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Drug-Induced DNA Damage in Cancer Therapy and Mechanisms of Chemoresistance

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ABSTRACT

Cancer chemotherapeutic agents consist of a wide range of drugs that follow the mechanism of inducing DNA damage to show their therapeutic effects in dealing with malignant or benign cells by inhibiting the ability to replicate and leading to cell death. However, the effectiveness of this method that limits the success of these therapies is the development of chemo-resistance in cancer cells. Resistance in the tumor cells can develop by various DNA damage response (DDR) mechanisms that detect and repair the DNA lesions, such as activation of ATM/ATR signaling pathways. These DNA repair responses help the tumor cells to replicate and survive despite exposure to anticancer drugs. This review discusses the different types of drug-induced DNA damage in cancer therapy and the mechanism of development of chemo-resistance in tumor cells. Furthermore, the article also provides an overview of different emerging strategies to overcome cancer therapy resistance for more effective and targeted cancer treatments.

Keywords: Drug-induced DNA damage; DNA damage response (DDR); Cancer chemotherapy; DNA repair mechanisms; Chemo-resistance; Anticancer drugs

1. INTRODUCTION

Cancer is a leading cause of mortality worldwide, and its prevalence has been increasing every year. Cancer occurs due to mutation of genes during replication, and these mutations cause changes in cellular function leading to the formation of malignant cells, which later rapidly grow to become tumor cells. The treatment of cancer through chemotherapy plays a central role in killing malignant cells. There are many anticancer drugs that show their therapeutic effects by inducing damage to the DNA of abnormally dividing tumor cells. DNA within the cells is essential for storing genomic information and ensures proper cellular function and replication. Cancer cells are known to have genomic instability, and yet they depend on the DNA damage response for survival and to maintain genome integrity. Chemotherapeutic agents are designed to act on cancer cells to induce DNA damage. These drugs interfere with DNA replication, transcription and chromosome segregation, ultimately leading to the generation of DNA double-strand breaks (DSBs). These DSBs are formed either directly or indirectly, causing cytotoxic lesions in cancer cells. [4,5]

However, despite the effectiveness of DNA-damaging agents, cancer cells are able to tolerate DNA lesions by adapting their innate DNA repair mechanisms to counteract the formation of DNA lesions. These mechanisms include bypass via repriming, activation of drug efflux pumps, error-free template switching (TS), error-prone translesion synthesis (TLS), and the emergency response to prevent drug-induced cell death. [6,7,8]

This review focuses on how chemotherapy induces DNA damage, which DNA repair pathways respond to damage, and how these pathways lead to resistance in cancer cells against chemotherapy.

2. REVIEW METHOD

A comprehensive literature search was conducted to identify relevant research articles related to drug-induced DNA damage and mechanisms of chemoresistance in cancer therapy. The search was performed using major electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Search terms included "drug-induced DNA damage," "chemoresistance," "DNA damage response," "anticancer drugs," and related terms. Inclusion criteria comprised peer-reviewed original research articles, review articles, meta-analyses, and clinical trial reports in the English language.

Additional studies were done by screening the reference lists of selected articles. The selected research articles were then thoroughly studied, and a comprehensive review was carefully constructed.

3. DNA DAMAGE IN CANCER THERAPY

Chemotherapeutic agents induce DNA damage through different mechanisms that disrupt structural complexity along with genomic stability. The principal categories of chemotherapy-induced DNA damage include: (1) base modifications and adducts resulting from alkylation; (2) intrastrand and interstrand DNA crosslinks; (3) single-strand breaks (SSBs); (4) double-strand breaks (DSBs); (5) replication stress and fork collapse; and (6) topoisomerase-mediated cleavable complex stabilization. The biological impact of each lesion type depends on its frequency, repairability, and the specific genomic location where it occurs. [9,10]

4. MECHANISM OF DRUG-INDUCED DAMAGE

4.1. Single-Strand Breaks

Single-strand breaks (SSBs) occur when the phosphodiester backbone of a DNA strand is disrupted. Although these lesions are generally less severe than double-strand breaks, accumulation of unrepaired SSBs can interfere with DNA replication and lead to genomic instability. [11] SSBs are primarily repaired through the base excision repair (BER) pathway, involving PARP1 binding and the XRCC1–DNA Ligase III complex. When PARP1 becomes trapped at SSBs by PARP inhibitors, the resulting complexes are converted to replication-dependent DSBs, which forms the basis of synthetic lethality in BRCA1/2-deficient cancers.

4.2. Double-Strand Breaks

Double-strand breaks (DSBs) represent one of the most severe forms of DNA damage. These lesions involve the simultaneous breakage of both strands of the DNA helix. If not properly repaired, DSBs can lead to chromosomal rearrangements, mutations, and cell death. [12,13] DSBs are the most cytotoxic form of DNA damage; a single unrepaired DSB can trigger apoptosis. Phosphorylation of H2AX at serine 139 (γH2AX) produces characteristic foci that serve as a quantitative biomarker of DSBs.

4.3. DNA Crosslinks

DNA crosslinks occur when chemical bonds form between DNA strands or between DNA and proteins. These lesions prevent strand separation during replication and transcription, making them highly cytotoxic to rapidly dividing cells. [14] Intrastrand crosslinks, such as the 1,2-d(GpG) adducts produced by cisplatin, are repaired primarily by NER. Interstrand crosslinks (ICLs) require coordinated action of the Fanconi anemia (FA) pathway, NER, translesion synthesis (TLS), and homologous recombination (HR) for repair.

4.4. Base Modifications and Oxidative Damage

Some anticancer drugs generate reactive oxygen species (ROS) that modify DNA bases. These oxidative lesions can disrupt base pairing and lead to mutations if not repaired. [15] Key lesions include O6-methylguanine (O6-MeG) adducts caused by temozolomide and 8-oxo-7,8-dihydroguanine (8-oxoG) produced by ROS. O6-MeG triggers futile MMR cycles that generate secondary DSBs. 8-OxoG is highly mutagenic, causing G:C→T:A transversions. Repair mechanisms include MGMT for O6-MeG and OGG1-initiated BER for 8-oxoG. [15,16]

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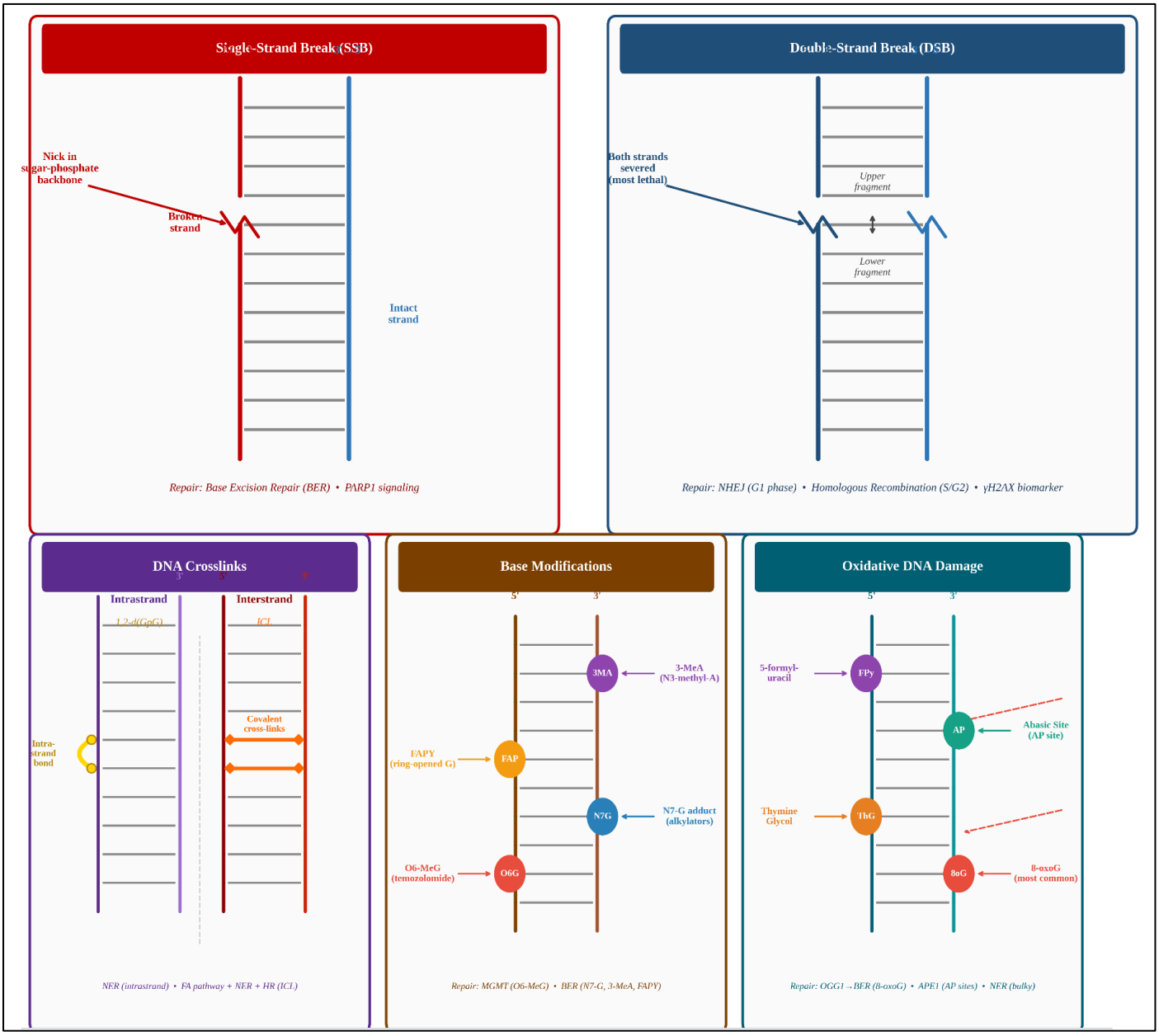

Figure 1. ***Types of drug-induced DNA damage.*** *(A) SSB: nick in one strand. (B) DSB: both strands severed. (C) DNA crosslinks: intrastrand (cisplatin 1,2-d(GpG)) and interstrand (ICL). (D) Base modifications: O6-MeG, N7-guanine, FAPY, 3-methyladenine. (E) Oxidative damage: 8-oxoguanine, thymine glycol, abasic (AP) sites.*

5. CLASSES OF ANTICANCER DRUGS THAT INDUCE DNA DAMAGE

5.1. Alkylating Agents

Alkylating agents constitute among the first chemotherapeutics used as treatment against lymphomas, leukemia, and Hodgkin's disease. They act by transferring alkyl groups to nucleophilic sites on DNA bases, predominantly the N7 and O6 positions of guanine and the N3 position of adenine, causing DNA adduct formation, crosslinks, and strand breaks. [17,77]

Approximately 10–20% of all cancer patients are prescribed platinum-based drugs during chemotherapeutic treatment. Cisplatin is the first platinum-based alkylating chemotherapeutic drug and is effective against testicular, ovarian, bladder, head and neck, and lung cancers. Cisplatin predominantly forms 1,2-intrastrand d(GpG) crosslinks (~65%) and ICLs (~5–8%), blocking replication and transcription, leading to apoptosis in rapidly dividing cancer cells. [18,19]

5.2. Topoisomerase Inhibitors

Topoisomerases relieve topological stress by transiently cleaving one (Topo I) or both (Topo II) strands of the double helix. [20] Topoisomerase I inhibitors include irinotecan and topotecan, which create SSBs that are converted to irreversible DSBs at replication forks. [21] Topoisomerase II inhibitors include doxorubicin, epirubicin, and etoposide, which stabilize the Topo II–DNA cleavable complex, generating DSBs throughout the genome. [22]

5.3. Antimetabolites

Antimetabolites interfere with the formation of RNA and DNA by generating structural analogs of nucleotide bases, leading to errors in replication and DNA damage. [23] Folate analogs like methotrexate inhibit dihydrofolate reductase (DHFR), reducing thymine nucleotide synthesis. [24,10] Pyrimidine analogs such as 5-FU inhibit thymidylate synthase, stopping thymidine production required for DNA replication. [25] Purine analogs such as fludarabine, cladribine, and mercaptopurine incorporate into DNA, eliminating the DNA chain causing DNA breaks if left unrepaired. [26]

5.4. Reactive Oxygen Species and Oxidative DNA Damage

Several chemotherapeutic drugs generate reactive oxygen species (ROS) as part of their mechanism of action. Bleomycin forms a complex with ferrous iron and molecular oxygen that cleaves DNA, producing single-strand and double-strand breaks with modified ends that are difficult to ligate. [27,28]

Table 1. Classification of chemotherapeutic agents and their mechanisms of DNA damage induction.

5	Mechanism of Action	Examples
Alkylating Agents	Mono-functional and bi-functional alkylation of DNA bases forming adducts and crosslinks	Procarbazine, Dacarbazine, Temozolomide Cyclophosphamide, Ifosfamide, Melphalan Cisplatin, Carboplatin, Oxaliplatin
Topoisomerase Inhibitors	Prevents re-ligation of topoisomerase I and II-induced DNA breaks, generating SSBs and DSBs	Topo I: Irinotecan, Topotecan Topo II: Doxorubicin, Epirubicin, Etoposide
Antimetabolites	Inhibits enzymes required for nucleotide synthesis and/or incorporates into DNA to stall replication forks	Folate analogs: Methotrexate Pyrimidine analogs: 5-FU, Gemcitabine Purine analogs: Fludarabine, Cladribine, Mercaptopurine
ROS Generators	Generation of free radicals that form complexes and cleave DNA backbone	Bleomycin

6. DNA DAMAGE RESPONSE (DDR) IN CANCER CELLS

6.1. Sensing and Signaling

The DNA damage response is a sophisticated signal transduction network that detects DNA lesions, amplifies the damage signal, and coordinates cell cycle progression, DNA repair, and cell fate decisions. [29,30] ATM is activated by DSBs via the MRN complex (MRE11–RAD50–NBS1) and phosphorylates H2AX at serine 139 (γH2AX). ATR is activated via ATRIP recruitment to RPA-coated ssDNA at stalled replication forks, phosphorylating CHK1 to enforce intra-S and G2/M checkpoints.

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6.2. Cell Cycle Checkpoints

DDR signaling activates cell cycle checkpoints at the G1/S and G2/M phases. The G1/S checkpoint is controlled primarily by the p53 tumor suppressor pathway, which upregulates p21CIP1/WAF1 to inhibit CDK2. [31] The G2/M checkpoint is mediated by CHK1 and CHK2, which phosphorylate and degrade CDC25C, thereby inhibiting CDK1 and preventing mitotic entry. [32]

Figure 2. ***The cellular DNA damage response (DDR) signaling cascade.*** *Double-strand breaks activate ATM via the MRN complex, leading to γH2AX formation, CHK2 activation, and p53 stabilization. Replication stress activates ATR, leading to CHK1 activation and S/G2 checkpoint enforcement.*

6.3. DNA Repair Pathways Relevant to Chemotherapy

Homologous Recombination (HR): HR repairs DSBs and ICLs during S and G2 phases using the sister chromatid as a template. Key mediators include BRCA1, BRCA2, RAD51, and PALB2. [33]

Non-Homologous End Joining (NHEJ): NHEJ is the main DSB repair mechanism in G1 phase, dependent on Ku70/Ku80, DNA-PKcs, and XRCC4–Ligase IV. NHEJ is error-prone, introducing small insertions or deletions. [34]

Nucleotide Excision Repair (NER): NER eliminates bulky, helix-distorting lesions such as platinum-DNA adducts via ERCC1-XPF-mediated incision. Elevated NER activity is strongly associated with platinum resistance. [35,36]

Mismatch Repair (MMR): MMR detects and corrects base-base mismatches. O6-MeG:T mismatches trigger futile MMR cycles generating secondary DSBs leading to apoptosis. Loss of MMR results in microsatellite instability (MSI-H). [37,38]

Fanconi Anemia (FA) Pathway: The FA pathway (22 FANC genes) coordinates repair of ICLs through integrated NER incision, TLS, and HR. Deficiency sensitizes cells to cisplatin and mitomycin C. [39]

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Figure 3. ***DNA repair pathways and chemotherapeutic targets.*** *G1-phase cells rely on NHEJ; S/G2-phase cells use HR. NER handles bulky adducts; MMR processes replication mismatches; BER removes oxidative and alkylated bases; the FA pathway mediates ICL repair.*

Table 2. Clinically advanced DDR-targeting agents: mechanisms, clinical stage, and resistance mechanisms.

Drug Class	Key Agents	Target / Mechanism	Clinical Stage	Resistance Context
PARP Inhibitors	Olaparib, Rucaparib, Niraparib, Talazoparib	PARP1/2 trapping; BER inhibition; synthetic lethality with HR deficiency	FDA-approved: BRCA-mut ovarian, breast, prostate, pancreatic	BRCA reversion; 53BP1 loss; ABCB1 efflux
ATR Inhibitors	Ceralasertib, Berzosertib, Elimusertib	ATR inhibition → S/G2 checkpoint abrogation; replication catastrophe	Phase I/II: ATM-deficient tumors + chemo	RAS mutations; ATR reactivation
CHK1 Inhibitors	Prexasertib, SRA737, UCN-01	CHK1 inhibition → G2/M checkpoint abrogation; premature mitosis	Phase I/II: p53-mutant tumors + gemcitabine/topotecan	WEE1 compensation; p21-mediated G1 arrest
WEE1 Inhibitors	Adavosertib (AZD1775)	WEE1 inhibition → CDK1/CDK2 activation → premature mitotic entry	Phase II: p53-mut ovarian, AML + cisplatin/carboplatin	p53 wild-type; CCNE1 amplification
DNA-PK Inhibitors	Peposertib (M3814), AZD7648	DNA-PKcs inhibition → NHEJ impairment → DSB persistence	Phase I/II: Advanced solid tumors + radiotherapy	HR upregulation; ATM-proficient tumors
BCL-2 Inhibitors	Venetoclax, Navitoclax, AMG 176	BH3 mimetics → apoptotic priming; displaces pro-apoptotic proteins	FDA-approved: CLL, AML; Phase I/II: lymphoma	MCL-1 upregulation; BCL-XL compensation

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7. MECHANISMS OF CHEMORESISTANCE

7.1. Classification of Chemoresistance

Chemoresistance is broadly classified as intrinsic or acquired. Intrinsic resistance reflects the genetic and epigenetic heterogeneity of tumor cell populations at the time of diagnosis. Acquired resistance develops through Darwinian clonal selection under therapeutic pressure, epigenetic adaptation, or non-mutational phenotypic plasticity. Clinically, resistance manifests as primary resistance, secondary resistance, and cross-resistance. [40,41]

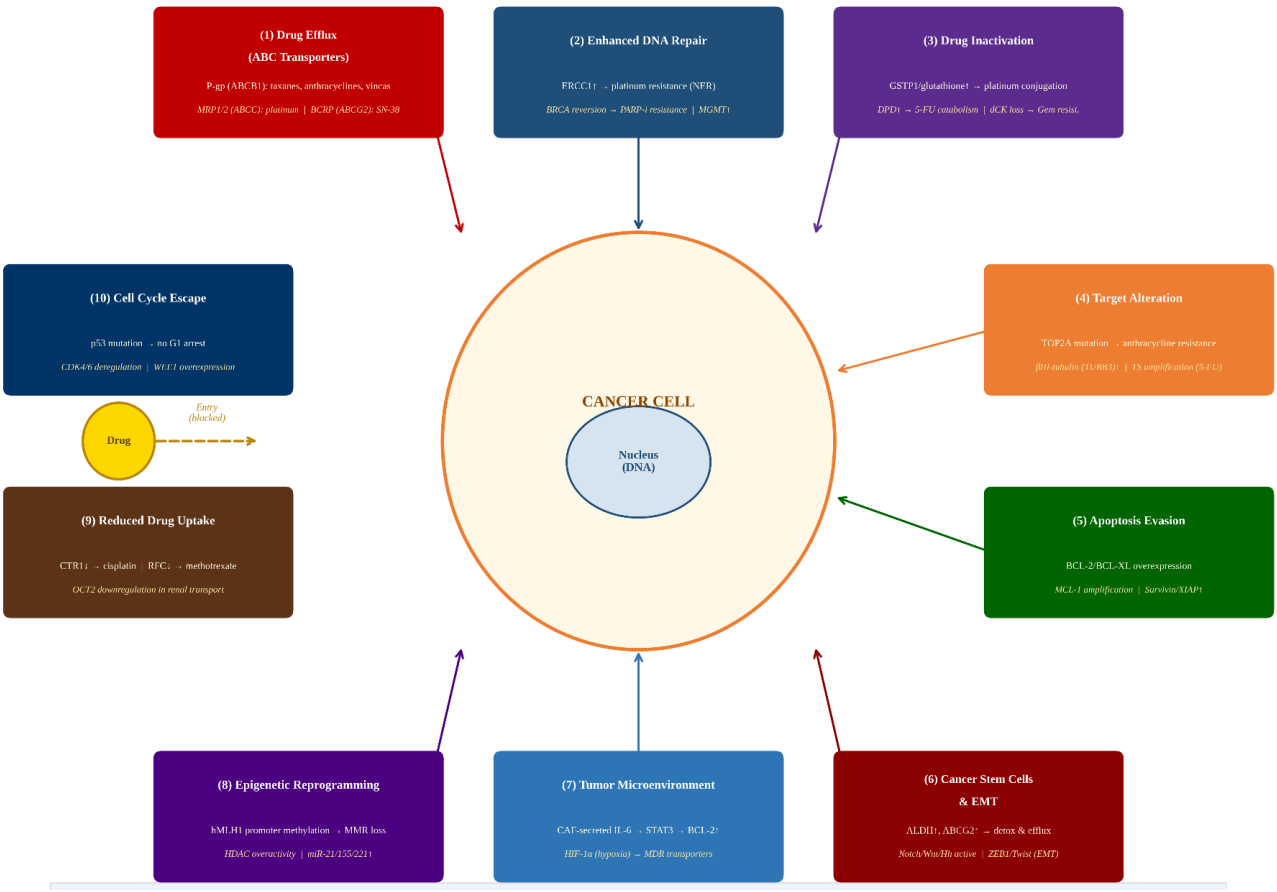

Figure 4. ***Molecular mechanisms of chemoresistance in cancer cells.*** *Ten integrated resistance mechanisms: (1) drug efflux via ABC transporters; (2) enhanced DNA repair; (3) drug inactivation; (4) target mutations; (5) apoptosis evasion; (6) epigenetic reprogramming; (7) tumor microenvironment; (8) cancer stem cell enrichment; (9) cell cycle escape; (10) reduced drug uptake.*

7.2. Enhanced DNA Repair as a Resistance Mechanism

Nucleotide Excision Repair and Platinum Resistance

Resistance to platinum compounds is strongly associated with upregulation of NER components, particularly ERCC1 and XPA. High ERCC1 expression correlates with shorter progression-free survival in cisplatin-treated lung adenocarcinoma and ovarian cancer. ERCC1 depletion restores platinum sensitivity in resistant cell lines, validating NER upregulation as a bona fide resistance mechanism. [35,42]

Homologous Recombination and PARP Inhibitor Resistance

Loss-of-function mutations in BRCA1/2 define HR-deficient cancers selectively sensitive to PARP inhibitors and platinum compounds through synthetic lethality. Resistance arises through somatic reversion mutations in BRCA1/2 restoring HR function. [43,44] Additional mechanisms include loss of 53BP1 or SHIELDIN complex components and upregulation of RAD51.

MGMT and Alkylating Agent Resistance

MGMT directly reverses O6-alkylguanine adducts in a stoichiometric, non-enzymatic mechanism. MGMT promoter methylation silences the gene, creating vulnerability to temozolomide in glioblastoma. MGMT overexpression is the primary determinant of resistance to temozolomide and other alkylating agents. [45,78]

7.3. Drug Efflux and Influx Alterations

ATP-binding cassette (ABC) transporters play dominant roles in multidrug resistance (MDR): P-glycoprotein (P-gp/ABCB1) effluxes vinca alkaloids, taxanes, anthracyclines, and epipodophyllotoxins; MRP1/2 transport drug-glutathione conjugates; and BCRP/ABCG2 mediates resistance to topotecan, irinotecan (SN-38), and methotrexate. [46,47] Reduced drug influx via CTR1 downregulation reduces cisplatin uptake in ovarian cancer. [48,24]

7.4. Drug Inactivation and Metabolic Resistance

Glutathione S-transferases (GSTs) catalyze the conjugation of glutathione to cisplatin, cyclophosphamide, and chlorambucil, facilitating their export via MRP transporters. High DPYD expression contributes to 5-FU resistance and DPYD polymorphisms predict fluoropyrimidine toxicity. [49,50,51] Deoxycytidine kinase (dCK) loss confers resistance to gemcitabine, cytarabine, and cladribine.

7.5. Drug Target Alterations

Tubulin mutations in β-tubulin isotypes (TUBB2A, TUBB3) impair taxane and vinca alkaloid binding; TUBB3 overexpression is associated with paclitaxel resistance and poor prognosis in lung, ovarian, and breast cancers. Topoisomerase II gene mutations reduce sensitivity to anthracyclines and etoposide. Amplification of thymidylate synthase (TYMS) reduces the inhibitory effect of 5-FU-derived FdUMP. [52,53]

Table 3. Key molecular biomarkers of chemoresistance with established or emerging clinical utility.

Biomarker	Resistance Mechanism	Drug(s) Affected	Detection Method	Clinical Utility
ERCC1 protein/mRNA	Enhanced NER of platinum-DNA adducts	Cisplatin, carboplatin, oxaliplatin	IHC, RT-PCR, FISH	Predictive in NSCLC, ovarian, gastric cancer
MGMT methylation	MGMT silencing → O6-MeG unrepaired → alkylator sensitivity	Temozolomide, BCNU	Pyrosequencing, MS-PCR, NGS	FDA co-approved biomarker for GBM (temozolomide)
BRCA1/2 mutation	HR deficiency → synthetic lethality with PARP-i; platinum sensitivity	Olaparib, rucaparib, niraparib, cisplatin	Germline/somatic NGS; LOH	FDA companion Dx for PARP-i (ovarian, breast, prostate)
MSI-H / MMR deficiency	Loss of MMR futile cycling → alkylator resistance; high neoantigen burden	TMZ (resistant); PD-1 blockade (sensitive)	PCR (MSI), IHC, NGS (TMB)	FDA tumor-agnostic: pembrolizumab for MSI-H/dMMR
ABCB1 (P-gp)	Drug efflux reducing intracellular taxane/anthracycline concentration	Paclitaxel, doxorubicin, vincristine, etoposide	IHC, RT-PCR, flow cytometry	Prognostic in AML, lymphoma, breast; no approved inhibitor
RRM1 (RNR M1)	Overexpression restores dNTP pools, reduces gemcitabine efficacy	Gemcitabine	IHC, RT-PCR	Predictive for gemcitabine resistance in NSCLC, pancreatic cancer
BCL-2/BCL-XL/MCL-1	Anti-apoptotic proteins block MOMP and cytochrome c release	Multiple cytotoxics; venetoclax sensitizes	IHC, BH3 profiling	FDA: BCL-2 IHC (venetoclax in CLL); BH3 profiling for functional sensitivity

8. STRATEGIES TO OVERCOME CHEMORESISTANCE

8.1. DDR Inhibitors as Chemosensitizers

PARP inhibitors are now approved for BRCA-mutant ovarian, breast, and prostate cancers, exploiting synthetic lethality and additionally sensitizing HR-proficient tumors to platinum-based chemotherapy by impairing BER and trapping PARP-DNA complexes at replication forks. ATR inhibitors sensitize tumors to cisplatin, gemcitabine, and topotecan by abrogating S and G2/M checkpoints. CHK1 and WEE1 inhibitors similarly abrogate the G2/M checkpoint and are being evaluated in combination with DNA-damaging agents in multiple Phase I/II trials. [54,55,56]

8.2. Epigenetic Therapies for Resistance Reversal

DNMT inhibitors (5-azacytidine, decitabine) reverse promoter hypermethylation of silenced chemosensitivity genes. HDAC inhibitors restore pro-apoptotic gene expression and have been combined with cytarabine in relapsed/refractory AML. EZH2 inhibitors (tazemetostat) targeting PRC2-mediated H3K27me3 silencing have entered clinical practice for follicular lymphoma. [57,58]

8.3. Targeting Drug Efflux and Delivery

Despite decades of research on P-gp inhibitors (verapamil, valspodar, tariquidar), clinical reversal of MDR has proven elusive due to pharmacokinetic interactions and dose-limiting toxicity. Current strategies include nanoparticle drug delivery systems that bypass ABC transporter-mediated efflux by endocytosis-dependent intracellular drug release, and antibody-drug conjugates (ADCs) such as trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan. [59]

8.4. Cancer Stem Cell Targeting

Emerging strategies for cancer stem cell (CSC) elimination include Notch gamma-secretase inhibitors, Wnt/porcupine inhibitors, and Hedgehog inhibitors (vismodegib). ALDH-targeting approaches and nanoparticle-mediated intracellular drug delivery circumvent ABC transporter-mediated efflux in CSC populations. Disulfiram, an ALDH inhibitor, is being evaluated in combination with chemotherapy in glioblastoma and breast cancer. [59,60]

8.5. Immunotherapy and the DDR

DNA-damaging chemotherapy induces tumor mutational burden (TMB), neoantigen expression, and release of damage-associated molecular patterns (DAMPs) that stimulate innate immune activation. STING pathway activation promotes innate and adaptive anti-tumor immunity. [62,63,64] MMR-deficient (MSI-H) tumors are responsive to PD-1 blockade, representing the first tumor-agnostic FDA approval (pembrolizumab for MSI-H/dMMR solid tumors, 2017). [38,64]

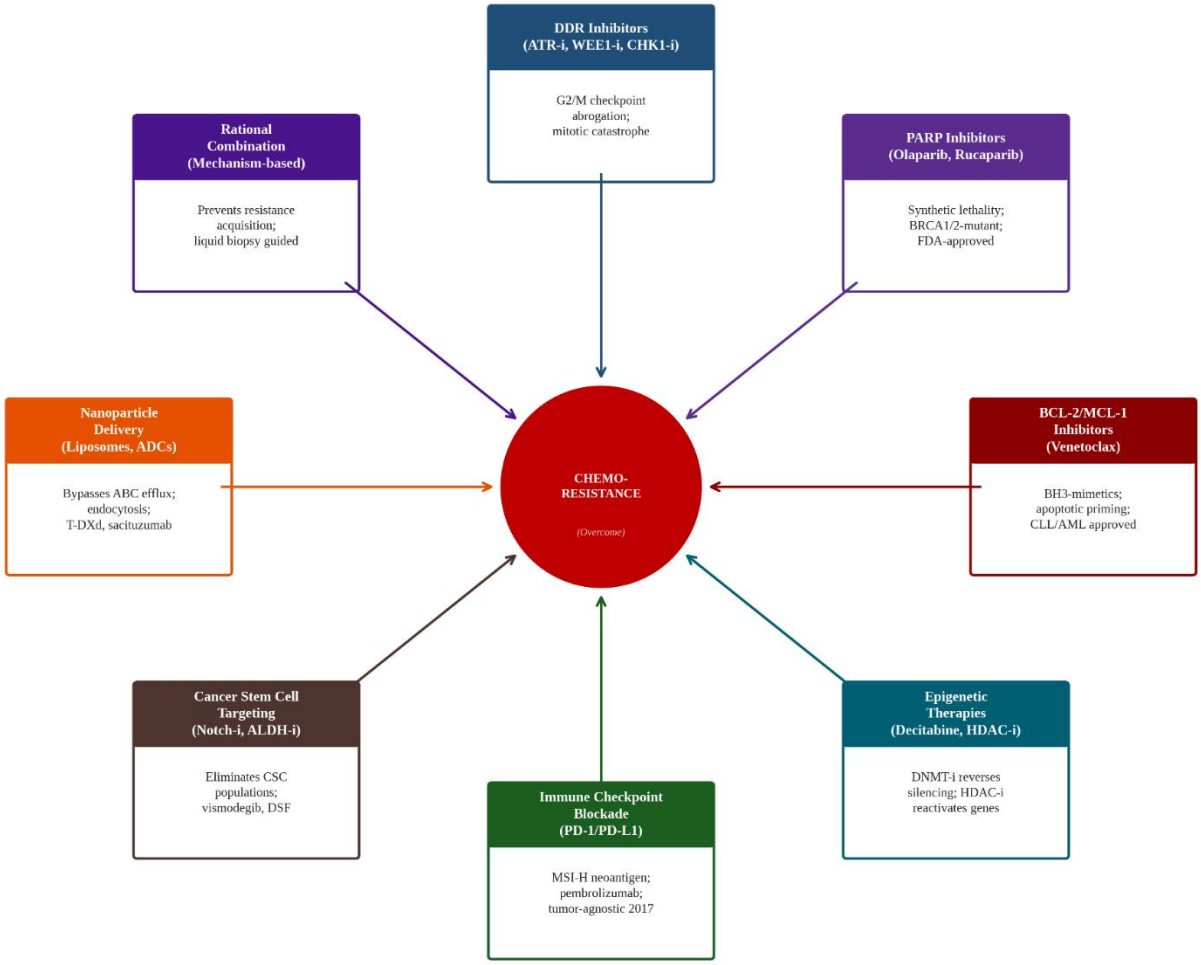

Figure 5. ***Eight principal therapeutic strategies targeting mechanisms of chemoresistance.*** *DDR inhibitors exploit checkpoint abrogation; PARP inhibitors exploit synthetic lethality; BCL-2/MCL-1 inhibitors restore apoptotic priming; epigenetic therapies reverse resistance-conferring silencing; immunotherapy exploits MMR deficiency; CSC-targeting eliminates resistant stem populations; nanoparticle delivery bypasses efflux; rational combinations prevent sequential resistance acquisition.*

9. FUTURE PERSPECTIVES AND CHALLENGES

The management of chemoresistant cancers will require integrated approaches that recognize tumor heterogeneity as the fundamental biological basis of resistance. Single-cell genomics and transcriptomics are revolutionizing our understanding of tumor heterogeneity and the clonal evolution of drug resistance. [65,66]

Liquid biopsy technologies, including circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and extracellular vesicles, are evolving into powerful tools for real-time monitoring of resistance evolution, detection of resistance-conferring mutations, and informing timely treatment modifications. [67,68]

The development of resistance-resistant therapeutic strategies, combination regimens designed a priori to prevent or delay resistance, remains the ultimate goal. This requires mechanistic understanding of resistance pathway interactions to design rational multi-agent combinations that prevent the sequential acquisition of layered resistance mechanisms. [69,80]

10. CONCLUSION

Drug-induced DNA damage represents both the therapeutic foundation of cytotoxic chemotherapy and the evolutionary pressure driving the selection of chemoresistant cancer cell clones. [1,6,40] The mechanisms by which cancer cells evade drug-induced genotoxicity are multifarious, interconnected, and context-dependent, encompassing enhanced DNA repair, drug efflux, enzymatic drug inactivation, target alteration, apoptosis suppression, epigenetic reprogramming, and cancer stem cell maintenance.

Substantial progress has been made in translating mechanistic insights into clinical strategies including PARP inhibitors exploiting HR deficiency, venetoclax targeting BCL-2 overexpression, and immune checkpoint inhibitors capitalizing on MMR deficiency. [43,70,38] Overcoming chemoresistance will require convergence of deep molecular characterization of individual tumors, rational mechanism-based combination strategies, novel drug delivery platforms, and real-time monitoring of resistance evolution, collectively advancing the goal of truly personalized cancer therapy.

AUTHOR CONTRIBUTIONS

Biswajeet Pillai: Conceptualization, literature search and review, writing of original draft, critical revision, and final approval of the manuscript.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise, related to the content of this manuscript.

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LIST OF ABBREVIATIONS

5-FU, 5-fluorouracil; ABC, ATP-binding cassette; ATM, ataxia telangiectasia mutated; ATR, ATM and Rad3-related; BER, base excision repair; BRCA, breast cancer susceptibility gene; CDK, cyclin-dependent kinase; ctDNA, circulating tumor DNA; DDR, DNA damage response; DHFR, dihydrofolate reductase; DSB, double-strand break; dCK, deoxycytidine kinase; ERCC1, excision repair cross-complementation group 1; FA, Fanconi anemia; GST, glutathione S-transferase; HR, homologous recombination; ICL, interstrand crosslink; MDR, multidrug resistance; MGMT, O6-methylguanine-DNA methyltransferase; MMR, mismatch repair; MSI-H, microsatellite instability-high; NER, nucleotide excision repair; NHEJ, non-homologous end joining; O6-MeG, O6-methylguanine; PARP, poly(ADP-ribose) polymerase; P-gp, P-glycoprotein; ROS, reactive oxygen species; SSB, single-strand break; STING, stimulator of interferon genes; TLS, translesion synthesis; TMB, tumor mutational burden.

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