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MINIREVIEWS

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Peer Reviewer of *World Journal of Clinical Oncology*, Mohammad-Salar Hosseini, MD, MPH, Doctor, Research Associate, Research Center for Evidence-Based Medicine, Tabriz University of Medical Sciences, Golgasht St., Tabriz, East Azerbaijan 51666, Iran. hosseini.msalar@gmail.com

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MINIREVIEWS

Progress in the research of cuproptosis and possible targets for cancer therapy

Jiang Wang, Lan-Zhu Luo, Dao-Miao Liang, Chao Guo, Zhi-Hong Huang, Guo-Ying Sun, Jie Wen

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Jiang Wang, Lan-Zhu Luo, Zhi-Hong Huang, Children Medical Center, Hunan Provincial People's Hospital, the First Affiliated Hospital of Hunan Normal University, Changsha 410013, Hunan Province, China

Dao-Miao Liang, Chao Guo, Department of Hepatobiliary Surgery, Hunan Provincial People's Hospital, the First Affiliated Hospital of Hunan Normal University, Changsha 410013, Hunan Province, China

Guo-Ying Sun, Department of Histology and Embryology, Hunan Normal University School of Medicine, Changsha 410013, Hunan Province, China

Jie Wen, Department of Pediatric Orthopedics, Hunan Provincial People's Hospital, the First Affiliated Hospital of Hunan Normal University, Changsha 410013, Hunan Province, China

Corresponding author: Jie Wen, PhD, Associate Professor, Department of Pediatric Orthopedics, Hunan Provincial People's Hospital, the First Affiliated Hospital of Hunan Normal University, No. 61 West Jiefang Rd, Changsha 410013, Hunan Province, China. cashwj@qq.com

Abstract

Developing novel cancer therapies that exploit programmed cell death pathways holds promise for advancing cancer treatment. According to a recently published study in Science, copper death (cuproptosis) occurs when intracellular copper is overloaded, triggering aggregation of lipidated mitochondrial proteins and Fe–S cluster proteins. This intriguing phenomenon is triggered by the instability of copper ions. Understanding the molecular mechanisms behind cuproptosis and its associated genes, as identified by Tsvetkov, including ferredoxin 1, lipoic acid synthase, lipoyltransferase 1, dihydrolipid amide dehydrogenase, dihydrolipoamide transacetylase, pyruvate dehydrogenase α1, pyruvate dehydrogenase β, metallothionein, glutaminase, and cyclin-dependent kinase inhibitor 2A, may open new avenues for cancer therapy. Here, we provide a new understanding of the role of copper death and related genes in cancer.

Key Words: Cuproptosis; Cuproptosis-related genes; Cancer; Targeted therapy

Core Tip: Developing novel cancer therapies that exploit programmed cell death pathways holds promise for advancing cancer treatment. Cuproptosis-related genes were identified by Tsvetkov, including ferredoxin 1, lipoic acid synthase, lipoyltransferase 1, dihydrolipid amide dehydrogenase, dihydrolipoamide transacetylase, pyruvate dehydrogenase α1, pyruvate dehydrogenase β, metallothionein, glutaminase, and cyclin-dependent kinase inhibitor 2A. Here, we provide a new understanding of the role of copper death and related genes in cancer.

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INTRODUCTION

Tsvetkov *et al*[1] have proposed an intriguing new form of programmed cell death related to the mitochondrial tricarboxylic acid (TCA) cycle, resulting in proteotoxic stress and copper-induced death, referred to as cuproptosis. These forms of oxidative-stress-induced cell death are characterized by mitochondrial stress, including the accumulation of fatty acylated mitochondrial enzymes and the loss of Fe–S cluster proteins[1]. The dysregulation of copper homeostasis promotes cancer growth and causes irreversible cellular damage. A variety of mechanisms have been suggested for the ability of copper to induce cell death, such as oxidative stress, proteasome inhibition, and antiangiogenesis[2].

The exact molecular mechanism underlying cuproptosis remains unclear, but recent studies have shed light on potential contributors. For instance, knockout of the ferredoxin (FDX) 1 gene attenuates copper ionophore-induced cell death. Additionally, genes associated with the loss of lipidated mitochondrial enzymes and Fe-S cluster proteins loss, such as lipoic acid synthase (LIAS), lipoyltransferase (LIPT) 1, and dihydrolipoamide transacetylase (DLAT), may contribute to cuproptosis[1,3].

Although the precise correlation between cuproptosis and cancer is yet to be fully understood, imbalances in copper homeostasis have been implicated in cancer growth and cause irreversible cellular damage. Copper metabolism *in vivo* and cancer therapy has been extensively studied[4,5]. Certain genes involved in the cuproptosis pathway, such as FDX1, may also play a role in cancer development, serving as a key regulator of proptosis and associated with poor prognoses in specific cancer types[6]. Here, we review the progress of copper ions in cancer therapy, the function of cuproptosis-related genes in cancer, and the possible target in cuproptosis.

COPPER IONS AND CANCER THERAPY

Recent studies have revealed three distinct mechanisms through which copper ions may induce cancer cell death. (1) Oxidative stress induction: Anticancer drug elesclomol has been found to exert its therapeutic effects through the transfer of copper ions to mitochondria, leading to oxidative stress[7]. Liu *et al*[8] demonstrated that flavonoids can induce mitochondrial apoptosis through modification of the redox cycle of copper ions; (2) inhibition of proteasomes: Chen *et al*[9] synthesized copper diethyldithiocarbamate [Cu(DDC)(2)] nanoparticles (NPs) that improved the resistance of prostate cancer to treatment. Copper-ion-mediated endoplasmic reticulum (ER) stress is induced by proteasome inhibition and accumulation of ubiquitinated proteins. Proteasome inhibitors like bortezomib and carfilzomib have been explored for their potential as cancer treatment options in the form of various complexes, such as clioquinol and dithiocarbamates[10]; and (3) reduce angiogenesis: Copper ions play a significant role in endothelial cell migration, proliferation, and fibronectin synthesis, crucial steps in angiogenesis[11,12]. However, copper depletion can act as an antiangiogenic switch, blocking the growth of endothelial cells and preventing their proliferation. By inhibiting copper transporters or chaperones like human antioxidant protein 1 and consolidation tumor ratio-1, in addition to direct capture of intracellular copper, copper imbalance can be induced, leading to antiangiogenic effects[13,14]. Combining this approach with vascular targeting techniques, such as immunotherapy, can enhance the cancer-killing effects[15]. The tumor microenvironment (TME) is a complex ecosystem where various immune cells interact and influence tumor growth and progression [16,17]. In the early stage of tumor growth, neutrophils promote inflammation and tumor cell apoptosis by releasing cytokines. However, in the middle and late stages of tumor formation, neutrophils contribute to angiogenesis, accelerating tumor progression and local infiltration. Different T cell populations are involved in TME, among which $CD8^+$ T cells can target and destroy tumor cells, secrete interferon, and inhibit angiogenesis. $CD4^+$ T cells coordinate immune responses, with Th1 cells promoting cancer and T regulatory cells promoting tumor formation and survival, by secreting auxin and cytokines, which then interacts with fibroblasts and epithelial cells. Although less prevalent than T cells, tumor-infiltrating B cells have antitumor effects, including antigen presentation to T cells, production of antitumor antibodies, and secretion of cytokines that promote cytotoxic immune responses. Regulatory B cells, in contrast, promote tumors by producing cytokines that promote the immunosuppressive phenotype in macrophages, neutrophils, and cytotoxic T cells. Tumor-associated macrophages (TAMs) are the predominant immune cells in the TME. They are involved in coordinating cancer-related inflammation and can release macrophage colony-stimulating factor to recruit TAMs, which have been implicated in cancer development. Moreover, TAMs can release epidermal growth factor,

modify cancer cells, and accelerate cell migration and metastasis. Medullary suppressive cells promote tumor invasion by weakening innate and adaptive antitumor responses.

In light of the mechanisms described above for copper ions in cancer treatment, copper complexes have been extensively studied for their potential in anticancer therapy (Figure 1). For instance, copper-amino acid sulfhydryl NPs can reduce Cu^{2+} to Cu^{+} when reacting with localized glutathione. The generated Cu^{+} then reacts with hydrogen peroxide, resulting in an increase in reactive oxygen species (ROS) levels. Excessive ROS can induce apoptosis of cancer cells[18]. A copper-containing complex known as Cu-tuberous sclerosis complex (TSC) is another widely used complex to enhance cytotoxicity of TSC and ROS production[19]. Chronic inflammation in the body can induce carcinogenesis and facilitate cancer spread. Copper complexes containing nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat inflammation and prevent cancer development (Table 1). In breast cancer stem-cell-like cells, Boodram *et al*[20] demonstrated that Cu-NSAID complexes could induce ROS accumulation, DNA damage, and cyclooxygenase-2 inhibition. Copper complexes with subcellular targeting properties can deliver more precise attacks on cancer cells. Kaur *et al*[21] reported that copper complexes containing polypyridine ligands could enter the ER in situ, leading to increased ROS levels and ER-stress-induced immunogenic cell death in cancer cells[22]. Although copper-complex-related therapies hold promise as a new anticancer strategy, their biocompatibility and application safety are critical challenges. Researchers have shown that copper complexes are cancer-killing, but long-term stability and biosafety tests remain to be conducted before these therapies can be translated into clinical applications.

THE ROLE OF CUPROPTOSIS-RELATED GENES IN CANCER

Cuproptosis remains an area of active exploration in its relationship with cancer. However, significant research has been conducted to understand the mechanisms through which cuproptosis-related gene molecules contribute to cancer development (Table 2). Figure 2 illustrates how these genes induce cuproptosis.

FDX1

FDX1 is a FDX protein primarily found in mitochondria, with diverse physiological functions, including the conversion of cytochromes during steroid hormone synthesis and vitamin D metabolism[23]. Shi *et al*[24] demonstrated that FDX1 is critical for Fe–S cluster biogenesis. Recent research has identified FDX1 as a key gene in the regulation of cuproptosis[25]. Zhang *et al*[26] study found that FDX1 expression did not significantly differ across clinical stages in most cancers. Although the reduction in FDX1 expression may not directly impact the growth, apoptosis, or cell cycle distribution of LUAD cells, it could affect their metabolism, as FDX1 knockout has been shown to promote glycolysis and fatty acid oxidation. Further investigations into the mechanisms of FDX1 in cancer pathogenesis revealed significant positive correlations between FDX1 expression and immune cells in most cancers. FDX1 has been associated with major histocompatibility complex, immune activation, immune suppression, chemokines, and chemotaxis[27]. Additionally, the products of factor receptors were positively coexpressed with FDX1, except for 1-aminocyclopropane-1-carboxylic acid and tetrahydrocannabinolic acid. This indicates that FDX1 expression is closely related to the immune response of cancer cells, which has implications for prognosis and represents a potential target for immunosuppressants[28,29]. Given the crucial role of copper ions in cuproptosis, the significance of FDX1 as a key gene in this process makes it an intriguing target for cancer therapy. Studies exploring its role may offer valuable insights as it directly influences the protein fatty acylation cycle, leading to the aggregation of these proteins and interference with respiratory chain iron-sulfur cluster proteins.

LIAS

LIAS encodes a protein belonging to the biotin and LIAS families. Located in the mitochondria, this Fe–S enzyme contributes to lipoic acid biosynthesis, serving as the final step in the process. Diseases like diabetes, atherosclerosis, and neonatal epilepsy are associated with a lack of LIAS expression. Current studies on the association between the LIAS gene and cancer have predominantly focused on lung cancer[29].

Using in situ hybridization and real-time quantitative PCR, Mabeta *et al*[30] investigated the differential expression of the LIAS gene in normal lung tissue and lung cancer samples. Their findings suggest that alteration in LIAS expression levels can promote lung cancer development, making LIAS an attractive target for novel therapies[29]. However further studies are warranted to confirm its therapeutic effectiveness.

LIPT1

As a member of the fatty acyltransferase family, LIPT1 encodes an enzyme that catalyzes the transfer of fatty acyl groups from fatty acyl-AMPs to specific lysine residues in fatty-acid-dependent enzymes. LIPT1-related disorders include fatty acyltransferase 1 deficiency and leukodystrophy[31]. While there have been relatively few studies on LIPT1 in cancer, Chen *et al*[32] conducted a systematic investigation of genes related to prognosis in bladder cancer using the pathological

Table 1 Copper-related compounds and their antitumor mechanism

Compounds	Mechanism	Ref.
Elesclomol	Transferring copper ions to mitochondria and increasing ROS level	Nagai *et al*[7]
Flavonoid drugs	Interfering with copper ion redox and inducing mitochondrial apoptosis	Liu *et al*[8]
(Cu(DDC)2)	Inhibiting proteasome and leading to ER stress activation	Chen *et al*[9]
Copper ion chelating agent	Inhibiting endothelial cell proliferation and angiogenesis	Zhou *et al*[15]
Copper ion transporter inhibitor	Inhibit endothelial cell proliferation and angiogenesis	Yee *et al*[13], Karginova *et al*[14]
NPs(Cu-CysNPs)	Reacting with glutathione to increase ROS level	Ma *et al*[18]
Cu-TSC	Inducing ROS accumulation	Sîrbu *et al*[19]
Cu-NSAID compound	Inducing ROS accumulation, DNA damage and COX-2 activity inhibition	Boodram *et al*[20]
Copper complexes containing polypyridine ligands	Increasing ROS level and inducing ER stress	Kaur *et al*[21]

ROS: Reactive oxygen species; TSC: Tuberous sclerosis complex; COX-2: Cyclooxygenase-2; NSAID: Non-steroidal anti-inflammatory drugs; (Cu(DDC)2): Copper diethyldithiocarbamate; ER: Endoplasmic reticulum.

Table 2 Functions of cuproptosis-related genes in cancer

Genes	Mechanism	Ref.
FDX1	FDX1 knockout promotes glycolysis and fatty acid oxidation and alters amino acid metabolism	Zhang *et al*[26]
LIAS	Involved in lipoic acid biosynthesis. Abnormally elevated transcript levels of LIAS contribute to the development of lung cancer	Burr *et al*[29]
LIPT1	Participating in the tricarboxylic acid cycle and is related to the prognosis of bladder cancer	Solmonson *et al*[31], Chen *et al*[32]
DLD		Wang *et al*[33]
DLAT	Converting pyruvate to acetyl-COA Promoting cancer cell growth by activating pentose phosphate pathway	Shan *et al*[40]
PDHA1	Inhibition of PDHA1 expression promotes glycolysis and cell proliferation	Zhuang *et al*[43]
	PDHA1 promotes mitochondrial lipid synthesis	Chen *et al*[45]
PDHB	Overexpression of PDHB inhibits the proliferation and invasiveness	Zhu *et al*[46]
MTF1	Induced co-expression of metallothionein with other genes involved in metal homeostasis contributes to tumor biogenesis and development	Günther *et al*[51]
GLS	Encoding K-type mitochondrial glutaminase and is dysregulated in many tumors	Choi and Park[52], Momcilovic *et al*[53]
CDKN2A	A cyclin with mutations and aberrant methylation in a variety of tumors	Zhao *et al*[56], Tam *et al*[60]

FDX1: Ferredoxin 1; LIAS: Lipoic acid synthase; LIPT1: Lipoyltransferase 1; DLD: Dihydrolipoamide dehydrogenase; DLAT: Dihydrolipoamide transacetylase; PDHA1: Pyruvate dehydrogenase alpha 1; PDHB: Pyruvate dehydrogenase beta; MTF1: Metallothionein; GLS: Glutaminase; CDKN2A: Cyclin dependent kinase inhibitor 2A.

atlas of the Cancer Genome Atlas. Their findings revealed a correlation between LIPT1 expression and bladder cancer prognosis[32]. However, further research is needed to elucidate the role of LIPT1 in other cancer types.

DIHYDROLIPOAMIDE DEHYDROGENASE (DLD)

DLD, encoded by the DLD gene, is an essential enzyme that significantly impacts cell metabolism, particularly pyruvate metabolism and the TCA cycle[33]. There is evidence that DLD could be used as a cancer-targeted therapy. In head and neck squamous cell carcinoma, DLD has been shown to be closely related to cystine deprivation and glutaminolysis. The biological function of DLD enhances mitochondrial KDH, MMP, and glutaminase activity. Increasing mitochondrial iron

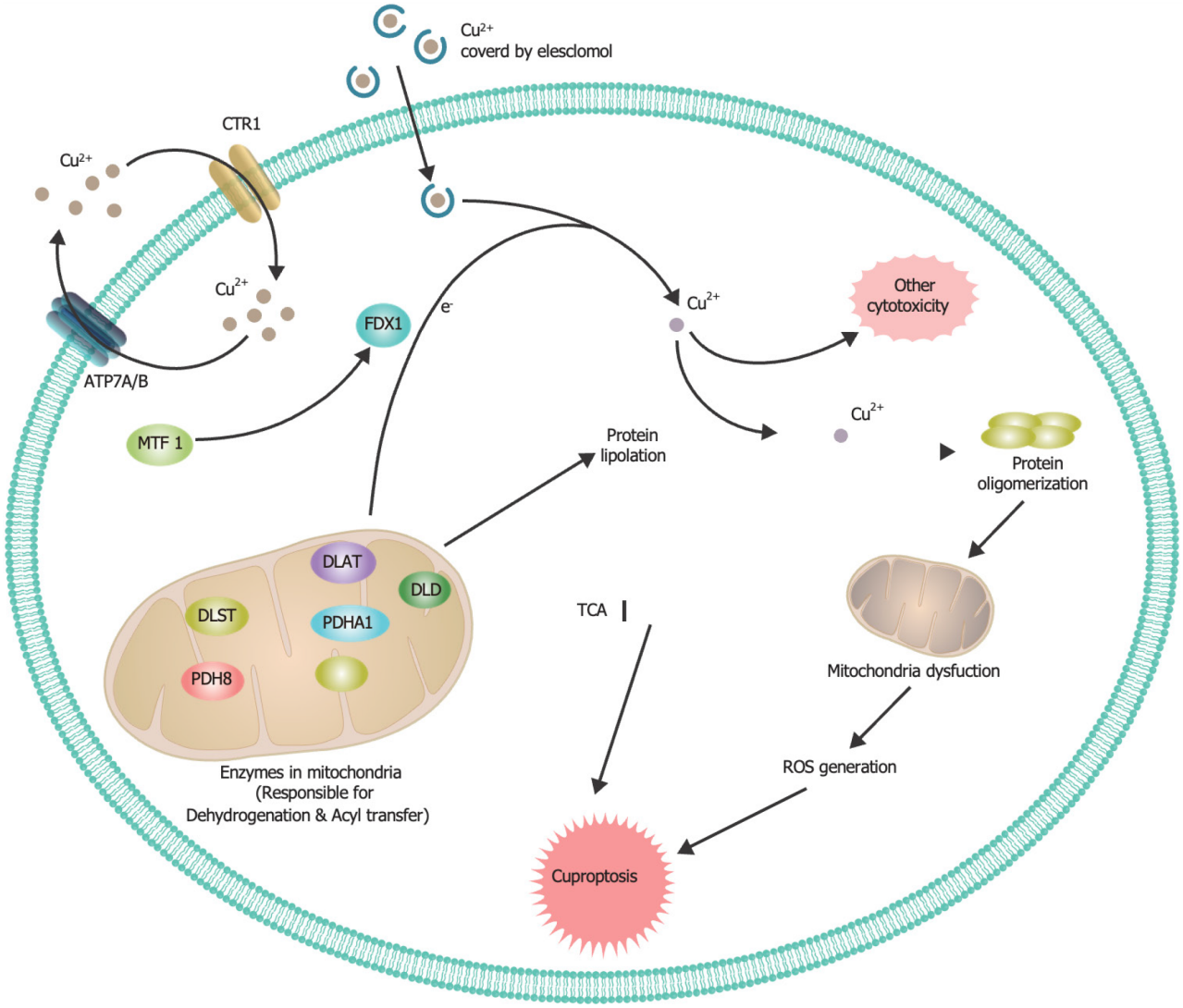

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Figure 1 Effects of excess copper and copper deficiency in cancer. Four copper-related pathways with cancer inhibition effects are described. Elesclomol mediates the entry of Cu^{2+} into the mitochondria and causes reactive oxygen species accumulation. Flavonoids interfere with copper ion oxidation and reduction, inducing mitochondrial apoptosis pathway activation. Copper diethyldithiocarbamate can inhibit proteasome and result in endoplasmic reticulum stress. Copper deficiency can suppress the proliferation and migration of endothelial cells and the formation of connexin, bridling tumor angiogenesis. TCA: Tricarboxylic acid; ROS: Reactive oxygen species; FDX1: Ferredoxin 1; MTF1: Metallothionein; CTR1: Consolidation tumor ratio-1.

levels can facilitate mitochondrial lipid peroxidation, or silencing DLD, which effectively reduces the proportion of cells undergoing death from cystine deprivation and reduces ROS levels in cystine-deprived cells. These processes have been closely related to cancer-programmed death[34]. Patients with endometrial cancer have exhibited abnormal levels of IgA and non-DLD IgG autoantibodies in their sera, indicating a correlation with mitochondrial DLD protein[35]. Comparing DLD protein expression levels between breast cancer and normal tissues revealed significant differences, highlighting the potential of DLD as a diagnostic and therapeutic target in breast cancer[36]. Using DLDH-based exogenous ROS to target skin cancer cells, Avraham *et al*[37] developed a method for targeting cancer cells, which could be a potential approach for melanoma treatment in the future.

DLAT

DLAT is an essential component of the pyruvate dehydrogenase complex, along with DLD and pyruvate dehydrogenase. This enzyme complex plays a crucial role in the synthesis of pyruvate acetyl-CoA. As the sole enzyme capable of converting citric acid into acetyl-CoA, DLAT can control the citric acid cycle–oxidative phosphorylation pathway, thus affecting the energy supply of cancer cells[38]. In gastric cancer cells, DLAT expression was significantly upregulated[39], making it a potential therapeutic target. DLAT promotes the growth of cancer cells by activating the pentose phosphate pathway[40]. Alternol, a compound that binds to multiple Krebs cycle enzymes, inhibits mitochondrial respiration and ATP production. This discovery offers a novel therapeutic strategy for treating prostate cancer[41].

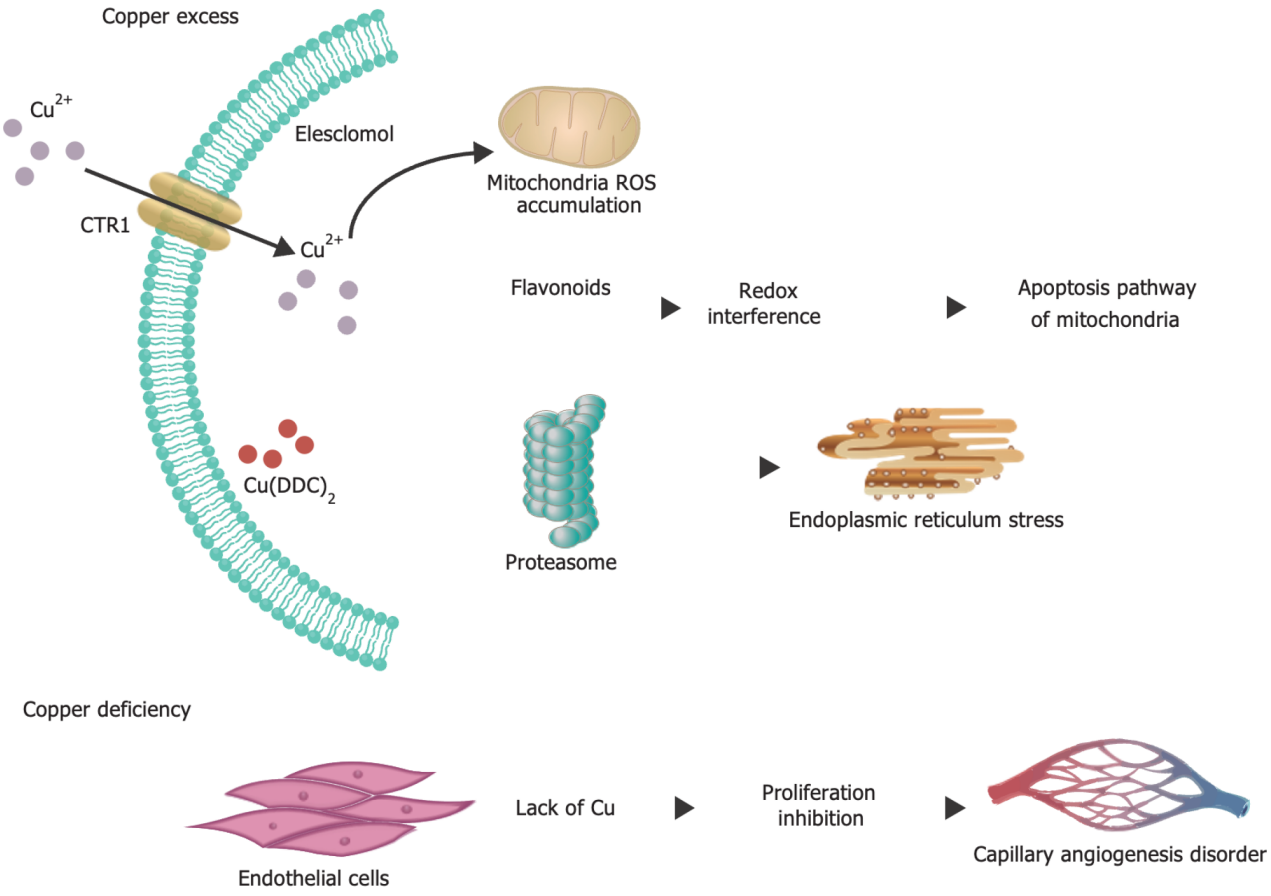

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Figure 2 General molecular biological process of cuproptosis. Copper can be transported into cells through the action of consolidation tumor ratio-1 and elesclomol encapsulation. When Cu^{2+} encapsulated by elesclomol enter the mitochondria, it gains an electron from ferrodoxin 1 (FDX1) (FDX1 expression can be promoted by metallothionein) and converts into Cu^{+}. Concurrently, proteins responsible for dehydrogenation and acyl transfer (dihydrolipoamide transacetylase, dihydrolipoamide S-succinyltransferase, dihydrolipoamide dehydrogenase, pyruvate dehydrogenase α1, and pyruvate dehydrogenase β) undergo electron loss and are liporated by lipoic acid synthase. Subsequently, Cu^{+} promotes the oligomerization of liporated proteins. This cascade of events leads to a series of phenomena, including reactive oxygen species accumulation, mitochondrial dysfunction, and tricarboxylic acid inhibition, ultimately culminating in cuproptosis. CTR1: Consolidation tumor ratio-1; (Cu (DDC)2): Copper diethyldithiocarbamate; FDX1: Ferrodoxin 1.

PYRUVATE DEHYDROGENASE α1 (PDHA1) AND PYRUVATE DEHYDROGENASE β (PDHB)

PDHA1 and PDHB encode subunits of the pyruvate dehydrogenase complex, an essential enzyme complex within the mitochondria responsible for catalyzing pyruvate oxidation to acetyl-CoA, connecting glycolysis and the TCA cycle.

PDHA1 inhibition can increase proliferation, glycolysis, and Warburg effect in certain cancer cells. Gastric cancer has been shown to downregulate PDHA1, and elevated expression of PDHA1 correlates with poor prognosis[42]. Downregulation of PDHA1 promotes the growth of gastric cancer. Exosomal miR-21-5p suppresses PDHA1 expression, thereby promoting glycolysis and cell proliferation in gastric cancer cells. PDHA1 expression in gastric cancer samples is negatively correlated with miR-21-5p levels[42]. Additionally, miR-21-5p/PDHA may influence ovarian cancer drug resistance through exosomal miR-21-5p-mediated regulation of PDHA1 expression[43]. The knockout strains had increased glycolysis, glucose intake, and glutamine consumption, while oxidative phosphorylation was inhibited, indicating enhanced Warburg effect and PDHA1. The proliferative capacity, angiogenic capacity, and drug resistance of the knockout esophageal cancer cells were significantly improved[44]. PDHA1 is closely associated with prostate cancer growth, where it is involved in mitochondrial lipid synthesis. Therefore, PDHA1 may be useful as a therapeutic target for prostate cancer[45].

PDHB also acts as a cancer suppressor gene. PDHB overexpression inhibits colon cancer cell proliferation, invasiveness, and glycolysis as it targets miR-146b-5p at the 3'-UTR end of the gene, promoting cancer cell growth[46]. Gastric cancer cells overexpressing PDHB exhibit reduced proliferation and migration[47]. PDHB inhibitors have also been shown to suppress cancer growth in various studies. For instance, reduced PDHB expression in non-small cell lung cancer indicates poor prognosis for patients[48], while PDHB may serve as a biomarker for breast cancer[49]. Thus, the progress made in the research on PDHA1 and PDHB in cancer highlights the broad potential applications of therapeutic drugs targeting these molecular targets.

METALLOTHIONEIN (MTF1)

MTF1 plays a crucial role in the treatment resistance of malignant cancers[50]. Cells stimulated with heavy metals, such as copper, trigger the production of products encoded by MTF1, leading to the induction of metal sulfur production. During tumor biogenesis and progression, coexpression of proteins and other genes involved in metal homeostasis is implicated. Notably, MTF1 is highly expressed in ovarian cancer tissues, and its high expression is associated with poor patient survival and disease recurrence[51]. MTF1 knockout can inhibit the epithelial–mesenchymal transition process of ovarian cancer cells, thereby suppressing their proliferation, migration, and invasion, indicating that MTF1 may serve as a novel biomarker and therapeutic target for ovarian cancer[50]. Given the multiple aspects of MTF-1 activities, monitoring changes in its expression and activity during cellular stress and cancer may prove valuable for cancer screening and prognosis studies.

GLUTAMINASE (GLS)

GLS encodes mitochondrial glutaminase K, which is dysregulated in many cancers. GLS can modulate promoter methylation modification and influence the clinical prognosis. In both in vitro and in vivo studies, GLS-targeted therapy has demonstrated its potential to inhibit cancer growth[52,53]. Similarly, GLS has been detected in clinical samples from breast cancer, esophageal cancer, head and neck cancer, and leukemia. The expression of GLS is associated with poor prognosis in statistical analysis. Therefore, GLS can be considered a prognostic biomarker for certain types of cancer[54]. However, its use as a prognostic biomarker remains controversial and further research is necessary to clarify its role and potential clinical applications[55].

CYCLIN-DEPENDENT KINASE INHIBITOR 2A (CDKN2A)

During cancer development, aberrant gene silencing is highly associated with cell cycle regulation. Dysregulation of CDKN2A, which encodes the p16INK4a protein, has been causally linked to the pathogenesis of various cancer types, contributing to cancer recurrence, poor prognosis, cancer genesis, and metastasis[56]. CDKN2A mutations are responsible for 20%-40% of familial cancers and 2%-3% of sporadic melanomas[57]. Nonsynonymous mutations of CDKN2A were found in approximately 16% (9/56) of cutaneous melanoma metastases[58]. Activation of CDKN2A has been reported in 95% of pancreatic adenocarcinoma cases due to promoter hypermethylation[59]. In lung cancer, CDKN2A inactivation has been observed in 75% of cases (30/40), including 16 homozygous deletions, 10 methylations, and four mutations[60]. CDKN2A gene mutations and abnormal methylation have also been reported in ovarian, gastric, and colorectal cancers, among others[56]. Reactivating CDKN2A genetically and epigenetically could offer promising approaches for cancer prevention and treatment.

DISCUSSION

Copper ion concentration in the human body is tightly regulated by a homeostatic mechanism to maintain trace levels, as excess copper becomes toxic and leads to cell death. However, the mechanism underlying copper-induced cytotoxicity is still unclear [61,62]. Recently, a novel form of cell death, cuproptosis, was discovered, which operates independently of known cell death mechanisms[1]. Cuproptosis-related genes were identified using CRISPR-Cas9 loss-of-function screens, which revealed seven positively regulated and three negatively regulated genes.

So far, the identified copper-ionophore-induced death genes include DLD, fatty acylated protein targets PDH complex including DLAT, PDHA, and PDHB. While studies on these genes in cancer have been more extensive[3], other components of the lipoic acid pathway, such as fatty acyl synthase LIAS and FDX1, remain relatively understudied in cancer, and further experiments are needed to verify their roles in different cancer types[1,3]. High cuproptosis activity status has been found to be a good prognostic indicator.

While some progress has been made in utilizing other types of programmed cell death for cancer treatment, there are still limitations in their application. Cuproptosis, being a novel form of programmed cell death, offers new perspectives on the correlation between its related genes and cancer prognosis. The combination of cuproptosis-targeted molecular drugs with existing therapies might open up new avenues for cancer treatment.

Currently, cuproptosis research is still in its infancy, and the existence of other signaling pathways for cell cuproptosis is not yet clear. Additionally, existing copper agents have poor targeting specificity and can cause serious side effects in patients undergoing treatment. These limitations and deficiencies impede the development and clinical implementation of cancer treatment strategies based on cuproptosis mechanisms.

In the future, researchers should focus on improving our understanding of the mechanism of cuproptosis in cancer cells and conducting thorough investigations into relevant mechanisms. Additionally, efforts should be directed towards developing copper-related formulations with high targeting and specificity (such as targeted nano-drug delivery systems) to maximize the targeting of cancer treatment while reducing toxic side effects. Lastly, it is necessary to develop and improve copper treatment plans in clinical practice in order to conduct relevant clinical trials and treatments for patients with cancer.

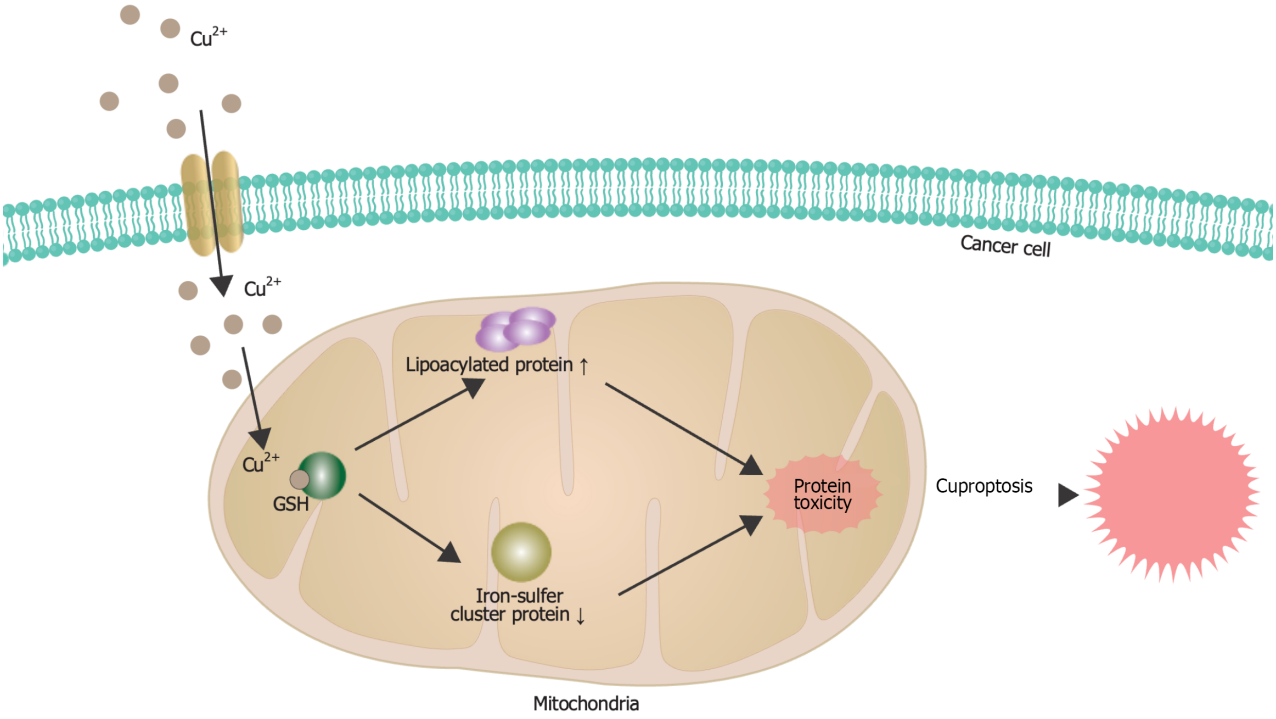

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Figure 3 The mechanisms underlying cuproptosis in cancer cells. GSH: Glutathione.

CONCLUSION

Cuproptosis is triggered by the direct interaction of copper ions with the fatty acylated components in the citric acid cycle of mitochondrial respiration. This interaction results in the aggregation of fatty acylated proteins and subsequent down regulation of Fe–S cluster proteins, leading to protein toxic stress and, ultimately leading to cell death (Figure 3). The elucidation of this mechanism provides a clear understanding of how previous copper ion drugs exert their antitumor effects. This provides potential possibilities for the clinical application of these drugs in antitumor therapy and also broadens the path for the development of new drugs targeting copper in the future.

FOOTNOTES

Author contributions: Wang J and Luo LZ contributed equally to this study, and share joint first authorship; Wang J wrote the paper; Luo LZ and Liang DM did the literature review; Guo C and Huang ZH did the data analysis; Luo LZ conceived and coordinated the study; Sun GY and Wen J contributed equally to this study, and are joint corresponding authors; All authors reviewed the results and approved the final version of the manuscript.

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MINIREVIEWS

Advances in drug resistance of triple negative breast cancer caused by pregnane X receptor

Zhou-Zhou Rao, Zhong-Wen Tang, Jie Wen

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Zhou-Zhou Rao, Department of Physiology, Hunan Normal University School of Medicine, Changsha 410003, Hunan Province, China

Zhong-Wen Tang, Jie Wen, Department of Pediatric Orthopedics, Hunan Provincial People's Hospital, the First Affiliated Hospital of Hunan Normal University, Changsha 410013, Hunan Province, China

Corresponding author: Jie Wen, PhD, Assistant Professor, Department of Pediatric Orthopedics, Hunan Provincial People's Hospital, the First Affiliated Hospital of Hunan Normal University, No. 61 West Jiefang Rd, Changsha 410013, Hunan Province, China. cashwj@qq.com

Abstract

Breast cancer is the most common malignancy in women worldwide. Triple-negative breast cancer (TNBC), refers breast cancer negative for estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2, characterized by high drug resistance, high metastasis and high recurrence, treatment of which is a difficult problem in the clinical treatment of breast cancer. In order to better treat TNBC clinically, it is a very urgent task to explore the mechanism of TNBC resistance in basic breast cancer research. Pregnane X receptor (PXR) is a nuclear receptor whose main biological function is to participate in the metabolism, transport and clearance of allobiological agents in PXR. PXR plays an important role in drug metabolism and clearance, and PXR is highly expressed in tumor tissues of TNBC patients, which is related to the prognosis of breast cancer patients. This reviews synthesized the important role of PXR in the process of high drug resistance to TNBC chemotherapeutic drugs and related research progress.

Key Words: Triple-negative breast cancer; Pregnane X receptor; Drug resistance; Cytochrome P450; Uridinediphosphate glucuronyl transferases; Glutathione transferases; ATP-binding cassette transporter

Core Tip: Treatment of triple-negative breast cancer (TNBC) is a difficult problem in the clinical treatment of breast cancer. It is a very urgent task to explore the mechanism of TNBC resistance in basic breast cancer research. Pregnane X receptor (PXR) is a nuclear receptor whose main biological function is to participate in the metabolism, transport and clearance of allobiological agents in PXR. This reviews synthesized the important role of PXR in the process of high drug resistance to TNBC chemotherapeutic drugs and related research progress.

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INTRODUCTION

Cancer and cardiovascular disease are the two leading causes of death in the world, which seriously endanger people's physical and mental health[1]. In recent years, the incidence of cancer has been showing an upward trend worldwide, and the growth rate and mortality rate of breast cancer in women are grim[2]. According to the overall cancer data in the world in 2020[3], breast cancer has exceeded lung cancer to become the number one malignant tumor in the world, accounting for 11.7% of all different types of cancer. The incidence and mortality of breast cancer rank the first in most countries in the world. Literature reports that in 2020, the number of new breast cancer cases in the world was more than 2.26 million, and the number of deaths reached 685000, among which Chinese patients accounted for 18.4% of all cases in the world[4]. Therefore breast cancer has become the most threatening malignant tumor that endangers women's health.

According to the different express of estrogen receptor (ER), human epidermal growth factor receptor 2 (HER-2), progesterone receptor (PR), and insufficient expression of proliferating cell nuclear antigen-67, breast cancer have been classified into several subtypes, these include: Luminal A, HER-2 overexpression, Luminal B and triple negative[5]. In all kinds of breast cancer, the type of breast cancer which is negative for PR, ER, and HER-2 is called triple-negative breast cancer (TNBC). It accounts for 10% to 20% of all types of breast cancer[6] and occurs mostly in young women[7]. TNBC mainly metastasize to the lung and brain, and its own biological characteristics make it have poor response to general local treatment and poor prognosis[8]. Although there have been great breakthroughs in the treatment of breast cancer recently, the treatment of advanced metastatic breast cancer (especially TNBC) is still a great clinical challenge. Although there are so many different subtypes in breast cancer, TNBC is the most clinically complex subtype to treat. Because the lackness of effective molecular targets, theraputic attempts for non-TNBC, such as endocrine therapy and HER2-targeted therapy, cannot benefit TNBC patients[9]. Poly (ADP-ribose) polymerase inhibitors and immune checkpoint-based immunotherapy have made important progress in preclinical and clinical research[10]. However, although these treatment strategies can benefit some patients, the overall benefit of all TNBC patients is still very limited. At present, chemotherapy is still an important treatment for TNBC[11]. However, TNBC is not all sensitive to chemotherapy, and the main reason for the failure of chemotherapy is the resistance of TNBC to chemotherapy[12]. In summary, this type of breast cancer is characterized by high degree of deterioration, high recurrence rate, high metastasis rate and low survival rate. It is particularly important to study the mechanism of chemotherapy resistance[13].

In 1998, when Kliewer *et al*[14] searched the mouse liver HHMI EST database, they found a sequence with high homology to the known nuclear receptor, and the protein encoded by this sequence can be activated by a series of natural or synthetic pregnane hormones, so they named it pregnane X receptor (PXR). Human PXR is expressed by the nuclear receptor subfamily 1 group I member 2 gene, located on chromosome 3q13-21, and consists of 10 exons and 9 introns, with a gene size of approximately 40 kb. In contrast to other nucleoid receptors, PXR possesses a large and somewhat flexible spherical ligand-binding domain, allowing it to bind a large number of compounds of different sizes and structures. Phosphorylation of residues at positions T248, Y249, and T422 of PXR is required for its ligand-activated function[15]. When PXR binds to its ligand, its conformation changes and activates the PXR pathway, which causes PXR to translocate from the cytoplasm to the nucleus and bind to the retinal X receptor to form a heterodimer, which in turn combine with the DNA response elements in the target gene's specific promoter region to regulate their transcription[16]. The main biological function of PXR is to participate in the metabolism, transport and clearance of xenobiotics including chemotherapeutic drugs[17]. There are three phases involved in the metabolic process of PXR: Phase I, metabolizing enzymes; Phase II, conjugating enzymes; phase III, transporter[18] (Figure 1).

Although PXR is mainly expressed in liver, intestinal and colon tissues, it has been found that it is also expressed in normal breast tissues, and its expression level is even higher in breast cancer tissues[19]. PXR can affect the expression of drug resistance-related genes, thereby enhancing the metabolism and clearance function of chemotherapy drugs in cancer cells[20], and then plays an important role in breast cancer[21]. Studies have shown that the expression of PXR increased in docetaxel-resistant TNBC cells and tumor xenograft mice[22]. This article reviews the role of PXR in the drug resistance mechanism of TNBC.

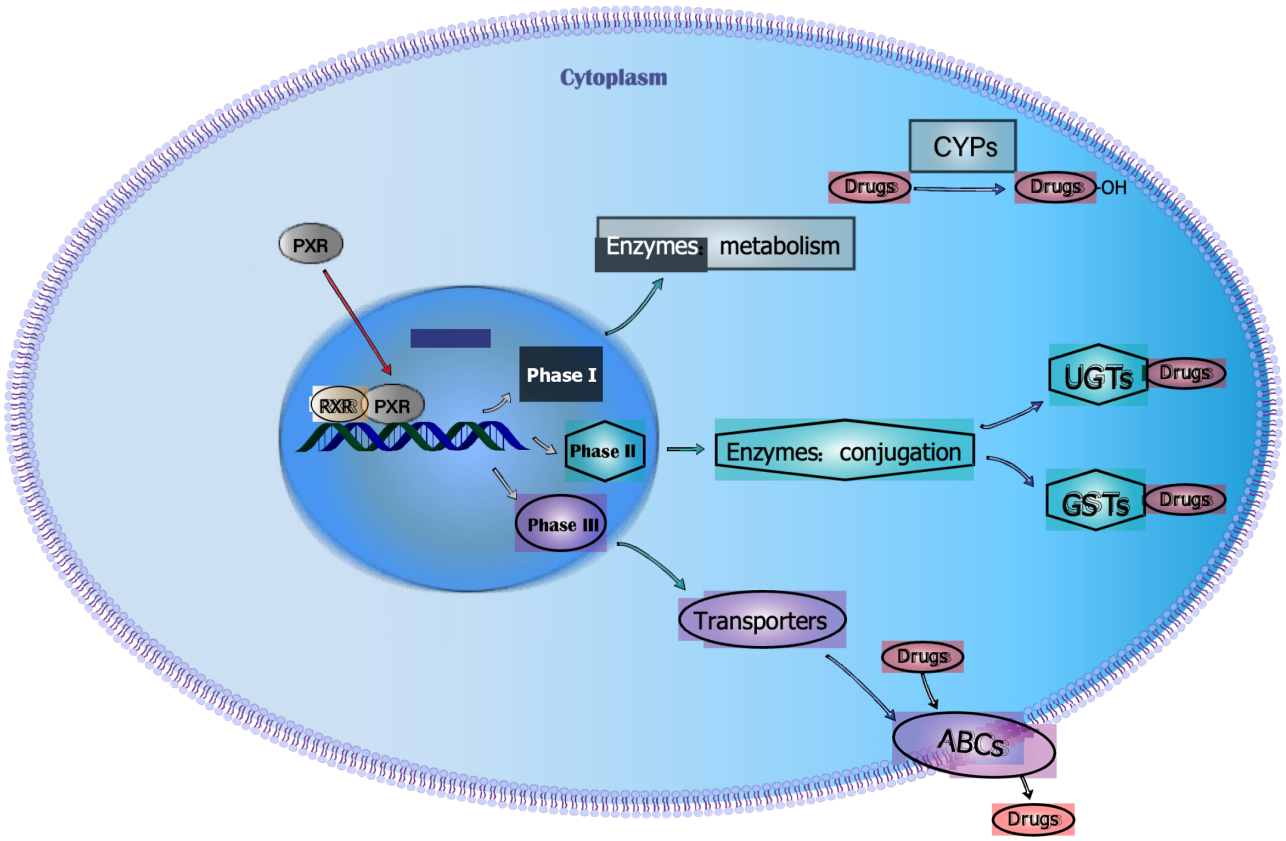

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Figure 1 Three phases in the chemotherapy drug resistance mechanism caused by pregnane X receptor in triple-negative breast cancer. RXR: Retinal X receptor; PXR: Pregnane X receptor; ABC: Adenosine triphosphate binding cassette; CYPs: Cytochrome P450s; UGTs: Uridine diphosphate glucuronosyltransferase; GSTs: Glutathione transferase.

PXR AND METABOLIZING ENZYMES IN PHASE I OF DRUG METABOLISM

Drug metabolizing enzymes refers a special kind of enzymes, which responsible for the metabolism function of a variety of substances such as exogenous chemicals and endogenous biological small molecules. Cytochrome P450 (CYP) is an important enzyme system involved in the metabolism of xenobiotics in cells. CYP was first discovered in rat liver microsomes in 1958[23]. CYP is named for its typical absorption peak at 450 nm wave length[24]. The rules for CYP nomenclature include: Different numbers after the family represent different families, different letters after the family represent different subfamilies, and different numbers after the subfamily represent different peptides[25]. There are 18 CYP families in human body, including 26 subfamilies and more than 50 different isoforms with catalytic functions[26]. Three families, CYP1, CYP2 and CYP3, account for nearly 70% of the human CYP family and response for most drugs' metabolism progress. It is the dominant superfamily enzyme system not only involved in the drug metabolism phase I, but also affected drug oxidation, reduction or hydrolysis[27]. For patients with liver cancer, clarifying the expression information of CYP, strengthening the monitoring of medication, adjusting the dose and frequency of drugs, and reducing drug resistance and side effects are of great significance for the precise treatment of anticancer drugs[28].

It is demonstrated by Murray *et al*[29] that CYP2S1, CYP4V2, CYP3A4, and CYP26A1 were connected to the final survive rate of breast cancer patients, which also indicated the potential of CYP as a marker for the clinical results of breast cancer patients. A large number of studies have shown that CYP enzymes are related to breast cancer drug metabolism. Among them, CYP enzymes have been experimentally confirmed to be: CYP3A4, CYP3A5, CYP2C8, CYP2C9, CYP2J2, CYP1A1, CYP1B1, CYP17A1, CYP2B6, CYP2D6, CYP2C19, *etc*[30-33]. Alexanian *et al*[34] reported the lower expressions of CYP4A11 and CYP4A22 in normal breast tissues than those in TNBC tissues. Overexpression of CYP3A4 can promote the metabolism of docetaxel in triple negative breast cancer stem cells and further induce reduced accumulation of chemotherapy drugs in cancer cells, leading to cell drug resistance[22]. Two major metabolic enzymes of paclitaxel (CYP2C8, CYP3A4) and other genes involved in taxane heterogenic metabolism (*e.g.*, CYP1B1) are associated with drug resistance in TNBC[35]. Numerous experiments have shown that CYP enzymes are significantly upregulated in TNBC patients [22,29,35]. Therefore, the association between CYP enzymes and tumor resistance in TNBC has attracted increasing attention.

It has been reported that activated PXR can transcriptically up-regulate the expression of CYP450 family members such as CYP3A4, CYP3A23, CYP2B6, CYP2B9, CYP2C55, CYP2C9 and CYP1A[36,37]. In experimental studies related to TNBC drug resistance, it has been confirmed that PXR can regulate the expression of CYP3A4, resulting in increased drug metabolism in TNBC, which is obviously related to TNBC chemotherapy resistance[22].

PXR AND CONJUGATIVE ENZYMES IN PHASE II OF DRUG METABOLISM

Conjugation enzymes in phase II of drug metabolism are mainly various transferases, such as glutathione transferase (GST) and uridine diphosphate glucuronosyltransferase (UGT)[30]. GST, as an important part of the detoxification system of the body, is responsible for catalyzing the combination of glutathione and drugs, and expelling the conjugate from the body under the action of multidrug resistant-related proteins, all of above made GST plays a detoxification role[38]. UGT is the most important enzyme involved in human phase II of drug metabolism, and about 40%-70% of drugs and traditional Chinese medicine are metabolized by UGT[39]. UGT and GST can make exogenous harmful substances into water-soluble harmless small molecular substances, and then excreted in the form of bile and urine.

In 1978, Lawrence *et al*[40] found that there was a glutathione peroxidase without selenium in the liver tissue of mice, named GST. The GST family plays a crucial role in cellular defense by catalyzing the coupling reaction of carcinogens to glutathione, thereby preventing cell damage. Any mutation in the gene that expresses this enzyme may alter the catalytic process, which in turn can alter drug bioavailability and may amplify or reduce drug efficacy and toxicity[41]. Multidrug resistance (MDR) mediated by the overexpression of GST is the main cause of chemotherapy failure in breast cancer[42]. Compared with non-TNBC cells, GSTP1 expression is higher in TNBC, and GSTP1 plays a crucial role in the chemoresistance of TNBC cells[43]. In GSTA1-overexpressing cancer cells, an unexpected lack of chemotherapeutic agents leads to enhanced cytotoxicity[44]. Overexpression of GSTA2 protects cancer cells from apoptosis can also induced by chemotherapeutic agents[45]. Upregulation of GSTA2 is associated with doxorubicin resistance[46]. A case-control study, which investigated children suffered acute lymphoblastic leukemia treated with different anticancer agents (vincristine, daunorubicin, cytarabine, *etc.*), showed that GSTM1 deficiency reduced the risk of recurrence by 18 times[47]. In addition, low survival rate was observed in patients with high GSTM1 expression who received high-dose cyclophosphamide, carmustine and cisplatin as initial chemotherapy for breast cancer[48]. Clearly, GST family is associated with drug resistance of breast cancer, and it also involved in the drug resistance of TNBC.

UGTs are a superfamily, so named because they mainly utilize uridine diphosphate glucuronic acid as a glycosyl donor. UGT catalyzes the binding of the substrate to the uridine diphosphate glucuronate group, making it more hydrophilic and conducive to elimination from the body. The human UGT superfamily is divided into two families based on nucleotide sequence similarity: UGT1A and UGT2[49]. The UGT1A gene cluster, encoded by a gene cluster located at 2q37, contains a total of 17 exons. UGT1A enzymes, especially UGT1A1, have been shown to be overexpressed in tumor tissues and play a role in anticancer drug resistance[50], as well as in TNBC[51]. Overexpression of UGT1A6 counteracts the cytotoxicity caused by the breast cancer chemotherapy drug methotrexate[52]. UGT2B7 can induce epirubicin resistance in breast cancer cells[53]. To sum up that UGT, as a conjugation enzyme in phase II of drug metabolism, plays a important role in breast cancer resistance. Although there are few reports on UGT family in TNBC, the only reports can also illustrate the role of UGT in tumor resistance.

Among the conjugated enzymes in phase II of drug metabolism, the target genes of PXR have been found to include UGT1A1, UGT1A6, UGT1A3, UGT1A4 and GSTA1, GSTA2, GSTA3, GSTM1, GSTM2, GSTM3, GSTM4[30]. The mechanism of which PXR regulates UGT and GST, further lead to drug resistance in TNBC may be one of the drug resistance mechanisms, but due to the lack of relevant reports, more experiments are needed to prove it.

PXR AND TRANSPORTERS IN PHASE III OF DRUG METABOLISM

The transporters in phase III of drug metabolism are mainly adenosine triphosphate binding cassette (ABC) membrane transporters, including MDR protein, multidrug resistation-associated protein (MRP) and breast cancer resistance protein (BCRP), which are mainly involved in drug transport and clearance[54].

ABC membrane transporters affect the therapeutic effect of drugs on malignant tumors by affecting the absorption and metabolism of drugs in cells. ABC transporters use adenosine triphosphate to efflux various compounds, including chemotherapeutic drugs of different structures and properties. A variety of ABC transporters are closely related to chemotherapy resistance of solid tumors including breast cancer, and increased drug efflux mediated by ABC transporters is the most common mechanism of MDR caused by drug efflux[55]. The ABC family of membrane transporters includes seven isoforms (ABCA-ABCG), among which the MDR protein 1 (MDR1/P-gp) gene is a membrane transporter encoded by the ABCB1 gene, with a relative molecular weight of 170 KDa, composed of 1280 amino acids, and located on the cell membrane. The energy released by ATP hydrolysis can be used to transport the hydrophobic and lipophilic drugs outside the cell, when MDR1/P-gp is overexpressed, drug efflux is increased through the role of efflux pump, thereby reducing the accumulation of drugs in cells and the effect of drugs on cells, thus causing drug resistance in tumor cells[56]. Overexpression of MDR has become an important mechanism of drug resistance mediated by TNBC, which is associated with poor outcome, reduced survival rate and chemoresistance of patients[57]. The MRP gene is a membrane transporter encoded by the ABCC gene, whereas BCRP is a membrane transporter encoded by the ABCG gene. In breast cancer related studies, ABCC1, ABCC3, ABCB1 and ABCG2 are associated with drug resistance [22,30,33]. Compared with other breast cancer subtypes, tmultidrug resistance protein-1 (ABCC1/MRP1), MDR protein-8 (ABCC11/MRP8) and BCRP (ABCG2/BCRP) is significantly overexpressed in TNBC[58,59], which is closely related to chemotherapy resistance[60].

PXR regulates a variety of proteins, including MDR protein (ABCB1, ABCB2), MDR associated protein (ABCC2, ABCC3, ABCC4, ABCC5) and so on. These enzymes are mainly bile acid transporters, which mediate the metabolism and excretion of bile acids, as well as the transmembrane transport and clearance of chemotherapeutic drugs[61]. Overexpression of PXR leads to increased cellular levels of resistance proteins such as ABCC1 and ABCG2[62,63]. Studies have

Table 1 Role of pregnane X receptor in the mechanism of drug resistance in breast cancer (including triple-negative breast cancer)

Phase	Resistance-associated proteins associated with PXR	Resistance-associated proteins associated with breast cancer	Resistance associated proteins associated with TNBC	Resistance related proteins known to be regulated by PXR in TNBC	Possible regulatory targets of PXR in TNBC (unconfirmed)
Phase I	CYP3A4, CYP3A23	CYP3A4, CYP3A5	CYP3A4	CYP3A4	CYP2C8
Enzymes metabolism	CYP3A11, CYP2B6	CYP2C8, CYP2C9	CYP4A11		
CYPs	CYP2C8, CYP2C9	CYP2J2, CYP1A1	CYP4A22		
	CYP2C19, CYP1A	CYP1B1, CYP17A1	CYP2C8		
	CYP2B9, CYP2C55	CYP2B6, CYP2D6	CYP1B1		
		CYP2C19, CYP2S1			
		CYP4V2, CYP26A1			
		CYP4A11, CYP4A22			
Phase II	GSTA1, GSTA2	GSTM1, GSTP1	GSTP1		
Enzymes conjugation	GSTA3, GSTM1	GSTA1, GSTA2			
GSTs	GSTM2, GSTM3				
	GSTM4				
UGTs	UGT1A1, UGT1A6	UGT1A, UGT2B7	UGT1A1		UGT1A1
	UGT1A3, UGT1A4				
Phase III	ABCB1, ABCB2	ABCC1, ABCC3	ABCC1	ABCC1	
Ttansporters	ABCC1, ABCC2	ABCB1, ABCG2	ABCG2	ABCG2	
ABCs	ABCC3, ABCC4	ABCC11	ABCC11		
	ABCC5, ABCG2				

PXR: Pregnane X receptor; TNBC: Triple-negative breast cancer; ABC: Adenosine triphosphate binding cassette; CYPs: Cytochrome P450s; UGTs: Uridine diphosphate glucuronosyltransferase; GSTs: Glutathione transferase.

also shown that PXR-mediated induction of ABCC2 seems to be involved in chemotherapy resistance in tamoxifen-resistant breast cancer [64,65]. PXR has been confirmed to regulate two membrane transporters ABCB1 and ABCG2 in TNBC[66]. Clearly, PXR-mediated upregulation of ABC membrane transporter family expression in TNBC cancer patients is one of the mechanisms of chemotherapy resistance in TNBC.

CONCLUSION

In conclusion, although PXR is mainly expressed in liver, intestinal and colon tissues, it is also expressed in normal breast tissues, and its expression level is even higher in breast cancer tissues[67-70]. PXR is associated with the phenotype of TNBC and is a powerful and independent poor prognostic factor[71]. PXR can accelerate the metabolism and clearance of chemotherapy drugs in TNBC through the regulation of three phases of the metabolism of chemotherapy drugs: phase I drug metabolism enzymes CYPs, phase II drug binding enzymes GSTs and UGTs, and phase III drug transporter ABCs, thus resulting in drug resistance (Table 1). Among them, experiments have confirmed that PXR can regulate the expression of CYP3A4, ABCC1, and ABCG2 in TNBC, resulting in TNBC drug resistance. In the future, researchers should focus on improving our understanding of the mechanism of PXR in TNBC drug resistance, including regulation of PXR and function of PXR independence of drug metabolism.

FOOTNOTES

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Country/Territory of origin: China

ORCID number: Zhong-Wen Tang 0000-0001-6201-4625; Jie Wen 0000-0002-5734-4678.

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MINIREVIEWS

Effectiveness and safety of COVID-19 vaccines in patients with oncological diseases: State-of-the-art

Nedelcho Ivanov, Boris Krastev, Dimitrina Georgieva Miteva, Hristiana Batselova, Radostina Alexandrova, Tsvetelina Velikova

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Nedelcho Ivanov, Department of Clinical Immunology with Stem Cell Bank, University Hospital Alexanrovska, Sofia 1431, Bulgaria

Boris Krastev, Medical Center Nadezhda, Medical Center Nadezhda, Sofia 1407, Bulgaria

Dimitrina Georgieva Miteva, Department of Genetics, Faculty of Biology, Sofia University St. Kliment Ohridski, Sofia 1164, Bulgaria

Hristiana Batselova, Department of Epidemiology and Disaster Medicine, Medical University, Plovdiv, University Hospital St. George, Plovdiv 6000, Bulgaria

Radostina Alexandrova, Department of Pathology, Institute of Experimental Morphology, Pathology and Anthropology with Museum, Bulgarian Academy of Sciences, Sofia 1000, Bulgaria

Tsvetelina Velikova, Medical Faculty, Sofia University St. Kliment Ohridski, Sofia 1407, Bulgaria

Corresponding author: Nedelcho Ivanov, FRCS (Hon), MD, PhD, Assistant Professor, Department of Clinical Immunology with Stem Cell Bank, University Hospital Alexanrovska, St. Georfi Sofiiski 1 str, Sofia 1431, Bulgaria. nedelcho.ivanov93@gmail.com

Abstract

Although the coronavirus disease 2019 (COVID-19) pandemic was declared to be no longer "a public health emergency of international concern" with its wide range of clinical manifestations and late complications, severe acute respiratory syndrome coronavirus 2 infection proved to be a serious threat, especially to the elderly and patients with comorbidities. Patients with oncologic diseases are vulnerable to severe infection and death. Indeed, patients with oncohematological diseases have a higher risk of severe COVID-19 and impaired post-vaccination immunity. Unfortunately, cancer patients are usually excluded from vaccine trials and investigations of post-vaccinal immune responses and the effectiveness of the vaccines. We aimed to elucidate to what extent patients with cancer are at increased risk of developing severe COVID-19 and what is their overall case fatality rate. We also present the current concept and evidence on the effectiveness and safety of COVID-19 vaccines, including boosters, in oncology patients. In conclusion, despite the considerably higher mortality in the cancer patient group than the general population, countries with high vaccination rates have demon-

strated trends toward improved survival of cancer patients early and late in the pandemic.

Key Words: COVID-19; COVID-19 vaccines; RNA vaccines; Cancer; Oncological; Safety; Efficacy; Immunogenicity

Core Tip: The coronavirus disease 2019 (COVID-19) pandemic has greatly impacted the lives of cancer patients. Their medical care has been challenging, given the competing risks of death from cancer and serious complications from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Cancer patients are at high risk of severe complications and death from COVID-19. Protective SARS-CoV-2 antibodies and cellular immune response are induced after infection or/and COVID-19 vaccination. Vaccines decrease the risk of hospitalization and death from COVID-19. Therefore, vaccination of specific vulnerable groups, such as oncological patients, and all people in general, will slow the virus spread and save lives.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has considerably impacted the lives of cancer patients. Their medical care has been challenging because of the competing risks of death from cancer or serious complications from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the likely higher lethality in immunocompromised hosts[1,2]. Furthermore, patients diagnosed with malignancies are at higher risk of developing severe COVID-19[3] and fatal outcomes due to the disease. Studies have demonstrated variable mortality rates among subjects with hematological cancers and solid tumors, with some reporting fatality cases of as much as 40% of the infected subjects[4]. Despite this considerably higher mortality than the one observed in the general population, trends towards improved survival during the evolution of the pandemic have already been demonstrated in Europe, and much of this could be a direct result of the rigorous COVID-19 vaccination in this region[5].

Since the beginning of the pandemic, hundreds of different therapeutic options have been studied, including those well-known in the treatment of other diseases, such as reoriented drugs. Amongst them are remdesivir (initially developed for hepatitis C treatment, tocilizumab-rheumatoid arthritis, hydroxychloroquine-malaria, lupus, *etc*), corticosteroids, plasma from donors who have recovered from COVID-19, monoclonal antibodies (casirivimab + imdevimab, bamlanivimab, sotrovimab, cilgavimab + tixagevimab, *etc*), Janus kinase inhibitors (baricitinib), and even mesenchymal stem cells[6,7]. Targeting both the virus itself and the host's immune response with variable effectiveness during the different stages of the disease. However, prevention in the form of COVID vaccines remains the most desirable option for the general population both in long-term health-related and financial terms. Cancer patients are no exception in this regard. But exactly how effective are vaccines in cancer patients compared to the general population? This is the question we will try to answer.

In this review, we elucidated to what extent patients with cancer are at increased risk of developing severe COVID-19 and what is their overall case fatality rate. We also present the current concept and evidence on the effectiveness and safety of COVID-19 vaccines, including boosters, in oncology patients.

SEARCH STRATEGY

We performed a modified form of a biomedical narrative review according to recent recommendations for writing[8]. First, we thoroughly searched the scientific bibliographic databases Medline (PubMed) and Scopus. We used relevant free-text and Medical Subject Headings terms, as follows: ("COVID-19" OR "SARS-CoV-2") AND ("cancer patients" OR "oncological patients") AND ("COVID-19 vaccine" OR "mRNA vaccine"). We confined the search from January 1, 2020 to June 20, 2023. Then we identified additional papers using the search engine Google Scholar. Information from advisory committee meetings was also added.

COVID-19 AND PATIENTS WITH ONCOLOGICAL DISEASES

Patients with oncologic diseases are affected by SARS-CoV-2 in many different ways. Similar to many other infections, COVID-19 poses an additional risk of a fatal outcome for cancer patients. However, it is challenging to say to what extent patients with malignancies are threatened by complications of severe infections. As oncological diseases and treatment

protocols are extremely diverse, it can be expected that the course of SARS-CoV2 infection would also be quite different [9-11].

The stage of disease, type of malignancy, and the sort and phase of the applied treatment modalities (surgery, chemotherapy, radiation therapy, and immunotherapy) introduce even more variables and more superimposing confounding factors, making this group of patients even more heterogeneous and difficult for overall risk assessment. Cancer patients who have recently undergone surgery or chemotherapy (especially during the induction phase with high-dose intensive regimens) are at a dramatically increased risk of death from COVID[12,13]. Side effects of chemotherapy, such as secondary immunodeficiency due to severe leukopenia and specific tissue toxicity due to some chemo- and immunotherapeutics, can significantly alter the course of COVID-19 infection, from worsening the patient's overall condition and increasing the risk of complications and death to masking or mimicking the radiological pulmonary signs (*e.g.*, immune checkpoint related pneumonitis)[13]. Finally, another confounding factor is the various therapeutic regimens used to treat infection in hospitals and intensive care units worldwide. Cancer patients are treated as high risk by default, which carries a risk (polypharmacy, drug interactions, adverse drug effects, acute kidney or liver failure, *etc*) [14].

Below, we present data from several studies that attempt to measure and objectify this risk. The first large-scale meta-analysis by 2020 done by Zhang *et al*[11] of 15 studies involving a total of 3019 patients from Europe, the United Kingdom, the United States, Canada, and Asia detected 22.4% circulating free RNAs (CFRs) in cancer patients with COVID-19, compared to 5.9% in noncancer patients. As in other patients, risk factors influencing the course and mortality are: Being over 65 years old, male sex, and having comorbidities (especially hypertension and diabetes). No significant difference in mortality was found between different continents. The study found that mortality in patients with lung cancer and hematological malignancies was highest, although the incidence of complications did not differ[11].

A study by Yang *et al*[15] involving 1575 patients, of whom 52 with various cancers (lung, colorectal, breast, cervical, thyroid, *etc*) showed that oncologic patients are at higher risk of presenting as severe/critical cases and are more likely to develop acute respiratory distress syndrome. Also, other life-threatening complications such as myocardial infarction and shock are significantly increased in frequency. Lower lymphocyte count, as well as higher concentrations of C-reactive protein, D-dimer, procalcitonin, interleukin 6 (IL-6), and lactate dehydrogenase, were reported to reach $P < 0.05$. Cancer patients are also more likely to have comorbidities, which, as it becomes clear in this study, contributes seriously to the overall higher CFR[15].

A meta-analysis of 122 papers and 9 studies, including a total of 805 patients by Afshar *et al*[16], demonstrated how heterogeneous the data on mortality in cancer patients are. They showed that cancer patients are more likely to be admitted to intensive care units, need invasive ventilation, and are more likely to die. The published CFR in the analyzed studies ranges from 5.5% to 60.0%, with a pooled CFR of 21%. However, the authors warn that these data should be interpreted cautiously due to the high heterogeneity and the small number of patients in most studies[16].

Large-scale survival analysis by Li *et al*[9] based on data from United Kingdom Biobank followed 4606 cancer patients (288 positives) and 4606 noncancer patients (275 positives) for 21 mo after the SARS-CoV2 test. The cumulative CFR of the positive cancer patients was six times higher than the negative ones. The hazard ratio was assessed for each specific malignancy in the study, and the results showed that hematological malignancies, melanoma, kidney, and uterine cancer had particularly high CFRs (up to 10 times higher than the noncancer controls). The authors emphasize the importance of timely vaccination in these groups of patients[9].

In contrast to the data above, a study by Brar *et al*[17] included 585 patients, 117 with active malignancies. It showed no statistically significant difference in morbidity or mortality in cancer patients *vs* the general population. Furthermore, the authors argued that the studies claiming the opposite did not consider confounding factors such as age, sex, and comorbidities. According to this study, cytotoxic treatment within 90 d of admission is not associated with worse outcomes[17].

A team from London published a study in onco-hematology patients, where 40% (14 of 35) of patients hospitalized with COVID-19 had succumbed to the infection[18]. In general, COVID-19 appears to have an increased risk of complications and mortality in a large proportion of cancer patients. In addition, besides the virus itself, the pandemic and the restrictive measures were associated with disrupted access to medical care, hindered timely diagnosis and treatment, the lack of follow-up of many patients and lower quality of life[19]. Studies have shown that since the beginning of the pandemic, the total number of newly diagnosed cancers has dropped substantially[20]. As many authors warned, this inevitably led to an increased frequency of advanced cancers at diagnosis. Delaying diagnosis and treatment resulted in lower chances of survival[21]. Yong *et al*[22] conducted a study in Canada using microsimulation models, which estimated that for colorectal cancers, suspending primary screening for only 6 mo will increase cancer incidence by about 2200 cases, of which about 960 will be lethal over time. Consequences that otherwise would be prevented by the screening program and early detection.

Furthermore, there are many other indirect ways the COVID-19 pandemic affects cancer patients' quality of life and mortality[13]. At the same time, the standard of living, the structure and stability of the health care system, and even political factors in connection with dealing with the pandemic play roles that should not be underestimated[23]. Knowing risk factors for the severity and mortality of COVID-19, cancer patients have their unique risk factors. They may include active and progressing cancer, type of cancer, administration of cytotoxic chemotherapy, radiation therapy, impaired immune system due to leukocytopenia, low immunoglobulin levels, long-lasting immunosuppression, comorbidities, and others.

Malignancies reported as comorbidities in patients hospitalized with confirmed COVID-19 in different countries are: (1) Malignancies in 7.2% in a cohort study with 138 adults with confirmed COVID-19 pneumonia in Wuhan, China, in January 2020[24]; (2) malignancies in 8% at admission in a cohort study with 1591 patients with laboratory-confirmed COVID-19 in Lombardy, Italy between February 20 and March 18, 2020[25]; and (3) Malignancies reported in 5.6% at

admission in a cohort study with 5700 patients with confirmed COVID-19 infection hospitalized in 12 New York City hospitals between March 1 and April 4, 2020[26].

In a cohort study of 928 adults with COVID-19 and current or past cancer diagnosis, solid tumors were found in 82%, including breast (21%), hematologic (22%), prostate (16%), gastrointestinal (12%), thoracic (10%), gynecologic (5%), and renal cell carcinoma (5%)[27,28]. The estimated overall mortality in the research was 13%: 20% for patients with multiple cancers, 18% for patients with hematological malignancies, and 12% for patients with solid tumors[27].

Zhang *et al*[11] showed the COVID-19 fatality rates in subgroup analysis: (1) By cancer type: 32.9% in patients with lung cancer; 34.2% in patients with hematologic cancer; 17.2% in patients with solid cancer; and (2) By cancer treatment: 25.6% in patients with chemotherapy, 27.6% in patients with surgery, 24.3% in patients with immunotherapy, 21.3% in patients with targeted therapy, and 20.5% in patients with radiation therapy[11].

Children with cancer and positive for COVID-19 are at higher risk of severe illness than children without cancer. The cohort study found that about 20% of pediatric cancer patients with COVID-19 experienced a severe infection, compared to 1%-6% of children in the general population[29]. Among patients with hematologic malignancy and laboratory-confirmed COVID-19, mortality was reported in 34% of adults and 4% of children[4].

We can summarize that the main challenges in cancer patients regarding COVID-19 are the often immunocompromised state (*e.g.,* due to leukocytopenia, low immunoglobulin levels, long-lasting immunosuppression), the treatment (*e.g.,* severe chemotherapy, radiation therapy), progression of cancer, comorbidities, and others.

IMMUNE RESPONSE IN CANCER PATIENTS

Cancer cells induce an immune suppressive microenvironment and use various mechanisms to "escape" the body's immune response. As a systemic disease, cancer causes a wide range of functional and compositional changes in the immune system and can affect the body's defenses against various pathogens[30,31].

Dendritic cells (DCs) are antigen-presenting cells with an essential role in originating and directing cellular and humoral immune responses, converging innate and adaptive immunity. DCs have been recognized as the most potent professional antigen-presenting cells[32].

Tumors use different strategies to alter DC maturation and function, such as: (1) The ability to influence the capacity of hematopoietic progenitor cells to differentiate into functional DCs[33,34]; (2) production of various immunosuppressive factors that block the maturation of CD34+ stem cells into DCs[35]; and (3) spontaneous apoptosis of DCs in peripheral blood of patients with breast cancer[36]. Quantitative and functional DC deficiencies have been widely observed in patients with several types of cancer including breast cancer[37,38], prostate cancer[38], non-small cell lung cancer[39,40], colon cancer[41], and melanoma[42].

Data have revealed that tumors disrupt normal hematopoiesis, leading to extramedullary hematopoiesis and myeloid skewing. The three branches of terminally differentiated myeloid cells (macrophages, DCs, and granulocytes) are essential for normal innate and adaptive immune response functioning. The tumor microenvironment alters myeloid cells and can convert them into potent immunosuppressive cells[43,44]. Lymphopenia caused by disease or treatment is frequent in oncology patients and affects their prognosis[45,46].

T cells, one of the primary arms of the adaptive immune response, are also affected in oncology patients. Cancer cells express various membrane and soluble T-cell inhibitory signals. For example, programmed cell death protein-ligand 1 linking to programmed cell death protein 1 on T cells results in decreased activation, proliferation, survival, and cytotoxicity[47]. The last discovery led to the development of checkpoint inhibitors, a breakthrough in immuno-oncology, which led to the 2018 Nobel Prize for Physiology or Medicine. Indoleamine 2,3-dioxygenase, a soluble enzyme physiologically expressed in many tissues, is overproduced in some cancers leading to tryptophan depletion in the tumor microenvironment. T cells, being highly sensitive to tryptophan deprivation, suffer significant functional impairment, promoting tumor growth[48]. An increased rate of CD4+CD25+ regulatory T cells with potent immunosuppressive properties in the peripheral blood of individuals with cancer diseases has been reported[49,50].

Additionally, regulatory B cells (Bregs) are a newly designated subset of B cells that play a central role in regulating immune responses associated with inflammation, autoimmunity, and cancer. Increased Bregs express immunosuppressive properties in gastric cancer through the secretion of anti-inflammatory molecules, such as IL-10, and facilitating the conversion of T cells to regulatory T cells[44,51,52]. Additionally, tumor progression is associated with the dysfunction of natural killer cells due to the combined action of tissue-specific and systemic factors[53]. All of these immune alterations in cancer patients contribute to the differences in immune response after vaccination, including after COVID-19 vaccine administration. Before the COVID-19 pandemic, we had an experience with influenza vaccine administration in patients with oncological diseases. Infectious complications resulting from bacterial, fungal, and viral (often due to reactivation of latent disease, primarily in patients with hematological malignancies) diseases are a severe cause of morbidity and mortality in cancer patients[54]. Oncology patients receiving chemotherapy are at increased risk of influenza virus infection and serious post-influenza complications. Cancer patients are eligible for influenza vaccination, although their response may be suboptimal due to immunosuppression associated with cancer itself and/or its treatment [55,56]. Data have shown that cancer patients receiving chemotherapy can respond to influenza vaccination[57].

Breast cancer patients receiving influenza vaccination during FEC (5-fluorouracil, epirubicin, and cyclophosphamide)-containing treatment regimens have exhibited significantly lower responses to influenza virus vaccination than healthy controls. Vaccination early during the chemotherapy cycle (day 4) induces better responses than vaccination on day 16 [58]. The summary of the available evidence reveals that immunization of individuals with malignancies is critical to their care and may protect them from significant morbidity and mortality associated with vaccine-preventable diseases[59].

COVID-19 VACCINES FOR PATIENTS WITH ONCOLOGICAL DISEASES-DATA ON OUTCOMES AND EFFECTIVENESS

Several available COVID-19 vaccines are now in use all over the world. Moderate or severely immunocompromised people should receive a vaccination to protect them from severe COVID-19 disease[60,61].

The efficacy of COVID-19 vaccines in cancer patients is a question of continuous research, with most studies using immunological parameters as surrogate endpoints for clinical outcomes. Clinical trials investigating immune response after COVID-19 vaccination often use seroconversion to SARS-CoV-2 spike (S) protein as an endpoint for vaccine efficacy. Other parameters such as anti-spike antibody titers, detection of neutralizing antibodies, and cellular immune response are usually explored as secondary endpoints[62]. Some authors, however, underscore the role of neutralizing antibodies as the immunological parameter, which probably best correlates with the level of protection after COVID-19 vaccination [63-65].

Both humoral and cellular immune responses to COVID-19 vaccines differ in patients with malignancies compared to noncancer patients; this is not only attributed to the immunosuppressive nature of the oncologic disease but also to the antitumor therapy itself and its direct impact on immune cells. While patients with solid tumors have seroconversion rates similar to the general population, the most significant concern regarding post-vaccination and post-infectious COVID-19 immunity lies with hematological malignancies, especially those where lymphocyte-depletion therapy is used. In support of this is the research of Monin *et al*[66], who presented interim results of a prospective observational study that explores the immunogenicity of one compared to receiving two doses of the COVID-19 vaccine in patients with cancer by assessing the humoral immune response between 151 patients (95 with solid tumors and 56 with hematological malignancies) and 54 healthy controls. Authors reported efficacy after the first dose in 94%, 38%, and 18% of control subjects, patients with solid tumors and hematological cancer, respectively. After the second dose, the response increased to 100% in controls, 95% in patients with solid cancers, and only 60% in the group with hematological malignancies[66].

When considering post-vaccination immunity in patients with cancer, we should consider that those with hematological malignancies are expected to show different levels of antibody response to COVID-19 vaccines compared to patients with solid tumors. One of the most substantial pieces of evidence in corroboration came from the CAPTURE trial [67]. This prospective clinical study assessed the humoral response after COVID-19 vaccination in more than 700 subjects with solid tumors or hematologic neoplasms, 585 of whom did not have previous SARS-CoV-2 infection. The trial demonstrated 85% and 54% seroconversion rates for anti-spike antibodies after the second dose in patients with solid tumors and hematological malignancies, respectively. However, the response observed among participants was not the same for all SARS-CoV-2 variants[68].

The authors announced substantial differences in neutralizing antibodies concerning viral genotypes from the CAPTURE trial: 83% of patients developed detectable levels of the original SARS-CoV-2 and only 54% of the delta variant. And while nearly two-thirds (62%) of patients with solid tumors elicit humoral response against delta variant, only 31% of those with hematologic malignancies did so[67]. The prospective cohort study of immune response to COVID-19 vaccination in cancer patients CAPTURE (NCT03226886) also showed that among 585 patients, the antibody rates after two doses of BNT162b2 or AZD1222 vaccines given over 12 wk were assessed. The results showed that seroconversion was 85% and 59% after two doses in patients with solid and hematological malignancies, respectively. Neutralizing antibodies against SARS-CoV-2 VOCs were detected in a small proportion of patients, mainly with solid cancers. Vaccine-induced T-cell responses were found in 80% of patients regardless of the vaccine or type of cancer[67].

In an attempt to overcome this relatively low rate of seroconversion in patients with blood cancers, Greenberger *et al* [69] conducted a large prospective cohort trial on nearly 700 patients vaccinated with three doses of the COVID-19 vaccine. It was estimated that antibody response indeed increased with the 3rd (booster) dose, so 43% of those without detectable antibodies after the 2nd dose demonstrated humoral response after the booster. However, about 20% of all hematological patients still failed to achieve a response even with 3 doses of vaccine[69]. In contrast to the plethora of research on humoral immunity after COVID-19 vaccination in cancer patients, the cellular immune response in this setting is considerably less studied. In a review article by Rüthrich *et al*[70], the authors tried to summarize what is currently known about the issue in patients with solid tumors and hematological malignancies, comparing data from COVID-19 vaccines and other "classical" vaccines. Although the assessment of T-cell immune response in the reviewed studies varied, most research used methods based on quantifying and characterizing pathogen-specific T cells and/or estimating T-cell function by cytokine measurement[70].

Observations on immune responses in patients with hematological malignancies revealed that although this population may lack adequate levels of neutralizing viral antibodies, especially after treatment with B cell-depleting agents such as anti-cluster of differentiation 20 monoclonal antibodies, COVID-19 vaccines are still able to produce protective cellular immunity. Solid evidence for the sufficient efficacy of T-cell response comes from a trial in patients with agammaglobulinemia who demonstrated improved COVID-19 infection outcomes after vaccination. However, cellular immunity could also be impaired in this specific patient population, and some of the significant factors for this are age, disease activity, immunosuppressive treatment, and low lymphocyte counts in circulation[70].

This discordance between humoral and cellular immune response could also be seen In patients with solid tumors. In this population, T-cell responses vary among different cancer subtypes and are determined mainly by the type of systemic antitumor treatment. Various studies have demonstrated wide ranges in terms of cellular immunity achieved after COVID-19 vaccination ranging from about 50% to nearly 90% of the vaccinated cases[71,72].

However, despite being generally higher than those observed in blood cancer patients, T-cell response in those with solid tumors remains significantly lower than in healthy controls. One of the most extensive trials reporting data on immune response in patients with solid tumors receiving systemic anticancer treatment is the VOICE study[73]. After recruiting nearly 800 subjects (240 without cancer), the authors assessed cellular immunity by measuring the SARS-CoV-2

spike-specific interferon gamma T-cell response after two vaccine doses. They reported cellular responses in 67%, 66%, and 53% of patients treated with chemotherapy, immunotherapy, or chemoimmunotherapy, respectively. Another interesting trial finding was that more than 40% of patients who did not elicit a humoral immune response could develop a T-cell response, highlighting the vaccine's 'double-edge sword' efficacy in this specific population. Similar to the model observed with the humoral response, whether the cellular response is affected by a booster dose is still an open question since there are conflicting data. Some studies have reported significant enhancement of the T-cell response after the 3rd dose, whereas others refute such assertions[73].

To date, most trials reporting COVID-19 vaccine efficacy in cancer rely on immunological endpoints and not so much on clinical outcomes. However, a recent study on infection rate and outcomes in vaccinated patients with solid tumors and hematologic malignancies has raised concern that despite vaccination, these patients remain at risk of worse outcomes compared to the general population[74]. Among fully vaccinated cancer patients, who experienced breakthrough SARS-CoV-2 infection, the hospitalization rate, intensive care unit admission (or required mechanical vaccination), and death rate are 65%, 19%, and 13%, respectively. This is mainly attributed to patients' comorbidities and the much worse COVID-19 prognosis in those with hematological malignancies.

In a prospective study conducted by Goshen-Lago *et al*[75], it was shown that patients with solid tumors demonstrated short-term efficacy and safety of the BNT162b2 vaccine. A follow-up study evaluated these outcomes at 6 mo after vaccination[76]. Participants were 154 patients with solid tumors and 135 controls (health workers). At 6 mo after vaccination, 122 patients were seropositive compared with 114 controls, and the serologic titers dramatically decreased almost equally in both cohorts. Efficacy and safety evidence of BNT162b2 vaccines shows that the serological profile in cancer patients after 6 mo resembles that of the general population[76].

A similar study was conducted by Barrière *et al*[77], who evaluated the immunogenicity of the BNT162b2 vaccine in patients with solid tumors. Serological analyses were performed during the first vaccination, during the booster dose (w3-w4), and 3-4 wk after the booster dose (w6-w8). The study reported the results for 122 of 194 evaluable patients with solid tumors who had at least two doses from January 2021 to March 2021. In the first analysis (w3-w4), 58 patients had neutralizing antibodies, although the median levels were significantly lower than in the control group. In the following analysis (w6-w8), the data showed the same anti-S seroconversion rate, demonstrating impaired immunogenicity of the BNT162b2 vaccine in cancer patients[77].

Shroff *et al*[78] also compared anti-S seroconversion to the BNT162b2 mRNA vaccine in patients with solid tumors on active cytotoxic anticancer therapy with healthy control participants. Neutralizing antibodies were found in 67% of cancer patients after the first immunization, and a follow-up analysis found a threefold increase in titers after the second or third doses. European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number 2021-000291-11 was conducted in patients with solid cancers, multiple myeloma, and inflammatory bowel disease[79]. The study is a prospective, open-label, phase four trial to monitor vaccine-specific antibody and cellular responses after booster vaccination with mRNA-1273 or BNT162b2. The data show that booster vaccination against SARS-CoV-2 reverses the lack of response and early antibody weakening in immunocompromised patients.

Another study on the efficacy and safety of heterologous booster vaccination with Ad26.COV2.S after BNT162b2 mRNA vaccine in cancer patients without antibody response was conducted in 2022[80]. The assessment was done directly before vaccination and 4 wk after. Ad26.COV2.S booster vaccination resulted in a serological response in 31% of nonresponders after a double dose of BNT162b2. Clinical trials with the number NCT04368728 reported results from individuals with a history of past or active neoplasms and up to 6 mo of follow-up after dose 2 of a placebo-controlled, observer-blinded trial of the BNT162b2 vaccine[81]. In participants with past or active neoplasms, two doses of the BNT162b2 vaccine improved efficacy and safety profile as in the overall trial population. No vaccine-related deaths were reported.

One of the first evaluations of the effectiveness of vaccination against breakthrough SARS-CoV-2 infections in cancer patients at a population level was done by Lee *et al*[82]. Analysis was performed in the cancer cohort by vaccine type (BNT162b2, ChAdOx1 nCov-19, or mixed, and other), cancer type and subtype, stage, date of cancer diagnosis, and anticancer treatment or radiotherapy. Data show that vaccination with different COVID-19 vaccines is effective in people with cancer, providing varying levels of protection against SARS-CoV-2 infection. However, it is lower in cancer patients than in the general population[82].

A single-arm prospective clinical trial was conducted with 106 cancer patients by Thakkar *et al*[83]. They received two doses of mRNA followed by one dose of AD26.CoV2.S vaccine or a third dose of mRNA vaccine. The results showed that a third dose induced immunity in cancer patients. Seroconversion was also assessed in 57% of patients who did not respond to primary vaccination. A fourth dose boosted the immune response by two-thirds. Some patients have neutralizing activity against the omicron variant[83].

In conclusion, all of these studies confirm that people with cancer are at increased risk of severe COVID-19 disease, hospitalization, and death after SARS-CoV-2 infection compared to the general population. The above data show that cancer patients have impaired overall vaccine effectiveness to the approved COVID-19 vaccines. Seroconversion in them decreases faster than in the control population. Although vaccination provides different levels of protection, there should be a global prioritization of the programs to boost vaccination for cancer people, considering the impact of other treatments.

There are still a lack of data on vaccine efficacy in cancer patients concerning novel virus variants like omicron[68]. Table 1 presents the studies on the effectiveness and safety of COVID-19 vaccination with different approved COVID-19 vaccines in oncological patients with solid tumors[5,63,66,67,69-71,73,75-84,84].

Table 1 Some of the more significant studies conducted on the efficacy and safety of COVID-19 vaccination with different approved COVID-19 vaccines in oncological patients with solid tumors

Ref.	Type of vaccine	Type of study	Subjects (diagnosis, other specific characteristics)	Data on efficacy	Data on safety (main side effects)
OnCovid study group [5]	NA	A multicenter observational registry-based study	All PTs included n = 2634 (100%); PTs with advanced tumor stage n = 1244 (46%); PTs with receipt of anti-cancer therapy within 4 wk of COVID-19 diagnosis n = 1305 (51.8%); malignancy type: Breast n = 493 (18.9%); gastrointestinal n = 476 (18.2%); gynecologic/genitourinary n = 530 (20.3%); hematologic n = 357 (13.7%)	The difference in the necessity of hospitalization due to COVID-19, oxygen therapy requirement, mechanical ventilation requirement, and 14-d CFR between PTs stratified across time five phases and two major outbreaks of the pandemic; hospitalization requirement: 1st phase-64.7% to 5th phase-42.7% (P < 0.01); proportion to PTs requiring oxygen: therapy, phase 1-62.6%, to phase 5-46.0% (P < 0.001); mechanical ventilation: Phase 1-12.1% to phase 5-11.8% (P = 0.01); CFR: 1st outbreak-25.6% to-2nd outbreak 16.2% (P < 0.001)	N/A
Khoury *et al* [63], 2021	mRNA and adenoviral vector vaccines			20.2% of subjects had (95%CI) 50% protective neutralization level	N/A
Monin *et al* [66], 2021	mRNA	Prospective observational study	PTs with oncologic disease n = 151: With solid cancer n = 95; with hematological malignancy n = 56; and HCs n = 54	Surrogate marker of efficiency: Seroconversion after 1st dose: 32 of 34 (94%) HCs, 21 of 56 (38%), PTs with solid cancer, 8 of 44 (18%) PTs with hematologic malignancies; after 2nd dose: 12 of 12 (100%) HCs; 18 of 19 (95%) PTs with solid, 3 of 5 (60%) PTs with hematologic malignancies	AE: Injection site pain within 7 d following the first dose in: 23 of 65 (35%) PTs with cancer; 12 of 25 (48%) HCs; no vaccine-related deaths were reported
Greenberger *et al*[69], 2021	mRNA and adenoviral vector vaccines	Retrospective cohort study	PTs with hematologic malignancies, n = 3300		
Ehmsen *et al* [71], 2021	mRNA	Prospective cohort study (comparison between groups with different malignancies; no HCs)	PTs with cancer, n = 524, of whom: 201 (38%) with solid cancer; 323 (62%) with hematologic cancer; 524 (100%) had a blood sample drawn at a median of 36 d after the second dose of vaccine; and 247 (47%) had a second blood sample drawn 3 mo after the second dose of the vaccine	Seropositivity rate for anti-S IgG 36 d after vaccination: PTs with solid cancer 187 of 201 (93%); PTs with hematologic cancer 215 of 323 (66%); seropositivity rate for anti-S IgG 3 mo after vaccination: PTs with solid cancer-86%, PTs with hematologic cancer-53%; anti-S IgG titers; between 36-d and 3-mo samples declined from a median of 429 BAU/mL to a median of 139 BAU/mL (P = 0.03, Student's t-test); T-cell reactivity: PTs with solid cancer-92 (46%), 70 (76%) mounted both CD4+ and CD8+ T-cell responses, 21 (23%) elicited only a CD8+ T-cell response, PTs with hematologic cancer-144 (45%), 81% were positive for both CD4+ and CD8+ T cells, 26 (18%) only elicited a CD8+ T cell response, 76% of the seronegative PTs did not elicit a T-cell response; PTs with solid cancer: only 1 of the 14 (7%) seronegative PTs elicited a T-cell response; PTs with hematologic cancer: 28 of 108 (26%) PTs elicited a T-cell response	N/A
Oosting *et al* [73], 2021	mRNA	Prospective, multicenter, non-inferiority trial	Cohort A: Individuals without cancer (control cohort); cohort B: PTs with SOTs, regardless of stage and histology, treated with immunotherapy; cohort C: PTs treated with chemotherapy; and cohort D: PTs treated with chemoimmunotherapy	Presence of SARS-CoV-2-binding antibodies after the second vaccination; at 28th d, 6 mo after 12 mo after a spike-specific T-cell response was defined as a two times or more significant increase in the number of spot-forming cells	N/A
Polack *et al* [84], 2020	mRNA vaccines	Placebo-controlled, observer-blinded, pivotal efficacy trial (randomized 1:1 vaccine *vs*	All PTs included n = 43548; PTs with liver disease n = 217 (0.6%)	95% efficacy (9 vaccinated *vs* 169 controls with COVID-19); 10 cases of severe COVID-19 infection *vs* 9 in the placebo group; flares: NR	Systemic AEs: (1) Fatigue (34%-51%); (2) headache (25%-39%); (3) fever (11%), injection site reactions; (4)

		placebo)			pain (71%-83%); (5) redness and swelling (< 7%); and (6) serious AE < 4%
Fendler *et al* [67], 2021	BNT162b2 or AZD1222 vaccines (CAPTURE, NCT03226886)	Prospective cohort study	585 PTs, the seroconversion rates after two doses of BNT162b2 or AZD1222 vaccines given over 12 wk were assessed	After two doses of BNT162b2 or AZD1222 vaccines given over 12 wk, seroconversion was 85% and 59% in PTs with solid and hematological malignancies, respectively; vaccine-induced T-cell responses were found in 80% of PTs regardless of the vaccine or type of cancer	N/A
Goshen-Lago *et al* [75], 2021	BNT162b2 vaccine	Prospective study	154 PTs with SOTs and 135 HCs (health workers)	In PTs with cancer with active intravenous treatment, 79% (n = 122) of the PTs had positive serologic test results, compared with 84% (n = 114) in the control group; analysis by age, sex, or disease stage has no significant differences within the PT cohort; 15% of the seropositive PTs became seronegative after 6 mo, comparable to the control group	N/A
Waldhorn *et al*[76], 2021	BNT162b2 vaccine	Prospective study	154 PTs with SOTs and 135 controls	6 mo postvaccination, 79% of PTs and 84% of HCs were seropositive (P = 0.32); dramatically decreased serology titer	
Shroff *et al* [78], 2021	BNT162b2	Phase 1 cohort trial	53 PTs with SOTs on active cytotoxic anticancer therapy and 50 healthy cohort	Neutralizing antibodies were detected in 67% of PTs with cancer after the first immunization, followed by a threefold increase in median titers after the second dose	AEs were mild: temperature, fever, headache, redness, and swelling on the injection site
Barrière *et al* [77], 2021	BNT162b2	VMO for vaccinated PTs under active treatment in the Department of Oncology of the Saint Jean Polyclinic, Nice, France	194 evaluable PTs with SOTs and 31 HCs	58 PTs had neutralizing antibodies, although the median levels were significantly lower than those in the control group; the data demonstrating impaired immunogenicity of the BNT162b2 vaccine in immunocompromised PTs; % of efficacy was not reported	N/A
Thomas *et al* [81], 2022	BNT162b2 mRNA	Phase 3 randomized clinical trial	3813 participants had a history of neoplasm: Most common malignancies were breast (n = 460), prostate (n = 362), and melanoma (n = 223)	Vaccine efficacy was 94.4% (95%CI) after up to 6 mo of follow-up post-dose 2	N/A
Wagner *et al* [79], 2022	mRNA-1273 or BNT162b2	Prospective, open-label, phase four trail	263 PTs with SOT, n = 63), MM, n = 70, IBD, n = 130 and 66 controls	1 mo after the two-dose primary vaccination, the highest nonresponder rate was found in MM PTs (17%); 6 mo after the second dose, 18% of PTs with MM, 10% with SOT, and 4% with IBD became seronegative compared to the control group; the vaccination with mRNA-1273 led to higher antibody levels than with BNT162b2; booster vaccination increased antibody levels 8-fold in seropositive individuals and induced responses in those with undetectable pre-booster antibody levels	N/A
Lee *et al*[82], 2022	BNT162b2, ChAdOx1 nCov-19, or mixed and other	Population-based test-negative case-control study	Cancer cohort comprised 377194 individuals, of whom 42882 had breakthrough SARS-CoV-2 infections; the control population consisted of 28010955 individuals, of whom 5748708 had SARS-CoV-2 breakthrough infections	Overall vaccine effectiveness was 69.8% in the control population and 65.5% in the cancer cohort; vaccine effectiveness at 3-6 mo was lower in the cancer cohort (47.0%) than in the control population (61.4%)	N/A
Reimann *et al*[80], 2022	Ad26.COV2.S after BNT162b2 mRNA		32 oncological nonresponders to double-dose BNT162b2	The overall response rate was 31%	Mainly mild local and systemic reactions
Thakkar *et al* [83], 2023	Two doses of mRNA or one dose of AD26.CoV2.S vaccine and administered a	Single-arm prospective clinical trial	cancer PTs	A third dose of the COVID-19 vaccine induces durable immunity in cancer PTs, leading to seroconversion in 57% of PTs who did not respond to primary vaccination; 18 PTs with blood cancer and severe immune suppression had no response after three	N/A

	third dose of mRNA vaccine	doses; and the fourth dose boosted the immune response by 2/3 of PTs, with neutralizing activity against the omicron variant

AE: Adverse event; CI: Confidence interval; CFR: Circulating free RNA; COVID 19: Coronavirus disease 2019; HCs; Healthy controls; IBD: Inflammatory bowel disease; MM: Multiple myeloma; NA: Not available; N/A: Not applicable; PT: Patient; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SOT: Solid tumor; VMO: Vaccine monitoring observatory.

COVID-19 VACCINES AND CHEMOTHERAPY INTERACTIONS

People with cancer often have an increased susceptibility to infections due to various factors, including cancer itself and/or, in some cases, the applied therapy, poor nutrition, and damaged physiological barriers. In addition, the incidence of neoplasia is highest in individuals aged 65 and over. When the immune system's effectiveness is weakened, the elderly often have concomitant diseases for which they can also take medications[54,85].

Regarding cancer chemotherapy, conventional antitumor chemotherapeutic agents kill actively proliferating cells, including bone marrow cells, and myelosuppression is one of clinical oncology's most common side effects[86]. Chemotherapy-induced neutropenia is a significant cause of hematological and dose-limiting toxicities of chemotherapy [87]. Some currently available anticancer drugs, such as methotrexate and cyclophosphamide, express immunosuppressive effects and impair peripheral T cells' proliferative and/or effector functions. Methotrexate is an antimetabolite of the antifolate type developed in 1947 and is included in the World Health Organization's List of Essential Medicines. Currently, it is widely used not only in clinical oncology (in the treatment of acute lymphoblastic leukemia, acute myeloid leukemia, meningeal leukemia and lymphoma, osteosarcomas, non-Hodgkin's lymphoma, breast and bladder cancers, *etc*.) but also as a first-line treatment in autoimmune, inflammatory diseases such as rheumatoid arthritis, psoriasis and Crone's disease[88-90]. Methotrexate has been found to disturb antibody response after pneumococcal vaccination[91,92]; the drug reduces circulating T helper 17 (Th17) cells and impairs plasmablast and memory B-cell expansion following pneumococcal conjugate immunization in patients with rheumatoid arthritis[93].

Cyclophosphamide is an alkylating agent synthesized in 1958 and used for decades in clinical practice in the therapy regimens of neoplasms (malignant lymphomas, multiple myeloma, sarcoma, breast cancer, disseminated neuroblastomas, retinoblastoma, ovarian adenocarcinoma, *etc*) and as an immunosuppressive agent for the treatment of autoimmune and immune-mediated diseases such as multiple sclerosis. Cyclophosphamide shows selectivity for T cells and is an immunosuppressant to prevent transplant rejection and graft-*vs*-host complications[94]. Cyclophosphamide has been associated with suppressing helper Th1 activity and enhancing Th2 responses[95]. This drug inhibits Th1/Th17 responses and increases the cells secreting anti-inflammatory cytokines such as IL-4, IL-10, and transforming growth factor beta [96]. A single administration of low-dose cyclophosphamide selectively suppresses regulatory T cells. The low-dose cyclophosphamide promotes antitumor immunity by selectively depleting regulatory T cells and enhancing effector T cell function. However, cyclophosphamide can also increase the number of myeloid-derived suppressor cells[97,98].

Treatment with tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib applied in the treatment of chronic myeloid leukemia is associated with loss of memory B-cell subsets and impaired humoral immune responses to 23-valent polysaccharide pneumococcal vaccine, likely due to the off-target kinase inhibitory activity of these drugs[99].

CONCLUSION

Data so far show that patients with cancer are at increased risk of severe COVID-19 and developing various complications mainly due to their immunocompromised state, type of treatment and comorbidities. Although cancer patients were excluded from vaccine trials, the investigations of post-vaccinal immune responses and the effectiveness of the vaccines showed that both humoral and cellular immune responses to COVID-19 vaccines differ in patients with malignancies compared to noncancer patients, and this is being attributed not only to the immunosuppressive nature of the oncologic disease but to the antitumor therapy itself and its direct impact on immune cells.

The evidence indicates that the efficacy of vaccinations could be impaired in cancer patients in line with a reduced rate of seroconversion and shorter duration compared to healthy controls. Despite these data, when focusing on the clinical outcomes instead of immunological endpoints regarding vaccine efficacy, COVID-19 vaccines demonstrated high effectiveness in preventing severe COVID-19 and infection-related death, and safety profile with comparable to healthy controls adverse effects in patients with solid tumors and hematological malignancies.

Despite the considerably higher mortality in the cancer patients group from COVID-19 than the general population, countries with high vaccination rates have demonstrated trends toward improved survival of cancer patients early and late in the pandemic. Nevertheless, vaccination of these patients and overall vaccination of the population has proven to significantly reduce the risk of complications and mortality of COVID-19 and should be promoted worldwide.

FOOTNOTES

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Country/Territory of origin: Bulgaria

ORCID number: Nedelcho Ivanov 0000-0002-7471-7368; Boris Krastev 0000-0003-4196-0828; Dimitrina Georgieva Miteva 0000-0002-5931-2426; Hristiana Batselova 0000-0002-6201-848X; Radostina Alexandrova 0000-0002-7699-6479; Tsvetelina Velikova 0000-0002-0593-1272.

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