ARSENOPLATINS VS COMBINATION OF PLATINUM DRUGS AND ARSENIC TRIOXIDE

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The serendipitous discovery of cisplatin and its approval as an anticancer agent by the FDA in 1978 marked the beginning of using metal complexes as anticancer drugs. Cisplatin is used to treat ovarian, bladder, testicular, and other cancers. Two other drugs, carboplatin (used for the treatment of advanced ovarian cancer) and oxaliplatin (used for the treatment of colorectal cancer and stage III colon cancer) were approved in 1989 and 1996, respectively. All three platinum drugs have two nitrogen donors in cis position. The geometrical isomer of cisplatin, transplatin, did not show efficacy in tumors, and for an extended period scientist believed that trans(N) platinum compounds were not effective against tumors. The main obstacle in using the FDA approved platinum drugs is intrinsic and acquired resistance, and an intensive search for structurally different platinum drugs is underway. Recently, trans(N)-platinum compounds emerged as anticancer agents that are active against cisplatin-resistant cell lines.

Arsenic trioxide is another inorganic drug that is FDA approved for the treatment of acute promyelocytic leukemia (APL). More than 90% of APL patients were cured with this drug. The success of arsenic trioxide in leukemia was not repeated in solid tumors due to the arsenic trioxide rapid renal clearance. A synergy effect exists between arsenic trioxide and cisplatin in several cancer cell lines. Inspired by these results, we synthesized arsenoplatins, small molecular compounds that combine platinum and arsenic pharmacophores in the form of one entity. NCI-60 screening of human tumor cell lines has shown that the first representative of this class of agents, arsenoplatin-1, is more potent than arsenic trioxide in all nine indications tested. ICP-MS experiments on AP-1 DNA adducts isolated from triple negative MDA-MB-231 cancer cell line treated by AP-1 confirmed the ability of arsenoplatin-1 to bind to DNA. After longer incubation time, we found that the Pt/As ratio in AP-1-DNA samples increases. This implies that the platinum-arsenic bond breaks in the cellular milieu and arsenic moiety releases from the AP-1-DNA adducts. Based on our results, arsenoplatin-1 acts as a dual pharmacophore anticancer agent which can deliver platinum and arsenic species to solid tumors. Arsenoplatin-1 also satisfies the Lipinski rule of five used to predict not only the permeability through the cell membrane, but also the overall drug-likeness.