic outcomes, reduced survival rates, significantly diminished quality of life, and potentially more fatal consequences than cancer itself if left untreated[4,5]. And compelling information suggests that complications and comorbidities are frequently associated with poorer clinical outcomes in cancer patients, particularly the elderly[7]. Thus, both complications associated with chemotherapy and pre-existing diseases represent vast chapters of oncology due to their prevalence, polymorphous manifestation, intricate interplay with cancer, and substantial influence on the well-being of those receiving cancer therapy.

A large body of literature has extensively investigated and documented the potential off-target toxicities of chemotherapeutic agents, as well as the underlying principles that contribute to the complications induced by chemotherapy[8–10]. The prevalence of comorbid disorders within cancer patients has also garnered the attention and interest of oncologists and scientists, and increasing evidence has shed light on their potential influence on and intimate relationship with cancer[11,12]. These studies offer valuable knowledge and facilitate a deeper understanding of complications and comorbidities associated with chemotherapy. To date, some guidelines are available for the evaluation and management of complications in cancer patients[13,14], nevertheless, seldom consensus has been achieved on how to manage comorbidity in the context of cancer. Regrettably, randomized clinical trials are prone to excluding so-called high-risk people, such as elderly adults and those with comorbidity. Consequently, this leads to insufficient clinical data, limited efficacy information, and suboptimal clinical outcomes within these populations[15,16]. The surging prevalence of cancer and the impending demographic shift towards an aging population in numerous nations underscore the desperate need for a more comprehensive and incisive understanding of cancer and its long-term sequela. In this particular context, our review aims to provide a state-of-the-art overview of the current body of knowledge regarding the predominant complications and comorbidities associated with chemotherapy. The primary focus of this review is to examine their impact on cancer treatment, especially chemotherapy, as well as the intricate mechanisms underlying the intimate relationship between cancer and its long-term sequela. In addition, this work presents an outline of the essential lessons to learn for improved management of both cancer and its complications or comorbidities. These lessons encompass strategies aimed at mitigating the adverse effects while maintaining the efficacy of chemotherapy, and potential approaches to targeting the overlapped mechanisms of cancer and its comorbidities, as well as an overview of cutting-edge preclinical cancer models and practical advice on the establishment of bio-faithful models for the research of complications and comorbid diseases associated with cancer and chemotherapy. The overarching purpose of this work is to pinpoint actionable avenues to improve the health-related quality of life for cancer patients suffering from complications and/or comorbid conditions.

2. Complications induced by anticancer chemotherapy

Following the T92 (Toronto 1992) complication grading, various alternative systems have been proposed for the classification of surgical complications, including the Clavien-Dindo classification (CDC) [17,18], the Accordion system[19], the Memorial Sloan Kettering system[20], the comprehensive complication index[21], and several others[22]. These systems serve as valuable references for categorizing postoperative complications and assessing their severity. Most of these classifications are extended alternatives and built upon the framework established by the CDC. This section will provide a concise overview of the prevalent complications induced by chemotherapy, categorized according to their anatomical locations, akin to the classification system employed by the CDC. In general, these issues encompass cardiovascular, neurological, skeletal, and other complications. Specifically, we also discuss potential causal chemotherapeutic agents, the observable symptoms, and probably responsible mechanisms related to the complications.

2.1. *Cardiovascular*

Many antineoplastic chemotherapeutic agents can cause acute or chronic cardiotoxicity, which results in a range of adverse effects including heart failure and myocardial infarction. Cardiovascular diseases become the second leading cause of death in cancer survivors after cancer recurrence, which has garnered the attention and interest both of cardiologists and oncologists, leading to a novel discipline, termed cardio-oncology[23]. In the field of cardio-oncology, the damage of chemotherapeutic drugs to myocardial tissues has been well recognized despite their treatment benefits. There are already a few good reviews highlighting the cardiotoxicities related to chemotherapy[24–26]. From asymptomatic left ventricular ejection fraction, arrhythmias, and cardiomyopathy, to myocardial infarction, and severely symptomatic congestive heart failure (CHF), cardiovascular complications induced by chemotherapy can vary greatly depending upon the treatment regimens and the development of diseases[27]. The increased cardiovascular risk is attributable to both the direct effects of cancer chemotherapy and the indirect influence of other risk factors: hypertension, diabetes, and cigarette smoking, for example.

Notably, the emergence of cardiovascular complications related to chemotherapy has become a significant issue with increasing cancer survivorship. Hence, a better understanding of cardiovascular toxicities induced by different chemotherapeutic agents facilitates improved prevention of and treatment for those complications and the cancer itself. Herein, this section will pay special attention to the chemotherapeutic agents that directly cause cardiotoxicities and result in the formation of cardiovascular complications.

Various chemotherapeutics have been reported to be able to invoke cardiotoxicity, covering almost all classes of traditional chemotherapy drugs such as anthracyclines, platinum compounds and 5-fluorouracil (5-FU)[25,28,29]. It is well known that severe cardiotoxicity can be induced by anthracyclines, a class of wide-spectrum antibiotic widely used as antineoplastic agents for hematological malignancies, soft tissue sarcomas and solid tumors. Doxorubicin, epirubicin, and idarubicin are the most frequently used anthracyclines, which remain the most effective anticancer drugs to date. However, congestive heart failure (CHF) and left ventricular dysfunction (LVD) have been recognized as short and long-term complications of anthracycline exposure, and the underpinning mechanisms of anthracycline cardiotoxicity are mainly thought to stem from the inhibition of topoisomerase 2 and mitochondrial biogenesis due to oxidative stress[29–32]. In addition to anthracyclines, platinum complexes can also induce cardiotoxicities and complications. Circulating platinum after platinum treatment can cause continuous damage to the vascular system, resulting in aging of the vascular system and consequent complications[31,33]. Myocarditis or heart failure can be provoked by other alkylating agents such as cyclophosphamide and ifosfamide, probably owing to excessive oxidative stress generated during their complex metabolic process[34]. Antimetabolites, 5-FU and purine analogs, for instance, can cause chest pain, arrhythmias, and myocardial infarction, which have been attributed to oxidative stress and vasospasm[31,35]. Mitotic inhibitors, especially taxanes, can cause ischemic heart disease and chronic heart failure potentially attributable to their harm to Purkinje system or autonomic control[31,34,36]. Extending chemotherapy to a broader scope, more therapeutic agents can be included as main contributors to cardiovascular toxicities and complications, for example, tyrosine kinase inhibitors in targeted therapy and HER-2 inhibitors in immunotherapy, which have been discussed in other papers[27,37].

Table 1 summarizes the representative chemotherapy drugs associated with cardiovascular complications.

Although the elucidation of mechanisms underlying neurological complications associated with chemotherapy has achieved enormous progress and the field of cardio-oncology has thrived robustly since its advent, the prognosis of such neurological complications remains strikingly poor, let alone systematic and mature management. This situation urgently calls for cooperation between multidisciplinary organizations and services, and the establishment of practical and cost-effective clinical models for the management of cardio-oncology programs. Fortunately, this problem has aroused vigilance from global researchers who have given their valuable suggestions and tentative solutions[38–40]. In proportion, the prevention of cardio-oncology also attracts great attention of scientists and oncologists *via* multi-modal approaches from pharmacologic cardio-protection to lifestyle therapy, risk management, surveillance strategy, and so forth[41,42]. Besides, it is also advocated that a specific gender-based point of view in the care process for cardio-oncology should be developed given the difference in biology, socio-economy, and culture due to gender inequality and gender differences[43].

2.2. *Neurological*

Although chemotherapy brings clinical benefits to cancer patients, mounting evidence indicates that long-term administration of chemotherapeutic agents causes pathological damage to the nervous system, leading to the incidence of neurological complications associated with chemotherapy[10,44]. The chemotherapy-induced neurotoxicity can manifest in numerous ways, such as headache, distal pain, visual loss, seizure, cerebellar dysfunction, and spinal cord damage with myelopathy[45]. While several articles have comprehensively reviewed neurological complications along with chemotherapy and systemic cancers, this section places more stress on those frequently diagnosed in patients with advanced cancer, in particular, representative complications such as peripheral neuropathy and cognitive impairment (also known as 'chemobrain'), as well as corresponding chemotherapeutic agents related to them[10,46,47]. A broad array of widely used chemotherapy agents, including platinum complexes, anthracyclines, vinca alkaloids, taxanes, and thalidomides have been reported to be neurotoxic to varying extents and able to induce neurologic

Table 1 Main symptoms and possible mechanisms of cardiovascular complications induced by representative chemotherapies.

Drug	Cardiovascular symptom	Possible mechanism	Ref.
Anthracyclines	Acute myocarditis, arrhythmias, LVD, CHF	Oxidative stress Inhibition of topoisomerase 2 Mitochondrial damage Inflammation	29,30,36,37
Alkylating agents (platinum complexes, cyclophosphamide, ifosfamide)	Arrhythmias, myocarditis, HF	Direct endothelial injury Oxidative stress Mitochondrial damage	31,32,37
Antimetabolites (5-FU, capecitabine, methotrexate)	Chest pain, myocardial infarction, cardiogenic shock, CHF	Vasospasm Endothelial injury Oxidative stress	33,37
Mitotic inhibitors (paclitaxel, docetaxel, vinca alkaloids	Ventricular tachycardia, cardiac arrhythmias, atrioventricular block, ischemia, HF	Damage on Perkinje system or autotomic control	32,34,37

5-FU, 5-fluorouracil; LVD, left ventricular dysfunction; CHF, congestive heart failure; HF, heart failure.

complications after long-term exposure[48,49]. The peripheral nervous system (PNS) remains extremely vulnerable to antineoplastic agents which may cause directly toxic effects on it and bring on the occurrence of chemotherapy-induced peripheral neuropathy (CIPN). Although the blood−brain barrier (BBB) prevents most chemotherapeutic drugs from directly intoxicating the central nervous system (CNS), receptor-mediated chemotherapy drugs, metabolites of anticancer agents, and released inflammatory cytokines during chemotherapy can transport across the BBB steadily, resulting in neurotoxicity to the CNS and consequent chemotherapy-induced cognitive impairment (CICI) and other complications[10]. The exact mechanisms involved in such complications are still unclear, yet increasing endeavors have been put into identifying the molecular, biochemical, and neurobiological pathways engaged[47,48,50−52]. To date, impaired neurogenesis, excessive oxidative stress, and neuroinflammation are believed among the main mechanisms by which neurological complications are induced both in CNS and PNS[53,54]. Other proposed mechanisms include damage to the BBB integrity, genetic predisposition, transporter-mediated uptake, and so forth[44,55].

The recognition of neurological complications related to specific chemotherapeutic agents can be crucial for cancer management and improvement of the quality of life of patients given that prevention and diagnosis of neurological complications are often difficult since many neurological disorders and illnesses show similar symptoms. Chemotherapy agents are rarely administered alone, but frequently in combination with other anticancer drugs and/or other therapeutic modalities. Thus, correct identification of responsible anticancer drugs to specific neurological complications affords rapid and proper modification of the offender, circumvention of extra testing, and potential discontinuation of irrelevant mediations. Herein, we summarize the antineoplastic agents associated with neurological complications both in PNS and CNS (Table 2)[45,47,52,56−63]. Chemotherapy agents related to peripheral neuropathy cover the majority of conventional anticancer drugs, including alkylating agents (platinum complexes), mitotic inhibitors (taxanes, epothilones, and vinca alkaloids), proteasome inhibitors (bortezomib), and antiangiogenic agents (thalidomides). The main symptoms of complications in PNS present as sensory, motor, and autonomic neuropathy. Whereas, neurological complications to the CNS are likely to be induced by antimetabolites (methotrexate, and 5-FU), and alkylating agents (ifosfamide, nitrosoureas, platinum compounds), among others. Unlike complications in PNS, neurological complications in CNS may manifest in different means, mainly acute/chronic encephalopathy, seizures, headache, visual loss, and cerebrovascular complications[58].

2.3. *Skeletal*

It is a sad fact that nearly all patients suffer from severe skeletal complications with advanced cancers where bone metastasis occurs in the late stage of cancer development, frequently in breast, prostate, lung, thyroid, bladder, and kidney cancers[64,65]. Skeletal complications, also called bone metastasis-associated complications, mainly include chronic bone pain, pathological fracture, hypercalcemia, spinal cord compression, and cancer cachexia[66]. These complications seriously impair the patients' quality of life and are responsible for increased risks of morbidity and mortality in cancer patients. The disseminated tumor cells invade the bone and disrupt normal bone homeostasis *via* interactions with the resident local microenvironment, leading to tumor growth in bone and consequential skeletal complications[67,68]. This underlying mechanism was termed "the vicious cycle" of bone metastasis[69,70]. Frequently, muscle loss accompanies the emergence of skeletal complications, skeletal muscle loss or sarcopenia has been identified as a predictive factor for clinical outcome and chemotherapy-induced complications, and it is also implied to be associated with decreased survival in cancer patients[71−73]. Recent findings suggested that such musculoskeletal complications induced by chemotherapy are predominantly attributed to bone-muscle crosstalk through endocrine signaling[74,75]. To address skeletal-related complications associated with chemotherapy, bisphosphonates are commonly used to prevent the emergence of associated skeletal complications, as well as other bone-targeted antiresorptive agents such as zoledronate, clodronate, pamidronate and ibandronate[76].

2.4. *Others*

2.4.1. *Chemotherapy-induced nausea and vomiting*

Nausea and vomiting are still among the most feared complications in cancer patients undergoing chemotherapy[77]. More than 90% of cancer patients are estimated to be under exposure to highly emetogenic chemotherapeutic agents, *e.g.*, platinum complexes, anthracyclines, and cyclophosphamides, while 30%−90% of cancer patients exposed to moderately emetogenic agents, *e.g.*, irinotecan, nitrosoureas, and low-dose anthracyclines[78]. Though acute chemotherapy-induced nausea and vomiting (CINV) can be effectively managed in most patients, delayed CINV remains a clinical challenge and poses a detrimental impact on patients' quality of life[78]. The pathophysiology of CINV is a complex process without comprehensive understanding and continues to be elucidated, involving contributory interaction between neurotransmitters and receptors located both in the CNS (brain) and PNS (gastrointestinal tract)[79,80]. Stimuli including chemotherapy administration transmitted *via* the peripheral pathway primarily cause acute emesis, while the central pathway is predominantly associated with delayed CINV. When left untreated, cancer patients might suffer from dehydration, electrolyte imbalance, chemotherapy discontinuation, and increased morbidity. Hence, the prevention and treatment of CINV are critically crucial and need to vary according to its forms, *e.g.*, acute, delayed, anticipatory, breakthrough, and refractory. Various guidelines are available to give reasonable recommendations for the management of CINV, including well-recognized National Comprehensive Cancer Network guidelines and the American Society of Clinical Oncology guidelines[81]. Neurokinin-1 receptor antagonists, serotonin (5-HT_3) receptor antagonists, dexamethasone, olanzapine, and palonosetron are among the most popular antiemetic prophylaxes for the control of CINV[82,83]. Interestingly, ginger and many other natural products showed beneficial effects against CINV probably by inhibiting 5-HT_3 receptors[84,85]. On top of that, computational modeling has been proposed to predict the risk of experiencing CINV in cancer patients with good accuracy[86].

2.4.2. *Infections*

Infection represents another fatal complication of cancers, and can strongly influence cancer incidence, morbidity, and mortality. According to a recent report, 13% of global new cancer cases (non-melanoma skin cancers excluded) are attributable to infections in 2018, and the first four culprits are *Helicobacter pylori*, human papillomavirus (HPV), hepatitis B virus (HBV) and

Table 2 Main symptoms and potential mechanisms of neurological complications caused by representative chemotherapies.

Drug		Neurological symptoms in CNS	Potential mechanism	Ref.	Peripheral neuropathy in PNS	Potential mechanism	Ref.
Alkylating agents	Platinum compounds (cisplatin, carboplatin, oxaliplatin)	Seizures, encephalopathy, visual loss, cerebrovascular complications	Vasospasm, increased BBB permeability, neurogenesis degeneration, neuronal damage, inflammation, transmitter dysregulation	47,59,60	Sensory, motor	Neuronal damage, ion channel disturbance, oxidative stress, inflammation	47,61–63
	Cyclophosphamide, ifosfamide	Encephalopathy, seizures	Neurogenesis degeneration, neuronal damage, inflammation	47,59	–	–	–
	Nitrosoureas (carmustine)	Encephalopathy, visual loss	Neuronal damage, increased BBB permeability, inflammation, oxidative stress	47,60	–	–	–
Mitotic inhibitors	Taxanes (paclitaxel, docetaxel)	Encephalopathy, seizures, visual loss	Inflammation, neuronal damage	47,59	Sensory, motor	Disruption of axonal transport, oxidative stress, inflammation, mitochondrial damage, neuronal injury	47,61–63
	vinca alkaloids	Encephalopathy, seizures, visual loss			Sensory, motor, autonomic		
	Ixabepilone	–	–	–	Sensory, motor		
Proteasome inhibitors	Bortezomib	–	–	–	Sensory, motor, autonomic	Mitochondrial damage, oxidative stress, inflammation	47,52,62,63
Antiangiogenic agents	Thalidomide, lenalidomide, pomalidomide	–	–	–	Sensory, motor, autonomic	Neuronal injury, oxidative stress, NF-κB inhibition	52,62
Antimetabolites	Methotrexate	Headache, seizures, encephalopathy	Neuronal damage, inflammation, dysregulated microglia, astrocytes and oligodendrocytes	47,59	–	–	–
	5-Fluorouracil	Encephalopathy, seizures, headache	Neuronal damage, inflammation, transmitter dysregulation	47,59,60	–	–	–
Antibiotics	Anthracyclines (doxorubicin, daunorubicin)	Encephalopathy, cerebrovascular complications	Neuronal damage, inflammation, neurotransmitter disturbance, oxidative stress	47,59	–	–	–

CNS, central nervous system; PNS, peripheral nervous system; BBB, blood–brain barrier; –, not applicable.

hepatitis C virus (HCV)[87]. Regrettably, China accounts for over one-third of these infection-attributable cancer cases, particularly those caused by *H. pylori* and HBV, which also predisposes them to gastric and hepatic cancer[87]. Except bacteria and viruses, it is becoming evident that fungi, protists, and even helminths could also contribute to the development of cancer[88,89]. The Infectious complications significantly impact the morbidity and mortality of cancer patients, especially those burdened with hematological malignancies where nearly 60% of deaths are directly associated with infections. In patients with solid tumors, infections are estimated to be either the primary or related cause of death in about half of the patients[90]. In addition to immune compromise and related comorbidities, cancer therapy-associated factors including chemotherapy are among the risk factors for infections in cancer patients. Despite procedures and devices used in the prognostic process, the emergence of neutropenia, disruption of anatomic barriers, and obstruction of healthy passages can considerably increase the infectious risk in patients with solid tumors[91]. Infections often occur in body sites hinging on the tumor sites, especially those locations enriched with epithelial and mucosal structures where microorganisms dwell, for example, skin, bloodstream, respiratory tract, and urinary tract[91].

Increasing evidence shows that patients undergoing chemotherapy are at significantly increased risk for developing infectious complications, mainly stemming from the unfavorable consequences due to adverse effects of chemotherapy, such as chemotherapy-induced neutropenia, disruption of normal biological barriers, and alterations in the host microbiome[92–94]. Chemotherapy regimens, especially those containing myelosuppressive agents, are often considered the main contributor to the emergence of neutropenia, followed by elevated susceptibility to infections in cancer patients[95]. Based on a comprehensive analysis, most cytotoxic agents (*e.g.*, alkylating agents, antimetabolic agents, anticancer antibiotics, platinum complexes, and alkaloids) enable to induce neutropenia, highlighting the need for more cautious management of elderly and underweight patients receiving chemotherapy[96]. Damage to and disruption of natural anatomic barriers, for instance, the skin and mucosal surfaces, is another common side effect of chemotherapy, facilitating the invasion of infective pathogens and the development of infectious complications[91] Anthracyclines, 5-FU, cisplatin, carboplatin, etoposide, cyclophosphamide, ifosfamide, methotrexate, vinblastine, and taxanes are among the common chemotherapeutic agents that frequently cause mucositis[97]. Furthermore, the injury to mucosal barriers is frequently associated with a changed host microbiome, thus detrimental dysbiosis and even antimicrobial resistance[92,98,99]. Additionally, antimicrobial prophylaxis, usually against Gram-negative organisms, is commonly given to patients with hematologic malignancies instead of those with solid tumors, leading to a higher prevalence of Gram-negative infections in these patients[91]. Fortunately, the prevention and control of infectious complications in cancer patients has garnered the attention of both oncologists and clinicians, and corresponding guidelines and practice advice have been set up to tackle infectious issues[100,101].

The progress of technology substantially underpins the prognosis of cancers and accompanying complications, especially the rapid development of computation capacity. Recently, artificial intelligence and machine learning have been utilized to predict chemotherapy-induced complications[9]. Besides, mechanistic pharmacokinetic and pharmacodynamic modeling also provides an important opportunity to predict cardiotoxicities of antineoplastic drugs for precision cardio-oncology[102]. Though the therapeutic effects of chemotherapy guarantee the basic survival of cancer patients, the suffering from chemotherapy-induced complications should not be ignored, and potential prevention and treatment of these complications should be carefully weighed and evaluated against the overall benefit of cancer treatment.

3. Pre-existing diseases with reciprocal influence on chemotherapy

It is increasingly common that patients are burdened with other diseases when newly diagnosed with cancers. Cancer patients with coexisting diseases (comorbidity) are reported to have poorer survival and lower quality of life[103–105]. A recent prospective cohort study covering 405,878 participants reveals that coexisting chronic diseases are neglected cancer risks, which contribute to over one-fifth of cancer incidence risk and over one-third of cancer mortality risk[106]. This phenomenon is particularly remarkable in elder people who account for more than 60% of cancer patients in high-income countries[103]. Observational data have shown positive correlations between several diseases and pan-cancer incidence, including cardiovascular diseases, pulmonary disorders, and diabetes. Based on the data from a regression analysis, hypertension (29.7%), pulmonary diseases (15.9%), and diabetes (13.5%) are the most common comorbidities, while lung cancer and colorectal cancer are the most common cancers with comorbid diseases, followed by prostate cancer, melanoma, and breast cancer[5]. The existence of comorbidities greatly interferes with the diagnosis and treatment of cancers, for the symptoms of comorbid diseases could be similar to those of cancers, and the practice of corresponding cancer therapies may be halted or canceled due to the effects of comorbidities, such as poor pulmonary and cardiac function[107]. In this section, we discuss these three most common comorbidities in cancer patients with specific stress on the potential interplay between these coexisting diseases and cancer, and possible influence on treatment management.

3.1. Hypertension

In response to the increased risk of cancer pathogenesis by cardiovascular diseases (CVD), a new term was coined reverse-cardio oncology, which was supported by epidemiological and preclinical studies[108,109]. According to a recent study of more than 27 million individuals, people with CVD have a 13% higher risk of developing cancer than those without CVD, and the risk rises to 20% in people with atherosclerotic CVD[110]. In fact, CVD and cancer race neck to neck as two leading causes of morbidity and mortality worldwide[111,112]. Hypertension, a forerunner and well-established risk factor of other cardiovascular diseases, has been recognized as the most common comorbid disease in patients with cancer[113]. Accumulating evidence suggests that hypertension and cancer share numerous risk factors, including diabetes, smoking, and obesity[114]. In addition to shared risk factors, the overlap of pathophysiological mechanisms is believed to contribute prominently to both conditions, such as inflammation, increased reactive oxygen species (ROS), and oxidative stress involved in both hypertension and cancer[114]. These common risk factors and pathophysiological mechanisms indicate the inevitable interplay between cancer and hypertension. The impact of cancer chemotherapy on CVD including hypertension has been discussed in the previous section, therefore, the opposite effect will be reviewed here.

Several investigations implied that hypertension itself may promote the development of certain cancers, especially kidney cancer, excluding the positive association between cancer and antihypertensive therapy[115−117]. Patients with hypertension showed a 2.5-fold increased risk of developing kidney cancer compared with those without hypertension in a study covering almost 300,000 European patients during a 6-year follow-up[118]. This finding was supported by a Korean national study with more than 9,746,000 participants during an 8-year follow-up that a significantly increased risk for kidney cancer was found in people with hypertension[119]. However, in the instances of breast, colorectal, endometrial, and bladder cancers, the influence of hypertension and antihypertensive medication on them seems uncertain with controversial conclusions in different analyses[120−122]. Despite the increased risk of cancer incidence, augmented cancer mortality (7%−15%) was found in cancer patients with hypertension compared to normotensive patients[123]. Apart from the impact on cancer incidence and mortality, the coexistence of hypertension also directly affects cancer therapy, particularly chemotherapy. As discussed in the previous section, several classes of chemotherapy drugs, anthracyclines for instance, are well known to cause cardiovascular damage in a dose-dependent manner. Recent studies imply that pre-existing hypertension, especially poorly controlled hypertension, significantly amplifies the risk of chemotherapy-induced cardiac adverse events, in particular cardiomyopathy and heart failure[124]. Similarly, evidence showed that cardiotoxicity associated with trastuzumab has been aggravated by the presence of hypertension[125]. Thus, pre-existing hypertension may compromise the clinical outcomes of cancer patients undergoing anthracyclines-/trastuzumab-based therapy, and pretreatment of hypertension becomes essential before commencing such anticancer therapies, particularly those having pro-hypertensive effects[126].

3.2. *Pulmonary diseases*

Similar to hypertension and other CVD, increasing evidence indicates that pulmonary diseases, particularly chronic obstructive pulmonary disease (COPD), promote the risk of developing several cancers, especially lung and colorectal cancers[127−129]. It is well-established that COPD is an independent risk factor for lung cancer, as the most prevalent comorbidity found in almost 37% of lung cancer patients[130]. A Korean national study involving 338,548 subjects indicated that the incidence rate of lung cancer is 6-fold higher in nonsmokers with COPD, and dramatically increases to 19-fold higher in ever-smokers with COPD compared to never-smokers without COPD[131]. Another population cohort study with 716,872 subjects showed that individuals with pulmonary tuberculosis (PTB) have an approximate 11-fold higher incidence of lung cancer[132]. And the overlap of COPD and PTB further boosts the risk of developing lung cancer[133]. Likewise, another nationwide investigation demonstrated that patients with idiopathic pulmonary fibrosis (IPF) have a 6-fold higher incidence rate of lung cancer than those without IPF[134]. These corroborate that pulmonary comorbidity spurs the risk of developing cancers and *vice versa*. The strong reciprocal effect between pulmonary diseases and cancers, specifically lung cancer, might stem from the shared pathogenic features both in genetic and epigenetic levels, for example, genetic aberration, immune dysfunction, lung microbiome, oxidative stress, and chronic inflammation[127,135−137].

In addition to the impact on cancer incidence, poorer survival and lower quality of life also result from the presence of concomitant pulmonary diseases in patients burdened with lung, laryngeal, and colorectal cancers[138−140]. Such phenomena could be partially explained by the fact that the existence of pulmonary comorbidities has extensively affected the prognosis and complicated the management and treatment of cancer patients with comorbid conditions. For instance, transthoracic needle biopsy might be inadvisable in lung cancer patients with severe emphysema or with diffuse lung fibrosis, thus resulting in imprecise diagnoses. In patients with COPD, surgery can be impossible due to insufficient respiratory function[141]. As a result, comorbidity significantly influences the outcome of clinical treatment, particularly chemotherapy, in patients with lung cancer[142]. In a similar way, pulmonary comorbidity affects the management, treatment choice, and outcome as well in patients with colorectal cancer, head and neck cancer, and esophageal cancer[143−145]. Hence, cancer screening could greatly benefit from prospective studies including patients with pulmonary diseases complying with reasonable risk score systems[146]. Additionally, therapeutics against pulmonary comorbidities, such as statin therapy for COPD, have shown chemo-preventive benefits in COPD patients against colon and lung cancers, implying that proper treatment of pulmonary comorbid conditions may reduce cancer risks and provide chemoprotective effects[147,148].

3.3. *Diabetes*

Apart from cardiovascular and pulmonary comorbidities, the concurrence of diabetes and cancer is highly prevalent nowadays with the aging population, and pre-existing diabetes is frequently thought to be a risk factor for cancer and associate with increased risk of cancer incidence and mortality[149−151]. Meta-analyses implied that the greatest risks (around 2-fold or higher) lie in cancers of the pancreas, liver, and endometrium, and moderate (around 1.2−1.5-fold) in cancers of the colon and rectum, breast, and bladder[150,152]. The association between diabetes and cancer has been supported by compelling shreds of evidence in epidemiological, clinical, and experimental research[153]. Several risk factors are shared both in diabetes and cancers, such as obesity, aging, smoking, alcohol, and physical inactivity[151,154]. Although the exact mechanisms behind this association need further elucidation, emerging data show that many pathophysiological contributors of diabetes can also fuel the carcinogenesis process during cancer progression, including hyperglycemia, hyperinsulinemia, dyslipidemia, inflammation, microbiome, epigenetic changes, and oxidative stress[153,155−157]. It is well recognized that many cancer chemotherapies may increase blood glucose concentration, particularly those involving glucocorticoids, thus leading to the emergence of hyperglycemia and even diabetes[158]. By contrast, the effects of anti-diabetic therapies on cancer are controversial. According to a recent meta-analysis involving 171 million participants with diabetes, biguanide use is inversely related to colorectal and liver cancers, thiazolidinediones with lower risks of breast, lung, and liver cancers, and insulins with lower risks of breast and prostate cancer[159]. On the other hand, insulin secretagogues are positively associated with a higher risk of pancreatic cancer, and insulins with higher risks of liver and pancreatic cancers as well[159]. Besides, the effect of metformin on cancer is also contentious, with some research showing protective and anticancer effects against several cancers in addition to its anti-diabetic efficacy, others demonstrating no significant difference[160−162]. Therefore, additional studies should be carried out to confirm the interplay between chemotherapy and diabetes,

as well as the influence of anti-diabetic therapies on cancer management. Furthermore, integrated clinical care has to be highlighted for cancer patients with diabetes[163]. Except for attempts at the practical level, machine learning has also been proposed to predict and diagnose cancer and diabetes using advanced algorithms with high accuracy[164].

This section witnesses the strong links between the most prevalent coexisting diseases and cancer that they share many risk factors in common and even foster the development of each other. Various potential mechanisms behind these connections have been clarified, but more are yet to be fully understood, for elucidating the mechanisms underlying the association between these comorbidities and neoplasia may offer hints for developing novel strategies for cancer prevention and prognosis. Meanwhile, the therapies for both comorbidities and cancer should be carefully checked in cancer patients burdened with comorbid conditions given that some cancer chemotherapeutic drugs might exacerbate the coexisting diseases and vice versa. Ideally, that some therapies could be efficacious against both conditions, which will be discussed in the next section.

4. Lessons to learn from cancer complications and comorbidities

Complications and comorbidities without proper management can result in more fatal consequences than the cancer itself, and they may greatly compromise the therapeutic effects of antineoplastic chemotherapies. We can see from previous discussions that our understanding of cancer and its complications and comorbidities is far from enough. There are many lessons (Fig. 1) that we have to learn from them to rationally design and deliver anticancer drugs, especially how to develop effective strategies to maximize the efficacy and minimize adverse effects of cancer chemotherapies, how to manage both conditions through targeting their common mechanisms, and how to establish rational animal models to rule out relevant mechanisms and translate basic research findings from bench to bedside.

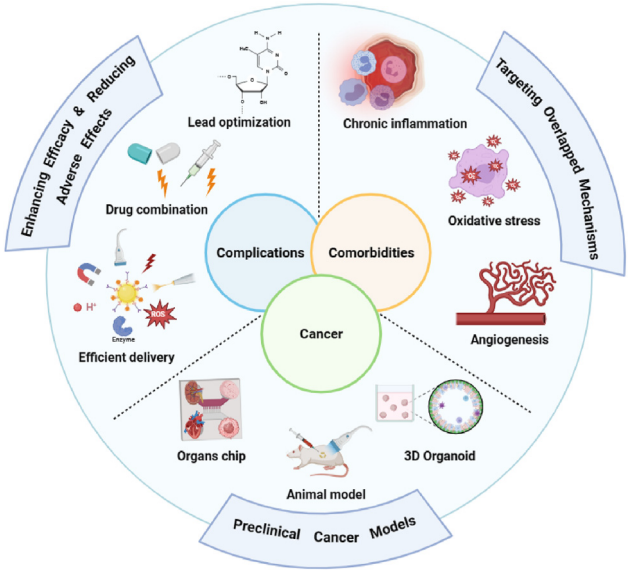

Figure 1 Lessons to learn for the research of complications and comorbidities associated with cancer chemotherapy.

4.1. Strategies to maximize the efficacy and minimize adverse effects of chemotherapy

As previously mentioned, the occurrence of complications and the aggravation of comorbid diseases stem in part from the adverse side effects and long-term sequela of anticancer chemotherapies despite barely satisfactory efficacy and enhanced survival. Approaches to addressing potential long-term consequences (*e.g.*, complications and comorbidities), are frequently ignored or underestimated, although adverse effects associated with chemotherapy have garnered more attention and massive attempts have been conducted to counteract their influence[165]. Thus, new strategies to reinforce tolerance and diminish sequela are urgently needed while minimizing adverse effects and maintaining the efficacy of chemotherapies. To achieve this goal, diverse strategies have been developed and trialed in the last decades, including lead optimization of effective molecules, drug combinations for better efficacy, and size control for effective delivery, among others.

4.1.1. Lead optimization

Lead optimization is a pivotal process in drug discovery to modify bioactive natural products and synthetic compounds in order to enhance or preserve desired properties of the molecules and meanwhile diminish structural defects[166]. Novel anticancer chemotherapeutics can be designed with favorable biological properties by this approach based on lead structures of existing bioactive molecules either from natural or synthetic sources. This strategy is a common occurrence in the history of anticancer drug development. For instance, the serendipitous discovery of cisplatin initiated the exploration of Pt(II) complexes for their potent antitumor effects and opened a new era of metal-based anticancer agents[167]. However, the instability and low bioavailability caused severe side effects and complications which greatly impeded the medical applications of these Pt(II) complexes. In this context, lead optimization emerged as a good solution by transforming the Pt(II) compounds into Pt(IV) prodrugs with better stability in blood circulation and similar efficacy when reduced into Pt(II) forms in cancer cells, thus significantly reducing the side effects on nonmalignant cells and tissues. Furthermore, Pt(IV) complexes have two additional axial ligands compared to their corresponding Pt(II) counterparts, which enables further chemical modification to improve the biochemical properties of the prodrugs, such as augmented water solubility, improved pharmacokinetic performance, better stability against degradation, favorable release in cancer cells, and even enhanced cytotoxicity[168]. There are many nice reviews on Pt(IV) prodrugs available so we are not going to plunge in here[169,170]. Similar optimization in the lead structures is abundant in almost all types of chemotherapeutic agents, such as gemcitabine in antimetabolites, paclitaxel in antimitotics, doxorubicin in antibiotics, and so forth[171–174].

From a chemical standpoint, this strategy can be further subdivided into three asymptotic stages[175]. The most straightforward modification is the direct maneuvering of functional groups on the lead compounds, including alteration or replacement of the functional groups, changing the ring systems, and isosteric substitution. Attempts in this stage are commonly empirical and intuition-driven, particularly in the manipulation of natural substances. Once the structure–activity relationships (SAR) of the bioactive molecules were primarily established, the second stage came to subsequently optimize the lead structures guided by the SAR. Generally, the optimization in this step is more rational based on the direction of SAR, and chemical and biological

information accumulated in the first stage. Anticancer agents derived from natural products by these two methods are estimated to occupy about one-third of small-molecule antineoplastic drugs[175]. Notably, the core structures of the molecules are basically not altered in these two stages so efficacy and pharmacokinetics are mainly affected by the modification while the chemical accessibility of the compounds is barely touched. Pharmacophore-oriented molecular modification represents the last approach to optimize the existing compounds or design novel molecules, which could change the structures significantly while holding the pharmacophores only[176]. In this case, recognized SAR hints could expedite the identification of pharmacophores and accelerate the process of drug discovery[177,178]. And it is frequently used to address the issues mingled with chemical accessibility of existing agents, in addition to the design and generation of novel drugs. This tactic is widely applied in modern pharmaceutical design and discovery, for example, scaffold hopping and structure-based drug design[176,179]. Moreover, other technologies can greatly facilitate the process of lead optimization, including experimental techniques (NMR-, MS-, and crystallography-based screening, etc.) and computational techniques (pharmacophore studies, quantitative SAR, molecular docking, dynamics analyses, etc.), especially when encountered with large chemical dataset and complicated macromolecular interactions[166,177,180].

4.1.2. *Drug combination*

Drug combination is another promising therapeutic strategy in cancer treatment in order to magnify efficacy, diminish adverse effects, and even overcome drug resistance[181]. Vast antineoplastic drugs were developed as mono-therapeutic agents and demonstrated encouraging efficacies in preclinical studies, but the failure rate was as astonishing high as 90% in following clinical trials in the US during 1993−2002[182]. Incorporating therapeutic agents rationally permits potential improvement of this dismal track record. In the latest decade, only 81 drug combinations were approved by the US Food and Drug Administration (FDA), 62% for solid tumors and the remaining for hematologic malignancies[183]. Two-thirds of these combinations include agents previously approved for monotherapy, the rest comprising new chemical/biological entities. Undoubtedly, the discovery of effective drug combinations demands tremendous effort and investment. Initially, chemotherapeutic agents used for combination therapies were often determined by empirical experiments to observe potential synergistic effects across different drug pairs. Compounds from natural sources have attracted intensive interest in combinational therapies, such as curcumin from turmeric, ginsenosides from ginseng, and quercetin from tea, among others[184−186]. These natural products are frequently employed as complementary medicine in cancer treatment largely owing to their capacity to enhance chemotherapeutic sensitivity and alleviate adverse effects induced by chemotherapy, and their anticancer mechanisms of action are also under intensive research[187,188]. Additionally, a high-throughput platform has been established to rapidly screen possible drug combinations against patient-derived models, permitting several prominent hits, especially meaningful for drug resistance[189]. More recently, guided by multi-omic molecular features, another large-scale study examined the potential synergistic effects of more than 2000 drug pairs in 125 breast, colon, and pancreatic cell lines in a high-throughput genomics screening platform, showing a disappointing rate of drug synergy with high context-dependence[181]. In fact, the number of possible drug combinations explodes exponentially along with the burgeoning expansion of the anticancer drug library, which makes experimental testing impractical and unfeasible. To accelerate the identification of effective drug synergy, the application of artificial intelligence and advanced computation becomes a sensible option for the screening and discovery of suitable therapeutic combinations[190]. Thus, the development of anticancer drug cocktails gradually transforms from empirical-driven experiments to target-guided modeling[191,192]. Compelling investigations are emerging in the field of computational prediction as well as the roaring establishment of corresponding datasets for anticancer combination therapies[192−195]. It is noteworthy that such *in silico* prediction requires adequate clarity of relevant chemical and biological mechanisms, concrete support of large-scale data collected in a standardized manner, network integration from different platforms, and creative collaboration across different institutions and fields. Besides, drug combination also offers an alternative approach to exploit the therapeutic value of various agents by drug repurposing[196]. On top of that, potential drug−drug interactions should be carefully evaluated and harmful drug cocktails should be avoided in anticancer combination therapies[197].

4.1.3. *Effective delivery*

In addition, effective delivery of antineoplastic agents has been embraced to offset the undesirable long-term sequela caused by chemotherapy while preserving or even enhancing favorable anticancer potency. The discovery of the enhanced permeability and retention (EPR) effect represented a hallmark in the history of chemotherapy and commenced the revolution of anticancer drug delivery, which depicted the phenomenon of defective vasculature and abnormal lymphatic drainage in solid tumors[198]. Since then, the research on size control of anticancer drug delivery systems (DDS) has been in full swing and many excellent reviews are available in relation to the history and development of delivery platforms with size control, especially anticancer micro- and nanomedicine[199−201]. Commonly, these micro/nanomedicines demonstrate multiple advantages over conventional small-molecule anticancer drugs, *e.g.*, improved pharmacokinetic properties with resulting prolonged plasma half-life, favorable accumulation in tumor with consequent enhanced anticancer efficacy, and decreased off-target effects in normal tissues followed by reduced adverse reactions[202]. Hence, size control of DDS for chemotherapeutic agents, for instance, micro- and nano-scale formulations, has sprung up as another useful strategy for enhancing therapeutic efficacy and reducing adverse effects.

Obviously, relying on the passive targeting brought forth by EPR effect itself is difficult to effectively deliver anticancer drugs into the central parts in tumors due to the heterogeneity of EPR effect both inter- and intratumorally[203]. Thus, various approaches have been explored to reinforce the EPR effects, such as EPR enhancement using adjuvant enhancers, tumor blood flow speed-up using angiotensin II, arterial infusion of therapeutics for better penetration, among others[204,205]. Instead of counting on the passive targeting only, increasing the active-targeting ability of DDS has been buttressed by a number of studies to represent another helpful strategy for effective anticancer drug delivery[206,207]. Harnessing the unique features of tumors to produce smart nanomedicines is an attractive approach to target tumors for effective drug delivery, *e.g.*, DDS sensitive to pH, ROS, enzymes, GSH, and overexpressed proteins, as well as those responsive to external stimuli, such as temperature, light, magnetic, ultrasound, etc.[208]. Furthermore, codelivery of natural products and

chemotherapeutics surges as an interesting anticancer approach due to the re-sensitizing capability of natural compounds to drug resistance and outstanding chemoprotective effects on normal tissues[209]. Emerging work implies that compared to their free forms, nanocomposite formulations of various chemotherapeutic drugs can effectively reduce multiple side effects, such as cardiotoxicity, neurotoxicity, nephrotoxicity, among others[210–212]. Despite reducing acute side effects, nanoformulations have displayed decreased long-term adverse effects including complications associated with chemotherapy[213,214]. Additionally, nanotechnology also holds significant promise for the management of common comorbidities (*e.g.*, CVD, diabetes, and pulmonary diseases) along with cancer chemotherapy[215–217]. Apart from nanotherapeutics, micro-sized carriers such as microparticles and microemulsions are also adopted for effective pulmonary delivery due to the physiological characteristics of pulmonary system[218]. Nevertheless, many concerns arise about the bio-safety, particularly toxicities resulting from small sizes of these micro/nanomedicines, which should be taken into consideration and be carefully evaluated when applying such DDS to anticancer therapies[219]. Moreover, the clinical translation of nanomedicines is unsatisfactory although a large body of literature surged about prominent preclinical researches on anticancer nanoparticles, therefore, some challenging issues must be taken into consideration when translating nanomedicines from bench to bedside, including patient stratification for better clinical response, rational design and constructure of nanomedicines, and selective combination with other therapy modalities, as well as controllable, reproducible and scalable production of nanomedicines[220–223].

Apparently, the strategies discussed above can work not only independently, but also in a combinational manner, such as the union of nanotechnology and drug pairs, blending of lead optimization and nanomedicine, or even all of them[224–226]. In addition to the strategies aforementioned, more approaches are contributing to the optimization of therapeutic efficacy and minimization of side effects of cancer therapies, such as immunotherapy, genetic therapy, and targeted therapy, which are not addressed here due to our confined review scope in chemotherapy[227–229].

4.2. Targeting shared mechanisms by one-key-two-birds strategies

As reviewed in previous sections, chemotherapeutic agents could exacerbate the pre-existing problems in cancer patients, in turn, the therapeutics against the comorbidities may also negatively affect the chemotherapeutic outcomes. Notably, diverse common mechanisms (Fig. 2) underlie the interplay between cancer and pre-existing diseases, and this fact provides profound therapeutic implications that it would be ideal to target these shared pathophysiological similarities to exert therapeutic efficacy against both conditions in one fell swoop, in order to avoid or mitigate the adverse interference between both therapies. Chronic inflammation, oxidative stress, and angiogenesis are among the overlapped mechanisms, and they will be discussed in this section as potential shared therapeutic targets for the treatment of both cancer and its long-term adverse consequences, in particular, comorbid disorders[230–232].

4.2.1. Chronic inflammation

As previously discussed, compelling evidence showed that chronic inflammation is involved in the onset and progression of cancer[233],

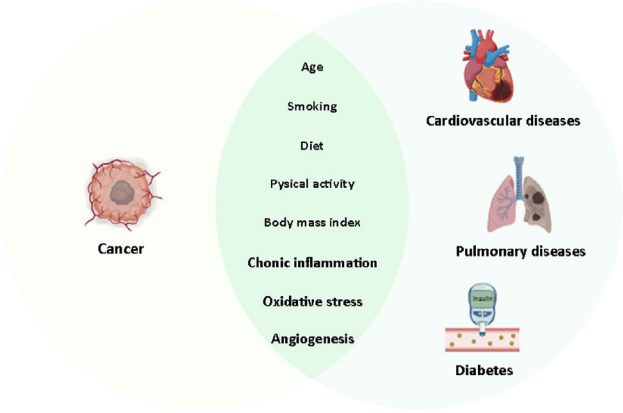

Figure 2 Representative overlapped risk factors between cancer and its comorbid conditions.

as well as cancer-associated complications and comorbidities[137,156,234]. It is well accepted now that chronic inflammation predisposes to the advancement of cancers, and tumors, in turn, can trigger and perpetuate inflammatory procedures to promote cancer development across all stages of tumorigenesis, including initiation, growth, invasion, metastasis, and recurrence[235]. Thus, the inflammatory process could be a shared therapeutic target for enabling one to troubleshoot tumor, complications and concomitant diseases in cancer patients. The mechanisms of how inflammation impacts every step during tumor development are complicated and continue to be elucidated, those in which both tumor-suppressing and tumor-promoting mechanisms coexist but the pro-tumorigenic prevail without tumor rejection[236]. Normally, inflammation is a healthy response of the innate immune system to body insults, *e.g.*, infection, stresses, metabolic dysfunction, and tissue damage, which helps restore tissue homeostasis and prevent function loss. In the context of cancer, the innate immunity goes astray, and persisting inflammation-induced signals are fed resulting in failed inflammation resolution, thus, chronic inflammation becomes an accomplice to foster tumor growth and development[235]. By contrast, the association between inflammation and cancer-associated complications and comorbidities (*e.g.*, cardiovascular diseases, diabetes, neurological side effects, pulmonary comorbid conditions, etc.) has been corroborated by extensive experimental data and clinical studies, although the mechanisms underlying such link are still not completely understood[237,238]. Therefore, inflammatory pathways could be attractive pharmacologic targets in attempts to control cancer and cancer-related sequela. Recent research displayed that inhibition of proinflammatory cytokines, like interleukins IL-1β, IL-6, and tumor necrosis factor-α (TNF-α), can effectively impede the development of COPD, cardiovascular events, diabetes, and cancer in the meantime, undermining the contribution of chronic inflammation to both malignancy and its long-term sequela[137,238]. Nuclear factor-kappa B (NF-κB) has been pointed out to play important parts in the inflammatory process linking chronic inflammation and cancer, its activation participating in all known cancer hallmarks, including enhanced proliferation and survival, stemness acquisition of cancer cells, promoted genetic and epigenetic alterations, drug resistance, and immune suppression[239]. Meanwhile, suppression of NF-κB showed preventive effects on diabetes development and insulin resistance, cardiovascular events, which are genetically related to diabetes,

chemotherapy-induced neuropathic pain, CVD, and other adverse effects[240−243]. Hence, the extensive involvement in cancer and cancer-related undesirable effects renders this transcriptional factor an appealing therapeutic target to free two birds with one key. In addition to regulation of these cytokines associated with chronic inflammation, many anti-inflammatory agents, especially natural products such as flavonoids and tea polyphenols, have been applied to the troubleshooting of both cancer and its adverse effects and showed effective modulation of inflammatory pathways, leading to reduced CVD, diabetes, neurodegenerative disorders, and inhibited carcinogenesis[244−246]. Recent studies showed that the peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathway plays a dispensable role in many cancers and diabetes, thus, thiazolidinediones as PPARγ agonists bring potential benefits to both cancer and diabetes mainly through the mediation of inflammation[247,248].

4.2.2. *Oxidative stress*

Oxidative stress, featuring imbalanced redox homeostasis between relatively excessive ROS (reactive nitrogen species included) and insufficient antioxidants, is believed to be involved in almost all chronic diseases and degenerative disorders, including cancer, CVD, neurologic disorders, diabetes, chronic obstructive pulmonary disease, among others[249]. ROS plays an important role in various molecular mechanisms to foster carcinogenesis, such as DNA damage, immune suppression, angiogenesis, invasion, metastasis, and drug resistance[249]. ROS could be a two-edged sword even for cancer cells since the appropriate concentration of ROS reinforces cell proliferation and survival while high ROS concentration is highly cytotoxic. ROS are highly reactive species that can react with macromolecules in cells, especially DNA, in which the pro-tumorigenic potential of ROS is thought to be rooted[250]. It is well accepted that compared to their non-malignant counterparts, cancer cells produce elevated ROS levels to drive hyperproliferation which, in turn, generates more ROS and pushes the redox balance away from the normal status, thus, they have to adapt multiple mechanisms to increasing the levels of antioxidants (*e.g.*, GSH, NADPH and thioredoxin) while, in the meantime, constraining the ROS thresholds to avoid unfavorable results from high ROS levels, *e.g.*, apoptosis or ferroptosis, in order to accommodate such aberrant redox homeostasis[250,251]. In the case of other diseases, ROS has been recognized as a crucial mechanism responsible for neurodegenerative disorders and pulmonary diseases and contributes to the pathology of CVD, diabetes, and infections, among others[249,252]. The contribution of oxidative stress to these diseases also arises from the reactivity of ROS with cellular macromolecules, such as DNA, lipids, and proteins, resulting in pathologically genetic and/or epigenetic alterations[253]. In cancer treatment, the cancer-killing capacity of many chemotherapeutics is known to accompany ROS generation and following chemotherapy-induced complications and comorbidities, *e.g.*, platinum complexes, anthracyclines, alkylating agents, epipodophyllotoxins, and the camptothecins[254].

Therefore, utilizing antioxidants to reduce oxidative stress represents an effective strategy for the prevention and treatment of both cancer and other chronic diseases[255]. This strategy can be fulfilled in diverse fashions, for instance, taking dietary supplements, such as unsaturated vitamins like vitamins A, C, and E, selenium, and other natural antioxidants like β-carotene, and polyphenols including flavonoids in vegetables and tea[256,257]. Various polyphenols such as quercetin, curcumin, and resveratrol have exhibited anticancer and cardio-protective benefits in a large body of literature, exerting beneficial effects against cancer, CVD, and diabetes largely *via* reduction of oxidative stress and restoration of redox homeostasis[258,259]. However, many natural antioxidants taken orally might possess poor bioavailability and compromise their antioxidant capability due to structural changes during metabolism[260]. Thus, appropriate formulations of antioxidants can relieve this problem as discussed in the previous section, including prodrug transformation, lead optimization, and nano-sized packaging, among others. Despite antioxidant intake, enhancing antioxidant defenses in normal cells while inhibiting antioxidant defenses in malignant cells could also be another appealing approach to implementing one-key-two-birds strategies[255]. As long as organisms highly depend on antioxidant enzymes to neutralize oxidants and restore oxidative damage, increasing antioxidant defense can be achieved by induction and enhancement of antioxidant enzymes, *e.g.*, heme oxygenase 1 (HO1), catalase, superoxide dismutase (SOD), glutathione peroxidase (GPX), as well as second-line GSH synthetase and reductase, and thioredoxin synthetase and reductase[260]. For example, GSH and HO1 inhibitors were delivered by nanocarriers to suppress the antioxidant defense system of cancer cells and enhance PDT efficacy[261]. Meanwhile, enhancement of antioxidant defenses using *Ulva lactuca* polysaccharides prevented breast carcinogenesis in Wistar rats[262]. In addition to antioxidants and antioxidant enzymes, ROS-related signaling pathways and biomarkers, *e.g.*, NF-κB, nuclear factor erythroid 2-related factor 2 (Nrf2), transforming growth factor beta (TGF-β), TNF-α, *trans*-4-hydroxy-2-nonenal (4-HNE), advanced glycation end products (AGE), malondialdehyde (MDA), protein carbonyl (PC), also unfold appealing therapeutic targets for imbalanced redox-mediated cancer and its sequela[263−265]. For instance, dietary isothiocyanate sulforaphane alleviated redox imbalance in diabetes and CVD by upregulation of the antioxidant defense system *via* modulation of Nrf2, NF-κB, and PPARγ signaling[266]. Furthermore, starting from the premise of good selectivity of the therapeutics, increasing ROS levels in tumors beyond their thresholds could be another audacious strategy to trigger apoptosis or ferroptosis of cancer cells, leading to cancer-targeted efficacy and diminished adverse effects[267]. The development of ferroptosis inducers is a vivid example of this approach, such as GPX inhibitors, system Xc^- inhibitors, iron chelators, and synthesis inhibitors of intracellular antioxidants (GSH and NADPH)[268].

4.2.3. *Angiogenesis*

Angiogenesis, the sprouting and stabilization of new blood vessels from pre-existing vascular structures, has garnered scientists' attention and interest in last three decades since the discovery of its negative contribution to numerous diseases, especially cancer and ocular diseases[269]. Physiological angiogenesis is a fundamental and critical process for embryonic and fetal development, as well as wound healing, skeletal recovery, menstrual cycle, and pregnancy in a healthy condition[270]. This process, in a normal condition, is tightly regulated by a range of proangiogenic and antiangiogenic signaling pathways, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), placenta growth factor (PlGF), fibroblast growth factor (FGF), angiopoietins (ANG), Notch, EphrinB (EphB), among others, which work in a complicated and highly coordinated manner[271]. Increasing evidence suggests that pathological angiogenesis is extensively involved in the development of many other diseases as well, *e.g.*, CVD, pulmonary diseases, diabetes, neurodegenerative disorders, skeletal issues, and others[270,272]. The angiogenetic

pathology usually commences from so-called "angiogenic switch", a process describing the imbalanced tilt between proangiogenic and antiangiogenic regulators toward activators, leading to the recruitment of independent blood supply in malignancies and dysregulation of tissue vascularization in other diseases, respectively[270,273]. Many excellent reviews are on hand describing dissect angiogenic mechanisms in different diseases, which will not be discussed here in detail[271,274–276]. The tumor-educated angiogenesis in malignancies is frequently manifested as upregulation of VEGF with significantly higher expression of VEGF in many types of solid tumors, probably resulting from tumor cell infiltration, metabolic alterations, and tissue hypoxia[271,277]. Similarly to cancers, overexpression of VEGF and dysfunctional angiogenesis also contribute to various other diseases, especially those closely connected with neovasculature (or "angiogenesis-dependent diseases", ADD), such as obesity, diabetes, CVD, pulmonary hypertension, diabetic retinopathy, neovascular age-related macular degeneration (AMD), and diabetic macular oedema (DME)[278,279]. Except tumorigenesis and neovascular-related disorders, the long-term adverse effects in cancer patients can in part be traced back to impaired angiogenesis manifested as accelerated vascular aging and dysfunction induced by chemotherapy[280]. Many first-line chemotherapeutic agents, for example, platinum complexes, anthracyclines, cyclophosphamides and taxanes, have long been reported to be associated with early vasculature senescence and endothelial dysfunction in cancer patients, and the flawed angiogenesis finally contributes to the emergence of subsequent complications and exacerbation of pre-existing comorbidities[281–283].

Given the significance and involvement of angiogenesis in tumors and ADD, targeting molecular pathways associated with the angiogenetic process holds great promise to use one to address both cancer and its complications and comorbidities[284]. Anti-angiogenic therapy represents a typical strategy for this purpose by using antiangiogenic molecules to inhibit the upregulated VEGF signaling[285]. The continual approval of bevacizumab since 2004 is a successful example of this strategy for the treatment of various cancers by inhibition of the VEGF pathway, including colorectal cancer, lung cancer, glioblastoma, cervical cancer, ovarian cancer, and hepatocellular carcinoma[286]. Except antibodies like bevacizumab, diverse angiopreventive agents and approaches have been explored in the field of oncology, including VEGF-targeted small molecules, combination therapies, anti-angiogenic nanomedicines, endothelial regulator degradation by proteolysis-targeting chimera (PROTAC), and so forth[287–289]. In the case of angiogenesis-dependent diseases, antiangiogenic therapy also showed high efficacy against retinal disorders by suppressing secretogranin III signal, Gorham−Stout disease through downregulation of VEGF signaling, CVD by promoting VEGF and FGF pathways, and others[290–293]. On the flip side of the coin, pro-angiogenesis could be another effective strategy for the troubleshooting of cancer and its long-term sequela. In the context of cancer, flawed vasculature usually is produced due to the dysregulated angiogenesis and quick extension of the local vascular system in tumors under the demanding need for oxygen and nutrients. This physiological characteristic is where the EPR effect stands, and can be harnessed in cancer treatment by a strategy called vascular normalization to break down the transport barrier and reshape the tumor microenvironment[294,295]. As well, pro-angiogenesis therapy by vascular normalization has drawn therapeutic interest for other diseases, particularly those linked with ischemic conditions including cancer and its complications and comorbidities associated with pathological angiogenesis[296,297]. Interestingly, although statins are first developed as a mainstay against CVD, low-dose statins have been proven to promote angiogenesis and resensitize tumors to chemotherapy probably *via* regulation of Ras signaling, meanwhile, statins present neuroprotective effects in brain diseases and mitigate diabetic syndromes by angiogenesis modulation *via* downregulation of VEGF and FGF[298]. Similarly, metformin, usually used as an antidiabetic agent, has proven to display benefits against CVD and cancers by regulating angiogenesis-associated microRNA[299]. This makes statins an attractive class of therapeutic agents for the one-key-two-birds strategy. In addition, fabulous angio-preventive properties have been found in a number of natural products, including polyphenols, alkaloids, polysaccharides, terpenoids, saponins, and Chinese herbal medicines, although their mechanisms of action need to be further clarified[300–302]. For example, the active compound from a traditional Chinese herbal medicine, ginsenoside Rb1 has demonstrated therapeutic potential against cancer, CVD, diabetes, and neurodegenerative diseases by exerting anti-angiogenic effects through PPARγ signaling pathway[303]. Moreover, knowledge database and computation of systems biology about angiogenesis have been established to better understand the underlying mechanisms of angiogenesis at genetic, molecular, cascade, cellular, tissue, and whole-body levels and facilitate further investigation on angiogenesis-associated diseases, which will also provide therapeutic clues for the treatment of cancer and complications and comorbidities related to cancer[304,305].

It is noteworthy that when channeled into the overlapped mechanism of tumor and its complications and comorbidities (Table 3), we find these factors discussed above often occur in a concomitant way in the pathology of cancer and other diseases, and sometimes they are regulated by specific but overlapping signaling pathways and molecules, implying that careful weighing and comprehensive evaluation are needed to implement novel strategies to target these shared mechanisms[306–309]. Apart from the mechanisms in common, age, smoking, physical inactivity, unhealthy diet, and obesity have all been recognized as risk factors for cancer and its prevalent complications and comorbidities. Thus, cancer patients burdened with complications and comorbidities should build healthy daily habits and could benefit from smoking cessation, abstinence from alcohol, and enhancement of physical exercise[310].

4.3. Preclinical cancer models for efficient drug testing and translation

Preclinical models are essential tools both for drug testing and pathological research in the field of cancer research, which simulate cancerous human bodies, bridging the gap from bench to bedside. In general, experimental models for cancer research (Fig. 3) can be categorized into three types based on their dimensions: *in vitro* conventional two-dimensional (2D) cell models, *in vitro* three-dimensional (3D) cell cultures, and *in vivo* animal models[311,312]. Traditional cancer monolayers are conventional 2D models that have been frequently used as fundamental tools for preliminary screening in cancer treatment mainly with respect to cell- and tissue-related investigations, which will not be addressed in this review**.** Herein, those cutting-edge 3D platforms and animal models that better mimic the living situation will be outlined and discussed, particularly in relation to complications and comorbidities associated with chemotherapy.

Table 3 Targeting overlapped mechanisms of cancer and its comorbid conditions.

Shared mechanism	Basic science evidence	Potential one-key-two-birds target	Ref.
Chronic inflammation	↑ Cancer development across all stages of tumorigenesis ↑ CVD, COPD, diabetes, and neurodegenerative disorders	IL-1β, IL-6, TNF-α, NF-κB, and PPARγ	137,238–244,247,248
Oxidative stress	↑ The initiation and progression of cancer ↑ The pathogenesis of CVD, pulmonary diseases, diabetes, infections, and neurodegenerative disorders	HO1, catalase, SOD, GPX, NF-κB, Nrf2, TGF-β, TNF-α, and PPARγ	249,252,255,258–266
Angiogenesis	↑Tumor progression with independent blood supply ↑ CVD, pulmonary hypertension, diabetic retinopathy, obesity, diabetes, neurodegenerative disorders, and skeletal issues	VEGF, PDGF, PlGF, FGF, ANG, Notch, EphB, and PPARγ	270–272,274,277–279,284,285,287–290,292,296–301,303

CVD, cardiovascular diseases; COPD, chronic obstructive pulmonary disease; IL, interleukin; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor-kappa B; PPARγ, peroxisome proliferator-activated receptor gamma; HO1, heme oxygenase 1; SOD, superoxide dismutase; GPX, glutathione peroxidase; Nrf2, nuclear factor erythroid 2-related factor 2; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; PlGF, placenta growth factor; FGF, fibroblast growth factor; ANG, angiopoietins; EphB, EphrinB.

4.3.1. 3D cell cultures

The term multicellular spheroid was coined in 1970 while experimental attempts at cancer research were first made far early in the 50s using 3D tumor cell aggregates[313]. Since then, studying neoplasia with 3D *in intro* models has changed the paradigm of experimental cancer research as they demonstrate better similarities to tissue environment and tumoral architecture of real tumors than their 2D counterparts[311]. Among 3D cell cultures, spheroids and organoids are the most common and promising *ex vivo* models in cancer research, both of which may possess 3D structures consisting of multiple cell lines. To date, the term organoid has been generally used to denote 3D multicellular co-cultures, although the Intestinal Stem Cell Consortium clarified their difference in 2012 lying in the cellular composition: spheroids are epithelial-only cultures and the organoids refer to those containing epithelial and mesenchymal-originated cells[314]. The incorporation of mesenchymal cells and resulting epithelial−mesenchymal interaction were suggested to ensure the long-term stability of the organoids[315]. Consequently, the composition distinctiveness results in the function ramification that spheroids are frequently regarded as mini-tissues while organoids are more complex than spheroids and often referred to as mini-organs[314]. Herein, the advances in 3D cancer models will be mainly focused on organoid models without stressing the distinction between spheroids and organoids due to the universal usage of "organoids" in most literature.

Recently, 3D organoid models are looming as exciting alternatives or complements to animal models in cancer research, especially in personalized medicine[316]. They have demonstrated high clinical relevance in therapeutic response and drug resistance, holding great promise in drug discovery for cancer treatment[317–320]. In addition to predictions of drug response and chemosensitivity, organoids also make considerable contributions to advancing clinical translation, particularly individualized

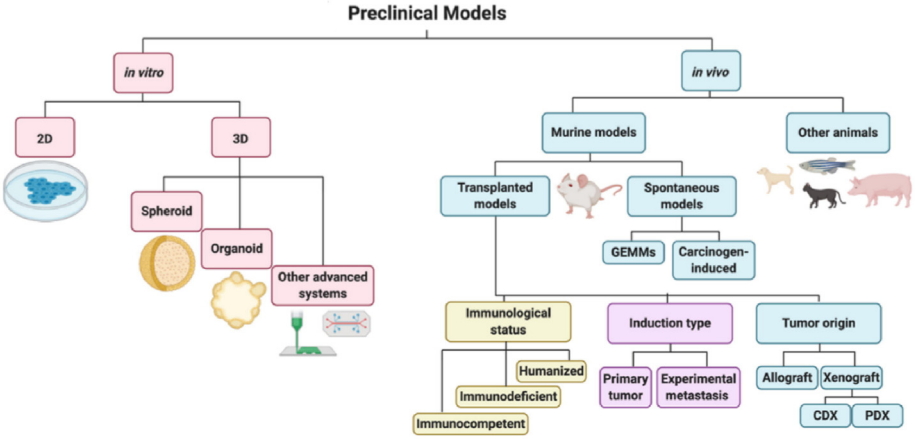

Figure 3 Preclinical models for cancer research. Reprinted with the permission from Ref. 312. Copyright © 2021 Elsevier B.V.

treatment regimens[321,322]. Their wide applications in cancer treatment are, in part, attributed to the potential to faithfully recapitulate the genetic and epigenetic key features of specific organs including diseased ones while providing versatility in genomic and environmental manipulation. Organoid models can be derived from two main sources, including differentiation from human stem cells and culture from patient-derived samples[323]. In the context of cancer research, organoid cancer models are often generated from patient-derived tumors, either liquid or solid biopsy samples, by direct dissection or dissociation and/or cell sorting to culture and form 3D organoids[316]. Cancer organoids have been widely cultured from a range of epithelial cancers, including brain, lung, colon, prostate, liver, breast, bladder, stomach, pancreas, esophageal, and endometrial cancers[316]. However, organoid modeling has its limitations, such as the inability to mimic non-epithelial cancers (sarcomas, leukemia, and lymphomas), incompetence to simulate multiorgan pathology, lack of tumor microenvironment, and unstandardized engineering for organoid culture[324,325].

In the case of complications and comorbidities associated with chemotherapy, organoids derived from pluripotent stem cells have been employed as promising preclinical models for studying chemotherapy-induced CNS toxicity and neuropathy[326,327]. Despite toxicities and complications in the nerve system, hepatic, mucosal, cardiovascular, kidney, and gastrointestinal adverse effects induced by chemotherapy are addressed as well in corresponding organoids[328−333]. Additionally, organoid models also demonstrate powerful tools for the study of common comorbidities with cancer, such as cardiovascular diseases, diabetes, and pulmonary diseases[334−336]. Nevertheless, organoids are unable to investigate chemotherapy-related complications and comorbidities in the presence of cancer burdens so far due to the limitation of modeling multi-organ systems. Fortunately, after the integration of body-on-a-chip technology, multi-organoid modeling might open up new avenues of such complex research on cancer and its long-term sequela, which have demonstrated interesting experimental results of tissue-tissue and multiorgan interactions[337,338].

Body-on-a-chip (also known as organs/organoids-on-a-chip, multiorgan-on-a-chip, or human-on-a-chip) refers to the microphysiological systems integrating multiple organs including cancers on the *in vitro* microfluidic cell culture devices to check responses to therapy[339]. Compared to static 2D and organoid models, they hold a few advantages: (a) they are able to mimic dynamic blood flow and specific tissue architecture, offering an essential research context with increased clinical relevance for studies related to neovascularization, cancer cell dissemination, and cancer metastasis, as well as drug delivery and PK−PD studies; (b) they can integrate real-time biosensors in the system, permitting facile and live monitoring of tissue state and activity; and (c) they enable the incorporation of multiple organs into a single system to study complex inter-organ communication such as crosstalk between cancer and other organs[339−341]. In the context of solid tumors, the so-called "tumor-on-a-chip" is emerging to study metastatic tumors and the interactions between tumors and TME[342]. For example, colorectal cancer and liver models are included on a chip for studying the metastasis into the liver[343]. Such multiorgan systems also could be a perfect platform for studying cancer-related sequela, including complications and comorbidities[344]. However, several challenges remain in this young technology, including technical hurdles, relatively low throughput, and lack of standardization in biological and technical frames[345]. Nevertheless, they are promising preclinical models and show the potential to decrease or even replace the use of animal models in appropriate scenarios.

4.3.2. *Animal models*

In addition to 2D and 3D cell models, animal models are usually used in the advanced stage of cancer research close to clinical translation, providing more complex and faithful modeling of cancerous bodies. The animals used range from small animals like zebrafish, mice, and rats, to large ones, pigs, dogs, and monkeys, for instance. In preclinical studies, small rodents are frequently used, especially mice and rats whose genome has been comprehensively investigated and exhibit close similarities to the human genome. These models can be generated by a variety of methods according to experimental purposes, including chemical induction, xenotransplantation, and gene programming. Excellent and comprehensive reviews are available concerning preclinical animal models on their history, development, and applications[346−348]. Herein, important animal models for cancer research are summarized with specific attention to their advantages and limitations in relation to chemotherapy-related complications and comorbidities.

According to the locations of transplantations and resources of carcinogens, animal models for cancer can be further subdivided into: (i) *ectopic xenografts* of tumor cells or tissue explants implanted into syngeneic or immune-compromised animals at different locations from the primary tumor sites; (ii) *orthotopic xenografts* of cancer cells or tissue explants implanted into the appropriate positions, recapitulating the local microenvironment where a primary tumor develops; (iii) *patient-derived xenografts* (PDX) of fresh human tumor tissues implanted into immunodeficient animals, thus maintaining the original genotype and phenotype of the primary tumors; (iv) *genetically engineered/transgenic mouse models* (GEMM) generated by mouse genetic engineering to allow the expression of oncogenes and/or inactivation of tumor suppressor genes; and (v) *carcinogen-induced models* in which tumors were induced by exposure to carcinogens, generally chemicals, *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, *N*-ethyl-*N*-nitrosourea, azoxymethane, among others[349]. In the context of chemotherapy-induced complications, the selection and utility of animal models become extremely demanding to study their mechanisms, reciprocal interactions, and effects between tumors and their surrounding environment. Researchers rely on animal models to study the pathogeneses of various complications or comorbidities associated with malignancies and attain therapeutic implications from them. In proportion to the complications and comorbid diseases reviewed afore, here the discussion of preclinical animal models will be stressed on those contributing to the most common long-term sequela along with chemotherapy.

Diverse preclinical *in vivo* models have been utilized to study the adverse effects on the cardiovascular system, and resulting complications or comorbid diseases related to chemotherapy drugs. Both rodent and nonrodent animal models are widely used to study cardiovascular toxicity and consequent complications associated with chemotherapy, ranging from zebrafish to mouse/rat to rabbit/swine[350]. Zebrafish models are extremely suitable for high throughput screening due to their small size, optical transparency, and facile maintenance. Despite most shared disease-causing human genes and ion channels, zebrafish can survive for several days with significant vascular defects and without cardiac output, permitting a better understanding of abnormalities deadly to mammals[351]. However, the distinct anatomic and physiological

differences (2-chamber heart without pulmonary circulation) from the human become an outstanding drawback of zebrafish models. Except zebrafish, rodents, especially mice or rats, are extensively used as *in vivo* models for cardiovascular studies, which are usually well-established for toxicity studying with various xenograft/transgenic models and specific antibodies at hand[352]. In contrast to zebrafish, these models share higher physiological similarities to humans, offering valuable insight into cardiovascular toxicities and complications coupled with chemotherapy. Most rodents used are young and healthy, which cannot accurately reflect comorbidities often existing in humans such as hypertension, hyperlipidemia, and diabetes. Although studies in rodents have demonstrated how prior chemotherapy exposure increases the vulnerability to additional cardiovascular impairments later in life, modeling cardiovascular toxicity or complications with preexisting comorbidities has not been attempted as yet[350]. Additionally, large animals such as rabbits, swine, and dogs are also employed for studies of chemotherapy-associated cardiovascular complications, allowing for further translation of critical research findings into clinical applications, despite decreased time- and cost-effectiveness and potential translation gap from humans[353]. Hence, there is an overwhelming lack of animal models that can faithfully recapitulate the intricate physiopathology of cardiovascular toxicities and complications in cancer patients in regard to potential comorbidities, age distribution, and possible multimodal therapies.

The evaluation of neurological complications in humans appears difficult since irreversible damage can be caused by the stimuli required for such testing and direct study in the clinical population has proven challenging[234,354]. Thus, animal models become crucial for understanding the underlying mechanisms and developing effective therapy for better management of neurological complications. Similarly, emphasis will be placed on animal models for peripheral chemotherapy-induced neuropathic pain and chemobrain, representative complications in PNS and CNS respectively. Chemotherapeutic agents have been administered to rodents to establish animal models of peripheral neuropathy associated with chemotherapy, which are helpful in revealing the etiology and manifestations of CIPN[354,355]. Only a few animal models of CIPN are established in the presence of a tumor load, which faces more concerns in ethical considerations and practical feasibility[356,357]. Although they can mimic clinical signs and symptoms of patients, they cannot fully replicate anatomical and neurophysiologic abnormality present in humans even with similar electrophysiological and histopathological changes to human malignancies. Moreover, most of these models are independent of the cancer which urges the use of chemotherapy and induce neuropathic pain as complications. Consequently, the clinical relevance of these animal models to human conditions has been questioned due to different pathophysiologies and uncertain pain processes[358]. With respect to cognitive impairment/chemobrain induced by chemotherapy, diverse animal models have been established and used to study the underlying mechanisms of CICI, including models of healthy animals and models of tumor-bearing animals[359]. In parallel to CIPN, healthy animals are used to predict the severity of cognitive dysfunction induced by chemotherapeutic agents and to explore potential therapeutic interventions in the absence of a tumor[359,360]. To increase clinical relevance, tumor-bearing animals are utilized to study the mechanisms and connection between chemobrain and tumors, where tumors are introduced by chemical induction or tumor cell xenografts[361,362]. Transgenic animals are also used to better simulate human tumorigenesis and study specific genetic factors related to cognitive deficits induced by chemotherapy[363,364]. So far, no standardization of animal models has achieved in the research area of neurological complications associated with chemotherapy, and few reports comply with the animal research: reporting of *in vivo* experiments (ARRIVE) guidelines, raising concerns about their reliability and reproducibility, regardless of the availability of various animal models[365].

Akin to neuropathic pain, bone pain is another type of cancer pain caused by chemotherapy. In the context of skeletal complications, it is noteworthy that the majority of animal models used are generated by inoculating cancer cells into animals, varying cancer types, injection techniques, and immunological background of the hosts depending upon the investigation purposes[366,367]. In this case, corresponding cancer cells can be injected spontaneously/systematically/locally into immunodeficient/syngeneic/humanized hosts. The "seed and soil" theory is suitable to explain the development of bone metastases[368]. With respect to the systemic models, the seeds (cancer cells) are injected systematically, and then accumulate in the preferred soil (bones). The systemic models are considered very close to real bone metastases given that they simulate the early stages from survival in circulation, extravasation, and dissemination to the bone to eventual dormancy and/or growth of bone metastases[369]. Unfortunately, tumors may arise in several sites more than the bones after the systematic injection of cancer cells which may perplex the evaluation of skeletal complications[370,371]. Therefore, models established by local injection of cancer cells have been used to exclude interference from other potential tumor sites. However, it should be noted that these inoculation models obviously cannot model the process starting from the primary tumors or pre-metastatic niches. To date, scarce models are found to outline the whole metastatic range from the primary tumor to final metastases and skeletal complications, in which the 4T1 syngeneic model of breast cancer represents one such model[369,370,372]. Due to the intrinsic connection with bone cancer pain, these models are also utilized to address cancer pain, another common complication along with late-stage cancers[373].

Animal models for the studies of chemotherapy-induced complications are also widely employed for the research on common comorbidities with cancer, *e.g.*, CVD, pulmonary diseases, and diabetes. The animal models used mainly include naturally mutant, chemical-induced, and transgenic models[351,374,375]. The main advantage of these animal models, particularly mouse/rat models, lies in the steady availability of existing techniques for model establishment and genetic manipulation. However, the limitations of these models should also be borne in mind, such as indispensable differences between animals and humans in genetics, anatomy, behavior, and physiology, among others. To minimize the gap, larger animal models have been developed, such as rabbit, cat, dog, swine, and non-human primate, though less large animal models with genetical engineering are available compared to rodents[375,376]. It should be noted that most animal models are established for the study of the comorbidities mentioned previously as independent diseases in a lack of any cancer burdens, which means they can offer limited information about the interactions between cancer and these comorbid conditions.

In general, a broad array of preclinical animal models is widely available and routinely deployed in laboratories for the research of chemotherapy-related complications and comorbidities, covering all categories aforementioned from xenografts to transgenic to

carcinogen-induced models. These models offer important tools to elucidate potential causal mechanisms, favor hypothesis validation, facilitate pathophysiological exploration, and enable testing of proof-of-concept diagnostic and therapeutic approaches, extensively bridging the translational gap between bench research and clinical application in this field. Despite these merits, close scrutiny has come to preclinical studies involving animal models. Increasing criticisms lie in unsatisfactory replication rates, appropriate interpretation of results to humans, and ensuing failures of clinical translation with massive investment[377,378]. These concerns also persist and the situation is even worse in the frame of chemotherapy-induced complications. More defined and faithful models are desperately needed for preclinical research of complications and comorbidities associated with chemotherapy, which present more complexity and specialization with respect to cancer itself. Obviously, complementary to clinical research, it is pragmatically impossible to ask for perfect animal models for complication/comorbidity studies. However, several principles should be taken into careful consideration for the design of animal models in the field of chemotherapy-induced complications[377,379]. First, the models must be grounded by a clear definition of human disease or condition being modeled which is a prerequisite for any useful animal model. Second, the purpose and frame of reference should be clarified to ensure the validity and utility of the animal model. Third, the essential attributes of the model must be in concordance with human disease or condition, in order to guarantee the bio-fidelity of the animal model. Fourth, the experimental outcome obtained in animal models should be confirmed by relevant clinical data for model validation. Rational design, conduct, and reporting of animal models in compliance with these principles help circumvent abuse of preclinical models, inaccurate interpretation of experimental results, and scientific misunderstanding in the field.

5. Conclusions and outlook

In the last few decades, the incidence of chemotherapy-induced complications and concurrence of pre-existing disorders in cancer patients are prevalent and have increased in tandem with prolonged cancer survival and aging population. Recent years have witnessed considerable progress and rapid scientific development in oncology, as well as a deeper understanding of complications and comorbidities associated with cancer treatment. Yet, enormous attention and effort cling to cancer while the influence of other conditions is frequently undervalued, and persistent afflictions from cancer-related complications and comorbidities are overwhelmed by the pursuit of "successful cancer treatment". The ongoing challenges posed by complications and comorbidities associated with cancer necessitate a paradigm shift in cancer care, from the current focus on separate specialties with limited cooperation, towards a more collaborative fashion emphasizing integrated efforts in prevention, screening, research, and management.

The most common complications and comorbidities associated with chemotherapy are reviewed, as well as their deliberate interactions with oncology and chemotherapy. Commonly, complications are thought to arise from the off-target toxicity of chemotherapeutic agents in non-malignant sites, while the comorbid diseases can sophisticate or even exacerbate cancer treatment *via* many overlapped mechanisms with malignancies. In light of these considerations, three lessons are summarized in this review learned from cancer and its long-term sequela: (a) anticancer efficacy-oriented strategies should be replaced by those mitigating the adverse effects while maintaining the efficacy of chemotherapeutics, in order to minimize the influence or even avoid the occurrence of chemotherapy-induced complications; (b) versatile therapeutic recipes effective against both cancer and its comorbidities should be explored and developed by targeting the overlapped mechanisms; and (c) the development of more comprehensive cancer models is desperately needed given the significant limitations imposed by current disease-specific preclinical models on the appropriate research for cancer-related complications and comorbidities. To our knowledge, our work is the first to propose the strategies of one-key-two-birds to manage cancer and its comorbid conditions with the same therapeutics.

We see opportunities to harness natural products for the combatting of cancer and its long-term sequela, due to their effectiveness in anti-proliferation, anti-inflammation, and antioxidation, as well as excellent chemo-protective and chemo-sensitive effects. Despite the profound therapeutical implications, further investigations should be carried out to clarify the precise mechanisms of action of these bioactive natural compounds. Furthermore, we also see the upcoming trend of coupling traditional research methods with the latest techniques, such as integration of computation capacity and machine learning for prediction and modeling of drug discovery, and coupling of in silico modeling and advanced 3D cell cultures with animals for better modeling of cancer and its complicated/comorbid conditions. Moving forward, the blank sheet in clinical data should be filled in because of the lack of participation of so-called high-risk populations, for example, elder people and those burdened with comorbidities, who should also be considered for clinical trials in the future, in order to collect precise clinical data of comorbidities and sufficient information reflecting accurate efficacy and side effects in these populations, providing sound support for clinical decision making, instead of extrapolation from younger and healthier subjects.

In summary, chemotherapy-induced complications and pre-existent diseases are important pieces in the puzzle of cancer research that should not be disregarded. To better manage neoplasia and its long-term sequela, there is a compelling need for further investigation into the underlying mechanisms, complex relationships, and potential resolutions, as well as appropriate preclinical models for studies associated with cancer-related complications and comorbidities. Additionally, it is imperative to foster more proactive cross-cutting endeavors from both clinical and nonclinical sectors. We hope that the overshadowed impact of complications and comorbidities will be underscored and addressed within the context of oncology management in the future, in order to practically improve the health-related quality of life of cancer patients. It is also anticipated that this concise review of complications and comorbidities associated with chemotherapy would provide a more comprehensive and long-term landscape for anticancer research and pave the way to future advances in corresponding fields.

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Author contributions

Chong Li and Xiaoman Mao contributed to the conception of the manuscript, drafted the manuscript, figures and tables. Shuang Wu and Dandan Huang participated in editing the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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