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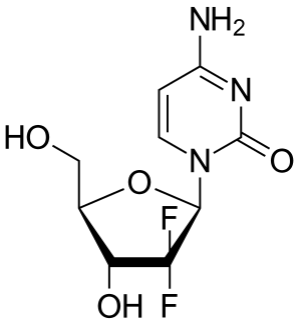
Gemcitabine

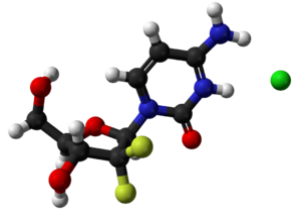
Gemcitabine, sold under the brand name **Gemzar**, among others,[1] is a chemotherapy medication used to treat a number of types of cancer.[2] These cancers include breast cancer, ovarian cancer, non-small cell lung cancer, pancreatic cancer, and bladder cancer.[2][3] It is given by slow injection into a vein.[2]

Common side effects include bone marrow suppression, liver and kidney problems, nausea, fever, rash, shortness of breath, and hair loss.[2] Use during pregnancy will likely result in harm to the baby.[2] Gemcitabine is in the nucleoside analog family of medication.[2] It works by blocking the creation of new DNA, which results in cell death.[2]

Gemcitabine was patented in 1983 and was approved for medical use in 1995.[4] Generic versions were introduced in Europe in 2009 and in the US in 2010.[5][6] It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.[7] The wholesale cost in the developing world is about US$24.41 to $316.99 per gram vial.[8] In the United Kingdom a 1 g vial costs the NHS approximately £155.[9]

Gemcitabine





Clinical data	
Pronunciation	/dʒɛm'saɪtəbi ː n/
Trade names	Gemzar, others[1]
Synonyms	2', 2'-difluoro 2'deoxycytidine, dFdC
AHFS/Drugs.com	Monograph (https://www.drugs.com/monograph/gemcitabine-hydrochloride.html)
Pregnancy	AU: D

Contents

Medical uses

Gemcitabine is used in various carcinomas. It is used as a first-line treatment alone for pancreatic cancer, and in combination with cisplatin for advanced or metastatic bladder cancer and advanced or metastatic non-small cell lung cancer. It is used as a second-line treatment in combination with carboplatin for ovarian cancer and in combination with paclitaxel for breast cancer that is metastatic or cannot be surgically removed.[10][11][12]

It is commonly used off-label to treat cholangiocarcinoma[13] and other biliary tract cancers.[14]

It is given by injection into a vein at a chemotherapy clinic.[2]

Contraindications and drug interactions

Taking gemcitabine can also affect fertility in men and women, sex life, and menstruation. Women taking gemcitabine should not become pregnant, and pregnant and breastfeeding women should not take it.[15]

As of 2014 drug interactions had not been studied.[11][10]

Adverse effects

Gemcitabine is a chemotherapy drug that works by killing any cells that are dividing.[10] Cancer cells divide rapidly and so are targeted at higher rates by gemcitabine, but many essential cells divide rapidly as well, including cells in skin, the scalp, the lining of the stomach, and bone marrow, resulting in adverse effects.[16]:265

The gemcitabine label carries warnings that it can suppress bone marrow function and cause loss of white blood cells, loss of platelets, and loss of red blood cells, that it should be used carefully in people with liver, kidney, or cardiovascular disorders, that people taking it should not take live vaccines, that it may cause posterior reversible encephalopathy syndrome, that it may cause capillary leak syndrome, that it may cause severe lung conditions like pulmonary edema, pneumonia, and adult respiratory distress syndrome, and that it may harm sperm.[10][17]

Very common (more than 10% of people develop them) adverse effects include difficulty breathing, low white and red blood cells counts and low platelet counts, vomiting and nausea, elevated transaminases, rashes and itchy skin, hair loss, blood and protein in urine, flu-like symptoms, and edema.[10][15]

Common adverse effects (occurring in 1–10% of people) include fever, loss of appetite, headache, difficulty sleeping, tiredness, cough, runny nose, diarrhea, mouth and lip sores, sweating, back pain, and muscle pain.[10]

Pharmacology

category	US: D (Evidence of risk)
Routes of administration	Intravenous
ATC code	L01BC05 (WHO (https://www.whocc.no/atc_ddd_index/?code=L01BC05))
Legal status	
Legal status	AU: S4 (Prescription only) UK: POM (Prescription only) US: ℞-only In general: ℞ (Prescription only)
Pharmacokinetic data	
Protein binding	<10%
Elimination half-life	Short infusions: 32-94 minutes Long infusions: 245-638 minutes
Identifiers	
IUPAC name	
CAS Number	95058-81-4 (http://www.commo

Gemcitabine is hydrophilic and must be transported into cells via molecular transporters for nucleosides (the most common transporters for gemcitabine are SLC29A1 SLC28A1, and SLC28A3).[18][19] After entering the cell, gemcitabine is first modified by attaching a phosphate to it, and so it becomes gemcitabine monophosphate (dFdCMP).[18][19] This is the rate-determining step that is catalyzed by the enzyme deoxycytidine kinase (DCK).[18][19] Two more phosphates are added by other enzymes. After the attachment of the three phosphates gemcitabine is finally pharmacologically active as gemcitabine triphosphate (dFdCTP).[18]

After being thrice phosphorylated, gemcitabine can masquerade as cytidine and is incorporated into new DNA strands being synthesized as the cell replicates.[2][18][19]

When gemcitabine is incorporated into DNA it allows a native, or normal, nucleoside base to be added next to it. This leads to "masked chain termination" as gemcitabine is a "faulty" base, but due to its neighboring native nucleoside it eludes the cell's normal repair system (base-excision repair). Thus, incorporation of gemcitabine into the cell's DNA creates an irreparable error that leads to inhibition of further DNA synthesis, and thereby leading to cell death.[2][18][19]

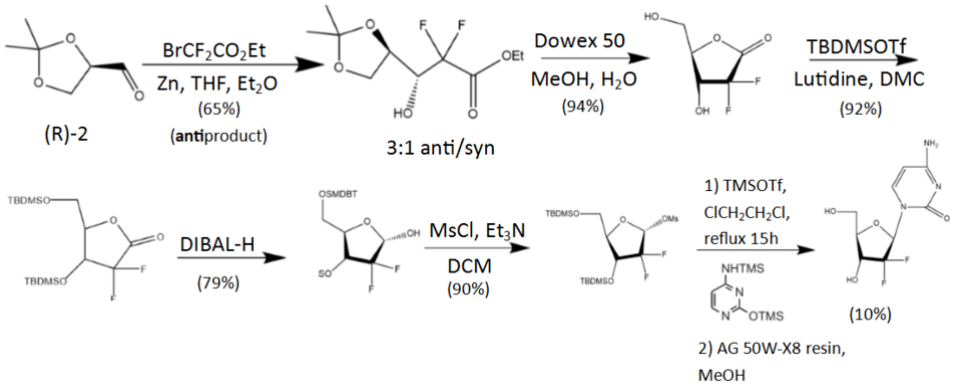
The form of gemcitabine with two phosphates attached (dFdCDP) also has activity; it inhibits the enzyme ribonucleotide reductase (RNR), which is needed to create new nucleotides. The lack of nucleotides drives the cell to uptake more of the components it needs to make nucleotides from outside the cell, which increases uptake of gemcitabine as well.[2][18][19][20]

Chemistry

Gemcitabine is a synthetic pyrimidine nucleoside prodrug—a nucleoside analog in which the hydrogen atoms on the 2' carbon of deoxycytidine are replaced by fluorine atoms.[2][21][22]

The synthesis described and pictured below is the original synthesis done in the Eli Lilly Company labs. Synthesis begins with enantiopure D-glyceraldehyde (R)-2 as the starting material which can made from D-mannitol in 2–7 steps. Then fluorine is introduced by a "building block" approach using ethyl bromoidfluroacetate. Then, reformatsky reaction under standard conditions will yield a 3:1 anti/syn diastereomeric mixture, with one major product. Separation of the diastereomers is carried out via HPLC, thus yielding the anti-3 gemcitabine in a 65% yield.[21][22] At least two other full synthesis methods have also been developed by different groups.[22]

	nchemistry.org/ChemicalDetail.aspx?ref=95058-81-4) ✓
PubChem CID	60750 (https://pubchem.ncbi.nlm.nih.gov/compound/60750)
IUPHAR/BPS	4793 (http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=4793)
DrugBank	DB00441 (https://www.drugbank.ca/drugs/DB00441) ✓
ChemSpider	54753 (http://www.chemspider.com/Chemical-Structure.54753.html) ✓
UNII	B76N6SBZ8R (https://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=B76N6SBZ8R)
KEGG	D02368 (http://www.kegg.jp/entry/D02368) ✓



Illustrates the original synthesis process used and published by Hertel et al. in 1988 of Lilly laboratories.

History

Gemcitabine was first synthesized in Larry Hertel's lab at Eli Lilly during the early 1980s. It was intended as an antiviral drug, but preclinical testing showed that it killed leukemia cells *in vitro*.[23]

During the early 1990s gemcitabine was studied in clinical trials. The pancreatic cancer trials found that gemcitabine increased one-year survival time significantly, and it was approved in the UK in 1995[10] and approved by the FDA in 1996 for pancreatic cancers.[3] In 1998, gemcitabine received FDA approval for treating non-small cell lung cancer and in 2004, it was approved from metastatic breast cancer.[3]

European labels were harmonized by the EMA in 2008.[24]

By 2008, Lilly's worldwide sales of gemcitabine were about $1.7 billion; at that time its US patents were set to expire in 2013 and its European patents in 2009.[25] The first generic launched in Europe in 2009,[5] and patent challenges were mounted in the US which led to invalidation of a key Lilly patent on its method to make the drug.[26][27] Generic companies started selling the drug in the US in 2010 when the patent on the chemical itself expired.[27][6] Patent litigation in China made headlines there and was resolved in 2010.[28]

Society and culture

ChEBI	CHEBI:175901 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:175901) ✓
ChEMBL	CHEMBL888 (https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/CHEMBL888) ✓
ECHA InfoCard	100.124.343 (https://echa.europa.eu/substance-information/-/substanceinfo/100.124.343)
Chemical and physical data	
Formula	$C_9H_{11}F_2N_3O_4$
Molar mass	263.198 g/mol
3D model (JSmol)	Interactive image (https://chemapps.stolaf.edu/jmol/jmol.php?model=c1cn%28c%28%3DO%29nc1N%29%5BC%40H%5D2C%28%5BC%40%40H%5D%28%5BC%40H%5D%28O2%29CO%29

	O%29%28F%29F)
SMILES	
InChI	
	(verify)

As of 2017, gemcitabine was marketed under many brand names worldwide: Abine, Accogem, Acytabin, Antoril, axigem, Bendacitabin, Biogem, Boligem, Celzar, Citegin, Cytigem, Cytogem, Daplax, DBL, Demozar, Dercin, Emcitab, Enekamub, Eriogem, Fotinex, Gebina, Gemalata, Gembin, Gembine, Gembio, Gemcel, Gemcetin, Gemcibine, Gemcikal, Gemcipen, Gemcired, Gemcirena, Gemcit, Gemcitabin, Gemcitabina, Gemcitabine, Gemcitabinum, Gemcitan, Gemedac, Gemflor, Gemful, Gemita, Gemko, Gemliquid, Gemmis, Gemnil, Gempower, Gemsol, Gemstad, Gemstada, Gemtabine, Gemtavis, Gemtaz, Gemtero, Gemtra, Gemtro, Gemvic, Gemxit, Gemzar, Gentabim, Genuten, Genvir, Geroam, Gestredos, Getanosan, Getmisi, Gezt, Gitrabin, Gramagen, Haxanit, Jemta, Kalbezar, Medigem, Meditabine, Nabigem, Nallian, Oncogem, Oncoril, Pamigeno, Ribozar, Santabin, Sitagem, Symtabin, Yu Jie, Ze Fei, and Zefei.[1]

Research

Because it is clinically valuable and is only useful when delivered intravenously, methods to reformulate it so that it can be given by mouth have been a subject of research.[29][30][31]

Research into pharmacogenomics and pharmacogenetics has been ongoing. As of 2014, it was not clear whether or not genetic tests could be useful in guiding dosing and which people respond best to gemcitabine.[18] However, it appears that variation in the expression of proteins (SLC29A1, SLC29A2, SLC28A1, and SLC28A3) used for transport of gemcitabine into the cell lead to variations in its potency. Similarly, the genes that express proteins that lead to its inactivation (deoxycytidine deaminase, cytidine deaminase, and NT5C) and that express its other intracellular targets (RRM1, RRM2, and RRM2B) lead to variations in response to the drug.[18] Research has also been ongoing to understand how mutations in pancreatic cancers themselves determine response to gemcitabine.[32]

It has been studied as a treatment for Kaposi sarcoma, a common cancer in people with AIDS which is uncommon in the developed world but not uncommon in the developing world.[33]

See also

- IMM-101

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