Current Status and Strategies for the Development of Platinum Antitumor Drugs

○Masahiko Chikuma, Takaji Sato and Seiji Komeda
(Dept. Pharm. Sci., Osaka Univ. Pharm. Sci.)

Cisplatin, a simple inorganic compound, has been one of the leading antitumor drugs for near 30 years, and hereafter cisplatin and its analogues will remain indispensable as a basic drug for combination therapeutic regimens. However, cisplatin has several drawbacks such as toxicity and drug resistance. Therefore, much attention has been focused on the development of new platinum complexes with improved pharmacological properties and a broader spectrum of activity to tumors. The recent advance of research on the molecular mechanisms of drug action and the cellular mechanisms of the emergence of resistance to cisplatin assists the rational design of new classes of platinum antitumor drugs, though details of both mechanisms still remain elusive. Information on DNA binding mode of platinum complexes, recognition and repair of DNA damage is instructive. Since several not *cis* but *trans* derivatives and not neutral but cationic complexes have been found to be active *in vitro* and *in vivo*, the early empirical structure-activity relationships of cisplatin analogues should be reevaluated. The hypothesis that platinum complexes, which bind to DNA in a different manner in comparison with cisplatin, will have different pharmacological properties has been tested, and now cationic multi-nuclear complexes and even *trans*-platinum complexes comprise unique classes of platinum-based antitumor agents with chemical and biological properties different from cisplatin. These new types of platinum complexes are often found to be effective against acquired cisplatin resistant tumor cells.

In conclusion, the following complexes appear to offer great potential as new antitumor agents:(1) Complexes with apparently different DNA interaction modes from cisplatin, which may circumvent intrinsic and acquired resistance to cisplatin through eluding the vigilance of DNA repair systems and (2) complexes with different tissue distribution or mechanisms of membrane transport which may exhibit a different spectrum of activity.

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