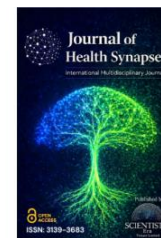


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Antitumor Antibiotics in Cancer Chemotherapy: Mechanisms, Clinical Use, Resistance and New Approaches to Selectivity

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ABSTRACT

Antitumor antibiotics are anticancer drugs of microbial origin that kill cells mainly by damaging DNA or by stopping it from being used as a template. They are antibiotics by pedigree only; none is used to treat infection. The clinically important members are the anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin), dactinomycin, bleomycin and mitomycin C. The enediynes, which are too toxic to give as free drugs, have found a clinical role as payloads on antibodies. This review follows these agents from mechanism to bedside. Anthracyclines intercalate into DNA, poison topoisomerase II and generate oxidative stress. Dactinomycin intercalates and blocks transcription. Bleomycin cuts DNA through an iron-dependent oxygen chemistry, mitomycin C has to be reduced inside the cell before it can cross-link DNA, and the enediynes cause double-strand breaks through a diradical intermediate. What limits all of them is a narrow margin between tumor kill and normal-tissue injury: cardiomyopathy with anthracyclines, pulmonary fibrosis with bleomycin, and marrow suppression across most of the group. Resistance adds a second limit and arises through drug efflux, altered targets, faster repair, defective apoptosis and tumor heterogeneity. Current development is aimed less at making these drugs stronger than at controlling where and when they act. We discuss liposomal and nanoparticle carriers, antibody–drug conjugates, hypoxia-activated chemistry, DNA-repair inhibitors, biomarker-guided selection and cardioprotection with dexrazoxane. We conclude that the older members of this family remain clinically useful, and that their greatest remaining value may lie in the chemistry they offer for building targeted agents.

1. Introduction

Chemotherapy still bears a large portion of the treatment load for cancer, especially when the disease has spread or when surgery is required to remove microscopic remaining tumors. Antitumor antibiotics occupy a peculiar place in the cytotoxic arsenal. They share a name with the medications used to treat

bacterial infections and were discovered by screening soil microorganisms, primarily *Streptomyces* species. That's where the similarities end. In the field of oncology, the term refers to origin rather than use: they are naturally occurring microbial compounds that disrupt DNA, preventing the growth of cancer

cells.[1]. The group's past serves as a helpful lesson on the need of natural product screening. One of the first antibiotics to exhibit anticancer action was actinomycin D. Among the most potent cytotoxic medications ever developed were daunorubicin and doxorubicin. Bleomycin introduced a novel mechanism that is dependent on molecular oxygen and bound iron. Drugs that are triggered by reduction are modeled after mitomycin C. Calicheamicin and other enediynes demonstrated in more recent decades that a substance too strong to provide systemically might be turned into a medication by using an antibody to guide it. None of these medications are simple to use. Because the DNA pathways they interfere with are not specific to cancer cells, each has a limited therapeutic window. The main limitations of anthracyclines are myelosuppression and cumulative cardiac damage, lung damage from bleomycin, marrow and mucosal toxicity from dactinomycin, and marrow suppression and renal and vascular problems from mitomycin C. Over the past thirty years, a large portion of the class's research has focused on expanding that window through modifications to molecular structure, delivery, schedule, or patient selection. Additionally, it is now evident that the response cannot be explained by DNA damage alone. Chromatin state, repair ability, topoisomerase expression, redox balance, drug transport, mitochondrial activity, and the surrounding microenvironment all influence whether a tumor dies. This is the organizing principle of this review and one of the reasons why two tumors with the same histology might react to the same drug very differently.

2. Scope and Approach

There was no attempt at a formal meta-analysis, and this review is narrative rather than methodical. Using search terms that combined the individual drug names with DNA damage, topoisomerase II, drug resistance, cardiotoxicity, pulmonary toxicity, liposomal delivery, and antibody–drug conjugates,

we consulted PubMed-indexed reviews and primary studies, National Cancer Institute drug information, and standard pharmacology references. We have tried to explain why a current mechanistic work differs from an earlier one in terms of emphasis. The evidence is arranged according to four questions: how the drugs kill cells, where they are used, why they don't function, and what is being done.

We focus on drugs that have a well-established or significant clinical history. Only when they elucidated a mechanism or produced a clinical product do experimental antibiotics emerge. Regimens and dosages are purposefully omitted. A review is not the right location to look them up because they depend on the patient, the type of tumour, and current guidelines.

3. Classes of Antitumor Antibiotics

Chemical structure and the manner in which each component damages DNA can be used to categorize the group (Table 1). In terms of clinical significance, anthracyclines are by far the most significant. The linked amino sugar lies in the minor groove of their planar anthraquinone chromophore, which slides across DNA base pairs to stabilize binding and make contact with topoisomerase II [2, 3].

Actinomycin D, or dactinomycin, is a chromopeptide. Two cyclic peptides are located in the minor groove, and a phenoxazone ring intercalates at guanine–cytosine sequences. RNA polymerase is unable to pass because the resultant complex is tight and takes a long time to dissolve [4,5]. A glycopeptide combination called bleomycin was isolated from *Streptomyces verticillus*. It cuts the sugar-phosphate backbone by binding DNA, chelating iron, and activating oxygen [6,7]. The quinone mitomycin C is essentially innocuous until it is reduced by a cellular enzyme, at which point it alkylates DNA [8,9]. Calicheamicin and other enediynes have a ring that, when activated, cyclizes into a diradical that may remove hydrogen atoms from both strands of DNA [10].

Table 1. Principal classes of antitumor antibiotics

Class	Representative drugs	Principal molecular effect	Main clinical limitation
Anthracyclines	Doxorubicin, daunorubicin, epirubicin, idarubicin	DNA intercalation; topoisomerase II poisoning; redox cycling	Cardiotoxicity, myelosuppression, efflux-mediated resistance
Chromopeptide	Dactinomycin	DNA intercalation; inhibition of transcription	Myelosuppression, mucocutaneous toxicity, extravasation injury
Glycopeptide	Bleomycin	Iron-dependent oxygen activation; DNA strand breaks	Pulmonary toxicity, skin toxicity
Mitomycins	Mitomycin C	Reductive activation; DNA alkylation and interstrand cross-links	Myelosuppression, renal and vascular toxicity
Enediynes	Calicheamicin (as ADC)	Diradical formation; DNA	Extreme potency; needs

	payload)	double-strand breaks	targeted delivery
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4. Mechanisms of Action

4.1 Anthracyclines and topoisomerase II

After more than 50 years of research, doxorubicin and daunorubicin continue to serve as the benchmarks for evaluating more recent anthracyclines [2,11,12]. Each has a tetracyclic aglycone attached to daunosamine, and slight modifications to either component affect toxicity, resistance profile, metabolism, and DNA affinity. For instance, the orientation of one hydroxyl group on the sugar is the only way that epirubicin and doxorubicin differ. However, there are differences between its cardiac tolerability and pharmacokinetics. The action of these medications cannot be explained by a single mechanism. Topoisomerase II poisoning is the most well-supported. In order to allow DNA to untwist during transcription and replication, the enzyme typically creates a brief double-strand break before resealing it. The cleavage stage of the enzyme is where anthracyclines trap it. The cell either suffers apoptosis or repairs the damage once the break becomes irreversible and the ATM and ATR kinases are triggered [13,14]. The sensitivity of proliferating tumor cells can be explained by their increased expression of the α isoform [15].

Chromatin is also altered by intercalation. Independent of DNA breakage, anthracyclines can cause cytotoxicity by evicting histones and disrupting nucleosome positioning [16]. Superoxide and other reactive oxygen species can be produced by one-electron reduction and reoxidation of their quinone ring (Section 4.3). The cell type and drug concentration appear to determine which of these activities predominates; older evaluations occasionally make this claim with greater certainty than the evidence supports.

4.2 Intercalation and transcriptional blockade

The insertion of a flat aromatic ring between neighbouring base pairs is known as intercalation. It alters how proteins interpret DNA and lengthens and unwinds the helix [17, 18]. However, cytotoxicity is seldom explained by intercalation alone. It puts anthracyclines at risk for topoisomerase poisoning. In the case of dactinomycin, the polymerase stalls and the drug's peptide arms lock it in place, making ribosomal RNA production one of the first processes to malfunction. The drug's exceptional effectiveness in some children tumours is likely due to the vulnerability of quickly developing cells to transcriptional stop.

4.3 Oxidative stress

Anthracyclines' quinone takes an electron from enzymes like mitochondrial complex I or NADPH-cytochrome P450 reductase and transfers it to oxygen. Superoxide, hydrogen peroxide, and, when free iron is present, hydroxyl radicals are

produced as a result of this pointless cycle. These have the ability to oxidise proteins, lipids, and nucleic acids. It's debatable how important this is for destroying tumours. Although concentrations in treated patients' plasma are likely too low for oxidative damage to be the primary anticancer mechanism, redox chemistry may be more important in the heart muscle due to its high mitochondrial content and weak antioxidant defences [2,19].

4.4 Bleomycin and strand cleavage

A metal-binding domain, a carbohydrate moiety important in cellular absorption, and a DNA-binding bithiazole tail are the three functional domains of bleomycin. The medication creates an activated combination with oxygen and ferrous iron that removes a hydrogen atom from the C4' position of deoxyribose. The strand is then severed once the sugar degrades [20,21]. A single bleomycin molecule can cause a double-strand break by cutting each strand sequentially, which makes the lesions difficult to heal [22]. Cleavage favours 5'-GT and 5'-GC sequences.

4.5 Reductive activation of mitomycin C

One prodrug is mitomycin C. The molecule loses its methoxy group and forms an aziridine ring when its quinone is reduced by DT-diaphorase (NQO1), cytochrome P450 reductase, and similar enzymes. Guanine is alkylated by the resultant electrophile, and an interstrand cross-link is produced by a second alkylation on the opposite strand [9,23]. Transcription and replication are both inhibited by a cross-link, which stops the strands from splitting. The medication has long been investigated as a means of targeting hypoxic tumour locations since reduction is preferred in areas with little oxygen [24].

4.6 Eneidiynes

The reactive core of the enediyne family is a ten-membered ring with two triple bonds on either side of a double bond. The ring forms a benzenoid diradical when cycloaromatization is initiated by a trigger, which is frequently a nucleophilic assault on a trisulfide in calicheamicin. At extremely low concentrations, the radical causes deadly double-strand breaks by removing hydrogen atoms from the DNA backbone on both strands [10,25]. The reason the free compounds didn't work as medications was because of their potency. Keeping them on an antibody until they get to the target cell is essential to their use.

5. How Cells Respond to the Damage

When two tumors are exposed to the same medication, their outcomes may differ. The reaction to harm is the decisive stage. Checkpoint kinases (ATM, ATR, CHK1, CHK2) and

p53 are activated by lesions. The cell stops and repairs if checkpoints are intact; if the damage is too great, apoptosis is triggered by the death-receptor and mitochondrial pathways. Repair capability is very important. Either non-homologous end joining or homologous recombination can repair double-strand breaks. A lengthier relay involving Fanconi anemia proteins, nucleotide excision repair, and homologous recombination is required for interstrand cross-links, the damage caused by mitomycin C. cancers with improved pathways may be abnormally resistant, while cancers without one of these routes may be abnormally vulnerable [14].

There are other outcomes besides apoptosis. Cells may divide with defective chromosomes and perish later in mitosis (a process known as a "mitotic catastrophe"), undergo senescence, or trigger autophagy. Drug concentration, exposure duration, cell-cycle phase, and genetic background all influence the chosen course. For example, cells with a faulty p53 checkpoint frequently enter mitosis with unresolved damage and only perish after aberrant division.

An further layer is added by the microenvironment. Reductive metabolism and repair are altered by hypoxia. Penetration is restricted in acidic, weakly perfused areas. Survival signals are released by immune and stromal cells. Cell-line potency should be interpreted cautiously since a medication that is lethal in a monolayer of cultivated cells may do far less in a solid tumor. Even while normal tissues rely on the same pathways and the treatment window may be narrow, the same reasoning justifies combining these medications with checkpoint control or repair inhibitors.

6. Clinical Applications

Antitumor antibiotics are nearly usually administered in combination with other drugs. In order to prevent a resistant clone from escaping and to ensure that no organ bears the whole burden, medicines with distinct mechanisms and toxicities are paired. The primary applications are shown in Table 2. It is not a list of authorized indicators; rather, it is a selection.

6.1 Anthracyclines

In oncology, doxorubicin is perhaps the most commonly used cytotoxic medication. It is a component of treatment plans for soft-tissue and bone sarcomas, Hodgkin and non-Hodgkin lymphomas, breast cancer, and a number of other malignancies. Epirubicin is mostly utilized for gastric and breast malignancies, whereas daunorubicin and idarubicin

continue to be essential components of induction treatment for acute leukemias. Pegylated liposomal doxorubicin was created especially to lower cardiac exposure and has fewer indications, including ovarian cancer, multiple myeloma, and AIDS-related Kaposi sarcoma [26,27].

The kind of tumor, the procedure, prior cumulative exposure, and cardiac state all influence the use of anthracyclines.

6.2 Dactinomycin

Dactinomycin plays a more limited role, yet it is difficult to substitute. Wilms tumor, rhabdomyosarcoma, Ewing sarcoma, prenatal trophoblastic disease, and some recurring or metastatic testicular malignancies are all treated with it [5]. The fact that a medication discovered in the 1940s is still used as a first-line therapy for many of these tumors indicates how effectively its mechanism works for them.

6.3 Bleomycin

Hodgkin lymphoma, germ-cell malignancies (including combination treatments for testicular cancer), and some squamous-cell carcinomas are all treated with bleomycin. In order to manage malignant effusions, it is also injected into the pleural space. Its primary draw is that it may be added to myelosuppressive combinations without exacerbating the toxicity of bone marrow suppression. Lung damage is the cost, necessitating dosage restrictions and careful observation [7,28].

6.4 Mitomycin C

Gastric, pancreatic, anal, bladder, and other malignancies have all been treated with mitomycin C. The NCI now includes a formulation administered locally for low-grade upper-tract urothelial cancer and advanced gastric or pancreatic adenocarcinoma following previous treatment [29]. A concept that is applicable to the entire class is demonstrated by topical and intravesical use: a medication with a low systemic therapeutic index can nonetheless be beneficial when used where it is required.

6.5 Eneidyne-derived conjugates

Gemtuzumab ozogamicin (anti-CD33) and inotuzumab ozogamicin (anti-CD22), two authorized conjugates of calicheamicin derivatives, are used to treat acute myeloid leukemia and acute lymphoblastic leukemia, respectively. These products best illustrate how a natural substance that is too hazardous for systemic use may be transformed into a useful medication by binding to a targeted antibody [10,25].

Table 2. Selected uses and limitations of individual agents

Drug	Selected established uses	Main advantage	Important limitation
Doxorubicin	Breast cancer, lymphomas, sarcomas, many combination	Very broad activity	Cumulative cardiotoxicity

	regimens		
Daunorubicin / idarubicin	Acute myeloid and lymphoblastic leukemias	Potent in hematologic disease	Myelosuppression; cardiotoxicity
Dactinomycin	Wilms tumor, rhabdomyosarcoma, Ewing sarcoma, gestational trophoblastic disease	High activity in selected curable tumors	Myelosuppression; tissue injury if extravasated
Bleomycin	Hodgkin lymphoma, germ-cell tumors, selected squamous-cell cancers	Little marrow suppression	Pulmonary toxicity
Mitomycin C	Selected gastrointestinal, pancreatic and urothelial cancers	Bioreductive cross-linking; usable locally	Myelosuppression; renal and vascular toxicity

7. Pharmacokinetic and Pharmacodynamic Considerations

The therapeutic index of these medicines is mostly determined by pharmacokinetics. Anthracyclines are widely distributed throughout tissues and metabolized in the liver. Certain metabolites, such as doxorubicinol, are less effective against tumors but may cause cardiac damage. As a result, hepatic impairment alters exposure and typically necessitates dosage modification [2]. Distribution is also altered by formulation: liposomal products circulate for a longer period of time and expose some normal tissues to less free drug.

Since the kidneys are primarily responsible for clearing bleomycin, decreased renal function increases exposure and the likelihood of damage. Bleomycin hydrolase, an enzyme found in many tissues but at low concentrations in the skin and lung, inactivates it, which likely accounts for the primary toxicity in these two organs [6]. Because mitomycin C's activation is dependent on tissue enzyme concentration and oxygen tension, it is more challenging to characterize. The tumor microenvironment has an impact on the drug's pharmacology [24, 30].

Time is also important. Long-term exposure causes both normal-tissue damage and cumulative DNA damage, and for some combinations, the order of delivery affects the outcome. Newer research attempts to assess medication exposure at the target location because plasma concentration is not a perfect proxy for what reaches the tumor. For this class, therapeutic drug monitoring is not customary. Body size, organ function, cumulative exposure, and reported toxicity are all taken into account when adjusting dosage in accordance with guidelines [31].

8. Adverse Effects and Their Management

8.1 Anthracycline cardiotoxicity

The issue that primarily restricts the usage of anthracyclines is cardiotoxicity. Its chance increases with cumulative exposure and may manifest during therapy, during the first year, or many years after. The estimated incidence of doxorubicin-related heart failure was about 5% at a cumulative dosage of 400 mg/m² and increased to approximately 26% at 550 mg/m²

in a retrospective analysis of three studies [32]. Risk factors include age, a history of cardiovascular illness, chest radiation, and concomitant use of cardiotoxic medications such as trastuzumab [33, 34].

It's likely a multifactorial process. The isoform found in non-dividing cardiomyocytes, topoisomerase II β , seems to be crucial since its deletion shields mice against doxorubicin cardiomyopathy [35]. Additional factors include decreased mitochondrial biogenesis, iron-dependent oxidative damage, and mitochondrial damage [19, 36]. The discovery that heart damage (mostly β -isoform) and tumor efficacy (mainly α -isoform) depend on distinct targets sustains the hope that the two can be pharmacologically separated.

Baseline cardiac evaluation, meticulous cumulative dose monitoring, and liposomal formulation selection are the first steps in prevention. The only medication that consistently demonstrates cardioprotection is dexrazoxane. A 2022 Cochrane review highlights the need to weigh benefits against drawbacks while endorsing a protective effect in adults [37]. Although the data was not very certain, a 2026 comprehensive review and meta-analysis found that dexrazoxane reduced the risk of clinical heart failure in adults [38]. Recovery is more likely when left-ventricular dysfunction is identified early and treated with heart-failure treatment [39].

8.2 Bleomycin pulmonary toxicity

Pneumonitis brought on by bleomycin may develop into fibrosis in certain cases. About 10% of treated individuals experience clinically significant pulmonary toxicity in documented series, and a small percentage of cases result in death [28]. Age, renal impairment, high cumulative dosage, previous or contemporaneous chest radiation, and high inspired oxygen concentrations—a factor that matters for anesthesia in patients who have received the drug—all increase risk. New respiratory problems in a treated patient should always be regarded carefully since early symptoms like dry cough or dyspnea are non-specific.

8.3 Myelosuppression and other toxicities

Anthracyclines, dactinomycin, and mitomycin C commonly cause marrow suppression, which often restricts recurrent dose. Additional side effects include hepatic or renal damage, mucositis, alopecia, nausea, and vomiting, depending on the medication. Extravasation of vesicants such as doxorubicin, daunorubicin, and dactinomycin might result in severe local necrosis. Prevention, dosage adjustment, supportive care, and, where appropriate, a change in formulation or regimen are the mainstays of management. In reality, oncology, pharmacy, and nursing teams collaborate on this task, and it is frequently their attention to detail—rather than the medication—that decides whether treatment can be finished safely.

9. Drug Resistance

Another reason a tumor that was initially receptive subsequently escapes is resistance. It might arise after treatment (acquired) or be there from the beginning (intrinsic), and a single tumor frequently contains many resistant subclones. They are chosen by the treatment itself.

9.1 Reduced drug accumulation

Overexpression of ATP-binding cassette transporters, particularly P-glycoprotein (ABCB1), which pumps the medication out of the cell, is the most well-known mechanism for anthracyclines. Since its discovery in relation to multidrug resistance, the protein has been discovered in leukemias and a number of solid malignancies [40, 41]. Nuclear drug levels are also decreased by modifications in intracellular trafficking, vesicular sequestration, and uptake [42]. This issue is still unresolved because the early clinical studies using P-glycoprotein inhibitors were generally unsatisfactory, partly because to the inhibitors' lack of specificity and alteration of the cytotoxic drug's pharmacokinetics.

9.2 Target alteration

Anthracyclines can trap fewer cleavage complexes when topoisomerase II expression is reduced or mutated [13,43]. A similar outcome may result from a change in the equilibrium between the α and β isoforms. Drug access to DNA may be further limited by chromatin remodeling.

9.3 Enhanced repair and altered activation

Cells can survive damages that would otherwise be fatal by faster homologous recombination, non-homologous end joining, base-excision repair, or cross-link repair; which route is important depending on the medication. Resistance to mitomycin C may also result from enzymes that detoxify the reactive intermediate or from a reduction in reductive activation. Resistance is seldom explained by a single marker since many enzymes might activate mitomycin [30]. There have been reports of increased hydrolase activity, decreased absorption, and higher antioxidant responses for bleomycin; nevertheless, hydrolase expression alone is not a reliable predictor of tumor response, indicating that resistance is multifactorial [6].

9.4 Evasion of apoptosis and tumor plasticity

If a tumor's death mechanism is compromised, it can withstand significant DNA damage. Altered mitochondrial apoptosis, overexpression of BCL-2 family members, and loss of TP53 activity can all change the result in favor of survival. Another pathway to relapse is drug-tolerant persister cells, which go into a slow-cycling condition and eventually become resistant populations. Table 3 lists the primary mechanisms along with suggested countermeasures.

Table 3. Resistance mechanisms and possible countermeasures

Mechanism	Consequence	Possible countermeasure
ABCB1 / P-glycoprotein efflux	Lower intracellular anthracycline concentration	Carrier-based delivery; transporter-independent analogues; rational combinations
Topoisomerase II alteration	Fewer trapped cleavage complexes	Agents with different targets; biomarker-guided selection
Enhanced DNA repair	Faster removal or tolerance of lesions	PARP, ATR or CHK1 inhibitors in selected settings
Antioxidant adaptation	Less oxidative killing	Context-dependent redox modulation
Altered mitomycin activation	Less reactive intermediate formed	Enzyme-directed or hypoxia-targeted strategies
Bleomycin degradation	Loss of active drug	Targeted delivery; mechanism-based patient selection
Defective apoptosis	Survival despite DNA damage	Combination with BCL-2 or survival-pathway inhibitors
Tumor heterogeneity	Selection of resistant subclones	Combination or adaptive schedules;

		molecular monitoring
Poor tumor penetration	Low drug level in distant regions	Nanoparticles, liposomes, local delivery, ADCs

Treatment failure in the entire class cannot be explained by a single cause. Rather than being a flaw that can be fixed with a single inhibitor, resistance is better understood as an evolutionary process. Finding the mechanism causing a certain tumor and selecting a companion treatment that targets it is the more practical objective.

10. Emerging Strategies

10.1 Liposomal and nanoparticle delivery

Nanocarriers have the ability to alter pharmacokinetics, increase tumor exposure, and decrease susceptible tissue exposure. The most well-known example is pegylated liposomal doxorubicin, which has equivalent anticancer effects in some circumstances but less cardiotoxicity than traditional doxorubicin, according to clinical trials [44, 45]. More recent particles are made to release medication in reaction to enzymes, pH, or redox conditions that are common in malignancies. Since improved permeability and retention—the basis for passive targeting—are far less in human malignancies than in many rat models, there is still a significant gap between promise and practice.

10.2 Antibody–drug conjugates

An antibody targeting a tumor-associated antigen, a linker, and a cytotoxic payload make up an antibody–drug combination. The payload is released when the linker is severed following the antibody's binding and internalization. One of the earliest payloads was calicheamicin, which is still used today. The technique is effective yet harsh when linker stability is low because of its potency, which is strong enough that only a small number of molecules entering the nucleus are sufficient to kill the cell [25]. Thus, payload release, linker chemistry, and antigen selection are critical.

10.3 DNA-repair inhibitors

Since these medications produce DNA lesions, preventing repair should theoretically make them more powerful. PARP, ATR, and CHK1 inhibitors are being studied as collaborators. Once more, selectivity is the main challenge because normal tissues use the same repair mechanisms and combined toxicity may be higher than anticipated. The tiny percentage of cancers having a clear, targetable defect limits the use of synthetic lethality, which offers a more selective logic in which a tumor already weak in one route is targeted through a second.

10.4 Hypoxia-directed therapy

In actuality, mitomycin C is not a selective hypoxic agent since it is also activated in well-oxygenated tissue, but it did

show that decrease in oxygen-poor areas may be exploited to concentrate cytotoxicity. More stringent oxygen dependency was incorporated into the design of later bio-reductive prodrugs. Reliable imaging or blood-based hypoxia indicators will likely be needed in the future to identify patients who may benefit.

10.5 Precision approaches and combination design

Repair flaws, transporter expression, topoisomerase levels, and redox phenotypes that affect medication susceptibility can all be found using molecular profiling. In theory, this enables an agent to be selected based on the characteristics of a tumor rather than merely its location. There are currently few proven prognostic biomarkers for the traditional antitumor antibiotics in use, and the most talked-about example of one that is still uncommon is TOP2A status in breast cancer.

Combinations require the same attention. A regimen may be rendered useless by overlapping toxicities, such as two cardiotoxic drugs or many myelosuppressive ones. Due to differences in repair kinetics and cell-cycle redistribution following the initial medication, certain pairings are only synergistic in a specific order. Such regimens are increasingly being found using computational modeling and high-throughput functional screening, and machine-learning techniques may aid in the prediction of resistance phenotypes and combinations. Until they have undergone experimental and clinical testing, such predictions remain theories.

11. Considerations for Pharmacy Practice

Many antitumor antibiotics are vesicants, and the majority are dangerous medications. Appropriate engineering controls, safety gear, verified compounding techniques, and proper waste disposal are all necessary for preparation. Pharmacists play a crucial role in the safety chain by monitoring lifetime anthracycline exposure, which cannot be accurately reconstructed from memory once a patient moves between centers, confirming the diagnosis and protocol, reviewing laboratory values and organ function, and verifying body-surface-area calculations.

Every medicine has its own watchpoints. Renal function and respiratory symptoms must be monitored when using bleomycin. Monitoring organ function and blood counts is necessary when using mitomycin C. Institutions should have a documented, drug-specific extravasation plan for each intravenous medication with vesicant potential since different medicines cause varying degrees of tissue damage. Preventable errors are decreased by staff education, independent double checks, and standard labeling.

It is important to report adverse events through national and institutional pharmacovigilance systems, particularly when older medications are used in novel combinations or formulations. Counseling should be straightforward: patients should understand which side effects are to be expected, which symptoms require immediate treatment, why monitoring tests are required, and which over-the-counter medicines or supplements should be avoided without guidance. Additionally, pharmacists can inform the oncology team and encourage adherence to oral supportive medications.

12. Discussion and Future Directions

These medications' continued use in therapeutic settings is not a historical coincidence. Despite their chemical differences, their methods are similar in that they rely largely on transcription, DNA integrity, replication, and redox balance—processes that are crucial to malignant cells. However, healthy tissue depends on those same mechanisms. Therefore, rather than relying just on a target present in tumors, selectivity is based on quantitative variations in proliferation rate, repair capability, drug dispersion, and stress tolerance. This explains the class's toxicity as well as its triumphs.

We believe that a single conceptual shift is more significant than any specific medication. The focus of development has changed from finding a more powerful chemical to improving exposure management. The most obvious examples are calicheamicin conjugates and liposomal anthracyclines. A far more powerful medication that harms healthy organs may not be as beneficial as a moderately active medication that is specifically administered to a tumor. This implies that a compound's ability to be linked to a targeting mechanism should be evaluated in addition to its cytotoxic efficacy when screening natural products.

There are still a few unanswered questions. Although encouraging, the data on dexrazoxane has limitations, and it is still up for dispute whether and to whom cardioprotection should be made more generally available [37, 38]. Prospective

trials have not demonstrated the value of tumor biomarkers for the older medications. The majority of attempts to overcome resistance, particularly efflux-mediated resistance, have been unsuccessful. The use of anthracyclines will be more influenced by cardio-oncology services as survival after cancer improves and late cardiac effects become a bigger part of the overall picture [34,39].

There are two worth mentioning research directions. Computational methods may expedite the creation of derivatives, and genome mining of microbial biosynthetic gene clusters may uncover novel scaffolds with unknown processes. Nevertheless, the translational challenge will remain the same as it has always been: translating exceptional molecular potency into therapeutic benefit that is both safe and repeatable.

13. Conclusion

A little yet effective component of cancer treatment is antitumor antibiotics. DNA is harmed by anthracyclines via redox chemistry, topoisomerase II poisoning, and intercalation. Transcription is blocked by dactinomycin. After reductive activation, mitomycin C cross-links DNA, while bleomycin cleaves it via iron-dependent oxygen activation. By offering extremely powerful payloads for antibody conjugates, enediyne have expanded the group.

The extent to which these medications can be used is still determined by toxicity and resistance. Resistance may result from efflux, target modification, repair, altered metabolism, and apoptotic abnormalities. Monitoring and individual risk assessment are necessary for cardiac, pulmonary, and bone marrow injuries. Future advancements in targeted administration, biomarker-based selection, logical combinations, and efficient cardioprotection are anticipated to come from improved selectivity rather than increased potency. There is still need for the older anticancer antibiotics. They continue to be effective medications and a rich supply of chemicals for the upcoming class of targeted medications.

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