Journal of Medical Sciences

ISSN 1682-4474

science alert

ANSInet
an open access publisher
http://ansinet.com

Review Article

J. Med. Sci., 13 (3): 160-168
1st April, 2013
DOI: 10.3923/jms.2013.160.168

Platinum Resistance: The Role of Molecular, Genetic and Epigenetic Factors

[1]Mohammed A. Ibrahim, [2]Kalkunte S. Srivenugopal and [3]Kakil Ibrahim Rasul

Active platinum compounds have important applications in treatment of number of malignant tumors and are used in the treatment of lung, ovarian, head and neck, testicular, cervical, colorectal and relapsed lymphoma. The success of platinum drugs in treatment of various types of cancers has been challenged by problems of intrinsic and acquired resistance. Biochemical and genetical studies have confirmed that platinum resistance is multifactorial and includes changes in drug transport leading to decreased drug accumulation, increased drug inactivation or detoxification, changes in DNA repair and damage bypass and alterations in the apoptotic cell death pathways. Molecular studies have revealed that genetic factors and epigenetic mechanisms are linked to platinum resistance. Proteomimetics might prove to be clinically useful as new anticancer agents capable of overcoming apoptosis resistance. The study summarizes the current and future trends of novel molecular discoveries which will find new ways to combat platinum resistance and permit the designing of patient-specific pharmacological interventions to circumvent platinum resistance and increase the drug efficacy.

Key words: Anticancer agents, epigenetic factors, platinum resistance, proteomimetics

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

For further information about this article or if you need reprints, please contact:

Mohammed A. Ibrahim
Princess Sumaya University for Technology, Amman, Jordan

ANSInet
Asian Network for Scientific Information

[1]Princess Sumaya University for Technology, Amman, Jordan
[2]TTUHSC School of Pharmacy, Amarillo, USA
[3]Weill Cornell Medical College and Hamad Medical Corporation, Qatar

INTRODUCTION

Chemotherapy is an important approach for treatment of various types of cancers, yet this type of treatment is facing the problem of drug resistance. Drug resistance was discovered in early days of cancer chemotherapeutic treatment by nitrogen mustard and recent investigations have shown that the problems of resistance encounter other active chemotherapeutic compounds (Goodman *et al*., 1946; Raguz and Yague, 2008). Several mechanisms are involved in development of drug resistance toward various antitumor agents, e.g., alteration in drug transport and metabolism, mutation and amplification of drug targets and others (Table 1). In addition, arising multidrug resistance creates thorny clinical problems which are difficult to overcome (Bidgoli *et al*., 2006; Garattini, 2007; Zahreddine and Borden, 2013). Another important point in this area of research is the genetic basis of resistance. The genetic mutational root of resistance was reported in cancer cells (Iwasa *et al*., 2006). Whereas other studies have shown that anticancer drug resistance and cross resistance are also under epigenetic control (Roberti *et al*., 2006; Ibrahim, 2010a). There are three main molecular epigenetic routes, DNA methylation, histone modifications and RNAi, which might lead to drug resistance in various types of cancers. In this connection, there are increasing support of possible involvement of epigenetic mechanisms in emerging of drug resistance in cancers cells and that the induction of epigenetic changes results in acquired resistance to cytotoxic drugs (Baker and El-Osta, 2003; Egger *et al*., 2004; Glasspool *et al*., 2006). For that, the aim of the present study is to review the recent advances of biochemical, genetic and epigenetic basis of platinum drugs resistance and their implication on cancer treatment.

PLATINUM DRUGS AND CANCER THERAPY

Active platinum compounds have important applications in treatment of number of malignant tumors. For almost three decades, they have been used in the treatment of lung, ovarian, head and neck, testicular, cervical, colorectal and relapsed lymphoma (Galluzzi *et al*., 2012). The best known compound in this group is cisplatin [cis-diammine-dichloroplatinum(II)] with MW of 300.1 and chemical formula (cis-$[PtCl_2(NH_3)_2]$), also known as cis-DDP (Rabik and Dolan, 2007). The bioactivity of cisplatin was first discovered more than four decades ago, it showed inhibitory effect against *Eschericia coli* (Rosenberg *et al*., 1969); since then it has been shown as an anti-tumor drug and was approved by FDA in 1978 (Galluzzi *et al*., 2012). The drug is currently widely used in treatment of advanced or metastatic tumor of small cell lung carcinoma and non-small cell lung carcinoma, head and neck cancers, testis and ovarian tumors (Chu, 1994; Yoshida *et al*., 1994; Jamal *et al*., 2006). In contrast to cisplatin, the transplatin which possess the amine ligands in the trans-position is not effective as an antitumor agent (Kelland *et al*., 1994; Rabik and Dolan, 2007). Because of the toxicities associated with cisplatin therapy, namely, the nephrotoxicity, neurotoxicity and ototoxicity (Cvitkovic *et al*., 1977; Kelland, 2007), two more platinum drugs with lower toxicity profiles were introduced to clinical practice. These are carboplatin [cis-diammine (cyclobutane-1,1-dicarboxylate-O,O') platinum(II)] and oxaliplatin [(1R, 2R)-cyclohexane-1,2-diamine](ethanedioato-O,O) platinum(II) which have fewer adverse effects but similar antitumor activity (Kidani *et al*., 1978; Harrap, 1985; Galluzzi *et al*., 2012). In addition, these studies have shown that the substitution of the chloride in cisplatin with bulky groups as in carboplatin and oxaliplatin leads to a slower dissociation of the compounds into electrophilic species that interact with nucleophilic centers in DNA (mainly guanine N7). Carboplatin is used for the treatment of ovarian cancer, while oxaliplatin is approved for treatment of colorectal cancer in association with 5-fluorouracil and folinic acid (the so-called FOLFOX protocol) (Harrap, 1985; Goldberg *et al*., 2004). However both drugs show cross resistance to cisplatin (Stordal *et al*., 2007; Galluzzi *et al*., 2012). The success of platinum drugs in cancer therapy has encouraged the investigators in this field to develop two more platinum drugs namely, picoplatin [amminedichloro (2-methylpyridine) Platinum] and

Table 1: Mechanisms of antitumor drug resistance

Mechanisms	Drugs or factors	References
Increased excision repair cross-complementing 1 protein expression	Platinum compounds	Martin *et al*. (2008)
Induced apoptosis	TRAIL	Zhang and Fang (2005)
Modification of drug metabolism	5-fluorouracil	Welsh *et al*. (2000)
Alteration in membrane transport	Antitumour nucleosides (cytarabine and fluorodeoxyuridine), alkylating agents	Fry and Jackson (1986)
Decreased accumulation	Platinum compounds, folate antimetabolites, nucleoside and nucleotide analogs	Gately and Howell (1993) and Zhou *et al*. (2008)
Somatic activating mutations	Gefitinib or erlotinib	Takezawa *et al*. (2012)

satraplatin [(OC-6-43)-bis(acetato) amminedichloro (cyclohexylamine) platinum] (Choy, 2006; Eckardt *et al*., 2009), which are undergoing clinical trials.

Now-a-days, cisplatin is considered the most prominent anticancer drug of platinum compounds. Its therapeutic action is unquestionable in treatment of solid tumors. It is worth noting that testicular cancer can be cured by treatment with cisplatin combined with bleomycin and etoposide (Rabik and Dolan, 2007). The authors also indicated in their work that cisplatin is also used in combination with carboplatin for treatment of ovarian, cervical, head and neck, non-small cell lung and lymphoma.

MODES OF ACTION OF PLATINUM DRUGS

The mechanisms of anticancer activity of platinum drugs are well studied. It is established that the primary target of cisplatin and other active platinum drugs is DNA, yet other biological targets are important, since the nucleophilic sulfhydryl groups present in glutathione (GSH) and proteins are also targeted for platination (Jamieson and Lippard, 1999). The involvement of the Multi-drug Resistance Proteins (MRPs) in the transport of in glutathione-platinum conjugates is also well known (Deeley *et al*., 2006; Zhou *et al*., 2008). Much research has been done on the aquation and pre-association multistage process of cisplatin and some of its derivatives binding to DNA and the formation of inter-/intra-strand cross-links. As a result of these studies their main mode of action has been proposed to be via covalent binding to DNA (Suntharalingam *et al*., 2013). Another recent study showed the critical role of B-ring hydroxyls of flavonols in their interactions with a cisplatin-bound double stranded DNA surface. These molecular interactions between cisplatin and flavonols increased the efficacy of cisplatin when combating cancer (Zwang *et al*., 2013).

DNA cross links can halt proliferation as a consequence of prevention of DNA replication and the signaling events leading to cell death (Crul *et al*.,1997). Carboplatin and oxaliplatin have similar modes of action and form identical lesions on DNA (Chaney *et al*., 2005; Rabik and Dolan, 2007). The intra-strand cross links formed by oxaliplatin treatment bends the double helix more than intra-strands formed by cisplatin and carboplatin, whereas inter-strand lesions induce even more steric changes in DNA (Misset *et al*., 2000; Di Francesco *et al*., 2002). The High Mobility Group (HMG) of proteins is known to bind the platinated DNA strongly, this binding increases the degree of distortion of platinated DNA and it has been suggested that these complexes may shield DNA from intracellular repair, leading to cytotoxicity (Park and Lippard, 2012). In addition, cisplatin can induce cells to undergo apoptosis (Jamieson and Lippard, 1999).

PROBLEM OF DRUG RESISTANCE

Cisplatin and the other two platinum drugs (carboplatin and oxaliplatin) form the most effective and widely used agents for treatment of solid tumors (lung, bladder, ovary and testicular carcinoma). However, the development of secondary resistance remains a major obstacle to clinical efficacy. It was reported that prolonged cisplatin treatment raise the frequency of emergence of resistant tumors (Kartalou and Essigmann, 2001; Allingham-Hawkins *et al*., 2010; Oliver *et al*., 2010). Mechanisms of resistance to these drugs are well studied and arise as a result increased levels of DNA repair, reduced uptake, inactivation by glutathione and other anti-oxidants (Rabik and Dolan, 2007).

An important drawback of emerging resistance to an anticancer drug is cross resistance to other antitumor drugs (Gottesman and Ling, 2006). It was reported that ovarian cancer cell lines with low to very high levels of resistance to cisplatin are 8-to 850-fold resistant to the epipodophyllotoxin derivative etoposide (Hamaguchi *et al*., 1993). Adriamycin-resistant sublines were found cross-resistant to MDR-related drugs, epirubicin, mitoxantrone, vincristine, etoposide and taxol but not the MDR-unrelated drug, mytomycin (Uchiyama-Kokubu and Watanabe, 2001). In a study carried out by Shen *et al*. (1998), cross resistance to methotrexate (MTX) and several metal salts was observed in cisplatin-resistant human hepatoma and a cervical adenocarcinoma cell lines. Accordingly, Multiple Drug Resistance (MDR) is an important cause of failures of chemotherapy; it provides a shield for tumor cells against various antitumor drugs.

GENES INVOLVED IN RESISTANCE TO PLATINUM DRUGS

The genetic factors that are involved in the mechanisms of drug resistance and cross resistance have been investigated. The genetic mutational basis of resistance was reported, in addition to the other important genetic mechanism leading to drug resistance via epigenetic routes (Iwasa *et al*., 2006; Roberti *et al*., 2006). The epigenetic routes refer to the role of three main molecular mechanisms, DNA methylation, histone modifications and RNAi on development of drug resistance in various types of cancers (Ibrahim, 2010a). Now-a-days, it is well established that epigenetic changes

Table 2: Genes involved in platinum drug resistance

Gene(s)	Mode of action	References
CTR1	Copper influx transporters	Safaei and Howell (2005)
ATP7A/ATP7B	Copper efflux transporters	Safaei *et al.* (2004)
MRP2	Multidrug resistant associated protein2	Li *et al.* (2004)
p53 and phosphorylated p53, ATM, Chk2, phospho-H2AX, p21cip1, bax, bcl2	DNA-damage-response/anticancer barrier	Siddik (2003) and Huang *et al.* (2005)
NER, ERCC1	Nucleotide excision repair	Ferry *et al.* (2000)
Overall glutathione content, γ-glutamyl cysteine synthetase (γ-GCS), glutathione S-transferase-pi, metallothionein, Redox-modulating proteins such as thioredoxin and glutaredoxin	Drug conjugation, drug inactivation, redox modulation	Chen and Kuo (2010) and Koberle *et al.* (2010)

Table 3: DNA methylation aberration of genes associated with cisplatin resistance

Gene(s)	Cell lines	Tumor	References
RASSF1A, HIC1	-	Male germ cell tumor (GCT)	Koul *et al.* (2002, 2004)
MGMT	-	Male germ cell tumor (GCT)	
SAT, C8orf4, LAMB3, TUBB, G0S2, MCAM and others	KB-3-1 and SCC25	-	Chang *et al.* (2010)

are involved in the induction of resistance to cytotoxic drugs and are more frequent than gene mutation (Shoemaker, 2000; Egger *et al.*, 2004; Glasspool *et al.*, 2006, Chang *et al.*, 2010). The modes of action associated with the expressions of some genes conferring resistance to platinum drugs were reported (Table 2). The products of these genes contribute to platinum drug resistance in one of following mechanisms: Copper influx/efflux transporters (Safaei *et al.*, 2004; Safaei and Howell, 2005), multidrug resistant associated protein MRP 2 (Li *et al.*, 2004), DNA-damage-responsive/anticancer barrier (Siddik, 2003; Huang *et al.*, 2005). Yeast strains were also used to investigate genes involved in cisplatin resistance. Homozygous diploid deletion pool of *Saccharomyces cerevisiae* was used systematically to identify three novel genes (PSY1-3, "platinum sensitivity") that when deleted confer sensitivity to the anticancer agents cisplatin, oxaliplatin and mitomycin C (Wu *et al.*, 2004).

ROLE OF DNA METHYLATION IN DEVELOPMENT OF CANCER AND DRUG RESISTANCE

Aberrations of genomic DNA methylation, loss of genomic methylation or hypermethylation, cause genomics malfunctions. These changes from normal state lead to development of diseases, e.g., cancers and drug resistance (Ibrahim, 2010a-c; Ibrahim, 2012). Several investigations had shown the role of DNA hypermethylation in the development of drug resistance. Nyce and her colleagues were able to show that chemotherapeutic drugs can induce DNA hypermethylation in cultured cells (Nyce *et al.*, 1986; Nyce, 1989; Nyce *et al.*, 1993). Whereas other investigators had reported that resistance to cisplatin was accompanied by over-expression of DNA methyltransferases (Wang *et al.*, 2001) and the resistance could be induced by over-expression of DNA methyltransferase genes (Qiu *et al.*, 2005). Similar results were obtained when human breast adenocarcinoma cells were treated with adriamycin (Segura-Pacheco *et al.*, 2006). More recent study by Kastl and his colleagues were able to demonstrate that changes in the DNA methylation machinery were associated with resistance to docetaxel in breast cancer cells (Kastl *et al.*, 2010). Chang and his colleagues provided further evidence that epigenetic promoter methylation was a frequent event during chronic cisplatin exposure and that secondary changes in gene regulation can play an important role in generating drug resistant phenotypes (Chang *et al.*, 2010). Changes in the DNA methylation patterns are observed in RASSF1A, HIC1 and MGMT genes of male germ cell tumor whereas other genes e.g., SAT, C8orf4, LAMB3 and others were observed in cell lines (Table 3). It is worth to mention that our search showed that several genes which are linked to the platinum drug resistance (Table 2) are prone to alteration of DNA methylation patterns, e.g., CTR1 (Stewart *et al.*, 2009), bcl2 (Hanada *et al.*, 1993), MDR1 (El-Osta *et al.*, 2002).

IMPACT OF REVERSAL OF DNA METHYLATION PROFILES ON DRUG RESISTANCE

It is possible to hypothesize that reversal of DNA aberration of cancer cells or drug resistance cells to normal states might be considered as promising approach for cancer therapy and overcoming the problem of anticancer drug resistance (Perez-Plasencia and Duenas-Gonzalez, 2006). One interesting approach to overcome platinum compounds resistance is to use DNA methylation inhibitors. A study carried out by group of researchers showed that treatment of HeLa cells with hydralazine and valproic acid lead to an increase in the cytotoxicity of gemcitabine, cisplatin and adriamycin (Chavez-Blanco *et al.*, 2006). Other research group led by

Candelaria showed that anticancer drug resistance which was associated with changes in the DNA methylation profiles could be reversed by epigenetic drugs (Candelaria *et al*., 2007). Research in this field is likely to lead to the development and discovery of epigenetic drugs especially from plant origin (Kirk *et al*., 2008; Link *et al*., 2010). These drugs might have future application in cancer therapy; in addition medicinal plants might be a good source for such epigenetic drugs (Ibrahim, 2010a; Jamal *et al*., 2010).

NEW NOVEL APPROACHES TO OVERCOME CISPLATIN RESISTANCE

Other ways to overcome cisplatin resistance have been investigated. A recent study showed that cisplatin resistant cells accumulate Reactive Oxygen Species (ROS), this observation might prove useful in targeted therapy (Wangpaichitr *et al*., 2012). Another approach has been directed to study the correlation between cisplatin resistance and factors involved in cell growth. It was possible to show that cisplatin resistance can be reversed by inhibition of modulators of cell growth (Wangpaichitr *et al*., 2008). In addition, there is strong evidence which points at the association of cisplatin resistance with apoptotic resistance. Research in this area has shown that this type of resistance is under control of apoptotic regulators (Crawford *et al*., 2011). An important group of proteins which are involved in apoptosis process belong to Bcl-2 family of proteins and includes two types of factors, pro-and anti-apoptotic, these are acting at the mitochondrial level (Hanahan and Weinberg, 2000; Susnow *et al*., 2009). BH3 domain is an interesting feature of these proteins, it is suggested that the interactions are mediated by this domain that consists of approximately 20 amino acids (Zhai *et al*., 2006; Lee *et al*., 2007). It is possible to identify or synthesize chemicals that mimic the BH3 domain and have anti-cancer activities (Fesik, 2005; Zhai *et al*., 2006). In this connection, ABT-737 is an example of one of the first small-molecule that binds to Bcl-xL, Bcl-2 and Bcl-w with high affinity (Lee *et al*., 2007). Since apoptosis resistance is a key feature, we believe that targeting this pathway with the BH3 mimetics, e.g., ABT-737, is a viable strategy for sensitizing cisplatin resistant tumors. It is worth mentioned that despite high affinity of ABT-737 for BcL-2, BcL-xL and BcL-w, many cell types proved refractory to ABT-737. It is worth mentioned that resistance in this case was attributed to the inability of ABT-737 to target Mcl-1 (Van Delft *et al*., 2006; Lee *et al*., 2007). On the other hand, a more recent study has shown the potential of this approach when used in combination with cytotoxic drugs (Joudeh and Claxton, 2012). Further, they reported that several agents target the function of anti-apoptotic Bcl-2 family members have entered clinical trials.

CONCLUSION

Cancer remains a major health problem with the incidence of solid tumors ever increasing, more so among women and the aging population. Platinum-based drugs, cisplatin, carboplatin and oxaliplatin form the most effective and widely used agents for these malignancies. Despite the powerful antitumor effects and reasonable improvement in the quality of life for many patients, the therapeutic efficacy of platinum drugs is limited because of intrinsic or acquired tumor resistance. DNA methylation is associated with resistance to active platinum compounds and some other important anticancer drugs. We believe that investigation of DNA methylation of genes, their products proved being involved in cisplatin resistance, will help in introducing molecular markers to detect acquired resistance to cisplatin and other platinum drugs in patients undergoing therapy. Furthermore, strong evidence points to the association of cisplatin resistance with apoptotic resistance resulting from the over expression of antiapoptotic Bcl-2 family of genes or under expression of the apoptotic regulators. It has also been shown that BH3 domains possess selectivity and have important applications in cancer therapy. Accordingly, it is expected that proteomimetics will have potential as anti-cancer therapeutics.

ACKNOWLEDGMENTS

The authors would like to thank the Princess Sumaya University for Technology, TTUHSC School of Pharmacy, Weill Cornell Medical College and Hamad Medical Corporation for supporting the research related to this publication.

REFERENCES

Allingham-Hawkins, D., A. Lea and S. Levine, 2010. ERCC1 expression analysis to guide therapy in non-small cell lung cancer. PLoS Curr., Vol. 2.

Baker, E.K. and A. El-Osta, 2003. The rise of DNA methylation and the importance of chromatin on multidrug resistance in cancer. Exp. Cell Res., 290: 177-194.

Bidgoli, S.A., M. Bagher, Z. Mansoor Djamali, F. Shamileh and A. Ebrahim, 2006. P-glycoprotein and topoisomerase II α expression in advanced gastric cancer patients: Association with clinicopathological findings. Int. J. Pharmacol., 2: 383-393.

Candelaria, M., D. Gallardo-Rincon, C. Arce, L. Cetina and J.L. Aguilar-Ponce *et al*., 2007. A phase II study of epigenetic therapy with hydralazine and magnesium valproate to overcome chemotherapy resistance in refractory solid tumors. Ann. Oncol., 18: 1529-1538.

Chaney, S.G., S.L. Campbell, E. Bassett and Y. Wu, 2005. Recognition and processing of cisplatin- and oxaliplatin-DNA adducts. Crit. Rev. Oncol./Hematol., 53: 3-11.

Chang, X., C.L. Monitto, S. Demokan, M.S. Kim and S.S. Chang *et al*., 2010. Identification of hypermethylated genes associated with cisplatin resistance in human cancers. Cancer Res., 70: 2870-2879.

Chavez-Blanco, A., C. Perez-Plasencia, E. Perez-Cardenas, C. Carrasco-Legleu and E. Range-Lope *et al*., 2006. Antineoplastic effects of the DNA methylation inhibitor hydralazine and the histone deacetylase inhibitor valproic acid in cancer cell lines. Cancer Cell Int., Vol. 6. 10.1186/1475-2867-6-2

Chen, H.H. and M.T. Kuo, 2010. Role of glutathione in the regulation of cisplatin resistance in cancer chemotherapy. Met. Based Drugs. 10.1155/2010/430939

Choy, H., 2006. Satraplatin: An orally available platinum analog for the treatment of cancer. Expert Rev. Anticancer Ther., 6: 973-982.

Chu, G., 1994. Cellular responses to cisplatin: The roles of DNA-binding proteins and DNA repair. J. Biol. Chem., 269: 787-790.

Crawford, N., A.D. Chacko, K.I. Savage, F. McCoy, K. Redmond, D.B. Longley and D.A. Fennell, 2011. Platinum resistant cancer cells conserve sensitivity to BH3 domains and obatoclax induced mitochondrial apoptosis. Apoptosis, 16: 311-320.

Crul, M., J.H. Schellens, J.H. Beijnen and M. Maliepaard, 1997. Cisplatin resistance and DNA repair. Cancer Treat. Rev., 23: 341-366.

Cvitkovic, E., J. Spaulding, V. Bethune, J. Martin and W.F. Whitmore, 1977. Improvement of Cis-dichlorodiammineplatinum(NSC119875): Therapeutic index in an animal model. Cancer, 39: 1357-1361.

Deeley, R.G., C. Westlake and S.P.C. Cole, 2006. Transmembrane transport of endo- and xenobiotics by mammalian ATP-binding cassette multidrug resistance proteins. Physiol. Rev., 86: 849-899.

Di Francesco, A.M., A. Ruggiero and R. Riccardi, 2002. Cellular and molecular aspects of drugs of the future: Oxaliplatin. Cell. Mol. Life Sci., 59: 1914-1927.

Eckardt, J.R., D.L. Bentsion, O.N. Lipatov, I.S. Polyakov and F.R. Mackintosh *et al*., 2009. Phase II study of picoplatin as second-line therapy for patients with small-cell lung cancer. J. Clin. Oncol., 27: 2046-2051.

Egger, G., G. Liang, A. Aparicio and P.A. Jones, 2004. Epigenetics in human disease and prospects for epigenetic therapy. Nature, 429: 457-463.

El-Osta, A., P. Kantharidis, J.R. Zalcberg and A.P. Wolffe, 2002. Precipitous release of methyl-CpG binding protein 2 and histone deacetylase 1 from the methylated human multidrug resistance gene (MDR1) on activation. Mol. Cell Biol., 22: 1844-1857.

Ferry, K.V., T.C. Hamilton and S.W. Johnson, 2000. Increased nucleotide excision repair in cisplatin-resistant ovarian cancer cells: Role of ERCC1-XPF. Biochem. Pharmacol., 60: 1305-1313.

Fesik, S.W., 2005. Promoting apoptosis as a strategy for cancer drug discovery. Nat. Rev. Cancer, 5: 876-885.

Fry, D.W. and R.C. Jackson, 1986. Membrane transport alterations as a mechanism of resistance to anticancer agents. Cancer Surv., 5: 47-79.

Galluzzi, L., L. Senovilla, I. Vitale, J. Michels and I. Martins *et al*., 2012. Molecular mechanisms of cisplatin resistance. Oncogene, 31: 1869-1883.

Garattini, S., 2007. Pharmacokinetics in cancer chemotherapy. Eur. J. Cancer, 43: 271-282.

Gately, D.P. and S.B. Howell, 1993. Cellular accumulation of the anticancer agent cisplatin: A review. Br. J. Cancer, 67: 1171-1176.

Glasspool, R.M., J.M.Teodoridis and R. Brown, 2006. Epigenetics as a mechanism driving polygenic clinical drug resistance. Br. J. Cancer, 94: 1087-1092.

Goldberg, R.M., D.J. Sargent, R.F. Morton, C.S. Fuchs and R.K. Ramanathan *et al*., 2004. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J. Clin. Oncol., 22: 23-30.

Goodman, L.S., M.M. Wintrobe, W. Dameshek, M.J. Goodman, A. Gilman and M.T. McLennan, 1946. Nitrogen mustard therapy: Use of methyl-bis(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. J. Am. Med. Assoc., 132: 126-132.

Gottesman, M.M. and V. Ling, 2006. The molecular basis of multidrug resistance in cancer: The early years of P-glycoprotein research. FEBS Lett., 580: 998-1009.

Hamaguchi, K., A.K. Godwin, M. Yakushiji, P.J. O'Dwyer, R.F. Ozols and T.C. Hamilton, 1993. Cross-resistance to diverse drugs is associated with primary cisplatin resistance in ovarian cancer cell lines. Cancer Res., 53: 5225-5232.

Hanada, M., D. Delia, A. Aiello, E. Stadtmauer and J. C. Reed, 1993. Bcl-2 gene hypomethylation and high-level expression in B-cell chronic lymphocytic leukemia. Blood, 82: 1820-1828.

Hanahan, D. and R.A. Weinberg, 2000. The hallmarks of cancer. Cell, 100: 57-70.

Harrap, K.R., 1985. Preclinical studies identifying carboplatin as a viable cisplatin alternative. Cancer Treat. Rev., 12: 21-33.

Huang, R.Y., M. Eddy, M. Vujcic and D. Kowalski, 2005. Genome-wide screen identifies genes whose inactivation confer resistance to cisplatin in *Saccharomyces cerevisiae*. Cancer Res., 65: 5890-5897.

Ibrahim, M.A., 2010a. Advances in genomic DNA methylation analysis. Biotechnology, 9: 459-468.

Ibrahim, M.A., 2010b. Perspective of DNA methylation in cancer research. Int. J. Cancer Res., 6: 188-201.

Ibrahim, M.A., 2010c. Prospects for DNA methylation research in psychiatric disorders. Trends Med. Res., 5: 1-15.

Ibrahim, M.A., 2012. An insight into the use of genome, methylome and gethylome in synthetic biology. Asian J. Applied Sci., 5: 67-73.

Iwasa, Y., M.A. Nowak and F. Michor, 2006. Evolution of resistance during clonal expansion. Genetics, 172: 2557-2566.

Jamal, A., R. Siegel, E.L. Ward, T. Murray, J. Xu, M. Smigal and J. Thun, 2006. Cancer Statistics. CA Cancer J. Clin., 56: 106-130.

Jamal, P., A.A. Barkat and A. Amid, 2010. Distribution of phenolics in various Malaysian medicinal plants. J. Applied Sci., 10: 2658-2662.

Jamieson, E.R. and S.J. Lippard, 1999. Structure, recognition and processing of cisplatin-DNA adducts. Chem. Rev., 99: 2467-2498.

Joudeh, J. and D. Claxton, 2012. Obatoclax mesylate: Pharmacology and potential for therapy of hematological neoplasms. Expert Opin Investig. Drugs, 21: 363-373.

Kartalou, M. and J.M. Essigmann, 2001. Mechanisms of resistance to cisplatin. Mut. Res., 478: 23-43.

Kastl, L., I. Brown and A.C. Schofield, 2010. Altered DNA methylation is associated with docetaxel resistance in human breast cancer cells. Int. J. Oncol., 36: 1235-1241.

Kelland, L.R., C.F. Barnard, K.J. Mellish, M. Jones and P.M. Goddard *et al*., 1994. A novel trans-platinum coordination complex possessing *in vitro* and *in vivo* antitumor activity. Cancer Res., 54: 5618-5622.

Kelland, L., 2007. The resurgence of platinum-based cancer chemotherapy. Nat. Rev. Cancer, 7: 573-584.

Kidani, Y., K. Inagaki, M. Iigo, A. Hoshi and K. Kuretani, 1978. Antitumor activity of 1,2-diaminocyclohexaneplatinum complexes against Sarcoma-180 ascites form. J. Med. Chem., 21: 1315-1318.

Kirk, H., W.T. Cefalu, D. Ribnicky, Z. Liu and K.J. Eilertsen, 2008. Botanicals as epigenetic modulators for mechanisms contributing to development of metabolic syndrome. Metabolism Clin. Exp., 57: S16-S23.

Koberle, B., M.T. Tomicic, S. Usanova and B. Kaina, 2010. Cisplatin resistance: Preclinical findings and clinical implications. Biochim. Biophys. Acta, 1806: 172-182.

Koul, S., J. Houldsworth, M.M. Mansukhani, A. Donadio and J.M. McKiernan *et al*., 2002. Characteristic promoter hypermethylation signatures in male germ cell tumors. Mol. Cancer, Vol. 1.

Koul, S., J.M. McKiernan, G. Narayan, J. Houldsworth and J. Bacik *et al*., 2004. Role of promoter hypermethylation in Cisplatin treatment response of male germ cell tumors. Mol. Cancer, Vol. 3.

Lee, E.F., P.E. Czabotar, B.J. Smith, K. Deshayes, K. Zobel, P.M. Colman and W.D. Fairlie, 2007. Crystal structure of ABT-737 complexed with Bcl-xL: Implications for selectivity of antagonists of the Bcl-2 family. Cell Death Differ., 14: 1711-1713.

Li, W.H., Y. Cui and J.R. Zhu, 2004. Methylated oligonucleotide inhibiting expression of human MRP2 and reversing multidrug resistance in hepatocellular carcinoma CellHepG2. Ai Zheng, 23: 900-904.

Link, A., F. Balaguer and A. Goel, 2010. Cancer chemoprevention by dietary polyphenols: Promising role for epigenetics. Biochem. Pharmacol., 80: 1771-1792.

Martin, L.P., T.C. Hamilton and R.J. Schilder, 2008. Platinum resistance: The role of DNA repair pathways. Clin. Cancer Res., 14: 1291-1295.

Misset, J.L., H. Bleiberg, W. Sutherland, M. Bekradda and E. Cvitkovic, 2000. Oxaliplatin clinical activity: A review. Crit. Rev. Oncol./Hematol., 35: 75-93.

Nyce, J., L. Liu and P.A. Jones, 1986. Variable effects of DNA-synthesis inhibitors upon DNA methylation in mammalian cells. Nucleic Acids Res., 14: 4353-4367.

Nyce, J., 1989. Drug-induced DNA hypermethylation and drug resistance in human tumors. Cancer Res., 49: 5829-5836.

Nyce, J., S. Leonard, D. Canupp, S. Schulz and S. Wong, 1993. Epigenetic mechanisms of drug resistance: drug-induced DNA hypermethylation and drug resistance. Proc. Natl. Acad. Sci. USA., 90: 2960-2964.

Oliver, T.G., K.L. Mercer, L.C. Sayles, J.R. Burke and D. Mendus *et al*., 2010. Chronic cisplatin treatment promotes enhanced damage repair and tumor progression in a mouse model of lung cancer. Genes Dev., 24: 837-852.

Park, S. and S.J. Lippard, 2012. Binding interaction of HMGB4 with cisplatin-modified DNA. Biochemistry, 51: 6728-6737.

Perez-Plasencia, C. and A. Duenas-Gonzalez, 2006. Can the state of cancer chemotherapy resistance be reverted by epigenetic therapy? Mol. Cancer, Vol. 5.

Qiu, Y.Y., B.L. Mirkin and R.S. Dwivedi, 2005. Inhibition of DNA methyltransferase reverses cisplatin induced drug resistance in murine neuroblastoma cells. Cancer Detect. Prev., 29: 456-463.

Rabik, C.A. and M.E. Dolan, 2007. Molecular mechanisms of resistance and toxicity associated with platinating agents. Cancer Treatment Rev., 33: 9-23.

Raguz, S. and E. Yague, 2008. Resistance to chemotherapy: New treatments and novel insights into an old problem. Br. J. Cancer, 99: 387-391.

Roberti, A., D. La Sala and C. Cinti, 2006. Multiple genetic and epigenetic interacting mechanisms contribute to clonally selection of drug-resistant tumors: Current views and new therapeutic prospective. J. Cell. Physiol., 207: 571-581.

Rosenberg, B., L. Van Camp, J.E. Trosko, V.H. Mansour, 1969. Platinum compounds: A new class of potent antitumour agents. Nature, 22: 385-386.

Safaei, R., A. K. Holzer, K. Katano, G. Samimi and S.B. Howell, 2004. The role of copper transporters in the development of resistance to Pt drugs. J. Inorg. Biochem., 98: 1607-1613.

Safaei, R. and S.B. Howell, 2005. Copper transporters regulate the cellular pharmacology and sensitivity to Pt drugs. Crit. Rev. Oncol./Hematol., 53: 13-23.

Segura-Pacheco, B., E. Perez-Cardenas, L. Taja-Chayeb, A. Chavez-Blanco, A. Revilla-Vazquez, L. Benitez-Bribiesca and A. Duenas-Gonzalez, 2006. Global DNA hypermethylation-associated cancer chemotherapy resistance and its reversion with the demethylating agent hydralazine. J. Transl. Med., Vol. 4. 10.1186/1479-5876-4-32

Shen, D.W., I. Pastan and M.M. Gottesman, 1998. Cross-resistance to methotrexate and metals in human cisplatin-resistant cell lines results from a pleiotropic defect in accumulation of these compounds associated with reduced plasma membrane binding proteins. Cancer Res., 58: 268-275.

Shoemaker, R.H., 2000. Genetic and epigenetic factors in anticancer drug resistance. J. Natl. Cancer Inst., 92: 4-5.

Siddik, Z.H., 2003. Cisplatin: Mode of cytotoxic action and molecular basis of resistance. Oncogene, 22: 7265-7279.

Stewart, D.J., J. Issa, R. Kurzrock, M.I. Nunez and J. Jelinek *et al*., 2009. Decitabine effect on tumor global DNA methylation and other parameters in a phase I trial in refractory solid tumors and lymphomas. Clin. Cancer Res., 15: 3881-3888.

Stordal, B., N. Pavlakis and R. Davey, 2007. Oxaliplatin for the treatment of cisplatin-resistant cancer: A systematic review. Cancer Treat. Rev., 33: 347-357.

Suntharalingam, K., O. Mendoza, A.A. Duarte, D.J. Mann and R. Vilar, 2013. A platinum complex that binds non-covalently to DNA and induces cell death via a different mechanism than cisplatin. Metallomics, (In Press).

Susnow, N., L. Zeng, D. Margineantu and D.M. Hockenbery, 2009. Bcl-2 family proteins as regulators of oxidative stress. Semin. Cancer Biol., 19: 42-49.

Takezawa, K., V. Pirazzoli, M.E. Arcila, C.A. Nebhan and X. Song *et al*., 2012. HER2 amplification: A potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site $EGFR^{T790M}$ mutation. Cancer Discovery, 2: 922-933.

Uchiyama-Kokubu, N. and T. Watanabe, 2001. Establishment and characterization of adriamycin-resistant human colorectal adenocarcinoma HCT-15 cell lines with multidrug resistance. Anticancer Drugs, 12: 769-779.

Van Delft, M.F., A.H. Wei, K.D. Mason, C.J. Vandenberg and L. Chen *et al*., 2006. The BH3 mimetic ABT-737 targets selective Bcl-2 proteins and efficiently induces apoptosis via Bak/Bax if Mcl-1 is neutralized. Cancer Cell, 10: 389-399.

Wang, C., B.L. Mirkin and R.S. Dwivedi, 2001. DNA (cytosine) methyltransferase overexpression is associated with acquired drug resistance of murine neuroblastoma cells. Int. J. Oncol., 18: 323-329.

Wangpaichitr, M., C. Wu, M. You, M.T. Kuo, L. Feun, T. Lampidis and N. Savaraj, 2008. Inhibition of mTOR restores cisplatin sensitivity through down-regulation of growth and anti-apoptotic proteins. Eur. J. Pharmacol., 591: 124-127.

Wangpaichitr, M., E.J. Sullivan, G. Theodoropoulos, C. Wu and M. You *et al*., 2012. The relationship of thioredoxin-1 and cisplatin resistance: Its impact on ROS and oxidative metabolism in lung cancer cells. Mol. Cancer Ther., 11: 604-615.

Welsh, S.J., J. Titley, L. Brunton, M. Valenti, P. Monaghan, A.L. Jackman and G.W. Aherne, 2000. Comparison of Thymidylate Synthase (TS) protein up-regulation after exposure to TS inhibitors in normal and tumor cell lines and tissues. Clin. Cancer Res., 6: 2538-2546.

Wu, H.I., J.A. Brown, M.J. Dorie, L. Lazzeroni and J.M. Brown, 2004. Genome-wide identification of genes conferring resistance to the anticancer agents cisplatin, oxaliplatin and mitomycin C. Cancer Res., 64: 3940-3948.

Yoshida, M., A.R. Khokhar and Z.H. Siddik, 1994. Biochemical pharmacology of homologous alicyclic mixed amine platinum(II) complexes in sensitive and resistant tumor cell lines. Cancer Res., 54: 3468-3473.

Zahreddine, H. and K.L.B. Borden, 2013. Mechanisms and insights into drug resistance in cancer. Front. Pharmacol., Vol. 4.

Zhai, D., C. Jin, A.C. Satterthwait and J.C. Reed, 2006. Comparison of chemical inhibitors of antiapoptotic Bcl-2-family proteins. Cell Death Differ., 13: 1419-1421.

Zhang, L. and B. Fang, 2005. Mechanisms of resistance to TRAIL-induced apoptosis in cancer. Cancer Gene Ther., 12: 228-237.

Zhou, S.F., L.L. Wang, Y.M. Di, C.C. Xue, W. Duan, C.G. Li and Y. Li, 2008. Substrates and inhibitors of human multidrug resistance associated proteins and the implications in drug development. Curr. Med. Chem., 15: 1981-2039.

Zwang, T.J., K. Singh, M.S. Johal and C.R. Selassie, 2013. Elucidation of the molecular interaction between cisplatin and flavonol(s) and their effect on DNA binding. J. Med. Chem., 56: 1491-1498.