Chapter 1 : Mechanism of Action of Cisplatin - Anti Tumor

Cisplatin, cisplatinum, or cis-diamminedichloroplatinum (II), is a well-known chemotherapeutic calendrierdelascience.com has been used for treatment of numerous human cancers including bladder, head and neck, lung, ovarian, and testicular cancers.

It was the first member of a class of platinum-containing anti-cancer drugs , which now also includes carboplatin and oxaliplatin. Cisplatin was discovered in It is used to treat various types of cancers, including sarcomas , some carcinomas e. Side effects Cisplatin has a number of side-effects that can limit its use: Nephrotoxicity kidney damage is a major concern. Adequate hydration and diuresis is used to prevent renal damage. The nephrotoxicity of platinum-class drugs seems to be related to reactive oxygen species and in animal models can be ameliorated by free radical scavenging agents e. Nephrotoxicity is a dose-limiting side effect. Common neurological side effects of cisplatin include visual perception and hearing disorder, which can occur soon after treatment begins. Recent studies have shown that cisplatin noncompetitively inhibits an archetypal, membrane-bound mechanosensitive sodium-hydrogen ion transporter known as NHE This noncompetitive interaction has been linked to hydroelectrolytic imbalances and cytoskeleton alterations, both of which have been confirmed in vitro and in vivo. Aprepitant combined with ondansetron and dexamethasone has been shown to be better for highly emetogenic chemotherapy than just ondansetron and dexamethasone. Audiometric analysis may be necessary to assess the severity of ototoxicity. Other drugs such as the aminoglycoside antibiotic class may also cause ototoxicity, and the administration of this class of antibiotics in patients receiving cisplatin is generally avoided. The ototoxicity of both the aminoglycosides and cisplatin may be related to their ability to bind to melanin in the stria vascularis of the inner ear or the generation of reactive oxygen species. Cisplatin can cause hypomagnesaemia, hypokalaemia and hypocalcaemia. The hypocalcaemia seems to occur in those with low serum magnesium secondary to cisplatin, so it is not primarily due to the cisplatin. Hemolytic anemia can be developed after several courses of cisplatin. It is suggested that an antibody reacting with a cisplatin-red-cell membrane is responsible for hemolysis. Most notable among the changes in DNA are the 1,2-intrastrand cross-links with purine bases. Interaction with cellular proteins, particularly HMG domain proteins, has also been advanced as a mechanism of interfering with mitosis, although this is probably not its primary method of action. Although cisplatin is frequently designated as an alkylating agent , it has no alkyl group and it therefore cannot carry out alkylating reactions. It is correctly classified as alkylating-like. Cisplatin resistance Cisplatin combination chemotherapy is the cornerstone of treatment of many cancers. Initial platinum responsiveness is high but the majority of cancer patients will eventually relapse with cisplatin-resistant disease. Many mechanisms of cisplatin resistance have been proposed including changes in cellular uptake and efflux of the drug, increased detoxification of the drug, inhibition of apoptosis and increased DNA repair. Its low activity is generally thought to be due to rapid deactivation of the drug before it can arrive at the DNA. It is toxic, and it is desirable to test batches of cisplatin for the absence of the trans isomer. In a procedure by Woollins et al. Although bacterial cell growth continued, cell division was arrested, the bacteria growing as filaments up to times their normal length. Cisplatin was approved for use in testicular and ovarian cancers by the U. Food and Drug Administration on 19 December When silver nitrate in water is added insoluble silver iodide precipitates and K2[Pt OH2 2 NH3 2] remains in solution. Addition of potassium chloride will form the final product which precipitates [24] In the triiodo intermediate the addition of the second ammonia ligand is governed by the trans effect. The trans product is then formed by reaction with hydrochloric acid.

Chapter 2 : Biochemical Mechanisms of Cisplatin Cytotoxicity | BenthamScience

Cisplatin-based combination chemotherapy regimen is a reasonable alternative to cystectomy in advanced/metastatic bladder cancer, but acquisition of cisplatin resistance is common in patients with.

Cisplatin Save Cisplatin is a chemotherapy medication used to treat a number of cancers. It is used to treat various types of cancers, including sarcomas , some carcinomas e. Side effects Cisplatin has a number of side effects that can limit its use: Nephrotoxicity kidney damage is a major concern. Adequate hydration and diuresis is used to prevent renal damage. The nephrotoxicity of platinum-class drugs seems to be related to reactive oxygen species and in animal models can be ameliorated by free radical scavenging agents e. Nephrotoxicity is a dose-limiting side effect. Common neurological side effects of cisplatin include visual perception and hearing disorder, which can occur soon after treatment begins. Recent studies have shown that cisplatin noncompetitively inhibits an archetypal, membrane-bound mechanosensitive sodium-hydrogen ion transporter known as NHE This noncompetitive interaction has been linked to hydroelectrolytic imbalances and cytoskeleton alterations, both of which have been confirmed in vitro and in vivo. Aprepitant combined with ondansetron and dexamethasone has been shown to be better for highly emetogenic chemotherapy than just ondansetron and dexamethasone. Audiometric analysis may be necessary to assess the severity of ototoxicity. Other drugs such as the aminoglycoside antibiotic class may also cause ototoxicity, and the administration of this class of antibiotics in patients receiving cisplatin is generally avoided. The ototoxicity of both the aminoglycosides and cisplatin may be related to their ability to bind to melanin in the stria vascularis of the inner ear or the generation of reactive oxygen species. Cisplatin can cause hypomagnesaemia, hypokalaemia and hypocalcaemia. The hypocalcaemia seems to occur in those with low serum magnesium secondary to cisplatin, so it is not primarily due to the cisplatin. Hemolytic anemia can be developed after several courses of cisplatin. It is suggested that an antibody reacting with a cisplatin-red-cell membrane is responsible for hemolysis. Most notable among the changes in DNA are the 1,2-intrastrand cross-links with purine bases. Interaction with cellular proteins, particularly HMG domain proteins, has also been advanced as a mechanism of interfering with mitosis, although this is probably not its primary method of action. Although cisplatin is frequently designated as an alkylating agent , it has no alkyl group and it therefore cannot carry out alkylating reactions. It is correctly classified as alkylating-like. Cisplatin resistance Cisplatin combination chemotherapy is the cornerstone of treatment of many cancers. Initial platinum responsiveness is high but the majority of cancer patients will eventually relapse with cisplatin-resistant disease. Many mechanisms of cisplatin resistance have been proposed including changes in cellular uptake and efflux of the drug, increased detoxification of the drug, inhibition of apoptosis and increased DNA repair. Two mechanisms have been suggested to explain the reduced anticancer effect of transplatin. Firstly, the trans arrangement of the chloro ligands is thought to confer transplatin with greater chemical reactivity, causing transplatin to become deactivated before it reaches the DNA where cisplatin exerts its pharmacological action. Secondly, the stereo-conformation of transplatin is such that it is unable to form the characteristic 1,2-intrastrand d GpG adducts formed by cisplatin in abundance. Although bacterial cell growth continued, cell division was arrested, the bacteria growing as filaments up to times their normal length. Cisplatin was approved for use in testicular and ovarian cancers by the U. Food and Drug Administration on 19 December Addition of potassium chloride will form the final product which precipitates [31] In the triiodo intermediate the addition of the second ammonia ligand is governed by the trans effect. The trans product is then formed by reaction with hydrochloric acid. Archived from the original on 21 December Retrieved 8 December Fischer, Janos; Ganellin, C. Archived from the original on 20 December Archived PDF from the original on 13 December International Drug Price Indicator Guide. BNF 69 69 ed. Archived from the original on 8 October Retrieved 13 November Einhorn LH 1 November Archived from the original on 22 April Annals of Internal Medicine. Lay summary â€" ScienceDaily. Wang, Dong; Lippard, Stephen J. Nature Reviews Drug Discovery. Trzaska, Stephen 20 June Stordal, B; Davey, M. Coluccia, Mauro; Natile, Giovanni January Anti-Cancer Agents in Medicinal Chemistry. Inorganic Chemistry 2nd ed. Archived from the original on 8 February Further reading

Riddell, Imogen A. Our Current Understanding of Their Actions". Development and Action of Anticancer Agents.

Chapter 3 : Cisplatin in cancer therapy: molecular mechanisms of action | Read by QxMD

Cisplatin is a chemotherapy medication used to treat a number of cancers. These include testicular cancer, ovarian cancer, cervical cancer, breast cancer, bladder cancer, head and neck cancer, esophageal cancer, lung cancer, mesothelioma, brain tumors and neuroblastoma.

Cisplatin is administered intravenously as short-term infusion in normal saline for treatment of solid malignancies. It is used to treat various types of cancers, including sarcomas , some carcinomas e. Side effects[edit] Cisplatin has a number of side effects that can limit its use: Nephrotoxicity kidney damage is a major concern. Adequate hydration and diuresis is used to prevent renal damage. The nephrotoxicity of platinum-class drugs seems to be related to reactive oxygen species and in animal models can be ameliorated by free radical scavenging agents e. Nephrotoxicity is a dose-limiting side effect. Common neurological side effects of cisplatin include visual perception and hearing disorder, which can occur soon after treatment begins. Recent studies have shown that cisplatin noncompetitively inhibits an archetypal, membrane-bound mechanosensitive sodium-hydrogen ion transporter known as NHE This noncompetitive interaction has been linked to hydroelectrolytic imbalances and cytoskeleton alterations, both of which have been confirmed in vitro and in vivo. Aprepitant combined with ondansetron and dexamethasone has been shown to be better for highly emetogenic chemotherapy than just ondansetron and dexamethasone. Audiometric analysis may be necessary to assess the severity of ototoxicity. Other drugs such as the aminoglycoside antibiotic class may also cause ototoxicity, and the administration of this class of antibiotics in patients receiving cisplatin is generally avoided. The ototoxicity of both the aminoglycosides and cisplatin may be related to their ability to bind to melanin in the stria vascularis of the inner ear or the generation of reactive oxygen species. Cisplatin can cause hypomagnesaemia, hypokalaemia and hypocalcaemia. The hypocalcaemia seems to occur in those with low serum magnesium secondary to cisplatin, so it is not primarily due to the cisplatin. Hemolytic anemia can be developed after several courses of cisplatin. It is suggested that an antibody reacting with a cisplatin-red-cell membrane is responsible for hemolysis. Most notable among the changes in DNA are the 1,2-intrastrand cross-links with purine bases. Interaction with cellular proteins, particularly HMG domain proteins, has also been advanced as a mechanism of interfering with mitosis, although this is probably not its primary method of action. Although cisplatin is frequently designated as an alkylating agent , it has no alkyl group and it therefore cannot carry out alkylating reactions. It is correctly classified as alkylating-like. Cisplatin resistance[edit] Cisplatin combination chemotherapy is the cornerstone of treatment of many cancers. Initial platinum responsiveness is high but the majority of cancer patients will eventually relapse with cisplatin-resistant disease. Many mechanisms of cisplatin resistance have been proposed including changes in cellular uptake and efflux of the drug, increased detoxification of the drug, inhibition of apoptosis and increased DNA repair. Two mechanisms have been suggested to explain the reduced anticancer effect of transplatin. Firstly, the trans arrangement of the chloro ligands is thought to confer transplatin with greater chemical reactivity, causing transplatin to become deactivated before it reaches the DNA where cisplatin exerts its pharmacological action. Secondly, the stereo-conformation of transplatin is such that it is unable to form the characteristic 1,2-intrastrand d GpG adducts formed by cisplatin in abundance. Although bacterial cell growth continued, cell division was arrested, the bacteria growing as filaments up to times their normal length. Cisplatin was approved for use in testicular and ovarian cancers by the U. Food and Drug Administration on 19 December When silver nitrate in water is added insoluble silver iodide precipitates and K2[Pt OH2 2 NH3 2] remains in solution. Addition of potassium chloride will form the final product which precipitates [31] In the triiodo intermediate the addition of the second ammonia ligand is governed by the trans effect. The trans product is then formed by reaction with hydrochloric acid.

Chapter 4 : The Molecular Perspective: Cisplatin

The limitations of using cisplatin in cancer chemotherapy are also associated with intrinsic and acquired resistance of tumor cells to this drug,15 Resistance to cisplatin is multi-factorial and, in general, may consist of mechanisms either limiting the formation of DNA adducts and/or operating downstream of the interaction of cisplatin with.

After completing this course, the reader will be able to: Describe the structure and action of cisplatin. It is a tiny molecule, composed of a platinum ion surrounded by four ligands arranged in a square. If you choose two amines and two chlorides as ligands, there are two ways to arrange them around the platinum ion. If the chlorides are arranged opposite one other, however, the compound has no activity. The reason for this difference becomes apparent when you look at the cellular target of cisplatin. Inside a cell, cisplatin loses its two chloride ions, creating a reactive species that forms bonds with DNA bases. Most of these cross-links are formed at sites where guanine and adenine are next to each other in the same strand, but in some cases, cisplatin can form links between the two strands. As you might imagine, these crosslinks cause severe problems when the cell attempts to read or replicate its DNA. The chloride ions in cisplatin are particularly important in its action as a drug. They are relatively stable when the drug is outside the cell, where the chloride concentration is normally high. But when the drug gets inside the cell and the chloride concentration drops, cisplatin loses its two chlorides, and they are replaced by water molecules. These water molecules are loosely bound and fall off easily, allowing the platinum to attack other molecules, such as DNA. In spite of this simple targeting mechanism, 9 out of 10 cisplatin molecules still get stuck on plasma proteins before they reach the nucleus. Unfortunately, cisplatin has significant limitations. Treatment with cisplatin causes severe side effects, and cisplatin is effective for only a specific range of cancers. Many crosslinking platinum compounds have been tested in an attempt to correct these disadvantages. In carboplatin, the chloride groups have been changed, resulting in better delivery to cells and fewer side effects. In oxaliplatin, the amino groups have been changed as well, forming a bulkier crosslink that is effective on a different range of cells. The detailed mechanism by which cisplatin kills cancer cells is still being actively studied, but apoptosis appears to play a central role. Resistance is a significant problem with cisplatin treatment: They reduce the amount of cisplatin reaching the nucleus, perhaps through the use of the mechanisms involved in the maintenance of copper levels. Once the platinum is bound to DNA, cells use their powerful nucleotide excision repair system to fix the problems. Testicular cancers appear to be particularly sensitive to cisplatin treatment because they are not as efficient in their repair mechanisms. Cancer cells also modify the proteins that sense damage and commit the cell to apoptosis, allowing platinated cells to bypass their normal checks and balances.

Chapter 5 : Cisplatin Efficacy: The Importance of Measuring Uptake in Cancer Cells | Technology Networks

Cisplatin is approved to be used alone or with other drugs to treat: Bladder cancer that cannot be treated with surgery or radiation therapy. Ovarian cancer that has metastasized (spread to other parts of the body).

References The discovery of cisplatin cis-diamminedichloroplatinum, or cis-DDP in the early s generated a tremendous amount of research activity as scientists strove to understand how the drug worked in the human body to destroy cancer cells. We now believe that cisplatin coordinates to DNA and that this coordination complex not only inhibits replication and transcription of DNA, but also leads to programmed cell death called apoptosis. As it turns out, however, formation of any platinated coordination complex with DNA is not sufficient for cytotoxic that is, cell-killing activity. The corresponding trans isomer of cisplatin namely, trans-DDP also forms a coordination complex with DNA but unlike cisplatin, trans-DDP is not an effective chemotherapeutic agent. Due to the difference in geometry between cis- and trans-DDP, the types of coordination complexes formed by the two compounds with DNA are not the same. It appears that these differences are critically important in determining the efficacy of a particular compound for the treatment of cancer. For this reason, a great deal of effort has been placed on discovering the specific cellular proteins that recognize cisplatin-DNA complexes and then examining how the interaction of these proteins with the complexes might lead to programmed cell death of cancer cells. Cisplatin is administered to cancer patients intravenously as a sterile saline solution that is, containing saltâ€”specifically, sodium chloride. The neutral compound then enters the cell by either passive diffusion or active uptake by the cell. Inside the cell, the neutral cisplatin molecule undergoes hydrolysis, in which a chlorine ligand is replaced by a molecule of water, generating a positively charged species, as shown below and in Figure 1. The cellular uptake of cisplatin and its targets. The effects of DNA on mitochondria are not well understood, but it is possible that damage to mitochondrial DNA resulting from cisplatin treatment contributes to cell death. The interaction of cisplatin with sulfur-containing enzymes is better understood and is believed to be involved in resistance of cells to cisplatin as discussed in the drug resistance module. We will briefly discuss the interaction of cisplatin with RNA. We will also describe the interaction of cisplatin with DNA in some detail and discuss why DNA is the target of cisplatin that is believed to be responsible for cell death. First, a single damaged RNA molecule can be replaced by newly synthesized material; studies have revealed that cisplatin does not affect RNA synthesis but that it does affect DNA synthesis. Also see the module on DNA. The DNA base pairs. Cisplatin coordinates to the N7 atoms of the purine guanine and adenine bases. The most important of these appear to be the ones in which the two chlorine ligands of cisplatin are replaced by purine nitrogen atoms on adjacent bases on the same strand of DNA; these complexes are referred to 1,2-intrastrand adducts. The purine bases most commonly involved in these adducts are guanines; however, adducts involving one guanine and one adenine are also found. The formation of these adducts causes the purines to become destacked and the DNA helix to become kinked, as shown in Figure 3. Notice the destacking of guanine bases, which would normally be parallel to one another. Since trans-DDP is inactive in killing cancer cells, it is believed that the 1,2-intrastrand adducts formed between cisplatin and DNA are important for the anticancer activity of cisplatin. Researchers have found that this binding affects both replication and transcription of DNA, as well as mechanisms of DNA repair. The effects of both cisplatin and trans-DDP on DNA replication were studied both in vitro using cell extracts outside the host organism and in vivo inside the host organism. In vitro studies on both prokaryotic bacterial and eukaryotic mammalian cells revealed that DNA adducts of both cisplatin and trans-DDP blocked the action of DNA polymerase, an enzyme necessary for replication. In particular, 1,2-intrastrand adducts of cisplatin with DNA all stopped polymerases from doing their job. Likewise, in vivo studies showed that cisplatin and trans-DDP inhibited replication equally well. Since other studies have shown that cisplatin is an effective antitumor agent but trans-DDP is not, these results suggest that DNA replication is not the only factor important for the clinical activity of cisplatin in destroying cancer cells. However, cisplatin does not appear to inhibit transcription, possibly leading to programmed cell death. Indeed, in vitro studies on cell extracts suggest that the most common cisplatinâ€”DNA adducts that is, 1,2-intrastrand adducts are not readily

repaired by the excision repair system see DNA module. It is dangerous to draw too many conclusions from these studies, however, because there may be mechanisms of repair present in the organism that are not apparent from studies on cell extracts alone. In this repair system before the damaged portion of DNA is even excised from the rest of the strand, it must be recognized by the cell. The cell detects DNA damage by the action of damage recognition proteins. Therefore, as a first step in studying the excision repair system, researchers looked for evidence of proteins attached to cisplatinâ€"DNA adducts. Several types of assays can differentiate between DNA that is bound to a protein and free DNA; researchers have been able to use these assays to isolate several proteins that bind to cisplatinâ€"DNA adducts. These proteins all contain a common portion that is, similar or even identical sequences of amino acids, which are the building blocks of proteins called a high mobility group HMG ; proteins in this class are called HMG-domain proteins. In vivo assays on yeast have also provided evidence that HMG-domain proteins are important for the activity of cisplatin: One theory asserts that if HMG-domain-containing transcription factors bind preferentially to the cisplatinâ€"DNA adducts, they could wreak havoc with the transcriptional machinery, possibly leading to cell death. A second theory suggests that when HMG-domain proteins bind to the cisplatinâ€"DNA adducts, the adducts would not be recognized by the repair machinery. Model for the inhibition of cisplatin adduct repair in the presence of HMG-domain proteins. This could interfere with the normal functions of the cell among them, replication and transcription and possibly trigger cell death. In Encyclopedia of Cancer, J. San Diego, CA, , Vol.

Chapter 6 : Cisplatin | Leaders in Pharmaceutical Business Intelligence (LPBI) Group

Abstract: Although cisplatin, cis-diamminedichloroplatinum(II), has been successfully used in the chemotherapy of cancer for more than 25 years, its biochemical mechanism of action is still unclear.

Nitric oxide NO , a gas with many biological functions in healthy cells, has also been implicated in the development of pathologies such as cancer. Nitric oxide may also play a role in chemotherapeutic reisitance. For example it had been known in the Melanoma study by Joshi et al. A new study from MIT reveals how NO-induced modifications may reduce cisplatin sensitivity in melanoma cells. This study focuses on how decreasing nitric oxide levels in melanoma cells increases their cisplatin sensitivity. The study also describes a possible mechanism for this effect: Also, for a description of other cancer-related targets of nitric oxide please see the posting by Dr. To read more background on nitric oxide and its role in disease etiology please see our e-book Perspectives on Nitric Oxide in Disease Mechanisms Biomed e-Books available on Amazon at: With that said, the following was adapted from the MIT site at http: The findings from Dr. The prognosis is generally worse for patients whose tumors have high levels of NO, said Luiz Godoy, an MIT research associate and lead author of the study. NO has many roles within living cells. At low concentrations, it helps regulate processes such as cell death and muscle contraction. NO, which is a free radical, is also important for immune-system function. Immune cells, such as macrophages, produce large amounts of NO during infection, helping to kill invading microbes by damaging their DNA or other cell components. They then treated the cells with cisplatin and tracked cell-death rates. The NO-depleted cells became much more sensitive to the drug, confirming earlier findings. It was already known that NO can alter protein function through a process known as S-nitrosation, which involves attaching NO to the target protein. S-nitrosation can affect many proteins, but in this study the researchers focused on two that are strongly linked with cell death and survival, known as caspase-3 and PHD2. The role of caspase-3 is to stimulate cell suicide, under the appropriate conditions, but adding NO to the protein deactivates it. This prevents the cell from dying even when treated with cisplatin, a drug that produces massive DNA damage. PHD2 is also involved in cell death; its role is to help break down another protein called HIF-1 alpha, which is a pro-survival protein. Godoy is now investigating how cisplatin stimulates that NO boost, and is also looking for other proteins that NO may be targeting.

Chapter 7 : Cisplatin | Revolvy

Cisplatin is an anticancer drug; Mechanism includes crosslinking of DNA, which triggers apoptosis. It is used to treat many types of cancers including testicular, lung, cervical, bladder, head and.

Inside the cell, the molecule undergoes hydrolysis of 1,1-cyclobutanedicarboxylate, becoming positively charged. Ctr1 is the high affinity copper transporter further described in Figure 4. Due to the pharmacodynamics of carboplatin, it has fewer side effects than its precursor cisplatin, although less potency, which might be due to differences in rates of adduct formation with DNA. These toxicity differences are probably due to the low reactivity rate of carboplatin with nucleophiles, since 1,1-cyclobutanedicarboxylate is a poorer leaving group than chloride Figure 3 Hah et al. The respective leaving groups are highlighted. Alkylation of a single strand of DNA can be repaired easily, but cross-linked inter strands such as those produced by bifunctional alkylating agents require more complex mechanisms of repair Rabik, Dolan, Inside the cell, recognition of the damage caused by platinum occurs through the repair machinery. In the context of chromatin, the repair system may require exposure of the damaged double-stranded DNA outwards from the nucleosome, which is the fundamental building block of chromatin. It is the configuration of the DNA rotation on the surface of histone octamer which defines nucleotides that are directed into the solvent and which are occluded by histones Kornberg, Lorch, Therefore, determining the connections between platinum in the DNA are located within the nucleosome is an important step in understanding the process of cell recognition. A key question is whether the adduct of platinum or the DNA sequence determines the configuration of the rotation of a DNA segment into the nucleosome and therefore how the platinum lesion is presented to the replication machinery, thereby affecting transcription and repair of the cell Danford et al. MMR is based on the recognition of DNA distortion caused by the presence of 6-thioguanine and adducts produced by carboplatin, generating an injury signal which might contribute to the initiation of apoptosis. Therefore, the loss of this repair mechanism can cause carboplatin resistance due to the inability to recognize the complex formed by DNA adducts with platinum drugs Fink et al. Some studies have provided evidence that the loss of MMR proteins is associated with drug resistance in ovarian tumors. Additionally, methylation in the MLH1 promoter the regulatory part of one MMR gene performs an important role in the resistance to cisplatin in ovarian cancer cells grown in vitro Zeller et al. Nucleotide excision repair NER is highly conserved and plays a key role in mediating resistance to drugs based on platinum Rabik, Dolan, Injuries that result in changes to the helical structure of DNA and interfere with the mechanism of replication and transcription are repaired by this route. One important protein in the repair pathway of nucleotide excision repair is cross-complementation group 1 ERCC1 , which is postulated to play an important role in the efficacy of the drug McWhinney, Goldberg, McLeod, The repair of caudate adducts by platinum agents mainly occurs through the NER pathway. Although all three types of intra-strand crosslinks 1,2-d ApG , 1. According to the work of Selvakumaran et al. Lower ERCC1 expression, evaluated based on mRNA expression or protein levels, is related to better outcomes in several cancers after platinum-based treatment De Castro et al. Da Costa Miranda et al. According to these authors, this expression was not either predictive or prognotic. However, the authors cite some drawbacks of the study, as the sample group was small and the study was conducted in a single center in Brazil. The manner whereby platinum drugs enter cells has traditionally been attributed to simple passive diffusion. However, some studies suggest that a number of mechanisms of uptake and efflux are active in the process, and altered regulation of these transporters is responsible for the reduced accumulation of drugs in resistant cells Hall et al. Anticancer drugs based on platinum, such as cisplatin, oxaliplatin and carboplatin, are captured by cells, followed by binding to DNA and cytotoxicity Wang, Lippard, Platinum uptake varies widely among different cell types and different types of tissues, and is a factor in the sensitivity and resistance of tumors Liu et al. Transporters of metals such as copper transporters, i. ATP7A is expressed in the epithelium of the intestine and other tissues, except the liver, whereas ATP7B is expressed in liver, kidney, and to a lesser extent in the brain Sprowl, Ness, Sparreboom, The uptake and efflux of carboplatin are apparently linked to the metabolism of copper; this pathway leads to the hypothesis that copper and

carboplatin can interfere with their mutual transport, thereby reducing the absorption of each other Ohashi et al. One of the main efflux pathways associated with copper, and apparently also associated with carboplatin efflux, is the detoxification mechanism mediated by glutathione and metallothionein Figure 4. Mechanism of detoxification of carboplatin within the cell. According to McWhinney, Goldberg and McLeod , the exclusion of the CTR1 gene in yeast results in a significant accumulation of three clinically available platinum analogs, including carboplatin. Forced overexpression of CTR1 in human ovarian cancer cells increases the absorption of platinum-based drugs, indicating that CTR1 plays a key role in the cellular accumulation of these drugs. Furthermore, high levels of ATP7A and ATP7B are associated with a poor response in patients with ovarian cancer receiving cisplatin or carboplatin-based chemotherapies Martinez-Balibrea et al. Hopefully, further investigations will be carried out so that we can identify the causal mechanisms of resistance to carboplatin, allowing more effective use of this highly effective product. The DNA repair pathway increases cell resistance to carboplatin, and activation of the NER or MMR pathway in addition to the detoxification mechanisms of carboplatin cytoplasmic mechanisms are known to be involved in resistance. Determining the causative mechanism of resistance to platinum agents in tumors and reducing the toxic side effects of these drugs in patients will be beneficial to a large number of cancer patients who receive these drugs. Neurotoxicity caused by the treatment with platinum analogues. Feasibility and safety of carboplatin plus paclitaxel as neoadjuvant chemotherapy for locally advanced cervical cancer: Why is it not used to predict response to platinum-based chemotherapy? Modifications of DNA by platinum complexes. 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the copper efflux transporter ATP7A mediates resistance to cisplatin, carboplatin, and oxaliplatin in ovarian cancer cells. Enhanced cisplatin cytotoxicity by disturbing the nucleotide excision repair pathway in ovarian cancer cell lines. Definitive radiochemotherapy of advanced head and neck cancer with carboplatin and paclitaxel. Novel strategies for reversing platinum resistance. Premature p34cdc2 activation required for apoptosis. ERCC1 and thymidylate synthase mRNA levels predict survival for colorectal cancer patients receiving combination oxaliplatin and fluorouracil chemotherapy. Polymorphic transporters and platinum pharmacodynamics. Mechanisms of resistance to cisplatin and carboplatin. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: A case of primary metastatic glassy cell carcinoma of the uterine cervix that responded to combined docetaxel and carboplatin. Excision repair cross-complementation group 1 ERCC1 in platinum-based treatment of non-small cell lung cancer with special emphasis on carboplatin: Cellular processing of platinum anticancer drugs. Molecular mechanisms of platinum resistance: The status of platinum anticancer drugs in the clinic and in clinical trials. Mismatch repair deficiency in ovarian cancer - Molecular characteristics and clinical implications. Candidate DNA methylation drivers of acquired cisplatin resistance in ovarian cancer identified by methylome and expression profiling. VATS lobectomy facilitates the delivery of adjuvant docetaxel-carboplatin chemotherapy in patients with non-small cell lung cancer. December 20, ; Accepted: This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License which permits unrestricted non-commercial use, distribution, and reproduction in any medium provided the original work is properly cited.

Chapter 8 : Carboplatin: molecular mechanisms of action associated with chemoresistance

Cisplatin: mode of cytotoxic action and molecular basis of resistance Zahid H Siddik,1 1Department of Experimental Therapeutics, Unit , The University of Texas M. D. Anderson Cancer Center, Holcombe.*

Mechanism of Action of Cisplatin Last Updated on Mon, 14 May Anti Tumor Broadening the chemotherapeutic arsenal depends on understanding existing agents with a view toward developing new modes of attack. In the 35 years since the discovery of the anti-tumor activity of cisplatin, laboratory studies have provided considerable information as to how the drug exerts its antitumor effects and how some tumors are, or become, resistant to this drug. Although a number of features of the mechanism underlying the anti-tumor effects of cisplatin have been thoroughly described, some still remain to be disclosed. There is a large body of experimental evidence that the success of platinum complexes in killing tumor cells mainly results from their ability to form various types of adducts with DNA. Cisplatin reacts with DNA in the cell nucleus, where the concentration of chloride is markedly lower than in extracellular fluids. The drug loses its chloride ligands in media containing low concentrations of chloride to form positively charged mono- and di-aqua species Figure It has been shown that only these aquated forms bind to DNA. Bifunctional cisplatin binds to DNA in a two-step process first forming mono-functional adducts preferentially at the guanine residues, which subsequently close to major intrastrand cross-links between adjacent purine residues 1,2-GG or 1,2-AG intrastrand cross-links. In all adducts, cisplatin is coordinated to the N7 atom of purine residues. The percentage of the 1,2-intrastrand adducts formed by cisplatin is larger than statistically expected so that this cross-link has generally been assumed to be the important adduct correlated with anti-cancer activity and was therefore most extensively investigated. These adducts induce a roll between the platinated purine residues, displacement of the platinum atom from the planes of the purine rings, a directional and rigid bend of the helix axis toward the major groove and a local unwinding. In addition, severe Figure Other minor adducts of cisplatin also induce several irregularities in DNA, the details of which have been reviewed elsewhere. The limitations of using cisplatin in cancer chemotherapy are also associated with intrinsic and acquired resistance of tumor cells to this drug. The formation of DNA adducts by cisplatin can be limited by reduced accumulation of the drug, enhanced drug efflux and cisplatin inactivation by coordination to sulfur-containing biomolecules including metallothioneins whose production may be increased as a consequence of cisplatin treatment. The second group of mechanisms includes enhanced repair of DNA adducts of cisplatin and increased tolerance of the resulting DNA damage. In human cells, cisplatin intrastrand adducts are removed from DNA mainly by the nucleotide excision repair NER system. There is also evidence that other cellular repair mechanisms, such as recombination or mismatch repair, can affect anti-tumor efficiency of cisplatin. It is generally believed that anti-tumor activity of cisplatin is mediated by the recognition of its DNA adducts by cellular proteins. The greatest attention has been paid to the studies of recognition of platinated DNA by HMGB1 and HMGB2 proteins which belong to architectural chromatin proteins and play some kind of structural role in the formation of functional higher order protein-DNA or protein-protein complexes or as signaling molecules in genetically regulated repair pathways. These structure-specific proteins bind selectively to the 1,2-GG or 1,2-AG adducts of cisplatin, but not to its 1,3-intrastrand cross-links. Extensive reviews addressing these questions have been recently published. They are, however, also recognized by a number of proteins which could block DNA adducts of cisplatin from damage recognition needed for repair Figure In this way these adducts can persist for sufficient time, which potentiates the anti-tumor effect of the drug. The other hypothesis based on the observation that a number of various proteins recognize cisplatin-modified DNA is that cisplatin-DNA adducts hijack proteins away from their normal binding sites, thereby disrupting fundamental cellular processes Figure Experimental support for these hypothetical aspects of the mechanism underlying anti-tumor activity of cisplatin or resistance of some tumors to this drug has been thoroughly reviewed recently. However, since apoptosis is a very complex process, a number of possible pathways still have to be explored for a complete understanding of the mechanism by which cisplatin triggers apoptosis. All the same, once you comprehend the causes of cancer and learn how to reverse those causes, you or your loved

one may have more than a fighting chance of beating out cancer.

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ABSTRACT. Carboplatin is a derivative of cisplatin; it has a similar mechanism of action, but differs in terms of structure and toxicity. It was approved by the FDA in the s and since then it has been widely used in the treatment of several tumor types.

Abstract Cisplatin, cisplatinum, or cis-diamminedichloroplatinum II , is a well-known chemotherapeutic drug. It has been used for treatment of numerous human cancers including bladder, head and neck, lung, ovarian, and testicular cancers. It is effective against various types of cancers, including carcinomas, germ cell tumors, lymphomas, and sarcomas. Its mode of action has been linked to its ability to crosslink with the purine bases on the DNA; interfering with DNA repair mechanisms, causing DNA damage, and subsequently inducing apoptosis in cancer cells. However, because of drug resistance and numerous undesirable side effects such as severe kidney problems, allergic reactions, decrease immunity to infections, gastrointestinal disorders, hemorrhage, and hearing loss especially in younger patients, other platinum-containing anti-cancer drugs such as carboplatin, oxaliplatin and others, have also been used. Furthermore, combination therapies of cisplatin with other drugs have been highly considered to overcome drug-resistance and reduce toxicity. This comprehensive review highlights the physicochemical properties of cisplatin and related platinum-based drugs, and discusses its uses either alone or in combination with other drugs for the treatment of various human cancers. A special attention is given to its molecular mechanisms of action, and its undesirable side effects. Cisplatin, Platinum-based drugs, Mechanisms of action, Cancer treatment 1. It is a white or deep yellow to yellow-orange crystalline powder at room temperature. It is slightly soluble in water and soluble in dimethylprimanide and N,N-dimethylformamide. Cisplatin is stable under normal temperatures and pressures, but may transform slowly over time to the trans-isomer IARC , Akron Cisplatin has a molecular weight of Cisplatin was first synthesized by M. Peyrone in and its chemical structure was first elucidated by Alfred Werner in Since the identification of cis-dichlorodiammineplatinum II cisplatin, r as the agent responsible for this activity, much interest has been generated in the use of coordination complexes of platinum, palladium, and other noble metals in the treatment of cancer. It was discovered to have cytotoxic properties in the s, and by the end of the s it had earned a place as the key ingredient in the systemic treatment of germ cell cancers. Among many chemotherapy drugs that are widely used for cancer, Cisplatin is one of the most compelling ones. It was the first FDA-approved platinum compound for cancer treatment in Kelland, This has led to interest in platinum II - and other metal-containing compounds as potential anticancer drugs Frezza, Hindo et al. Cisplatin is clinically proven to combat different types of cancers including sarcomas, cancers of soft tissue, bones, muscles, and blood vessels. Although such cancers have recently received better prognosis and therefore have become less life threatening Desoize and Madoulet, , significant challenges remain with regard to their cure. Also, because of drug resistance and considerable side effects, combination therapy of cisplatin with other cancer drugs have been applied as novel therapeutic strategies for many human cancers. In this research, we aim to provide a comprehensive review of the physicochemical properties of cisplatin and related platinum-based drugs, to discuss its uses either alone or in combination with other drugs for the treatment of various human cancers, to examine its molecular mechanisms of action, and to discuss it potential side effects. Cisplatin and Other Platinum-Containing Drugs Since the early seminal work in the preclinical and clinical development of cisplatin, several thousand analogues have been synthesized and tested for properties that would enhance its therapeutic index. About 13 of these analogues have been evaluated in clinical trials, but only one carboplatin has provided definite advantage over cisplatin and achieved worldwide approval. Figure 1 presents the chemical structures of cisplatin and four of its analogs including carboplatin, oxaliplatin, ormaplatin and enloplatin.