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A REVIEW OF HUMAN CARCINOGENS

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ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer

World Health Organization

ETOPOSIDE IN COMBINATION WITH CISPLATIN AND BLEOMYCIN

Etoposide, cisplatin, and bleomycin were considered by a previous IARC Working Group in 1999 (IARC, 2000). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

1.1.1 Etoposide

Chem. Abstr. Serv. Reg. No.: 33419-42-0
Chem. Abstr. Name: Furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one, 9-[4,6-*O*-(1*R*)-ethylidene-*β*-D-glucopyranosyl]oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-, (5*R*,5a*R*,8a*R*,9*S*)-
IUPAC Systematic Name: Furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one, 9-[(4,6-*O*-ethylidene-*β*-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)
Synonyms: Celltop; Etopophos; Eposin; furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one, 9-[(4,6-*O*-ethylidene-*β*-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-, [5*R*-[5a,5ab,8aa,9b(*R**)]]-; 4′-demethyl-1-*O*-[4,6-*O*-(ethylidene)-*β*-D-glucopyranosyl]epipodophyl-lotoxin; 4′-demethylepipodophyllotoxin 9-(4,6-*O*-ethylidene-*β*-D-glucopyranoside); 4′-demethylepipodophyllotoxin ethylidene-*β*-D-glucopyranoside; Toposar; Vepesid(e); pyrano[3,2-*d*]-1,3-dioxin, furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one deriv.
Description: White to yellow-brown crystalline powder; white to off-white crystalline powder [phosphate salt] (McEvoy, 2007)

(a) *Structural and molecular formulae, and relative molecular mass*
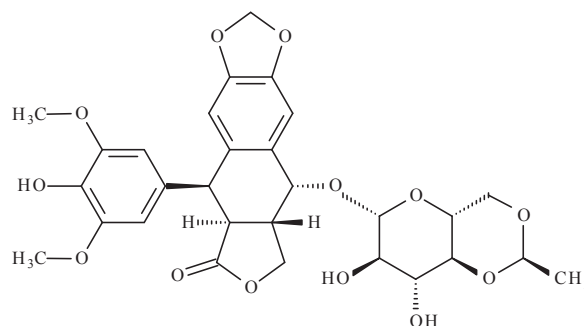
$C_{29}H_{32}O_{13}$
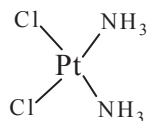Relative molecular mass: 588.6

1.1.2 Cisplatin

Chem. Abstr. Serv. Reg. No.: 15663-27-1
Chem. Abstr. Name: Platinum, diam-minedichloro-, (SP-4–2)-
IUPAC Systematic Name: Azane; dichloroplatinum
Description: Yellow to orange crystalline powder ([McEvoy, 2007](#))

(a) Structural and molecular formulae, and relative molecular mass

$Cl_2H_6N_2Pt$
Relative molecular mass: 300.0
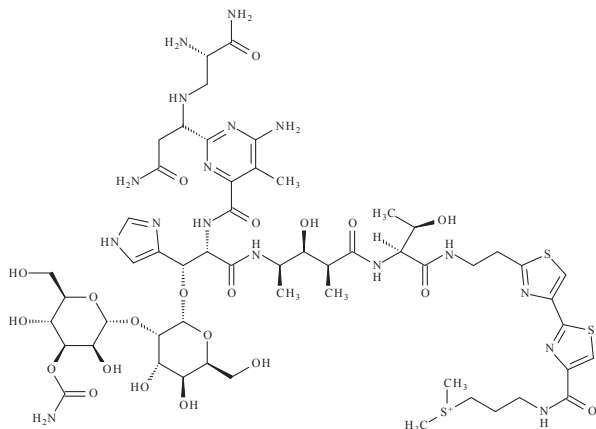
1.1.3 Bleomycin

Chem. Abstr. Serv. Reg. No.: 11056-06-7
Chem. Abstr. Name: Bleomycin
IUPAC Systematic Name: Bleomycin
Description: Cream-coloured, amorphous powder [sulfate salt] ([McEvoy, 2007](#))

(a) Structural and molecular formulae, and relative molecular mass

$C_{55}H_{84}N_{17}O_{21}S_3$
Relative molecular mass: 1415.6

1.2 Use of the agents

Information for Section 1.2 is taken from [McEvoy (2007)](#), [Royal Pharmaceutical Society of Great Britain (2007)](#), and [Sweetman (2008)](#).

1.2.1 Etoposide

(a) Indications

Etoposide is a semisynthetic derivative of podophyllotoxin with antineoplastic properties; it interferes with the activity of topoisomerase II, thus inhibiting DNA synthesis, and is most active against cells in the late S- and G_2-phases of the cell cycle. It is used, usually in combination with other antineoplastics, in the treatment of tumours of the testis, small cell cancer of the lung, and in acute leukaemias.

(i) Testicular neoplasms

Etoposide or etoposide phosphate may be used intravenously as a component of various chemotherapeutic regimens for the treatment of refractory testicular tumours in patients who have already received appropriate surgery, chemotherapy, and radiation therapy. Etoposide alone can be used in the treatment of disseminated non-seminomatous testicular carcinoma (Stage III), and in patients whose disease is refractory to cisplatin-containing combination chemotherapy. Cisplatin-containing combination chemotherapy regimens are used as initial therapy in patients with Stage III or unresectable Stage II non-seminomatous testicular carcinoma. For the initial treatment of advanced non-seminomatous testicular carcinoma, regimens containing cisplatin and bleomycin, in combination with etoposide, are used.

(ii) Cancer of the lung

Etoposide has been widely used for the treatment of lung cancer. Etoposide is used intravenously (either as etoposide or etoposide phosphate) in combination chemotherapy regimens for the treatment of small cell lung

carcinoma; etoposide also has been used orally, either alone or as a component of combination therapy for this cancer. Furthermore, etoposide has been used in conjunction with a platinum agent (i.e. cisplatin or carboplatin) and ifosfamide with mesna.

Etoposide is also used as part of first- or second-line combination chemotherapy regimens for the treatment of non-Hodgkin lymphoma, Hodgkin lymphoma, acute myeloid leukaemia, a variety of paediatric solid tumours, acute lymphocytic leukaemia, and in high-dose conditioning programmes before haematopoietic stem-cell transplantation.

(b) Dosage

Etoposide is administered orally and by slow intravenous infusion. Etoposide phosphate is administered by intravenous infusion.

The usual intravenous dose of etoposide ranges from 50–120 mg/m^2 daily for 5 days. Alternatively, 100 mg/m^2 has been given on alternate days to a total of 300 mg/m^2. The usual oral dose of etoposide is 100–240 mg/m^2 daily for 5 consecutive days. Courses may be repeated after 3–4 weeks.

Etoposide is available as a 50 mg liquid-filled capsule and as 100, 150, 200, 250, 500 mg and 1 g (20 mg/mL) solutions for injection concentrates and for intravenous infusion. Etoposide phosphate is available as 500 mg and 1 g (of etoposide) solutions for injection, and 100 mg (of etoposide) solutions for injection and intravenous infusion.

(c) Trends in use

No information was available to the Working Group.

1.2.2 Cisplatin

(a) Indications

The antineoplastic cisplatin is a platinum-containing complex that may act similarly to the alkylating agents. Its antineoplastic actions are cell-cycle non-specific and are dependent upon its *cis* configuration; they appear to be related to its hydrolysis in the body to form reactive hydrated species. Although it causes immunosuppression, stimulation of the host immune response against the tumour has been suggested as contributing to cisplatin's antineoplastic action.

Cisplatin is used in the treatment of tumours of the testis, usually as a major component of combination chemotherapy regimens, and particularly with bleomycin and etoposide (BEP), or with bleomycin and a vinca alkaloid. It is also used to treat metastatic ovarian tumours, cervical tumours, lung cancer, advanced bladder cancer, and squamous cell carcinoma of the head and neck.

(b) Dosage

Lower doses are generally used for combination chemotherapy regimens than in single agent therapy; 20 mg/m^2 or more is given once every 3–4 weeks. A dose of 20 mg/m^2 daily for 5 days every 3–4 weeks has been used in combination chemotherapy for the treatment of testicular tumours.

Various analogues of cisplatin have been developed or investigated including those with fewer adverse effects (e.g. carboplatin, nedaplatin), an altered spectrum of activity (oxaliplatin), or activity on oral dosage (satraplatin).

Various adjustments to the administration of cisplatin have been suggested in an attempt to improve its effectiveness while reducing its toxicity.

Toxicity is reported to be reduced when cisplatin is given by continuous intra-arterial or intravenous infusion. It has also been suggested that giving cisplatin in the evening rather than in the morning results in less damage to renal function, apparently because of circadian variations in urine production. However, another study found that morning, rather than evening, doses of cisplatin resulted in less renal damage.

(c)   Trends in use

No information was available to the Working Group.

1.2.3 Bleomycin

(a)   Indications

Bleomycin is an antineoplastic antibiotic that binds to DNA and causes strand scissions, and is probably most effective in the G_2- and M-phases of the cell cycle. It is used to treat malignant disease particularly squamous cell carcinomas, including those of the cervix and external genitalia, oesophagus, skin, and head and neck; Hodgkin lymphoma and other lymphomas; malignant neoplasms of the testis and malignant effusions. It has also been tried in other malignancies, including carcinoma of the bladder, lung, and thyroid, and some sarcomas, including Kaposi sarcoma.

Bleomycin is often used with other antineoplastics, with etoposide and cisplatin (BEP) in testicular tumours, and with doxorubicin, vinblastine, and dacarbazine (ABVD) for Hodgkin lymphoma. Bleomycin is given as the sulfate by either the intramuscular, intravenous, or subcutaneous route. It may also be given intra-arterially or instilled intrapleurally or intraperitoneally. Bleomycin hydrochloride has also been given parenterally for malignant neoplasms, and bleomycin sulfate has been applied topically for the local treatment of skin tumours.

(b)   Dosage

Doses are calculated in terms of the base, and are given in units, but the units used for preparations in the United Kingdom, which were formerly equivalent to those of the United States Pharmacopoeia (USP), are now international units equivalent to those of the European Pharmacopoeia. Because 1000 international units is equivalent to 1 USP unit, the United Kingdom doses now appear to be a thousand times greater than those previously in use, or than those in use in the Unites States of America, and care is recommended in evaluating the literature.

In the United Kingdom, the licensed dose as a single agent for squamous cell or testicular tumours is 15000 international units (15 USP units) three times a week, or 30000 international units twice a week, by intramuscular or intravenous injection, although in practice, treatment of malignancy will generally be with combination regimens. This may be repeated, at usual intervals of 3–4 weeks, up to a total cumulative dose of 500000 international units. The dose and total cumulative dose should be reduced in those over 60 years of age (see below). Continuous intravenous infusion at a rate of 15000 international units per 24 hours for up to 10 days or 30000 international units per 24 hours for up to 5 days may also be used. In patients with lymphoma, a dose of 15000 international units once or twice weekly by intramuscular injection has been suggested, to a total dose of 225000 international units. Dosage should be reduced in combination regimens if necessary. In the treatment of malignant effusions, a solution of 60000 international units in 100 mL of 0.9% sodium chloride may be instilled into the affected serous cavity. Treatment may be repeated as necessary up to a total cumulative dose of 500000 international units depending on the patient's age.

In the USA, licensed doses for lymphomas as well as squamous cell and testicular neoplasms are 250–500 international units/kg (0.25–0.5 USP units/kg), or 10000–20000 international units/m^2 (10–20 USP units/m^2), given once or twice weekly. In view of the risk of an anaphylactoid reaction, it has been suggested that patients with lymphomas should receive two test doses of 2000 international units (2 USP units) or less initially. In patients with Hodgkin lymphoma, once a 50% response has been achieved it may be maintained with 1000 international units (1 USP unit) of bleomycin daily, or 5000 international units (5 USP units) weekly.

In the United Kingdom, licensed product information suggests that a total dose of 500000 international units (500 USP units) should not be exceeded. Total cumulative dose should not exceed 300000 international units in patients aged 60–69 years, 200000 international units in those aged 70–79 years, and 100000 international units in those aged 80 years and over; the weekly dose should be no more than 60000, 30000, and 15000 international units, respectively. In the USA, the maximum total dose is 400000 international units (400 USP units); it is generally agreed that patients receiving 400000 international units or more are at increased risk of pulmonary toxicity.

Dosage should be reduced in patients with renal impairment.

(c)   Trends in use

No information was available to the Working Group.

2. Cancer in Humans

A previous *IARC Monograph* ([IARC, 2000](#)) reviewed studies of cancer in humans following exposure to etoposide, and concluded that the combination of etoposide, bleomycin and cisplatin was carcinogenic, causing acute myeloid leukaemia in humans; but was unable to draw a separate conclusion about the carcinogenicity of etoposide alone ([Table 2.1](#)).

In the current evaluation, a large number of cohort studies published in the 1990s were re-assessed ([Ratain *et al.*, 1987](#); [Pedersen-Bjergaard *et al.*, 1991](#); [Pui *et al.*, 1991](#); [Curtis *et al.*, 1992](#); [Bajorin *et al.*, 1993](#); [Bokemeyer & Schmoll, 1993](#); [Nichols *et al.*, 1993](#); [Smith *et al.*, 1993](#), [1999](#); [Sugita *et al.*, 1993](#); [Winick *et al.*, 1993](#); [Haupt *et al.*, 1994](#), [1997](#); [Heyn *et al.*, 1994](#); [Bokemeyer *et al.*, 1995](#); [Boshoff *et al.*, 1995](#); [Parkin *et al.*, 1997](#); [Duffner *et al.*, 1998](#); [Kollmannsberger *et al.*, 1998](#); [Yagita *et al.*, 1998](#)). A cumulative total of over 50 cases of acute myeloid leukaemia or myelodysplatic syndromes were reported in patients who had received etoposide for the treatment of a range of malignant diseases. These studies generally reported substantial increases (of the order of 10- to 100-fold) in the incidence of leukaemia compared to general population rates, as well as increases in leukaemia incidence with higher intensity administration of etoposide. [The Working Group noted that interpretation of many of these studies was limited by the difficulty in distinguishing the role of etoposide from that of other potentially leukaemogenic agents that had been received by the patients in the studies. However, in several studies, other agents involved in treatment of participating patients were recognized as being non-leukaemogenic.]

In an Italian study of patients treated for Langerhans cell histiocytosis ([Haupt *et al.*, 1994](#), [1997](#)), a large increased risk of acute myeloid leukaemia, based on five cases, was found after treatment with etoposide alone, or in combination with agents that are not recognized to cause leukaemia.

In cohort studies of germ-cell tumours in men, treatment with etoposide, cisplatin and bleomycin was associated with an increased risk for acute myeloid leukaemia ([Pedersen-Bjergaard *et al.*, 1991](#); [Bajorin *et al.*, 1993](#); [Bokemeyer & Schmoll, 1993](#); [Nichols *et al.*, 1993](#); [Bokemeyer *et al.*, 1995](#); [Boshoff *et al.*, 1995](#); [Kollmannsberger *et al.*, 1998](#)). On the basis of the data from these studies, the Working Group estimated a relative risk for acute myeloid leukaemia approximately 40 times greater than that of the general population.

A large increased risk for acute myeloid leukaemia was also found in one cohort study of lung cancer patients treated with etoposide, cisplatin and vindesine ([Ratain *et al.*, 1987](#)).

[Table 2.2](#) shows results from a case–control study investigating 61 cases of leukaemia or myelodysplastic syndromes following solid

Table 2.1 Cohort studies of the risk for secondary acute myeloid leukaemia or myelodysplastic syndromes after treatment of germ-cell tumours with etoposide-containing regimens

Reference Study location	Study Population	Cumulative dose of etoposide (mg/m²)	No. of patients	Additional chemotherapy or radiotherapy	No. of observed cases	Follow-up period (yr)	Relative risk (95%CI) for AML or MDS	Cumulative incidence (95%CI) for AML or MDS	Comments
Pedersen-Bjergaard et al. (1991) Denmark	212 men diagnosed in 1979–89	1800–3600		Cisplatin, bleomycin	5 (4 AML, 1 MDS)	5.7	336 (92–861) (AML)	4.7% (SE, 2.3) at 5.7 yr (AML + MDS) 11% (SE, 5.0) at 5.7 yr (AML)	
		1800–2000	130		0				
		2000–3600	82		5				
Bajorin et al. (1993) New York, USA	340 men diagnosed in 1982–90	800–5000		Cisplatin, cyclophosphamide	2 (AML)	≥ 5	NR	< 1% at 5 yr for 1 AML who received etoposide only	1 case also received cyclophosphamide
Bokemeyer & Schmoll (1993) Germany	293 men diagnosed in 1970–90	≤ 2000	221	Cisplatin, bleomycin, vinblastine, anthracyclines, dactinomycin, ifosfamide	3 (1 ALL, 2 solid tumours)	Median, 5.1	2.3 (0.1–13)	1.0% (0.0–2.2) at 5 yr	SMR for etoposide-treated patients
		> 2000	72		0				
Nichols et al. (1993) Indiana, USA	538 men diagnosed in 1982–91	1500–2000		Cisplatin, bleomycin, ifosfamide	2 (AML)	Median, 4.9	66 (8–238)	NR [< 1% at 5 yr for AML]	3 cases observed in another group [size unknown] of patients treated with 2000 mg/m² (n=2) and 4400 mg/m² (n=1) etoposide
Bokemeyer et al. (1995) Germany	128 men diagnosed in 1983–93	Median cumulative dose:			1 (AML)	Median, 4.5	[30–35] (NS)	0.8% (0–2.3) at 4.5 yr	Etoposide-treated patients; possible overlap with study by Bokemeyer & Schmoll (1993)
		3750	22	Cisplatin, bleomycin, ifosfamide	1 (AML)	6.1			
		3800	50	Cisplatin, bleomycin	0	5.2			
		3800	41	Cisplatin, ifosfamide	0	3.4			
		5300	15	Carboplatin, ifosfamide, autologous stem-cell rescue	0	2.3			

Table 2.1 (continued)

Reference Study location	Study Population	Cumulative dose of etoposide (mg/m²)	No. of patients	Additional chemotherapy or radiotherapy	No. of observed cases	Follow-up period (yr)	Relative risk (95%CI) for AML or MDS	Cumulative incidence (95%CI) for AML or MDS	Comments
Boshoff et al. (1995) United Kingdom	679 men diagnosed in 1979–92	720–5000		Vincristine, methotrexate, cisplatin, bleomycin, actinomycin D, cyclophosphamide, vinblastine, carboplatin	6 AML, 4 solid tumours	Median, 5.7; 2 ($n = 541$); > 5 ($n = 331$)	150 (55–326) based on 3 cases who received 7-agent regimen	NR	Mediastinal germ cell-cancer patients included in patient population but none of them developed secondary tumour
		≤ 2000	636		4 (AML)				
		> 2000	25		2 (AML)				
Kollmannsberger et al. (1998) Germany, France	302 men, 15–55-yr old diagnosed in 1986–96	2400–14000			4 AML, 2 MDS in mediastinal germ-cell cancer patients	Median, 4.3	SIR, 160 (44–411)	1.3% (0.4–3.4) at 4.3 yr	Mediastinal germ-cell cancer patients included in patient population
		First-line therapy, 2400–6000	141	Cisplatin, ifosfamide, autologous stem-cell support	2 (AML)	3.5			161 patients included after failing first-line therapy
		2400–14000	161	Cisplatin, cyclophosphamide, ifosfamide, carboplatin, autologous stem-cell support	2 (AML)	4.8–5.6			

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; MDS, myelodysplastic syndromes; NR, not reported; NS, not significant; SE, standard error; SIR, standardized incidence ratio; SMR, standardized morbidity ratio; yr, year or years

Table 2.2 Case–control study of secondary leukaemia and treatment of primary tumour with etoposide-containing regimen

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assess-ment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95%CI)	Adjustment for potential con-founders	Comments
Le Deley et al. (2003) France 1980–99	61 patients with leukaemia or MDS following first malignancy after 1980	196 controls patients with cancer but no secondary leukaemia matched by age, sex, year of diagnosis of first cancer and minimum survival	Medical records	Leukaemia	< 1.2 g/m^2 etoposide and < 170 mg/m^2 anthracyclines	8	1.0 (ref)	Type of first tumour, dose of anthracyclines	Exposure to etoposide alone not provided
					More in one or the other category	42	7 (2.6–19)		

CI, confidence interval; MDS, myelodysplastic syndromes; ref, reference

tumours among children in France (Le Deley et al., 2003). The risk for leukaemia increased strongly with cumulative dose of etoposide in multivariate analyses.

3. Cancer in Experimental Animals

As per the previous IARC evaluation of etoposide (IARC, 2000), a single study was evaluated. The incidence of leukaemia was not increased in wild-type ($Nf1^{+/+}$) and heterozygous ($Nf1^{+/−}$) neurofibromatosis-1 ($Nf1$) gene knockout 129/Sv mice treated by gastric intubation for 6 weeks with 100 mg/kg body weight/week etoposide (Mahgoub et al., 1999).

Bleomycin and cisplatin were each evaluated in previous *IARC monographs*. In animals, there was *limited evidence* for the carcinogenicity of bleomycin in animals, and *sufficient evidence* for the carcinogenicity of cisplatin (IARC, 1987a).

4. Other Relevant Data

Etoposide, cisplatin and bleomycin have very different profiles in terms of cellular uptake and generation of potentially cytotoxic lesions, but all three have actions that result in DNA damage leading to carcinogenicity.

4.1 Absorption, distribution, metabolism, and excretion

The general pharmacology of etoposide has been reviewed in Hande (1992). It is highly protein-bound in plasma with a free plasma fraction of approximately 6%, and its uptake into cells, which occurs by passive diffusion, is relatively slow (Tannock et al., 2002). In contrast, efflux can be driven by active outward transport mechanisms such as P-glycoprotein and members of the MRP (multidrug resistance

protein) family (Brock et al., 1995). The main intracellular target-binding proteins for etoposide are topoisomerase IIα and IIβ, and it is likely that the IIα isoenzyme is the more biologically important target (Errington et al., 1999). Studies using V79 cells have indicated that the distribution of topoisomerase IIα is highly dependent on its phosphorylation, and that phosphorylation promotes its location to the nucleus (Oloumi et al., 2000).

After intravenous administration, cisplatin is bound to plasma proteins, with the protein-bound drug thought to be biologically inactive (Johnsson et al., 1998), while the free drug is transported both in and out of cells by cupric ion transporters (Safaei & Howell, 2005). Inside the cell, cisplatin can react with protein sulfhydryl groups but is not sufficiently chemically reactive to react directly with DNA. Reaction with sulfhydryl groups of glutathione, however, makes it susceptible to the multidrug resistance transporter MRP2, which may also determine its intracellular concentration (Borst et al., 2000).

Bleomycin comprises a mixture of chemical entities that are strongly bound in biological fluids to divalent ions such as copper. It appears to be transported into the cell by high-affinity L-carnitine transporters (Aouida et al., 2004), but does not seem to be a substrate for P-glycoprotein-mediated efflux (Kang et al., 2000).

4.2 Mechanisms of carcinogenesis

4.2.1 Induction of DNA damage

Etoposide, once bound to topoisomerase IIα, does not impede the ability of this enzyme to form double-stranded breaks but does impede the religation of DNA (Osheroff, 1989), leading to the formation of a stabilized DNA–topoisomerase II complex. This complex can generate double-stranded DNA breaks. In addition, collision of advancing DNA replication fork with etoposide–topoisomerase complexes can

lead to the formation of double-stranded DNA breaks (Baldwin & Osheroff, 2005; Tanaka *et al.*, 2007).

Cisplatin, under the low chloride ionic environment within the cell, reacts with water and the resulting monohydrate form reacts with DNA, predominantly at the N^7 position of guanine (Go & Adjei, 1999; Wang & Lippard, 2005; Bell *et al.*, 2006). The remaining chloro ligand is also replaced by water and leads to reaction with a second purine; the most common complexes are d(GpG) and d(ApG) intrastrand complexes, with a smaller proportion of interstrand complex formation. The formation of a complex bends the double helix (Takahara *et al.*, 1995), and promotes the binding of a variety of proteins containing high-mobility group domains (Huang *et al.*, 1994). Subsequent events in human cells are still not completely clear.

Bleomycin, once inside the cell, binds to guanosine–cytosine-rich portions of DNA by partial intercalation of the bithiazole ring. A portion of the molecule binds to divalent metals including iron, the active ligand, and copper, an inactive ligand. Molecular oxygen is then converted to reactive oxygen species in an iron-catalysed reduction, which generate several DNA lesions (Burger, 1998). One type of lesion is a DNA double-strand break, while another is a DNA lesion, which upon DNA replication can lead to a double-strand DNA break. Bleomycin is less cytotoxic to cells that are in the G_1-phase of the cell cycle (Mirabelli & Crooke, 1981).

4.2.2 Mutational consequences of DNA damage

Interference with the ability of DNA polymerase to synthesize a cDNA strand, which is a function of all three of these drugs, is thought to lead to several effects including mutations, sister chromatid exchange, and chromosomal aberrations (Kaufmann, 1989). Each of these individual drugs (etoposide, cisplatin and bleomycin) induces sister chromatic exchange and aneuploidy (IARC, 1987b, 2000; Pommier *et al.*, 1988; Chibber & Ord, 1989; Au *et al.*, 2001; De Mas *et al.*, 2001; Cantero *et al.*, 2006). Of the three drugs, the strongest evidence for drug-induced cancer is provided by etoposide, which induces monocytic and myelomonocytic leukaemia through a specific chromosomal translocation (Kudo *et al.*, 1998), and this may be a general response to topoisomerase II poisons (Ferguson & Baguley, 1996).

Acute myeloid leukaemia develops in patients previously treated with epipodophyllotoxin-type topoisomerase II inhibitors such as etoposide and teniposide, and frequently exhibits distinctive characteristics that allow it to be distinguished from acute myeloid leukaemia induced by other agents (such as alkylating agents) or acute myeloid leukaemia that occurs spontaneously (Pedersen-Bjergaard & Rowley, 1994; Pedersen-Bjergaard *et al.*, 2006). The induced leukaemias are typically classified as the monocytic or myelomonocytic subtypes, have short latency periods of 2–3 years, and frequently exhibit balanced translocations involving the myeloid–lymphoid or mixed lineage leukaemia (*MLL*) gene (also known as acute lymphoblastic leukaemia-1 (*ALL-1*), human trithorax (*HRX*), and human homologue of *Drosophila* trithorax gene (*HTRX-1*)) located on the long arm of chromosome 11 (11q23). *MLL* encodes a transcription factor that plays a role in the regulation of haematopoietic development (Fidanza *et al.*, 1996; Hess *et al.*, 1997). Recent studies have shown that the four most common *MLL* translocation partner genes (*AF4*, *AF9*, *ENL*, and *AF10*) encode nuclear proteins that are part of a network involved in the methylation of lysine 79 of histone H3 proteins (H3K79 methylation) (Meyer *et al.*, 2006), indicating an important role for this pathway in induced leukaemias.

Approximately 85% of treatment-related leukaemia patients who exhibit 11q23 translocations have previously been treated with

topoisomerase-II-inhibiting drugs, primarily etoposide or anthracyclines (doxorubicin, daunorubicin) (Bloomfield *et al.*, 2002; Mauritzson *et al.*, 2002). Etoposide has also been shown to induce breakages, rearrangements, and translocations within the *MLL* gene in experimental systems (e.g., mouse embryonic stem cells and in haematopoietic CD34+ cells in culture, including human long-term repopulating haematopoietic stem cells) (Blanco *et al.*, 2004; Libura *et al.*, 2005, 2008; Sung *et al.*, 2006). This provides strong evidence of a causal link between etoposide exposure and *MLL* translocations in a crucial target cell for leukaemogenesis (Allan & Travis, 2005). In addition, topoisomerase II recognition sites are located close to the breakpoints in many of the treatment-related leukaemias seen in patients, providing additional evidence for the role of topoisomerase II in the formation of the translocations (Allan & Travis, 2005).

The ability of various *MLL* chimeric genes formed through translocation to transform mouse haematopoietic cells has been demonstrated by several investigators (Corral *et al.*, 1996; Dobson *et al.*, 1999; Lavau *et al.*, 2000; So *et al.*, 2003; Wang *et al.*, 2005). Upon expression of the chimeric gene or infusion of gene-expressing cells, the mice exhibited altered haematopoiesis, which progressed to more serious myeloproliferative disorders that mimicked the corresponding human disease. In most of these studies, the mice developed frank leukaemias (Corral *et al.*, 1996; Dobson *et al.*, 1999; Lavau *et al.*, 2000; Forster *et al.*, 2003; So *et al.*, 2003). However in one study (Wang *et al.*, 2005), treatment with a mutagenic agent such as γ-radiation or *N*-ethyl-*N*-nitrosourea was necessary for the manifestation of leukaemia.

4.3 Synthesis

Combined therapy with bleomycin, etoposide and cisplatin, a common form of chemotherapy for testicular germ-cell malignancies, has led not only to a large number of long-term survivors but also to a significant proportion of patients with secondary malignancies. Mechanistic studies of these three drugs have demonstrated that each is genotoxic, with evidence of induction of DNA damage, chromosomal aberrations, and aneuploidy. Etoposide is distinguished from the other two drugs by its ability to induce chromosomal translocations affecting the *MLL* gene, which are often seen in patients that develop therapy-related acute myeloid leukaemia.

Etoposide in combination with cisplatin and bleomycin is carcinogenic via a genotoxic mechanism.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of etoposide in combination with cisplatin and bleomycin. Etoposide in combination with cisplatin and bleomycin causes acute myeloid leukaemia.

There is *limited evidence* in humans for the carcinogenicity of etoposide alone.

There is *inadequate evidence* in experimental animals for the carcinogenicity of etoposide alone.

No data were available to the Working Group for the carcinogenicity of etoposide in combination with cisplatin and bleomycin in experimental animals.

Etoposide in combination with cisplatin and bleomycin is *carcinogenic to humans (Group 1)*.

Etoposide is *carcinogenic to humans (Group 1)*.

In making the overall evaluation of etoposide alone, the Working Group took into consideration the following:

• The acute myeloid leukaemias induced by drugs, including etoposide, that target topoisomerase II exhibit distinctive characteristics (i.e. morphology, latency, and karyotypes) that

allow them to be distinguished from leukaemias induced by alkylating agents.

• The high frequency of 11q23 translocations in the leukaemias associated with etoposide treatment and the localization of the breaks within the *MLL* gene, a gene involved in haematopoiesis.

• The clustering of the breakpoints within the *MLL* gene in the leukaemias induced by drugs that target topoisomerase II, and the presence of topoisomerase II recognition sites near these breakpoints.

• The ability of etoposide to induce breakages, rearrangements, and translocations within the *MLL* gene in model systems including long-term repopulating human haematopoietic stem cells, an important target cell for leukaemogenesis.

• The ability of the chimeric *MLL* genes resulting from 11q23 translocations to alter haematopoiesis, and to induce leukaemias in mice.

• The observations that bleomycin and cisplatin exert their genotoxic effects through mechanisms not involving inhibition of topoisomerase II.

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