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From old alkylating agents to new minor groove binders

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Contents

Abstract

Alkylating agents represent the oldest class of anticancer agents with the approval of mechloretamine by the FDA in 1949. Even though their clinical use is far beyond the use of new targeted therapies, they still occupy a major place in the treatment of specific malignancies, sometimes representing the unique option for the treatment of refractory tumors. Here, we are reviewing the major classes of alkylating agents, with a particular focus on the latest generations of compounds that specifically target the minor groove of the DNA. These naturally occurring derivatives have a unique mechanism of action that explains the recent regain of interest in developing new classes of alkylating agents that could be used in combination with other anticancer drugs to enhance tumor response in the clinic.

Keywords: Alkylating agents; DNA adducts; DNA repair; O6-methylguanine; DNA crosslinks

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1. Introduction

Alkylating agents were first used as chemical weapons during the First World War. They induced severe vesicant effects that were accompanied by bone marrow aplasia and pancytopenia several days following intoxication. This fortuitous observation led to the first experimentation of mustard gas as anticancer agents to target carcinogen-induced tumors in mice [1]. In the early 30s, the first trials in men showed interesting durable responses in patients with skin cancers and sarcomas [1]. Despite the Geneva Convention in 1925, a vast research program was secretly carried out by the *US Office of Scientific Research and Development* in order to identify new chemical weapons. Another major trigger for the discovery of alkylating agents' anticancer activity was the accidental spill of sulphur mustards that occurred during World War II in the Italian harbor of Bari. On December 2nd 1943, 17 ships were destroyed by a surprise raid of the German aviation, including the SS John Harvey vessel that secretly transported a cargo of more than 100 tonnes of mustard bombs. Among soldiers that were exposed, a significant rate of severe lymphoid hypoplasia and myelosuppression was observed. This led to further investigations of nitrogen mustards as potential anticancer agents by Gilman and Goodman who showed remarkable activity in the treatment of lymphomas. These results were only published in 1946 [2] but were rapidly followed by the FDA approval of the first alkylating agent, mechlorethamine (Mustargen) in March 1949, and the development of a number of new classes of compounds. Even though their clinical use is far beyond the use of new targeted therapies, they still occupy a major place in the treatment of specific malignancies and sometimes represent the unique option for the treatment of refractory tumors (Table 2). Here, we are reviewing the main classes of alkylating agents with a specific emphasis on the new generations of compounds that show a rather unique mechanism of action. Used as single agents or in combination with DNA repair inhibitors, these new derivatives represent promising therapeutic alternatives for tumors refractory to standard treatments.

2. The mechanism of DNA alkylation

Alkylating agents are electrophilic entities that react with nucleophilic moieties of DNA or proteins resulting in the covalent transfer of an alkyl group [3,4]. The cytotoxic effect of these agents is mainly due to the alkylation of DNA bases that can impair essential DNA processes such as DNA replication and/or transcription. The chemical reaction of alkylation is summarized in Fig. 1A where RX refers to the alkylating agent and X a negatively charged atom such as chlorine, and where R'H is the nucleophilic target of alkylation. Alkylation is a nucleophilic substitution (SN) in which the hydrogen atom (leaving group) is substituted by the alkyl group of the alkylating agent [3,4]. There are two types of nucleophile substitutions (SN1 or SN2) depending on the number of steps of the reaction (Fig. 1B). SN1 reaction involves the formation of a stable carbocation with a planar structure which can be attacked by the nucleophile on both sides with equal probability, leading to a racemic product. Conversely, SN2 reaction implies the formation of a short-lived intermediate in which the leaving group is not completely detached and the nucleophile almost linked covalently, leading to an inversion of the configuration of the asymmetric carbon [4].

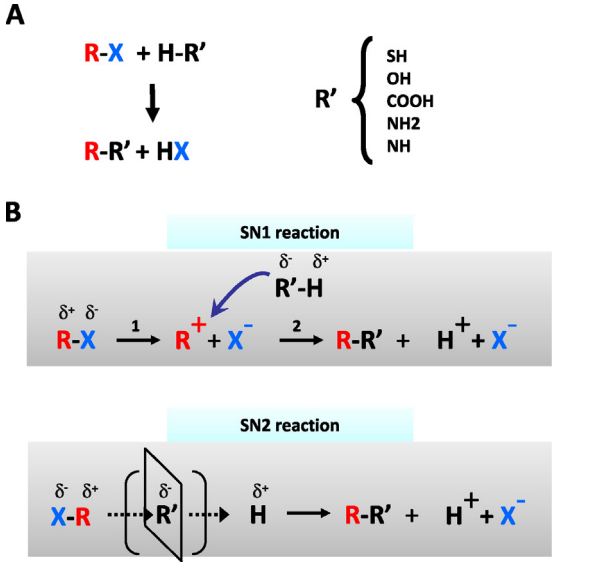

Fig. 1. (A) The reaction of alkylation in which RX represents the alkylating agent with its alkyl group (R) and a halogen atom (X), usually chlorine, and R'H the nucleophilic target of alkylation where the hydrogen atom of hydroxyl, amine, carboxyl, or sulfhydryl groups, is substituted. (B) The two types of nucleophile substitutions (SN1 and SN2).

3. The different targets of DNA alkylation

DNA is the main target of alkylation [3–5]. While monofunctional agents generate covalent adducts with the target molecule (Fig. 2a–c), bi-functional derivatives can form cross-links (inter-strands or intra-strand) in DNA or between DNA and proteins (Fig. 2d–h). There are preferential sites of alkylation in DNA depending on the nature of the nucleophile and of the alkylating agent [6–8]. In general base alkylation predominantly occurs on position guanine N7 and O6, adenine N1 and N3, and cytosine N3 [7,9,10]. The use of Mitomycin C and of the new classes of minor groove binders also revealed guanine N2 as a target of DNA alkylation (Fig. 3). Alkylation on other sites such as adenine N6, N7, thymine O2, N3, O4, or cytosine O2 were also observed, but to a lower extent (Fig. 3 and Table 1) [8,11]. While alkylation on O6G, N1G, N2G, or O4T results in stable DNA adducts [12], alkylation on other positions lead to chemically unstable adducts that are converted to DNA damage by opening of the base ring [8,12] (Fig. 4). That is especially the case for

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