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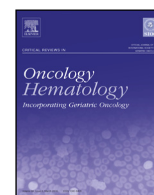

Review

Integrated scientific data bases review on asulacrine and associated toxicity

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ABSTRACT

Asulacrine (ASL), a weakly basic and highly lipophilic drug was synthesized in 1980's in cancer research laboratory of Auckland by modifications to the acridine portion of amsacrine on 3-, 4- and 5-substitution patterns. In contrast to its precursor amsacrine (m-AMSA), ASL was effective not only against leukemia and Lewis lung tumor system but also a wide variety of solid tumor. Its metabolic pathway is not same to amsacrine hence different side effects, hepatotoxicity and excretion was observed. Asulacrine is under phase II clinical trials and has showed promising results but its toxicity especially phlebitis is stumbling block in its clinical implementation. This review is an effort to give a possible clue, based on scientifically proven results, to the researchers to solve the mystery of associated toxicity, phlebitis. Review covers the available literature on asulacrine and other acridine derivatives regarding pharmacology, pharmacokinetics, quantitative structure activity relationship and toxicology via electronic search using scientific databases like PubMed and others. To date, all abstracts and full-text articles were discussed and analyzed. The tabulated comparisons and circuitry mechanism of ASL are the added features of the review which give a complete understanding of hidden aspects of possible route cause of associated toxicity, the phlebitis.

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Abbreviations: AAG, α-acid glycoprotein; AHMA, 3-(9-acridinylamino)-5-hydroxymethylaniline; A. Oxidase, aldehyde oxidase; ASL, asulacrine; COX-2, cyclooxygenase-2; CRL, cancer research laboratory; DACA, *N*-[2-(dimethylamino)ethyl] acridine-4-carboxamide; DPC, DNA protein cross-links; GSH, glutathione; G6P, glucose 6 phosphate; G6PD, glucose-6-phosphate dehydrogenase; HK, hexokinase; HOCl, hypochlorous acid; HSA, human serum albumin; HUVECs, human umbilical vascular endothelial cells; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; MAPK p38, mitogen activated protein kinase p38; mAQDI, quinonediimine; m-AMSA, amsacrine; MPO, myeloperoxidase; NF-κB, nuclear factor-κB; NO, nitrous oxide; NOX, NAD(P)H oxidase; NSCLC, non-small cell lung cancer; o-AMSA, ortho derivative of AMSA; PEP, phosphoenolpyruvate; PIP, post injection precipitation; PKC, protein kinase C; PKM2, phosphokinase isoform M2; QSAR, quantitative structure activity relationship; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen metabolites; SSB, single-strand breaks; TBA, thiobarbituric acid-reactive; TNFα, tumor necrosis factor α; topo II, topoisomerase II; 6PGL, 6 phospate glyceraldehyde.

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1. Introduction

DNA intercalating anilinoacridine derivative, Asulacrine (ASL) (CI-921: NSC 343 499) was developed by the Cancer Research Laboratory (CRL) in Auckland during anticancer drug development. While working on a class of molecules known as AMSA compound (acridinylaminomethanesulfonanilides) possessing reversible binding to DNA, a compound amsacrine (m-AMSA) (acridinylmethanesulfonanilide) (Fig. 1) received attention in 1978 and was approved for human trials. In 1984, m-AMSA was the first pharmaceutical, to be registered for clinical use in New Zealand. The antileukemic activity of m-AMSA was quiet comparable in both acute lymphoblastic leukemia and acute non-lymphoblastic leukemia (Arlin et al., 1980) but not useful for advanced non-Hodgkin's lymphoma (Warrell et al., 1980) and other variety of solid tumors (Hornedo and Van Echo, 1985). The limited activity of m-AMSA against solid tumors and to improve permeation and administration persuaded the researchers to synthesize comparatively weak basic and high lipophilic drug by modifications to the acridine portion of m-AMSA on 3-, 4- and 5-substitution patterns. Based on desired physical properties and antitumor activity in leukemia and lung tumor models, the 4-methyl-5-methylcarboxamide derivative (asulacrine) (Fig. 1) of m-AMSA was chosen for clinical trial among 200 compounds. Asulacrine (ASL) is under phase II clinical trials. Some important explorations of ASL are listed in Table 1.

In clinical trials, ASL showed promising data in the treatment of breast and lung cancers as shown in Table 1 (Fyfe et al., 2001) and its comparison to m-AMSA is shown in Table 2.

It is a wide spectrum anticancer drug. Asulacrine showed selective cytotoxicity with markedly increased life-extension against a wide variety of tumors. Alongside comparison of the mutagenicity of ASL and m-AMSA showed no substantial differences at similar toxicity (Ferguson et al., 1988). Amsacrine has been regarded as genotoxic being clastogenic and mutagenic with heritable chromosomal disorders (Allen et al., 1988a,b, 1994). Principal toxicities of ASL apart from m-AMSA, included leukopenia, marked phlebitis, and mild nausea and vomiting among 150 patients during phase II trial of drug in advanced malignancies (Harvey et al., 1991; Sklarin et al., 1992). Infact, ASL caused pain following intravenous infusion. A high incidence of phlebitis (53%), inflammation of the veins, was the most significant complication when administered in a 5% glucose solution (0.5–1 mg mL^{-1} as isethionate salt, pH 4.5) (Sklarin et al., 1992; Fyfe et al., 2001) which hampered the further characterization and development of ASL. Superficial thrombophlebitis has been characterized with, as shown in Fig. 2, (1) high concentration of thiobarbituric acid-reactive (TBA) substances and myeloperoxidase (MPO) and Reactive oxygen metabolites (ROS) (Glowinski and Glowinski, 2002), (2) chronic tissue hypoxia, (3) decreased antithrombin III activity and activated coagulation, (4) extravasation and (5) increased apoptosis. Reactive oxygen metabolites cause lipid peroxidation, oxidative modification of proteins and carbohydrates, leading to destruction of lipid membranes and organelles, denaturation of enzymatic and structural proteins and of polysaccharide components of the interstitium, activation of signaling pathways and disturbance of glucose level directly or indirectly. All of these processes are involved in vascular pathology (Glowinski and Glowinski, 2002). Free radicals activate blood platelets and influence components of haemostasis leading to thrombotic complications (Glowinski and Glowinski, 2002). Reactive oxygen species produced by NADPH oxidase, polymorphonuclear leukocytes and activated coagulation increase platelet adhesion to capillaries hence blood flow stoppage (Tyml, 2011; Jancinova et al., 2004). One may expect that underline cause of phlebitis associated with ASL may be either oxidative stress and/or free radicals leading to extravasation or other vascular complications. To understand this phenomenon, it was important to go through the important characteristics of drug in comparison to its precursor (m-AMSA) and other anilinoacridine drugs.

2. Physicochemical attributes

According to relative mobility by thin layer chromatography, ASL was more lipophilic than its precursor with decreased acridine base strength (pKa 6.40) and higher association constant for double-stranded calf thymus DNA, shown in Table 2 (Baguley et al., 1984). Unlike m-AMSA, multivariate equations modeling can rationalize these physicochemical properties of ASL as increased retention in tumor and delayed excretion to predict the selective anti-leukemic activity with maximum life extension at selective dose and vice versa (Baguley et al., 1981).

3. Pharmacological activity

Like other acridine derivatives such as m-AMSA and o-AMSA (ortho derivative of AMSA), ASL has been approved for DNA destabilization by intercalation as determined by circular DNA-binding test, demonstrated by equilibrium dialysis and spectrophotometric methods as well as fluorescence studies and thermal denaturation measurements (Hudecz et al., 1981; Waring, 1976). Some acridine drug derivatives have been arranged in Table 3 with their mechanism of action and known activity.

Drug–induced DNA destabilization is considered in relation to (i) the length of the locally destabilized DNA and (ii) the potentially associated bend in the DNA helix, which varies according to the compound's nature (Lenglet and David-Cordonnier, 2010). AMSA compounds bind selectively to DNA probably between each 4 or 5 base pairs. However in case of ASL, the unwinding angle of 18° (corrected for the proportion of unbound drug) is slightly less than that of m-AMSA (20.5°) ethidium (26°) (Baguley et al., 1984). Amsacrine is also known as mammalian DNA topoisomerase II (topo II) inhibitor or more precisely topo II poison. Amsacrine becomes trapped on DNA as part of an enzyme-DNA complex which is detected and quantified in mammalian cells as protein-linked single-strand breaks (SSB) and/or DNA protein cross-links (DPC) using the alkaline elution technique. Asulacrine works by ternary complex producing equivalent number of SSB and DPC in agreement with topo II inhibitors (Covey et al., 1988; Schneider et al., 1988; Denny, 2002). Formation of DPC and SSB seems in close relationship with the mechanisms leading to cell death and cytotoxicity respectively, which varies from drug to drug depending upon dose potency.

4. Pharmacokinetic assessment

Asulacrine expressed non-linear pharmacokinetics in mice intravenously best fitted to compartment model I showing 1.44 times longer half-life and 1.8 fold area under curve in tumor compared with m-AMSA as shown in Table 2, indicating efficient uptake and retention of ASL by the tumor in agreement to physicochemical properties (Kestell et al., 1988). In comparison to m-AMSA, the greater distribution or tissue uptake of ASL might be partly responsible for its greater anticancer activity in vivo (Paxton and Jurlina, 1986) as well as for higher affinity for Jurkat and U937 versus bone marrow as compared to m-AMSA (Ching et al., 1990). The drug was highly (80% of dose) associated with plasma proteins in one hour incubation with mouse blood (Kestell et al., 1988) and excreted in feces of mice by 72 h after intravenous injection (Robertson et al., 1988).

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