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Recent advances in clinical management and uses of conventional and novel therapies

Topoisomerase II inhibitors

*Kenneth R. Hande**

777 Preston Research Building, Vanderbilt University Medical Center, Nashville, TN 37232, United States

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ABSTRACT

Topoisomerase II is an enzyme essential for DNA replication, chromosome condensation and chromosome segregation. Inhibitors of topoisomerase II are important drugs used in the therapy of many neoplasms including breast cancer, lung cancer, testicular cancer, lymphomas and sarcomas. This paper reviews the mechanism of action, toxicities, pharmacology and clinical use of topoisomerase II inhibitors including etoposide, teniposide, doxorubicin, daunorubicin, epirubicin, idarubicin and mitoxantrone. New information regarding these agents and on topoisomerase II inhibitors under development is highlighted.
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1. Introduction

DNA topoisomerases are nuclear enzymes that make transient strand breaks in DNA to allow a cell to manipulate its topology [1,2]. Topoisomerase I makes single-strand breaks. Topoisomerase II makes double-strand breaks and passes double-stranded DNA through the nick to allow relaxation of over-coiled DNA [3]. Topoisomerases are highly conserved enzymes essential for the survival of all eukaryotic organisms. There is little sequence homology between topoisomerase I and II (Table 1). Topoisomerases function in DNA replication, chromosome condensation, and chromosome segregation. Several currently approved chemotherapeutic drugs interfere with the action of topoisomerases. Currently available topoisomerase I inhibitors are irinotecan (CPT-11) and topotecan. FDA-approved topoisomerase II inhibitors are etoposide, teniposide, doxorubicin, idarubicin, epirubicin, and mitoxantrone. This chapter will review critical concepts and update new information regarding topoisomerase II inhibitors.

2. Epipodophyllotoxins

2.1. *Etoposide*

2.1.1. *Mechanism of action*

Topoisomerase II is a multi-subunit enzyme which uses ATP to pass an intact helix through a transient double-stranded break in DNA to modulate DNA topology [4]. After strand passage, the DNA backbone is religated and DNA structure restored. Etoposide prevents topoisomerase II from religating cleaved DNA [5]. Etoposide thus converts topoisomerase II into a poison that introduces high levels of transient protein-associated breaks in the genome of treated cells.

Topoisomerase II exists as two highly homologous isoforms, alpha and beta, which differ in their production during the cell cycle. The alpha isoform concentration increases 2–3-fold during G2/M, and orders of magnitude is higher in rapidly proliferating cells than in quiescent cell populations. The alpha isoform appears to be the target of etoposide [6]. The beta enzyme does not change significantly during the cell cycle and could potentially be a target in slow growing cancers. Two scissile bonds are formed per every topoisomerase II-mediated double-stranded DNA break. Results of DNA cleavage and ligation assay studies indicate a two-site model for the action of etoposide against human topoisomerase II alpha. This model suggests that drug interactions at both scissile bonds are required in order to increase enzyme-mediated double-stranded DNA breaks [7].

There does not appear to be a single DNA binding site for etoposide-topoisomerase II targeted breaks. However, selected hot spots may be present for DNA binding (see sections on drug toxicity). The cell-signaling pathways that lead to apoptosis following topoisomerase-induced DNA damage are not completely understood. Current research

* Tel.: +1 615 322 4967; fax: +1 615 343 7602.
E-mail address: Kenneth.Hande@Vanderbilt.Edu.
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Table 1 – DNA topoisomerases

Topoisomerase I	Topoisomerase II
100 kDa	170 kDa; 180 kDa
Makes single-strand DNA breaks	Makes double-strand DNA breaks
ATP independent	ATP dependent
Genes located on chromosome 20q12	Gene located on chromosomes 17q21 and 3p24
	Two types, alpha and beta

is attempting to elucidate the mechanisms involved [8]. Caspases are a group of cysteine proteases that orchestrate apoptosis. Robertson et al. have identified caspase 2 as an important link between etoposide-induced DNA damage and the engagement of the mitochondrial apoptotic pathway [9]. Caspase 2 activates caspase 8 resulting in mitochondrial damage and subsequent downstream caspase 9 and 3 activation [10]. Caspase 3 appears critical for apoptosis-associated chromatin margination, DNA fragmentation, and nuclear collapse. Cells lacking caspase 3 are resistant to etoposide [11]. Caspase 10 appears to trigger a feedback amplification loop that amplifies caspases 9 and 3 [12]. Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) augments the expression of caspases induced by etoposide [13,14].

Other cell-cycle control proteins are also important mediators in etoposide-induced apoptosis. P53, c-Myc and BAFF have been identified as pathways utilized to arrest cell cycle progression and induce apoptosis in certain cell lines exposed to etoposide [15]. Etoposide activates two pathways which lead to G2M arrest, one which depends on the presence of P53 while the other is P53 independent [16]. The presence of bcr-abl, which prolongs G2M arrest and allows for DNA repair mechanisms, decreases the cytotoxicity of etoposide. Cells with dysfunctional early G2/M checkpoint control (such as ataxia-telangiectasia mutated deficient fibroblasts) have increased chromosomal abnormalities following etoposide exposure [17].

Resistance to etoposide arises through multiple mechanisms. Mutations at ser-1106 in the topoisomerase II molecule abrogate phosphorylation of the enzyme and reduce sensitivity to etoposide [18]. Rapid repair of DNA breaks caused by etoposide can also lead to drug resistance. Repair occurs through the single-strand invasion pathway of homologous recombination or by non-homologous DNA end-joining [19]. The repair of potentially lethal DNA damage by etoposide appears to be dependent on functioning FLT3 [20]. Resistance to etoposide is noted in cells that have the multidrug resistance (MDR) phenotype. By modifying the structure of etoposide to make it a prodrug, etoposide analogs have been developed which are active, in vitro, against MDR resistant tumors [21].

2.1.2. *Toxicity*

Common toxicities from etoposide include bone marrow suppression, nausea, vomiting, and alopecia. At very high doses, such as those used with bone marrow transplantation regimens, mucositis becomes the dose-limiting toxicity. Liver toxicity, fever, and chills may also occur with high-dose therapy. Palmar-plantar eruptions and irritation of the anal canal have been associated with etoposide use [22].

Hypersensitivity reactions, including vasomotor changes in the pulmonary and gastrointestinal systems, may also occur following etoposide (or teniposide) use. These reactions may result from the Tween 80 needed to solubilize etoposide. These reactions can usually be ameliorated with steroids, histamine blockade, and/or using a slower infusion rate [23]. Etoposide phosphate, a water-soluble pro-drug that is rapidly converted to etoposide by endogenous phosphatases [24], may reduce the risk of a hypersensitivity reaction since no solubilizer is required. Etoposide phosphate has been safely used in patients who have had a hypersensitivity reaction to etoposide [25]. Etoposide phosphate appears to have kinetics similar to etoposide, even in the transplant setting [26].

The most serious adverse event associated with etoposide is the development of acute myelogenous leukemia [27,28]. On the basis of current clinical evidence, the World Health Organization has identified etoposide as carcinogenic to humans [29]. Therapy-related acute myelogenous leukemia also occurs with other topoisomerase II inhibitors [30,31]. Various studies have shown that topoisomerase II inhibitors target selected binding sites at translocation breakpoints leading to MLL, AML1-ETO, PML-RARA and NUP98 rearrangements [32,33]. Etoposide-related leukemia develops relatively early after therapy (2–3 years). Most often (70% of cases), etoposide-related leukemia is distinguished by a balanced translocation involving the mixed-lineage leukemia (MLL) gene on chromosome 11. In vitro exposure of mouse embryonic stem cells to etoposide results in MLL fusions [34]. The MLL gene is more sensitive to topoisomerase II induced cleavage than other genes such as RUNX1 and MLLT3 [35,36]. Lovett et al. has found that not only etoposide, but also its metabolites (etoposide quinone and etoposide catechol) enhance DNA topoisomerase II cleavage near the MLL translocation breakpoints [37]. MLL rearrangements occur through cleavage events in MLL and the translocated gene in which both breaks become stable, DNA ends are processed and then undergo ligation [38]. The double-stranded DNA breaks in the MLL gene may not be directly linked to topoisomerase II exposure. Hars et al. [39] suggest that the DNA breaks generated in the MLL locus are the result of caspase activation of DNase by etoposide. MLL breakpoints can occur in stem cells found in cord blood and in fetal hepatic hematopoietic stem cells, potentially explaining the development of infant leukemia resulting from in utero exposure to topoisomerase II inhibitors [40].

The incidence of secondary leukemia from etoposide use and the factors increasing the risk of leukemia have varied from study to study. With rare exceptions, the risk for development of acute myeloid leukemia (AML) does not exceed 5% in patients treated for solid tumors, even with high cumulative doses of topoisomerase II inhibitors. The National Cancer Institute Cancer Therapy Evaluation Program, using data from 12 studies, calculated a 6-year rate of secondary leukemia of 0.7–3.2% after epipodophyllotoxin therapy [41]. The available data on testicular cancer suggest that the risk of secondary leukemia is dose-related with etoposide doses totaling more than 2 g/m^2 resulting in a 2–3% cumulative risk [42]. In a multicenter study of 61 secondary leukemia cases [43], the risk of secondary AML was associated with increasing expo-

sure to etoposide (RR = 7 for patients receiving a total dose of 1.2–6.0 g/m^2 etoposide or teniposide). Doses over 6 g/m^2 were associated with a 93-fold (range 9.9–87%) increased risk of leukemia development. Risks were highest in patients treated for Hodgkin's disease or osteosarcoma. Patients treated for non-Hodgkin's lymphoma and acute lymphocytic leukemia have been reported to have a higher (>5%) rate of AML induction [43,44]. The reasons for the difference in incidence are not clear, but are likely due to variations in treatment schedules and use of concurrent chemotherapy agents.

Host factors have been implicated in placing patients at higher risk for developing topoisomerase II inhibitor-related AML. Three predisposing factors recently identified include a paucity of CYP3A4 variant genotypes [45], an increased frequency of GSTM1 and GSTT1 null genotypes [46], and a lower activity of thiopurine methyltransferase activity [47]. Chronic thiopurine therapy is associated with an increased risk of etoposide-associated secondary neoplasms. Thiopurine treatment results in thioguanine substitution into DNA. Krynetskaia et al. [48] have shown that deoxythioguanosine substitution near the topoisomerase II cleavage site alters cleavage by topoisomerase II in the presence of etoposide. This finding may provide an explanation behind the interaction between thiopurine- and topoisomerase II-inhibitors. Remissions rates from therapy-related AML can be high; however, remissions from therapy-related AML are usually brief and the prognosis is poor [49].

2.1.3. *Pharmacology*

Etoposide is poorly soluble in water. For intravenous use, etoposide is dissolved in a solubilizer composed of polysorbate 80, polyethylene glycol, and alcohol and diluted to a concentration less than 0.4 mg/ml to avoid precipitation. These additives are believed to induce the hypersensitivity reactions occasionally seen with etoposide infusion.

Approximately one-third of intravenously administered etoposide is excreted in the urine. Less than 2% of an administered etoposide dose is excreted into bile as intact drug [50]. Etoposide clearance is modestly decreased in patients with renal dysfunction [51], but not in patients with hepatic obstruction [52]. Hepatic glucuronidation accounts for 25% of etoposide's clearance. Etoposide is converted primarily by UGT1A1 to the phenolic glucuronide metabolite [53]. Etoposide is also metabolized to a reactive catechol metabolite by cytochrome P450 3A4. The catechol AUC is only 1–2% that of etoposide [54]. However, the catechol metabolite, like etoposide, is cytotoxic. Mild to moderate liver dysfunction does not require a dose reduction and does not increase etoposide toxicity, even with hyperbilirubinemia [52]. Etoposide is highly bound to plasma proteins with only 6–8% being non-bound. Since free drug is biologically active, conditions that decrease protein binding or decrease albumin may increase the pharmacological effect of a given drug dose.

Only a few drug interactions have been identified that involve etoposide. Neither doxorubicin nor ifosfamide change etoposide clearance [55]. No significant interaction is seen between the platinum agents (cisplatin and carboplatin) and etoposide [56]. Grapefruit juice, an inhibitor of cytochrome P450 metabolism, does not alter etoposide kinetics [57]. However, concomitant use of prednisone induces etoposide clearance, possibly through induction of P-glycoprotein (PgP) [58]. Patients receiving glucocorticoids may be relatively under dosed as induction of PgP may increase renal or biliary clearance. Inhibitors of PgP delay etoposide clearance, increasing toxicity [59]. Daily use of etoposide induces metabolism to the catechol metabolite. Zheng et al. [54] found significantly higher etoposide catechol AUCs on day 5 of a 5-day course of etoposide compared with day 1 of treatment.

Etoposide's antineoplastic activity is highly dependent on the schedule of drug administration [60]. Slevin et al. found that 100 mg/m^2 of etoposide given to small-cell lung cancer (SCLC) patients daily for 5 days had a significantly greater response rate compared to a 24-h infusion of 500 mg/m^2 (89% *vs.* 10%), despite producing similar AUCs [61]. Etoposide infusions that provide prolonged low-plasma etoposide levels (>1 μg/ml) can produce antitumor responses in SCLC. The duration of exposure may impact the plasma concentration of etoposide required to achieve antitumor response [62].

The efficacy of low-dose, long-term etoposide therapy in preclinical models generated enthusiasm for oral etoposide, since this would theoretically be a convenient way of providing long-duration therapy for patients. Unfortunately, the bioavailability of oral etoposide ranges from 40 to 80% and varies with dose [63]. Oral absorption is linear up to doses of 250 mg, but decreases with doses greater than 300 mg. Etoposide has been administered via a vaginal ovule as a potential means of treating cervical lesions. High cervical tissue etoposide concentrations were noted with lack of any systemic absorption [64].

Both intravenous and oral etoposide have significant variability in plasma drug exposure. Oral etoposide administration results in greater variability in drug exposure than does intravenous administration [65]. Changing etoposide doses in patients with reduced creatinine clearance alters variability only modestly (±9%). In children, the inter-patient variability of AUC is decreased when doses are given based on body surface area rather than weight [66]. Children with Down's syndrome may have delayed etoposide clearance [67].

2.1.4. *Clinical use*

Etoposide has been used for treatment of a wide variety of malignancies, including lung cancer, germ-cell malignancies, leukemias, non-Hodgkin's lymphoma, Kaposi's sarcoma, soft tissue sarcomas, and neuroblastoma [68]. Edick et al. have correlated the etoposide AUC achieved in leukemia patients treated with etoposide and their response to therapy [69]. Median etoposide AUCs were higher in patients who achieved a complete response than in patients who did not achieve a CR (24 μmol/l *vs.* 14 μmol/l; $p = 0.06$). Toxicity was primarily noted in patients who maintained a plasma etoposide concentration over 1.7 μM for more than 8 h daily. This suggests that an adequate plasma drug concentration must be obtained for a therapeutic response, but that higher, more prolonged plasma etoposide concentrations produce greater toxicity. Monitoring plasma etoposide infusions and adjusting doses can result in attaining, within 10%, a target plasma etoposide concentration [70].

The addition of etoposide to CHOP chemotherapy for aggressive lymphomas has recently been found to improve 5-

year event-free survival compared to CHOP alone [71]. Selected leukemia types may be more sensitive to etoposide than others. In children with pre-B cell leukemia, the presence of the t(12:21)(p13:q22) resulting in the ETV6/RUNX1 fusion gene appears particularly sensitive to etoposide [72]. Mechanisms that explain such sensitivity remain to be defined.

2.2. *Teniposide*

Teniposide is an analogue of etoposide approved for use in the United States in 1993, 10 years after etoposide was approved. Teniposide use has been limited primarily to the treatment of childhood lymphomas and leukemias and for treatment of CNS malignancies. However, it may have clinical efficacy equivalent to etoposide given its similar preclinical activity and toxicities. Few studies comparing the activity of these two agents have been performed.

2.2.1. *Mechanism of action*

Teniposide's mechanism of action is similar to that of etoposide. Both drugs damage DNA by interaction with topoisomerase II to form cleavable complexes that prevent religation of DNA leading to double-strand DNA breaks. It has been proposed that the topoisomerase II–DNA covalent complex arrests transcription and triggers 26S proteasome-mediated degradation of topoisomerase II beta. Using various topoisomerase II inhibitors, Xiao et al. [73] found that the proteosomal degradation of topoisomerase II beta induced by formation of a topo II–DNA complex is due to transcriptional arrest, but not DNA damage. Teniposide prefers to form stabilized cleavable complexes at DNA sites bound to the nuclear matrix [74]. The rate of topoisomerase II–DNA complex formation with teniposide correlates with DNA damage but not with cytotoxicity [75].

2.2.2. *Toxicity*

Teniposide's toxicities are like those of etoposide: myelosuppression, alopecia, mucositis, nausea, and vomiting. Acute myelogenous leukemia with 11q23 chromosome changes occur following teniposide therapy [76]. Hypersensitivity reactions appear more frequently with teniposide infusions than etoposide infusions.

2.2.3. *Pharmacology*

In vitro, teniposide is about 10-fold more potent than etoposide in killing malignant cells. Since both agents have relatively similar abilities to inhibit topoisomerase II, the greater in vitro cytotoxicity is likely due to better cellular uptake [77]. Equitoxic teniposide doses are approximately one-third less than those of etoposide.

Teniposide has less water solubility, a lower renal clearance (10%), and is more tightly bound to plasma proteins than etoposide (less than 1% of the total plasma teniposide is unbound). Certain drugs, such as cyclosporine, increase the unbound fraction of teniposide resulting in increased toxicity [78]. Teniposide also has a longer drug half-life and greater biliary clearance than does etoposide. Anticonvulsants, such as phenobarbital and phenytoin, increase teniposide clearance, presumable by increasing hepatic metabolism [79]. This increased clearance results in a lower efficacy of teniposide chemotherapy in children with ALL who are receiving seizure medications [80,81].

2.2.4. *Clinical use*

Teniposide has been used as a component of therapy for pediatric patients with poor prognosis acute lymphocytic leukemia. Although teniposide is not a major component of therapy for any adult neoplasms, it has antitumor activity in small cell lung cancer, Kaposi's sarcoma, bladder cancer, leukemias, and lymphomas [82,83]. A Phase III study comparing teniposide with or without whole brain radiation therapy for brain metastases from small cell lung cancer demonstrated a 57% response rate in the combined-modality arm, which was significantly different from the 22% response in the teniposide-alone arm. However, overall survival was not altered [84]. BCNU plus teniposide increased survival over BCNU alone when given in combination for treatment of primary glioma [85]. Because of its use in CNS tumors and the frequent concomitant use of seizure mediations in this population, drug interactions between teniposide and anti-epileptic medications must be remembered.

3. Anthracyclines

Anthracycline antibiotics are commonly used antineoplastic agents with activity against breast cancer, leukemias, lymphomas, and sarcomas. Anthracyclines inhibit topoisomerase II [86]. Anthracyclines also intercalate into DNA and form reactive metabolites that interact with many intracellular molecules. Thus, the biologic effects of the anthracyclines may not be based solely on topoisomerase II activity [87]. Anthracyclines currently approved for use in the United States are doxorubicin, daunorubicin, epirubicin, and idarubicin.

3.1. *Mechanism of action*

Anthracyclines react with cellular constituents in various ways. Their planar aglycone moiety can insert between adjacent DNA base pairs (intercalation). Anthracyclines cause single- or double-stranded DNA breaks. They modify the ability of nuclear helicases to dissociate duplex DNA into single DNA strands [88]. Anthracyclines can undergo one- and two-electron reduction, since they are members of the quinone family, producing reactive compounds that damage macromolecules and lipid membranes [89]. Finally, the anthracyclines poison topoisomerase II in a manner similar to etoposide. The ability of anthracycline analogues to poison topoisomerase II correlates with the cytotoxic potential of the drug [86].

Anthracyclines trigger apoptotic cell death through complex signaling pathways. Nuclear factor kappa B activation and I kappa B alpha degradation are early events triggered by anthracyclines [90]. Cathepsin B is expressed via NF-kappa B [91]. TRAIL, p53, and the FAS/FAS-ligand system are additional pathways used for anthracycline apoptosis in various cell lines [92,93]. The presence of p21 (waf1/cip1/sdi1), a cyclin dependent kinase inhibitor, suppresses doxorubicin inducing apoptosis [94]. Doxorubicin decreases sumoylation of KAP1

(transcriptional cofactor KRAB domain-associated protein 1) which induces p21 expression [95].

3.2. *Resistance*

Anthracycline resistance can result from over expression of transport proteins, such as PgP or other multi-drug resistance transport proteins. Most clinical trials attempting to overcome development of anthracycline resistance have used inhibitors of PgP, such as cyclosporine and cyclosporine analogs. These clinical trials have been largely disappointing as the high concentrations of the inhibitors needed to block PgP exacerbate the toxicity of the chemotherapeutic agent by delaying anthracycline clearance. PSC 833 decreases daunorubicin clearance 2-fold and decreases the clearance of daunorubicinol 3-fold [96]. A recent Phase I trial of a third-generation P-glycoprotein inhibitor (GF120918) found few side effects from the PgP inhibitor and minimal effect on doxorubicin kinetics at plasma GF120918 concentrations blocking PgP in vitro [97]. Depsipeptide, an inhibitor of histone deacetylase, and all trans retinoic acid (ATRA) both upregulate P-glycoprotein expression and may potentially induce resistance to anthracycline treatment [98]. Inducers of nitric oxide synthesis [99] and inhibitors of the cyclooxygenase-2 enzyme [100] prevent expression of MDR associated proteins and could be used in new strategies to overcome anthracycline resistance.

3.3. *Toxicity*

The acute, dose-limiting toxicity of anthracyclines is myelosuppression. Myelosuppression occurs more frequently with infusion than with bolus administration. Other acute toxicities include nausea, vomiting, alopecia, and mucositis. Anthracyclines cause severe local tissue reactions if extravasation occurs during infusion. The resulting ulcers can progress over weeks, be slow to heal, and occasionally require skin grafting.

The most serious toxicity associated with anthracyclines is cardiotoxicity. Three types of cardiotoxicity have been defined based on timing of symptoms. Acute cardiotoxicity starts immediately after infusion and can include arrhythmias and, rarely, pericarditis. Symptomatic management is appropriate. There is little correlation between acute toxicity and development of chronic toxicity. Late-onset cardiomyopathy appears months to years after treatment is completed. In children treated with anthracyclines, subclinical cardiotoxicity may not become overt until patients are adolescent or adult. The mechanism underlying the cardiotoxic effects of anthracyclines is generally accepted to be the generation of free radicals involving iron–doxorubicin complexes that damage cardiac cellular membranes. Free radicals enhance endothelial nitric oxide synthase production which causes apoptosis in myocytes [101]. Iron chelating agents can reduce anthracycline cardiotoxicity (see below). However, chelation of iron does not completely protect cells from doxorubicin cytotoxicity [102]. Doxorubicin free radical metabolites reduce the protein C receptor on endothelial cells of blood vessels down-regulating the protein C anticoagulant pathway and perhaps triggering intravascular thrombus formation [103].

The frequency and severity of anthracycline cardiotoxicity in adults has been correlated, in retrospective studies, to the total dose of anthracycline administered and to the drug administration schedule with bolus administration appearing to cause greater risk of heart failure than continuous infusion [104]. The percentage of adult patients with doxorubicin-related congestive heart failure (CHF) is 5% at a cumulative dose of 400 mg/m^2, rising to 16% at a dose of 500 mg/m^2, 26% at a dose of 550 mg/m^2, and 48% at a dose of 700 mg/m^2 [105]. In children, a 2.8% incidence of CHF has been reported 6 years following administration of a mean cumulative dose of 300 mg/m^2 of an anthracycline [106]. There is growing evidence that the frequency of heart failure increases with longer follow-up in children. Congestive heart failure was noted in only 1.5% of 265 patients following a median of 34 months after a mean total dose of 300 mg/m^2 doxorubicin [107]. However, a 10% incidence of CHF was found in a group of 229 patients followed for 15 years after treatment receiving a similar dose of doxorubicin [108]. In addition to the development of overt heart failure, measurable cardiac abnormalities can be detected in 25–30% of adult patients treated with a median dose of 300 mg/m^2 doxorubicin [109]. Male sex, older age, higher doses of doxorubicin, radiotherapy and obesity increase the risk of cardiac toxicity. The concomitant use of other medications such as trastuzumab and paclitaxel increase the risk of anthracycline cardiotoxicity. Paclitaxel and docetaxel, at low concentrations, stimulate formation of the toxic metabolite doxorubicinol which may be the cause of increased cardiotoxicity [110]. Troponin plasma concentrations may be a sensitive means of assessing early doxorubicin cardiotoxicity. Troponin-T plasma concentrations are elevated in 30% of children treated with doxorubicin, positively correlate with dose of doxorubicin given, and occasionally remain elevated for months [111]. Levels of brain naturetic peptide (BNP) do not appear to be predictive of the development of reduced left ventricular ejection fraction [112].

Several strategies to decrease the risk of anthracycline cardiotoxicity have been evaluated. Continuous infusion anthracycline therapy has not been shown to offer a significant cardioprotective advantage over bolus drug administration [113,114]. Dexrazoxane, an iron-chelating agent, can decrease the acute risk of cardiac toxicity presumably by preventing formation of iron-catalyzed free radicals. There have been 16 published clinical trials, nine of them randomized, using dexrazoxane with anthracyclines that have demonstrated increased cardio-protection for patients taking dexrazoxane with no decrease in antineoplastic activity [115]. Dexrazoxane reduces cardiac injury, as measured by troponin T, associated with the use of anthracyclines in childhood ALL without compromising the anti-leukemic efficacy of treatment [116].

Chemical modifications of the anthracyclines have been explored in an attempt to reduce cardiac toxicity. Liposomal formulations of doxorubicin and daunorubicin have been developed. By encapsulating drug in liposomes, anthracyclines have a longer half-life and may preferentially accumulate in tumor tissue rather than cardiac tissue, thereby providing selectivity. Pegylated liposomal doxorubicin causes less cardiomyopathy than free doxorubicin. The median anthracycline dose producing cardiotoxicity is higher for lipo-

somal doxorubicin (785 mg/m^2) compared to conventional doxorubicin (570 mg/m^2) ($p = 0.0001$; hazard ratio, 3.56) [117]. In metastatic breast cancer patients, cardiotoxicity is reduced from 21 to 6% when liposomal doxorubicin has been compared to conventional doxorubicin [118]. The median cumulative dose of liposomal doxorubicin at the onset of cardiotoxicity was 2220 mg/m^2 versus 480 mg/m^2 for doxorubicin in this study. Liposomal doxorubicin (Doxil, Caelyx) appears to provide comparable antineoplastic efficacy against breast cancer compared to regular doxorubicin [119]. Liposomal doxorubicin preparations have less nausea, vomiting and alopecia than standard doxorubicin but have a significantly increased risk of palmar-plantar erythrodysesthesia (hand–foot syndrome) and mucositis [120]. Four skin toxicities have been reported with liposomal doxorubicin: hand–foot syndrome (40% of patients), diffuse follicular rash (10%), intertrigo-like eruption (8%), and formation of new melanotic macules (5%) [121]. Pegylated doxorubicin may have less cardiotoxicity than doxorubicin allowing greater cumulative drug doses [122].

At equally myelosuppressive doses, epirubicin has been proposed to be less cardiotoxic than doxorubicin [123]. Compared to doxorubicin, epirubicin has greater sequestration into vesicles and impaired efficiency of electron addition to form reactive oxygen species, which may limit cardiotoxicity [124]. Ryberg et al. have proposed using a maximum cumulative dose of 900 mg/m^2 of epirubicin (where the incidence of symptomatic cardiotoxicity was found to be 4%) [125]. However, Meinari et al. have found evidence of abnormal diastolic function in 38% of patients receiving relatively low (360–450 mg/m^2) doses of epirubicin and a drop in LVEF below 50% in 11% of these patients. These data suggest epirubicin may have greater cardiotoxicity than initially suggested [126]. A large systematic literature review found inadequate evidence to indicate that epirubicin was less cardiotoxic than doxorubicin at equimolar doses [127].

Unfortunately, treatment of anthracycline-induced cardiotoxicity, once developed, is less then optimal. Use of ACE inhibitors produces a transient improvement in heart function but heart failure redevelops after 2–6 years of ACE therapy [128]. New solutions to the problem of anthracycline cardiotoxicity continue to be evaluated [129].

Acute myeloid leukemia is a rare but serious complication of anthracycline-based chemotherapy (see Sections 2.1 and 4). Crump et al. found the probability of secondary acute leukemia to be 1.7% among 539 breast cancer patients treated with epirubicin [130]. In a large, retrospective review, AML/MDS was seen in 0.6% of 9796 breast cancer patients receiving adjuvant epirubicin [131]. The risk of AML/MDS increased in relationship to the dose of epirubicin per cycle and the cumulative dose of epirubicin is given.

3.4. *Pharmacology*

The anthracyclines have many similar pharmacokinetic properties. Anthracycline elimination occurs primarily through hepatic metabolism and biliary excretion. Urinary exertion of intact drug accounts for less than 10% of anthracycline clearance. Hepatic dysfunction (or obstruction) results in higher rates of mucositis and myelosuppression, but not increased cardiotoxicity [132]. Anthracycline pharmacokinetics are highly variable, with an almost 10-fold inter-patient variation in the AUC despite standardization of the dose based on body surface area [132,133]. Normalization for body surface area reduces variability by less than 2% [133]. Decreased doxorubicin distribution and clearance has been noted in elderly patients in some studies [126] but not others [134]. Greater toxicity was reported in patients receiving 60 mg/m^2 liposomal doxorubicin in patients over 70 compared to younger patients [135]. Doxorubicin metabolites accumulate in ascites and are cleared more slowly from the peritoneal compartment than from serum [136]. This delayed metabolite clearance has the potential to increase toxicity in patients with large third space fluid collections.

Anthracyclines are metabolized to 13-dihydro (alcohol) derivatives that are more toxic than the parent compounds. Doxorubicinol is twice as cardiotoxic as doxorubicin, and daunorubicinol is six times more cardiotoxic than daunorubicin [137]. Daunorubicin and idarubicin are more rapidly metabolized to their alcohol metabolite than are doxorubicin or epirubicin. The 13-dihydro anthracycline derivatives have minimal cytotoxicity except for idarubicinol. Samuel has suggested that parent drug contributes nearly all of the cardiotoxicity resulting from doxorubicin administration, but daunorubicin only causes about 25% of cardiac damage with daunorubicinol causing the remaining 75% [137].

Two FDA-approved liposomal formulations of doxorubicin, Doxil and Myocet, and one of daunorubicin, daunoxone, are currently available. Liposomal encapsulation extends the duration of drug exposure and alters the pharmacodynamic properties of anthracyclines [138–140]. The nature and extent of these alterations depends on the lipids used in the liposome formulation. Myocet carries doxorubicin in phosphatidylcholine and cholesterol while Doxil (Caelyx in Europe and Canada) utilizes pegylated lipids. Myocet releases half of its doxorubicin within 1 h and 90% within 24 h. In contrast, Doxil releases less than 10% of doxorubicin within 24 h (half-life of 45–90 h). The change in drug release alters the toxicity profile. Myocet causes myelosuppression and mucositis while Doxil therapy produces palmar-plantar erythrodysesthesia and mucositis. Less than 12% of a dose of pegylated liposomal doxorubicin is excreted in the urine. However, in a retrospective review, patients with renal insufficiency receiving pegylated doxorubicin had greater mucocutaneous and hematologic toxicity than expected [141].

Daunoxone has dose-limiting toxicity of febrile neutropenia [142]. Liposomal daunorubicin has a half-life of 5.3 h with low concentrations of daunorubicin and daunorubicinol persisting in plasma for 72 h following daunoxone administration [143]. Liposomal daunorubicin has markedly different pharmacokinetics compared to standard daunorubicin. First, liposomal encapsulated daunorubicin produces mean plasma AUC levels 100–200-fold those seen with regular daunorubicin at comparable doses due to decreased total body clearance. Second, the volume of distribution at steady state is 200–500-fold lower than for the non-liposomal drug. The plasma AUC of daunorubicinol is similar or greater than that of free daunorubicin for comparable doses.

Several important drug interactions affecting anthracycline kinetics and toxicity are important to recognize. When

paclitaxel is given prior to doxorubicin, the peak doxorubicin plasma concentrations increase significantly, drug clearance is reduced, and increased cardiotoxicity is noted as compared to the opposite sequence [144]. This interaction is caused by taxane inhibition of PgP-mediated anthracycline clearance. Effects on doxorubicin kinetics are noted up to 24 h after paclitaxel administration. The use of paclitaxel prior to epirubicin also results in increased myelosuppression and increased AUC of epirubicin and metabolites [145].

Epirubicin is inactivated via formation of epirubicin glucuronide. The specific UDP-glucuronosyltransferase (UGT) responsible for this inactivation is UGT2B7 [146]. Fortunately, currently recognized polymorphisms in UGT2B7 do not affect the rate of epirubicin glucuronidation. The amount of UGT2B7 present in hepatic microsomes increases with age which could result in increased epirubicin toxicity in very young children [147]. Epirubicin can be safely given to patients with chronic renal failure on dialysis [148]. Plasma, tumor and subcutaneous tissue concentrations of epirubicin have been measured following intravenous drug delivery. Mean epirubicin exposure in subcutaneous tissue is similar to that found in tumor tissue. However, C_{max} and AUC values in tissues are only 1% and 11%, respectively, of plasma values [149].

3.5. *Clinical uses*

Anthracyclines continue to be used to treat a wide variety of neoplasms including breast cancer, lymphoma, Kaposi's and soft tissue sarcomas, ovarian cancer, and leukemia. Higher doxorubicin plasma concentrations and AUCs have been correlated with an increased frequency of induction of complete remission in children with acute myeloid leukemia [150]. Doxorubicin is the most commonly used anthracycline. No anthracycline analogues have been found to be superior to doxorubicin in the treatment of solid tumors [151]. Epirubicin is an epimer of doxorubicin. It has similar antineoplastic activity compared with doxorubicin and is used primarily as therapy for breast cancer.

Daunorubicin has minimal activity in solid tumors, but it is an important agent for therapy of acute leukemias [152]. Idarubicin is an analogue of daunorubicin used primarily in AML therapy. While there has been some suggestion that idarubicin may have a survival advantage compared with daunorubicin, the actual differences in survival are minimal. Idarubicin has significant oral bioavailability [153]. Oral idarubicin use has been evaluated in elderly patients with AML [154] and showed high toxicity and lack of efficacy in this patient population.

Liposomal encapsulated doxorubicin (Doxil, Caelyx) has activity against breast cancer [155,156], Kaposi's sarcoma, head and neck cancer [157], ovarian cancer [158], and prostate cancer [159]. Liposomal doxorubicin is not active against recurrent SCLC [160], hepatocellular cancer [161], endometrial cancer [162], pancreatic cancer [163], gastric cancer [164], or advanced colorectal carcinoma [165].

An aerosolized formulation of doxorubicin has been developed in an attempt to find a delivery method with less systemic toxicity for treatment of pulmonary metastasis. In a recently reported Phase I trial [166], no systemic drug toxicity was noted up to an inhaled dose of 9.4 mg/m^2 doxorubicin. However, dose limiting pulmonary toxicity was noted at an inhaled dose of 9.4 mg/m^2.

4. Mitoxantrone

Mitoxantrone is an anthracenedione that targets topoisomerase II. It is the only agent of its class approved for clinical use [167]. Mitoxantrone lacks the ability to form the quinone-type free radicals thought to account for anthracycline cardiotoxicity. It has been purported, but not demonstrated, to have less cardiac toxicity than anthracyclines at equivalent cytotoxic doses.

4.1. *Mechanism of action*

Mitoxantrone binds to topoisomerase II resulting in cleavable complexes that induce DNA strand breaks. Mitoxantrone's poisoning of topoisomerase II, with resultant DNA damage, is a critical signal for NF-kappa B activation and induction of apoptosis [168]. Induction of apoptosis requires the integrity of functional DNA-damage response genes [169].

4.2. *Drug resistance*

Mitoxantrone resistance can develop through several mechanisms: altered topoisomerase II activity, decreased intracellular drug accumulation, increased glucuronidation, and altered nuclear/cytoplasmic distribution of drug [170]. An ABC half-transporter mitoxantrone efflux pump (also termed BCRP, MXR or ABCP) is located on chromosome 4q22 [171]. Transcription of this gene results in 2.4-kb mRNA encoding a 655-amino acid polypeptide localized to the plasma membrane [172]. Increased expression of the MXR/BCRP/ABCP is found in clinical samples from patients with relapsed or refractory acute myeloid leukemia [173]. Several immunosuppressants (cyclosporin, tacrolimus, and sirolimus) inhibit BCRP and can potentiate the cytotoxicity of mitoxantrone [174]. Selected flavonoids are also inhibitors of BCRP [175]. Mitoxantrone cellular transport is also mediated by other transport proteins such as MPR-1 and ABCB1 (MDR1) [176].

4.3. *Pharmacology*

Mitoxantrone is highly protein bound (78%) with a large volume of distribution 1000–4000 l/m^2 [177]. Hepatic metabolism is the primary mechanism for clearance [178] with 6–11% of mitoxantrone being cleared by the kidney. No adjustment in dosage is necessary for mild to moderate renal dysfunction. Hepatic dysfunction likely leads to increased AUC due to decreased drug elimination but firm data are lacking. Inhibition of PgP by cyclosporine decreases mitoxantrone clearance by 42% [179].

4.4. *Toxicity*

The primary dose-limiting toxicity of mitoxantrone is myelosuppression. Other potential toxicities include nausea, vomiting, alopecia, and cardiotoxicity. At doses that produce equivalent nadirs in WBC and platelet counts (75 mg/m^2 of

doxorubicin vs. 15 mg/m^2 of mitoxantrone), nausea, vomiting and alopecia are less frequent with mitoxantrone than with doxorubicin [180]. With commonly used dosages, approximately twice as much mitoxantrone can be given before heart failure develops when compared with doxorubicin. The incidence of heart failure in patients receiving a mean dose of 60 mg/m^2 mitoxantrone is less than 0.2% [181]. Although mitoxantrone is believed to be associated with reduced cardiotoxicity, because of the methodological limitations of reported studies, the exact risk factors for and incidence of mitoxantrone cardiotoxicity remain unclear [182].

Mitoxantrone may be more leukemogenic than anthracyclines [183]. The relative risk of AML or myelodysplasia (MDS) was 15.6 for breast cancer patients treated with mitoxantrone compared to a matched untreated control. The relative risk for breast cancer patients treated with anthracyclines was 2.7. Saso et al. [184] have estimated an actuarial risk of leukemia development at 1.1 and 1.6%, 5 and 10 years following treatment with mitoxantrone (10 times the risk of general population). The incidence of acute myeloid leukemia in patients treated with mitoxantrone as a single chemotherapy agent for multiple sclerosis was estimated to be only 0.07% in another study [185].

Acute promyelocytic leukemia (APL) is a secondary cancer associated with chemotherapy treatment of breast cancer [186]. Mitoxantrone use has been implicated in half of these APL cases. Most cases are associated with a 15:17 chromosomal translocation [187]. Mitstry et al. demonstrated that mitoxantrone therapy results in clustering of chromosomal breakpoints within an 8-bp region of the PML gene [187]. This mitoxantrone-related PML hotspot corresponds to a preferred site of topoisomerase II-mediated cleavage. Doxorubicin and etoposide also induce topoisomerase II to cleave at this APL hotspot. However, etoposide (as mentioned earlier) is most often associated with MLL translocations while mitoxantrone is associated with treatment related APL. This suggests that different topoisomerase II-directed chemotherapeutic agents predispose patients to different chromosomal translocations.

4.5. *Clinical uses*

Mitoxantrone is used primarily in therapy for breast cancer, leukemia, lymphoma and prostate cancer. Because of the anticipated reduced toxicity with mitoxantrone as compared to doxorubicin, mitoxantrone has been incorporated into selected chemotherapy regimens for patients with a poor performance status who are believed to be at significant risk for doxorubicin toxicity. In most selected head to head comparisons, response rates, and survival seem to be similar when mitoxantrone is substituted for doxorubicin [188]. Mitoxantrone has been evaluated in several unique clinical scenarios. Mitoxantrone has demonstrated activity in elderly and poor prognosis AML patients. However, mitoxantrone offers no advantage over other anthracyclines [189]. High dose mitoxantrone is no more effective than standard drug doses in treatment of breast cancer [190]. Mitoxantrone and prednisone for hormone-refractory prostate cancer delays disease progression and improves quality of life without altering survival. Mitoxantrone has been used for therapy of multiple sclerosis [191].

5. Novel topoisomerase II inhibitors

Novel topoisomerase II inhibitors are being investigated for their potential as clinically useful antineoplastic agents. The bisdioxopiperazines (ICRF-193, ICRF-187 [dexrazoxane], merbarone, and aclarubicin) are compounds that block the catalytic activity of DNA topoisomerase II but do not stabilize the DNA–topoisomerase II cleavable complex. ICRF-193 results in an accumulation of closed clamp conformations of topoisomerase II on DNA interfering with DNA transcription [192].

Drugs that potentially inhibit both topoisomerase I and topoisomerase II enzymes include intoplicin, TAS-103, XR5000, triterpenoids and F11782 [193]. F11782 inhibits catalytic activity of the topoisomerases without interacting with DNA, which gives it a novel mechanism of action [194]. TAS-103 is primarily a topoisomerase II inhibitor but may have minimal activity against topoisomerase I [195]. A Phase I trial of TAS-103 found the primary toxicity of this drug to be myelosuppression [196].

Several other classes of compounds including makaluvamines [197], bioflavonoids (flavones, favonols, and isoflavones) [198], nitrofurans (thanatop) [199], quinoxaline (XK469) [200], and radicol (also an inhibitor of heat shock protein) [201] have been identified as inhibitors of topoisomerase II. The clinical activity of these compounds has yet to be determined.

Several analogs of the anthracyclines are in various stages of clinical development. PNU-159548, an alkycycline daunorubicin derivative, has demonstrated antineoplastic activity in animal models with reduced cardiotoxicity compared to doxorubicin [202]. Ethonafide is an anthracene-containing derivative of amonafide which inhibits topoisomerase II and may have less toxicity than other anthracene-containing agents [203]. Amirubicin, a synthetic 9-aminoanthracycline, has been approved for clinical use in Japan for the treatment of lung cancer [204]. The hydroxyl metabolite of this agent, amirubicinol, has significant cytotoxicity and accounts for 15% of parent drug clearance.

Since several topoisomerase II inhibitors have demonstrated significant antineoplastic activity against a variety of cancers in man, continued studies looking at new agents that target this enzyme will undoubtedly be performed. Hopefully, agents with even greater activity or less toxicity will be identified from these investigations.

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