Dissection of the Role of Multidrug Resistance Protein in Cancer

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Abstract: Cancer is a major public health problem worldwide, with the mortality estimated to grow for years, especially with the belated access to care due to the pandemic of coronavirus disease 2019. Despite the emergence of various oncology therapies during the past several decades, multi-drug resistance remains an important challenge in cancer healing, especially in chemotherapies. This review includes the classification of chemotherapeutic agents. As over 90% of mortalities in chemotherapies are caused by multi-drug resistance, this study also elaborates the mechanisms of multi-drug resistance, with a deep insight into distinct types of multidrug resistance proteins and the inhibitors related to them. The mechanisms of multidrug resistance proteins are yet to be fully understood, and a few novel inhibitors of multidrug resistance proteins are still under development. Thus, there are challenges for effective chemotherapies overcoming multi-drug resistance. However, a few oncology treatments, such as immunotherapy and targeted drug delivery via DNA nanostructure have weakened the impact of multi-drug resistance. The aim of this review is not only to demonstrate the latest data on the studies of multi-drug resistance but also to offer information to those who are searching for novel oncology therapies with higher cure rates, and plan to contribute to future multidrug resistance studies as well as the emerging discoveries on mechanisms of MRPs.

1 INTRODUCTION

As a major public health problem worldwide, cancer is a group of diseases. Several cells in the body grow rapidly, spread beyond their boundaries, and invade other parts of the body (National Cancer Institute 2007, WHO 2021). The mortality rate of cancer increased in most of the 20th century until it peaked in 1991. Then with the boom in the detection and treatment of cancer, the mortality by 31% between 1991 and 2018, which means 3.2 million deaths caused by cancer were prevented. Various cancer therapies, including chemotherapy, surgery, radiotherapy, immunotherapy, and biologically targeted therapy, contribute to the effectiveness of chemotherapy as the most common oncology treatment (Bugde et al. 2017).

Either extracted from plants or synthetic compounds, chemotherapeutics can be classified into alkylating agents, topoisomerase inhibitors, antimetabolites, mitotic spindle inhibitors, and others according to the mechanism of action (Bukowski, Kciuk, Kontek 2020). Alkylating agents can cause the transfer of alkyl groups to the DNA guanine residues or intra or inter-strand cross links, leading to DNA base mispairing and the inhibition of strand separation in the process of DNA synthesis (Nussbaumer, Bonnabry, Veuthey, Fleury-Souverain 2011). Topoisomerase inhibitors include topoisomerase I inhibitors (topotecan, irinotecan) and topoisomerase II inhibitors(teniposide, etoposide, doxorubicin, anthracyclines), both of which can lead to DNA strand breakthrough manipulating topoisomerases in DNA replication (Bax, Murshudov, Maxwell, Germe 2019). Antimetabolites

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have interference in pathways of fundamental biosynthesis, perturb the synthesis of DNA or RNA, incorporate analogs of purine/pyrimidine with different structures into DNA, or result in DNA strand breaks by restraining a group of enzymes, for instance, DNA polymerase, dihydrofolate reductase (Marchi, O'Connor 2012). Mitotic spindle inhibitors sustain activation of the spindle assembly checkpoint (SAC), lengthening mitotic arrest, eventually resulting in the cell's death. The entire inhibition procedure is conducted in mitosis or in the G1 phase of the following cell cycle (Sinha, Duijf, Khanna 2019). Besides the chemotherapeutic agents above, other chemotherapeutic agents with distinct mechanisms exist, for instance, tyrosine kinase inhibitors, antibiotics, proteasome inhibitors, some particular enzymes, including l-asparagincase, are non-homogenous (Bukowski, Kciuk, Kontek 2020).

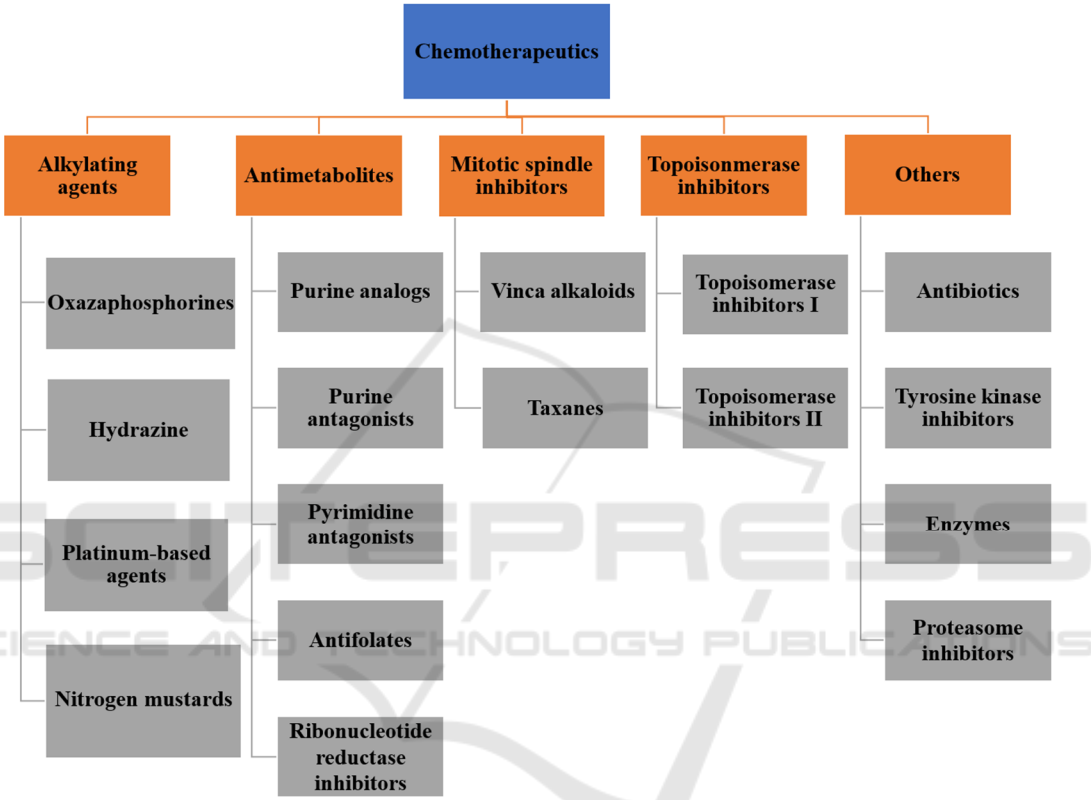


Figure 1: Classification of chemotherapeutics depending on their mechanism of action

However, the major challenge faced in cancer chemotherapy is the less effective treatment due to multidrug resistance (MDR), which remains the second cause of death in developed countries (Garcia-Mayea, Mir, Masson, Paciucci, LLeonart 2020). MDR in oncology is defined as the ability of resilience against drugs that are different in function and structure. It was first discovered in experiments with cultivated cells done by J.L. Biedler in 1970 (Biedler, Riehm 1970). Previous studies indicate that multidrug resistance can appear before or during the treatment, and it can be either acquired in the process of chemotherapy or just inherent (Harris, Hochhauser 1992).

Mechanisms of MDR can be divided into several categories: (1) promoted efflux of drugs by transporters on the membrane of cancer cells, of which ATP-binding cassette (ABC) transporters function as main transporters (Chun, Kwon, Nam, Kim 2015); (2) resistance to chemical substances caused by microenvironment changes, for example, cancer stem cell regulation (Li, Lei, Yao, et al. 2017); (3) mutation in drug targets or feedback activation of other targets and signaling pathways (Li, Lei, Yao, et al. 2017); (4) decrease in drug uptake by influx transporters; (5) promoted adaptability of cancer cells enhanced by regulation of miRNA as well as epigenetic regulation; (6) pathways of. apoptotic signaling blocked as a result of altered level of B cell lymphoma (BCL) family proteins expression or mutant p53 pathway; (7) prompted metabolism of xenobiotics (Bukowski, Kciuk, Kontek 2020).

MDR is most commonly led by the overexpression of ABC, with a family of 49 human membrane transporters involved in diverse physiologic processes, in which P-glycoprotein (P-gp), multidrug resistance-associated proteins (MRPs), breast cancer resistance protein (BCRP) are included (Liu 2019). P-glycoprotein (P-gp, MDR1/ABCB1), as the first member of the ABC transporter family, was found in drug-resistant Chinese hamster ovary cells in 1976 by Victor Ling functioning as an ATP binding cassette (ABC) transporter (Juliano, Ling 1976). Experiments indicate that the gene of P-gp, which was later renamed ABCB1, can lead to drug resistance when transfected into sensitive cells. Multidrug resistance-associated protein 1 (MRP1/ABCC1), as the second member of the ABC transporter family, discovered by Cole et al. (Cole, Bhardwaj, Gerlach, et al. 1992), can form resistance to vincristine etoposide, doxorubicin (Mirski, Gerlach, Cole 1987). Different from P-gp, which mainly transports hydrophobic chemicals, the substrates of MRP1 and are amphipathic organic acids with large hydrophobic groups with a wide range of diversity in structure. MRP1 also transports endobiotics, for instance, hormones, pro-inflammatory molecules, antioxidants, which P-gp doesn't export (Kumar, Jaitak 2019). Breast cancer resistance protein (BCRP/ABCG2), as the third member of the ABC transporter family, was first reported by Doyle et al. in 1998, named from the drug selected breast cancer cell line, i.e., MCF-7. Unlike P-gp or MRP1, both of which are full transporters, BCRP is considered as the shortest ABC transporter with one TMD and one NBD. Through flocking by homodimerization or heterodimerization with a disulfide bridge at Cys 603, BCRP gains its full function (Kumar, Jaitak 2019).

2 MULTIDRUG RESISTANCE PROTEINS (MRPS)

The ATP-binding cassette (ABC) transporters are participants of a protein superfamily that are recognized to transport intracellular and extracellular materials, including metabolic products, lipids and sterols, and xenobiotic drugs, and multidrug resistance proteins (MRPs) belong to the largest subfamily C in the ABC transporter superfamily (Zhang, Wang, Gupta, Chen 2015). MRPs include MRP1, MRP2 or cMOAT (the canalicular multispecific organic anion transporter), MRP3, MRP4 (cMOAT-B), MRP5 (cMOAT-C), MRP6, MRP7, MRP8, and MRP9. The extended expression of MRP is one of the integral motives of multidrug resistance. MRPs have been implicated in mediating multidrug resistance in tumor cells to many degrees as the efflux extrude chemotherapeutic compounds (or their metabolites) from malignant cells, so MRPs are the groundwork for chemotherapeutic resistance of many malignant tumors (Chen, Tiwari 2011).

2.1 Multidrug Resistance Protein 1 (MRP1)

MRP1(ABCC1) was once discovered in 1992, the predominant member of the MRP subfamily-associated MDR (Ma, Hu, Wang, et al. 2014). The MRP1 gene is positioned in the lengthy arm 13.1 bands of human chromosome 16 with a molecular weight of 190 kDa. The structure of MRP1 consists of two transmembrane domains (TMD) and two nucleotide-binding domains (NBD), and an extra N-terminal TMD-TMD0, in which TMD is accountable for substrate recognition, binding, and transport. At the same time, NBD is concerned with ATP binding and hydrolysis to grant strength for transport (Johnson, Chen 2017). MRP1 transports a range of therapeutic agents as properly as a variety of physiological substrates. It may also play a role in improving drug resistance in a range of cancers, including lung cancer, breast cancer, persistent lymphocytic leukemia, acute lymphocytic leukemia, prostate cancer, and pediatric neuroblastoma (Munoz, Henderson, Haber, Norris 2007). MRP1 is expressed in the liver, kidney, intestine, brain, and other tissues, transporting structurally numerous necessary endogenous substances (e.g., leukotriene and conjugated estrogen) and heterogeneous biological and their metabolites, such as a number conjugates, anti-cancer drugs, heavy metals, organic anion, and lipids, with features concerned in inflammation, detoxification, and oxidative stress (Nasr, Lorendeau, Khonkarn, et al. 2020, He, Li, Kanwar, Zhou 2011).

2.2 Multidrug Resistance Protein 2 (MRP2)

ABCC2 encodes MRP2, which was once first identified and cloned from rat liver cells. MRP2 not only exists in tumor cells but also in the small intestine, liver, kidney, placental barrier, and blood-brain barrier (Zhang, Wang, Gupta, Chen 2015, ostendorp, Beijnen, Schellens 2009). Similar to MRP1, MRP2 has two MSDs characteristic of ABC transporters, in addition to a third NH2-terminal MSD (MSD0) and a COOH-terminal region. Sequences

inside MSD0 of MRP2 are required for its activity and plasma membrane trafficking, as are sequences within its COOH terminal region (Chen, Tiwari 2011). MRP2 promotes the excretion of drugs and chemicals, especially MRP2 mediates ATP-dependent outflow of various drugs and chemical compounds (including glucosidic acid, sulfate, and glutathione complexes), so drugs and chemical substances can be eliminated from cells (Wen, Joy, Aleksunes 2017).

2.3 Multidrug Resistance Protein 3 (MRP3)

The amino acid sequence homology of MRP3 and MRP1 is the highest, about 58%. MRP3 used to be often positioned in the basement membrane of hepatocytes and more often than expressed in the adrenal gland, kidney, small intestine, colon, pancreas, and gallbladder. However, the expression stage of MRP3 was once low in the lung, spleen, stomach, and tonsil (Zhang, Wang, Gupta, Chen 2015, Chen, Tiwari 2011). One of the features of MRP3 is to mediate the transport of anionic complexes and optimize the endogenous lipophilic substances, exogenous resources, and glycosides of bile sulfate. At the same time, it can also preserve the stability of bile acid metabolism and adjust the transport of soluble compounds in bile (Pérez-Pineda, Baylón-Pacheco, Espíritu-Gordillo, Tsutsumi, Rosales-Encina 2021).

2.4 Multidrug Resistance Protein 4 (MRP4)

MRP4 (ABCC4) was first discovered in human T lymphoid cell lines in 1999. MRP4 is a vast substrate-specific carrier, dispensed in nearly all tissues and cells, inclusive of lung, ovary, testis, kidney, intestine, liver, brain, pancreas, prostate, and more than a few blood cells, and expressed in a range of human tissues (examples are the basolateral and apical plasma membranes from the liver and kidneys) (Pérez-Pineda, Baylón-Pacheco, Espíritu-Gordillo, Tsutsumi, Rosales-Encina 2021). MRP4 (MOAT-B) is a lipophilic anion efflux pump capable of conferring resistance to huge varying from substrates, including nucleotide analogs, MTX, and glutathione (GSH). Compared with other transgenic egg whites, ABCC4 has a typical ABC transporter core structure, specifically two transmembrane domains and two nucleotide-binding domains (Zhang, Wang, Gupta, Chen 2015). MRP4 is a plausible therapeutic target for MDR. MRP4 was once noticeably expressed in myeloid progenitors, and various endogenous molecules are transported out of cells. MRP4 protects cell function through 6-mercaptopurine (6-MP) efflux. However, it can make most cancer cells resistant to anticancer drugs and limit the sensitivity of the tumor to radiotherapy and chemotherapy (Ma, Hu, Wang, et al. 2014).

3 INHIBITORS

3.1 MRP1 Inhibitor - Sulindac

Sulindac appears to have favourable characteristics as a potential MRP-1 inhibitor since in vitro inhibition is evident at concentrations achievable in serum with standard doses of the agent. Also, sulindac is relatively nontoxic and well-tolerated because of the small number of NSAIDs that might be used, especially when used in an acute setting. The primary biological metabolites and certain analogues of it have been demonstrated to have pro-apoptotic actions. Sulindac potentially inhibition of MRP-1-mediated doxorubicin resistance coupled with other activities such as anti-angiogenesis, which has been described for sulindac and led to a potentiation of the toxicity of doxorubicin without using toxic concentrations. Also, sulindac is able to potentiate the anti-tumour activity of doxorubicin in some animal models (Anticancer Research 2004).

3.2 MRP1 and MRP2 Inhibitor - Nonsymmetrical 1, 4-Dihydropyridines

It is non-symmetrical compounds that have been investigated to inhibit MRP1 and MRP2, both with a non-symmetric framework. It is developed by novel non-symmetrically substituted 1,4-dihydropyridines in a different approach than the known so-called one-pot reaction. The reaction mixture consists of the afore-described three compounds to result in the molecular 1,4-dihydropyridine scaffold. Nonsymmetrical 1,4-Dihydropyridines express MRP1 and MRP2 using the fluorescent carboxyfluorescein diacetate (CFDA) as MRP substrate. The respective cells were pre-incubated with the potential inhibitors, and then the fluorescent substrate was added. The substrate uptake was measured by flow cytometry detecting the corresponding fluorescence of the respective cells. The fluorescence was related to the untreated control cells measured to give a fluorescence activity ratio (FAR) value (Pharmaceuticals 2020).

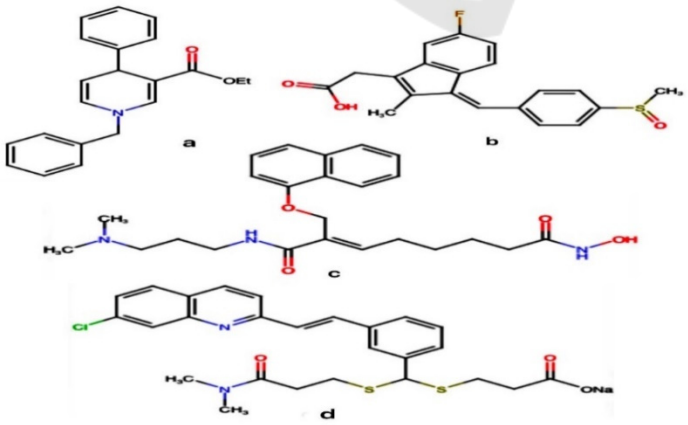
3.3 MRP3 and MRP4 Inhibitor - CG200745

CG200745, (E)- N(1)-(3-(dimethylamino)propyl)-N(8)-hydroxy-2-((naphthalene-1-loxy) methyl) oct-2-enediamide, is a recently developed HDAC inhibitor. As a novel, HDAC inhibitor, CG200745, is an intravenous hydroxamate-based pan-HDAC inhibitor. Its inhibitory effect on cell growth has been demonstrated in several types of cancer cells, including prostate cancer, renal cell carcinoma, and colon cancer in mono- and combinational-therapy with other anticancer drugs. CG200745 was well tolerated at the tested doses with no dose-limiting toxicities in the first human study. The effect of CG200745 on pancreatic cancer cell apoptosis was tested by Western blot analysis, which indicated that CG200745 increased the expression of pro-apoptotic proteins, BAX, and p21. CG200745 induced the expression of apoptotic proteins (PARP and caspase-3) and increased the levels of acetylated histone H3. CG200745 with gemcitabine/erlotinib showed significant growth inhibition and synergistic antitumor effects in vitro. In vivo, gemcitabine/erlotinib and CG200745 reduced tumor size up to 50%. CG200745 enhanced the sensitivity of gemcitabine-resistant pancreatic cancer cells to gemcitabine and decreased the level of ATP-binding cassette-transporter genes, especially MRP3 and MRP4. The novel HDAC inhibitor, CG200745, with gemcitabine/erlotinib, had a synergistic anti-tumor effect on pancreatic cancer cells. CG200745 significantly improved pancreatic cancer sensitivity to gemcitabine, with a prominent antitumor effect on gemcitabine-resistant pancreatic cancer cells (Scientific Reports 2017).

3.4 MRP4 Inhibitor - MK-571

MK571 is a multidrug resistance protein-1, multidrug resistance protein-2, and multidrug resistance protein-4 (MRP1, MRP2, and MRP4) inhibitor. It has been widely used to demonstrate the role of Mrp2 in the cellular efflux of drugs, xenobiotics, and their conjugates. Increasing the dosing concentration of MK-571 in the in vivo study is restricted by its solubility. Higher exposure of MK-571 in blood cells and tissues may increase the intracellular concentration of Methotrexate caused by MRP4 inhibition. MK-571 was selected as the concomitant drug possessing inhibitory potency for MRP transporters, demonstrating a typical bile-excretion pharmacokinetic property. It is efficient in inhibiting MRP1, MRP2, and MRP4 in cancer therapy (etm 2012).

Suppressing drug efflux is an important aim in many drug development programs, so as in cancer therapy. Chemically modifying or redesigning an anticancer drug to completely bypass MRPs is challenging. But no specific rules have been found, as they can recognize diverse structures that permeate cellular membranes. At the same time, modifications of an anticancer drug without diminution of drug potency are much harder. In comparison, drug delivery systems offer seemingly innumerable possibilities and provide the potential for safer and high-dose delivery of anticancer drugs while using noninvasive tracking techniques that are target-specific. In these cases, controlling drug release inside the cells could be significant, and the exploration of inhibitors is of great importance for our future.



a: MRP1 and MRP2 inhibitor - Nonsymmetrical 1,4-Dihydropyridines
b: MRP1 inhibitor -Sulindac
c: MRP3 and MRP4 inhibitor -CG200745
d: MRP4 inhibitor - MK-571

Figure 2. The structure of inhibitors.

Table 1: Structure and function of MRPs and related inhibitors (NR: not report).

MRPs	Chromosomal localization	Exon coding	Amino acids	Physiological function	major drugs	substrate inhibitors	Reference
MRP1	6p13.11-13	31	1531	Maintain the dynamic balance of GSH in vivo and protect cells from the toxic damage of bilirubin	amycin, vincristine, etoposicIe, Methotrexate, camptothec, Irinotecan, and its active metabolites SN-38, cyclophosphamide	diphenylsulfamide, benzazolone, Indometacin, Verapamil, quercetin, Genistein, cyclosporin A, steroids, glibenpiride, Glucovance	(Bakos, Homolya 2007, Wei, Sun, Liu 2010)
MRP2	10q23-24	32	1541	Transport of hydrophobic, uncharged molecules or water-soluble anionic compounds	cisplatin, etoposicIe, Vinblastine, camptothec, Methotrexate, Olmesartan, lopinovir	furosemide	(Kruh, Belinsky, Gallo, Lee 2007)
MRP3	17q21.3	31	1527	Transport bile salts and various organic acids, E217βG can be transported efficiently	etoposicIe, acetaminophen, glucuronic acid glycosides, vincristine, Methotrexate	etoposicIe, Methotrexate	(Chu, Huskey, Braun, Sarkadi, Evans, Evers 2004)
MRP4	13q32.1	31	1325	It plays a key role in the protection of cells and cell signaling pathways by regulating the redistribution and excretion of various inhibitory cell growth drugs, antiviral drugs, antibiotics, and cardiovascular drugs in vivo and in the kidney	Methotrexate, 6-mercaptopurine ,6-thioguanine, Adefovir, topotecan	celecoxib, rofecoxib, diclofenac	(Russel, Koenderink, Masereeuw 2008)
MRP5	3q27	NR	1437	It mediates the signal transduction process of biological cells and binds GSH and its compounds and even heavy metals	6-mercaptopurine, 6-thioguanine, Adefovir, heavy metals, S-GSH	Diprophenyl sulfamide, sulphinpyrazone , benzbromarone,	(Homolya, Váradi, Sarkadi 2003)
MRP6	16p13.1	31	1503	S-conjugated GSH transport is associated with pulmonary elastic fibrosis	leukotriene C4(LTC4), N-hexyl cis-butene diimide, S-GSH, dinitrophenol, podophylloside, doxorubicin, cisplatin, Daunorubicin	Indometacin, disulfonamide, Benzbromarone	(Hendig, Langmann, Kocken, et al. 2008)

MRP7	6p12-21	22	1492	Modulate the transport effects of E217βG	17-β-D-glucuronside, paclitaxel, Vinblastine, SN-38, amycin, carboplatin	imatinib	(Chen, Hopper-Borge, Belinsky, Shchavelev, Kotova, Kruh 2003)
MRP8	16q12.1	28	1382	Transport of nucleotides, transport of glycocholate and taurocholate	5-FU, Adefovir, Methotrexate, Chile Acid	NR	(Che, Guo, Belinsky, Kotova, Kruh 2005)
MRP9	16q12.1	29	1359	Transport nucleotides, immune markers of breast cancer	NR	NR	(Zhou, Wang, Di, et al. 2008)

4 CONCLUSIONS

This paper reviews the status and trend of research of the last five years based on the papers published in major educational technology journals. In summary, this paper shows that:

- the current status of cancer epidemiology with the pandemic of COVID-19;Bottom: 4,2 cm;
- the oncology treatments correlated to multidrug resistance; Right: 2,6 cm.
- molecular mechanism of multidrug resistance
- the classification and insight of multidrug resistance protein; Bottom: 4,2 cm;
- the definition, physicochemical property, and function of MRPs inhibitors. Right: 2,6 cm.

Due to the coronavirus disease 2019 (COVID-19) pandemic, the situation of oncology treatment in 2020 was relatively distinct. A short-term decrement in cancer incidence is followed by the growth in advanced-stage disease, causing increased mortality, resulting from delays in diagnosis and treatment caused by unavailable or belated access to care. Unfortunately, the consequence of COVID-19 is estimated to last for years to qualify, which burdens cancer therapy, even more, making effective tumor treatments of significance. The findings included in this paper could be good references for those searching for novel oncology therapies with higher cure rates, and plan to contribute to future multidrug resistance studies and the emerging discoveries on mechanisms of MRPs. In addition, the insight could be helpful to future researches on inhibitors of MRPs as well.

However, provided with cancer treatments in existence, multidrug resistance can be avoided in immunotherapy, or weakened by targeted drug delivery via DNA nanostructure.

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