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Cancer Chemotherapy and Biotherapy: Principles and Practice

FIFTH EDITION

Bruce A. Chabner, MD

Director of Clinical Research
Massachusetts General Hospital Cancer Center
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Dan L. Longo, MD

Division of Hematology
Brigham and Women's Hospital
Deputy Editor
New England Journal of Medicine
Boston, Massachusetts

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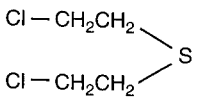
CHAPTER 14

Alkylating Agents

PART A: CLASSICAL ALKYLATING AGENTS

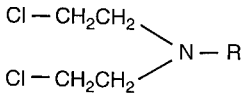
Stanton L. Gerson, Alina D. Bulgar, Lachelle D. Weeks, and Bruce A. Chabner

The alkylating agents are antitumor drugs that act through the covalent binding of alkyl groups to cellular molecules. This binding is mediated by reactive intermediates formed from a more parent alkylating compound. Historically, the alkylating agents have played an important role in the development of cancer chemotherapy. The nitrogen mustards mechlorethamine (HN_2, "nitrogen mustard") and tris(β-chloroethyl)amine (HN_3) were the first nonhormonal agents to show significant antitumor activity in humans.[1,2] The clinical trials of nitrogen mustards in patients with lymphomas evolved from the observation that lymphoid atrophy, in addition to lung and mucous membrane irritation, was produced by sulfur mustard during World War I. Antitumor evaluation[3] showed that the related but less reactive nitrogen mustards, the bischloroethylamines (Fig. 14A-1), were less toxic and caused regression of lymphoid tumors in mice. The first clinical studies produced dramatic tumor regressions in some patients with lymphoma, and the antitumor effects were confirmed by an organized multi-institution study.[1,2] This demonstration of efficacy encouraged further efforts to find chemical agents with antitumor activity, leading to the wide variety of antitumor agents in use today. Nonclassical alkylating agents include methylating agents such as procarbazine and temozolomide and are discussed later in this chapter. Alkylating agents, despite the enthusiastic development of targeted agents, continue to occupy a central position in cancer chemotherapy, both in conventional combination regimens and in high-dose protocols with hematopoietic cell transplantation (HCT). Because of their linear dose-response relationship in cell culture experiments,[4] these drugs have become primary tools used in HCT for a variety of diseases. Better appreciation of resistance mechanisms and development of targeting agents to block these resistance pathways promise to improve the efficacy of alkylating agents.



A

Bischloroethylsulfide (sulfur mustard).



B

Bischloroethylamine (nitrogen mustard general structure). —R = $—CH_3$ in mechlorethamine. —R = $—CH_2CH_2Cl$ in tris(β-chloroethyl)amine.

FIGURE 14A-1 Structures of bischloroethylsulfide and bischloroethylamine. **A.** Bischloroethylsulfide (sulfur mustard). **B.** Bischloroethylamine (nitrogen mus-

Alkylating Reactions

An alkylation reaction can occur by two mechanisms: S_N1 and S_N2. In S_N1 reactions, the rate-limiting step is the formation of a carbonium ion that can react rapidly with a nucleophile. This reaction follows first-order kinetics with a rate that depends solely on the concentration of the alkylating agent. In contrast, S_N2 reactions follow second-order kinetics and depend on the concentrations of both the alkylating agent and the nucleophile. Such reactions involve a transition-state entity formed by both reactants that decomposes to form the alkylated cellular constituent. Agents such as chloroethylnitrosoureas, through a S_N1-type of mechanism, can form covalent adducts with oxygen and nitrogen atoms in DNA. Compounds with S_N2 predominant mechanisms, such as busulfan, tend to react more slowly, with little alkylation of oxygen sites. Because alkylating agents are designed to produce reactive intermediates, the parent compounds typically have short elimination half-lives of less than 5 hours.

As a class, the alkylating agents share a common target (DNA) and are cytotoxic, mutagenic, and carcinogenic. The activity of most alkylating agents is enhanced by radiation, hyperthermia, nitroimidazoles, glutathione depletion, and inhibition of DNA repair. They differ greatly, however, in their toxicity profiles and antitumor activity. These differences are undoubtedly the result of differences in pharmacokinetic features, lipid solubility, ability to penetrate the central nervous system (CNS), membrane transport properties, detoxification reactions, and specific enzymatic reactions capable of repairing alkylation sites on DNA.[5-7] Application of techniques

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LE

A.1 *Key features of selected alkylating agents*

	Cyclophosphamide	Ifosfamide	Melphalan	BCNU	Busulfan	Bendamustine
hanism of action	All agents produce alkylation of DNA through the formation of reactive intermediates that attack nucleophilic sites.					
hanisms of esistance	Increased capacity to repair alkylated lesions, for example, guanine O^6-alkyl transferase (nitrosoureas, busulfan) Increased expression of glutathione-associated enzymes, including γ-glutamyl cysteine synthetase, γ-glutamyl transpeptidase, and glutathione-S-transferases Increased ALDH (cyclophosphamide) Decreased expression or mutation of p53					
e/schedule mg/m²)	400–2,000 IV	1,000–4,000 IV	8 PO qd × 5 d	200 IV	2–4 mg qd	70–100 mg daily, on day 1 and 2 of a 28-day cycle
	100 PO qd					
bioavailability	100%	Unavailable	30% (variable)	Not known	50% or greater	?
macokinetics	3–10 (parent)	7–15 (parent)	1 (parent)	0.25–0.75[a] (nonlinear increase with dose from 170 to 720 mg/m²)	2–3 h	0.5 (parent)
rimary elimination $t_{1/2}$ (h)	1.6 (aldophosphamide) 8.7 (phosphoramide mustard)					
abolism and xcretion	Microsomal hydroxylation activates, then chemical decomposition	Microsomal hydroxylation activates, then chemical decomposition	Spontaneously decomposes	Decomposes to active and inert products; also P450-mediated inactivation	Enzymatic conjugation with glutathione	Chemical decomposition
	Hydrolysis to phosphoramide mustard (active) and acrolein	Hydrolysis to iphosphoramide mustard and acrolein	20%–35% excreted unchanged in urine			
	Excretion as inactive oxidation products	Excretion as inactive oxidation and dechloroethylated products				Excretion primarily in feces
icity						
e Marrow	Acute, platelets spared	Acute but mild	Delayed, nadir at 4 wk	Delayed, nadir 4–6 wk	Acute and delayed marrow aplasia	Acute but mild
er	Hemorrhagic cystitis, cardiac toxicity, IADH	Hemorrhagic cystitis, encephalopathy	—	Pulmonary fibrosis, renal failure, hypotension	Addisonian syndrome, seizures, pulmonary fibrosis, venoocclusive disease	Mucositis, infections, tumor lysis syndrome
autions	Use MESNA with high-dose therapy	Always coadminister MESNA	Decomposes if administered over <1 h	—	Monitor AUC with high-dose therapy Induces phenytoin metabolism	

reference 296.
, area under the concentration time curve; BCNU, bischloroethylnitrosourea; IADH, inappropriate antidiuretic hormone syndrome; IV, intravenously; MESNA, ercaptoethane sulfonate; PO, per os; $t_{1/2}$, plasma half-life.

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