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The Drug

The path to curing cancer has been a long and expensive one. While the discovery of a universal cure is currently being strongly pursued, several treatments have been created to treat the various subtypes of this disease. One of these treatments includes the drug capecitabine. Capecitabine otherwise known as xeloda is a chemotherapeutic agent that is taken orally. The ability of this chemotherapeutic agent to be taken orally instead of intravenously is convenient to patients and also indicates that the stomach is able to absorb this drug. Xeloda falls under the classification of a prodrug in which it enters the body as an inactive compound that is later converted into an active compound upon metabolism. Xeloda enters the body as pentyloxycarbonyl-5′-deoxy-5-fluorocytidine (CAP). This compound is designed to pass through mucosal membranes unaltered and capitalize on the enhanced enzymatic activity found in cancer cells to better produce the active form of this drug. Many of these enzymes operate optimally in cancerous cell therefore xeloda specifically targets cancerous cells. This drug undergoes three enzyme modulated conversion reactions (Mainly in the liver) in which carboxylesterase converts 5′-deoxy-5-fluorouridine to 5′-deoxy-5-fluorocytidine (5′-DFCR). Cytidine deaminase then converts 5′-DFCR to 5′-deoxy-5-fluorouridine (5′-DFUR). Lastly circulating 5′-DFUR is converted to the active 5-fluorouracil compound (5-FU) through the use of thymidine phosphorylase. This product will prevent the manufacture of new DNA and RNA thereby inhibiting DNA replication and slowing the rate of cell growth and cancer (Desmoulin et al., 2002).

The Disease

The disease cancer is caused by an uncontrollable increase in the rate of cell division. This often leads to abnormal cell sizes and cell counts in areas where high cell division does not normally occur. Increasing the size and rate of cell growth has great consequences on the cell as maintaining normal metabolic and cellular functions grow more difficult. Often the loss of cellular function and eventually organ function occurs. Unfortunately this disease is not constraint to one location as one of this diseases greatest properties is its ability to metastasize to new tissue. Through the use of the circulatory or lymphatic systems, malignant cancer cells can break free of infected tissue and invade other areas of the body. Cancer has also proven to be quite adaptable. As new anti-cancer drugs arise the cancer cells are exposed to different selection pressures. While the majority of the cancer cells may die those that survive produce a new resistant strain through the processes of clonal expansion, clonal selection and genetic diversification (Greaves, 2012). Therefore, when combining its detrimental effects on cellular functions and its ability to evade many treatments, it is no surprise that this disease claims millions of lives each year.

One major form of cancer that xeloda is specifically used for is breast cancer. The two major forms of breast cancer are ductal carcinoma and lobular carcinoma. Ductal carcinoma is the more prevalent of the two conditions and is classified as cancer cells that infect the lining of the milk ducts. Lobules are the structures that supply milk to the milk ducts; therefore lobular carcinoma is the invasion of lobular cells with cancerous cells. However both of these types of cancer originate from the terminal duct lobular unit, thus the terminology given to each form of cancer can be misleading (Sainsbury et al., 1994). There are two types of ductal carcinoma. Invasive ductal carcinoma (IDC) occurs when cancer cells in the milk ducts invade the tissue of the breast and is thus able to metastasize across the body by using the circulatory or lymphatic system. Ductal Carcinoma in situ (DCIS) is the non-invasive form of breast cancer in which the cancer cells have not invaded the breast tissue and therefore will remain localized within the milk ducts. Unlike ductal carcinoma, invasive lobular carcinoma (ILC) is the only form of cancer for the lobular cells in which cancer cells that originate in milk-producing glands invade other areas of the organism (Yelland et al., 1991).

The other major form of cancer that xeloda is used as treatment for is colon cancer. Colon cancer occurs within the tissues of the colon and rectum, where rapid cell growth prohibits normal function. Common symptoms of this disease include rectal bleeding, constipation, loss of weight and anemia. Colon cancer
is not restricted to the tissue of the gastrointestinal tract as by a similar manner to breast cancer. Through the invasion of cancer cells through the bowel walls, the cancer is able to metastasize to other areas of the body using the circulatory and lymphatic systems (Stefanik, 2000).

The Discovery Process

In an effort to help treat both breast and colon cancer non-specific chemotherapeutics are used. While many different types of chemotherapy exist, chemists are looking to find novel pharmaceuticals that both enhance the effects of the drug and reduce the amount of strain that the patient must endure. Xeloda was synthesized for the purpose of hopefully providing these improvements by increasing the drugs specificity for cancerous cells and reducing the strain endured by the patients by option of an oral treatment instead of an intravenous treatment. Xeloda and its intermediate 5′-deoxy-5-fluorouridine (5′-DFUR) are prodrugs of 5-fluourouracil (5-FU). However simply using 5-fluourouracil alone is not effective as it uses the enzyme dihydropyrimidine dehydrogenase. This enzyme is not selective for cancerous cells and will often damage epithelial cells, bone marrow and many other healthy cell types. Therefore the need for a pharmaceutical that can bypass this enzyme was well needed and pursued. In 1993 the first active compound of xeloda was synthesized by Nippon Roche at the Kamakura Research Centre (Jarosinka et al., 2011). The main feature of this new compound was its ability to concentrate 5-fluorouracil inside tumor cells, thus vastly increasing the specificity of this cytotoxic drug. The chemists were able to accomplish this feature by bypassing the enzymedihydropyrimidine dehydrogenase using three enzymes that are specific for tumor cells. This therefore decreases the amount of collateral damage to other cells. Although this drug was synthesized in 1993, it was not until 2005 that the Food and Drug Administration approved xeloda as a treatment for colon and breast cancer.

Synthetic Synthesis of Xeloda

Xeloda was first synthesized from D-ribose and cytosine compounds in a series of sequential chemical reactions which ultimately bore an 18% chemical yield of the drug. D-ribose is first introduced to methanol and acetone in a highly acidic environment. This transforms D-ribose into methyl-(2,3-O-isopropyliden-D-ribofuranoside). This compound was then treated with tosyl chloride in a pyridine medium which creates a tosylate structure. Reaction of the tosylate with sodium iodide converts this intermediate compound into an iodide methyl type compound. This compound is then reduced using hydrogen gas with palladium producing methyl-(5-deoxy-2,3-O-isopropyliden-D-ribofuranoside). This is then hydrolyzed using an acidic solution and reacted with acetic anhydride. To remove any impurities from the compound at this point in xeloda synthesis the melting point of the compound was exploited such that the purified product could be obtained through recrystallization (Fei et al., 2004).

Upon the purification of the main compound tested, the chemists had synthesized a major intermediate compound in 5-deoxy-1,2,3-tri-O-acetyl-D-ribofuranose. While this compound was initially tested for efficacy it was determined that this compound was not an efficient chemotherapeutic. Therefore further modifications were necessary. While many minor modifications were made thus producing many similar derivative structures, three specific modifications were found to increase the affinity of this compound for the desired enzyme thus resulting in the production of more product compound. These modifications include glycosidation of the compound using 1,2,3-tri-O-acetyl-5-deoxyribose, acylation of the compound and hydrolysis of an acetyl group (Shimma et al., 2000).

Every chemical reaction and modification currently reported has been performed to chemically alter the initial D-ribose compound. The next sequences of modifications involve the initial compound of cytosine. Cytosine is first transformed into 5-nitrocytosine using nitric and sulfuric acid. This compound is then reacted with 1,1,1,3,3,3-hexamethyldisilazane which will produce the compound 5-nitrocytosine trimethylsilyl. This final compound of the cytosine pathway is now reacted with the final compound produced in the D-ribose pathway to produce the standard xeloda product. Upon minor modifications the final xeloda structure of pentyloxy carbonyl-5′-deoxy-5-fluorocytidine was created (Fei et al., 2004).

Trials Animal Testing

Similar to many other drugs that have a significant impact on human, xeloda had to undergo animal testing before being approved for clinical trials. Using primarily mice and monkeys the efficacy of the 5′-DFCR compound to undergo enzymatic conversion with the enzyme carboxylesterase and many of its
derivatives were tested. The two compounds that stood out as having a high susceptibility to carboxylesterase were capecitabine (Xeloda) and a derivative compound in galocitabine. In isolated animal tissues where the appropriate enzymes are found galocitabine was found to be much more effective than capecitabine in mice. However, what was troubling about this derivative was the inability for the drug to cross the specific tissue membranes in a full living system as a very large percentage of the drug was found in both the monkey's and mice's blood. Thus this certain derivative was deemed ineffective in living systems. For capecitabine however, very low amounts of his compound was found trapped in the blood plasma. Therefore combining this with capecitabine's high susceptibility for carboxylesterase made capecitabine the greatest choice to move forward with (Shimma et al., 2000).

Testing the efficacy of this drug in animals afflicted with specific tumors was the next area of research that needed conducting. Upon artificially inducing tumors in several mice vectors, different dosages of this drug along with several structurally similar drugs were administered to each specimen to find the optimal concentration at which this drug operates, to observe which drug had the greatest impact on host survival and to determine at what concentration this pharmaceutical becomes toxic. Unsurprisingly capecitabine proved to be the most effective agent in keeping its hosts alive and reducing tumors. However the dosages recorded were of little importance in the application of the drug to higher organisms (Kolinsky et al., 2009).

Clinical Trials Phases

Clinical Trials Phase One

Upon the efficacy of capecitabine in animals being determined, the next phase was to determine the effects and efficiency of this drug on human patients. Since chemotherapeutics are highly toxic, phase one trials began on individuals who were unhealthy and had been diagnosed with either breast or colon cancer. Upon testing patient blood and tissue samples they determined that the maximum tolerated dose of xeloda was found to be 3000 mg/m² when administered once a day for 2 weeks, followed by one week of no treatment. Common symptoms that indicated that the concentration was beginning to become toxic were diarrhea and leukopenia. Before treating patients with xeloda, researchers first found out the overall resistance that the participants had to other chemotherapeutics such as paclitaxel and anthracycline. Patients who were resistant to both of these drugs were then introduced to xeloda and the overall response rate and survival of these patients significantly increased. The amount of side effects suffered by patients also decreased when using xeloda and the percentage of drug failures drastically declined from approximately 50% in the paclitaxel and anthracycline to approximately 10% in xeloda. In addition to this certain dosage levels were determined that revealed levels of efficacy and levels of toxicity.

Clinical Trials Phase Two:

This phase of trials was performed to determine the response rate, toxicity and overall survival rate of xeloda in patients with the appropriate cancer. For the patients to be eligible for inclusion in this study they must be 18 years or older and have the specific cancer without having undergone any other form of treatment for at least a year. The treatments began with patients taking xeloda twice daily for two weeks at a concentration of 1000 mg/m². However this concentration proved to be too toxic for patients as they experienced symptoms of diarrhea and neutropenia thus the concentration was reduced to 900 mg/m². These treatments were administered for 36 weeks where at every two week interval the patients' blood was tested and the size of their tumor measured. Upon gathering all data and running statistical analyses, it was apparent that xeloda at 900 mg/m² was effective for treating people affected with colorectal and breast cancer as the tumor response rate was much greater than the researchers initially predicted. When using this treatment, the median time until disease progression (For those who the drug failed) was also approximately one and a half months longer and the time taken for the drug to fail was approximately two and a half months longer than other treatments. The overall survival time of the patients were also significantly longer than other treatments. Finally upon further analyses of tumor cells, it was evident that there was increased expression of thymidine phosphorylase in patients treated with xeloda. This enzyme contributes to the increased survivability and delayed disease progression in patients (Meropol et al., 2006).

Clinical Trials Phase Three:

This last phase is conducted to test the effects of this drug on a larger scale and to gain some consistency on their prior results. The effects of xeloda were tested on patients along with the effects of the intravenous bolus fluorouracil plus leucovorin, as this drug was the standard treatment for colon cancer. This phase of trials includes 1987 patients who are 18 years or older. Of these patients, 1004 people randomly received oral
capecitabine (Xeloda) while the remaining 983 participants received bolus fluorouracil plus leucovorin. Patients treated with xeloda were given dosages of 1250 mg/m² twice daily and those given bolus fluorouracil plus leucovorin were given dosages of 20mg/m² followed immediately by a dose of 425 mg/m² for the first five days in a 28 day cycle. Patients were examined every six months for two years through the use of thoracic radiography. Upon large scale analysis of the patients and statistical analyses of the results it was evident that xeloda is slightly more capable than fluorouracil plus leucovorin at completely eradicating the disease in patients as the rate of disease-free survival is 64.2 percent in xeloda as opposed to 60.6 percent in the alternative. In addition to this, relapse-free survival in capacetabine was greater than in fluorouracil plus leucovorin. Most importantly the overall survival rate was slightly greater in xeloda at 81.3 percent as opposed to fluorouracil plus leucovorin at 77.6 percent (Twelves et al., 2005). Therefore from this particular study it appears that xeloda is a better treatment option than the standard treatment. When comparing these results to many other similar studies taken in different areas of the world it is very clear that xeloda is the better option for colon cancer treatment.

ADMET

The ability of any drug to be absorbed, properly distributed, metabolized and exit the body is essential for any drug to perform its function properly. By examination of blood and tissue samples from patients treated with xeloda, researchers determined that xeloda reaches peak concentration in blood 90 minutes after consumption and the levels of the final 5-fluorouracil reach its maximal value 120 minutes after consumption. One of the greatest features of xeloda is its ability to be absorbed through the stomach. This occurs by the process of disintegration in which the pill is completely broken down in the stomach and absorbed here. This drug can be absorbed in the intestines if the pill does not disintegrate. However when any food is taken with this drug, the concentration of both compounds are drastically reduced in the body as absorption is interfered with.

Another great feature xeloda possesses is its specificity in its distribution pattern. Once xeloda is absorbed through the gastrointestinal tract, the compound enters the blood stream so that it may be distributed throughout the body. Since this compound’s main enzymes (carboxylesterase, cytidine deaminase and thymidine phosphorylase) involved in its conversion to 5-fluorouracil operate optimally in cancer cells, xeloda is able to concentrate 5-fluorouracil within cancer cells. Therefore healthy cells are fairly well excluded from cytotoxic attack. While these three enzymes aid in the specificity of this drug in interacting with cancer cells, they are also pivotal enzymes that cause the metabolism of starting material pentyloxy carbonyl-5′-deoxy-5-fluorocytidine to the active 5-fluorouracil compound (See Page One “The Drug”).

Once the 5-fluorouracil has performed its function it must exit the body before toxic concentrations accumulate. Approximately 97 percent of this drug is excreted in the urine with the remaining percentage excreted in the feces. Instead of simply excreting 5-fluorouracil, this compound undergoes enzyme-catalyzed conversion to the less toxic 5-fluoro-5,6-dihydro-fluorouracil compound. This is then converted to 5-fluoro-ureido-propionic acid by dihydropyrimidinase and finally converted to α-fluoro-β-alanine. This compound is the major form of xeloda found in urine.

As mentioned earlier, toxic concentrations of xeloda in the body usually cause diarrhea and cardiotoxicity. However other common effects of toxic concentrations include renal insufficiency, birth defects, neutropenia and many other serious symptoms.

References


Illustrations

Illustration 1

Figure 1: This illustrates the pathway the xeloda undergoes in the body.
Illustration 2

Figure 2: This illustrates where the cancer cells invade breast tissue.
This figure illustrates the superiority of xeloda over FPL. It has greater survivor rate and lesser fail rate. Twelves, C.; Wong, A.; Burris, H.; Cassidy, J.; et al. Capecitabine as adjuvant treatment for stage III colon cancer.