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Research question: A comparison of Fluorouracil and Docetaxel in the treatment of gastric cancer

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Abstract. Cancer is a serious lethal disease that is prevalent worldwide. This disease is mainly due to the development of abnormal cells that divide without any control. These abnormal cells, also known as tumor cells, can destroy normal body tissue. Causing numerous deaths around the world. Gastric cancer, commonly known as stomach cancer, is the cancer to be discussed in depth in this essay. It is one of the most prevalent and lethal cancers worldwide. Its cases and mortality rates vary significantly across different regions, reflecting differences in diet, genetics, and medicine access. Gastric cancer presents substantial challenges in medical treatment. The disease's complexity also leads to the exploration of various treatment methods. Among many pharmacological options, Fluorouracil and Docetaxel are two significant medicines that are worth discussing in depth. Fluorouracil and Docetaxel are both used in chemotherapy. However, they have distinct mechanisms and properties. Fluorouracil is a pyrimidine analog used to inhibit DNA synthesis of cancerous cells, while Docetaxel is a taxane that targets microtubules. They all played a vital role in treating cancer. Nevertheless, their comparative effectiveness and safety remain in debate. This essay aims to provide a depth comparison of Fluorouracil and Docetaxel. Focusing on their chemical structure, mechanisms of action, delivery modes, resistance, and toxicity, in the treatment of gastric cancer. Offering a better comprehension of two drugs, which are used for their optimal use in patient care.

Keywords: Gastric cancer, Fluorouracil, Docetaxel, Chemotherapy.

1. Introduction

Before the comparison of Fluorouracil and Docetaxel in the treatment of gastric cancer, a basic understanding of cancer and the stomach is needed.

Cancer affects 1/3 of people in the United States, which is a pretty high percentage.

Cancer cells can develop because of mutation. Mutations can happen because of the presence of cancer-causing agents. Mutations are random changes to the base sequence of genes. After mutation, cells can become cancerous. These cells will undergo uncontrolled cell division. Forming tumors. Just like Figure 1. showed.

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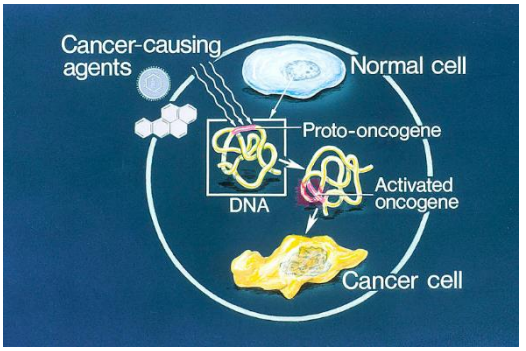

Figure 1. The process of cancer cell formation

Cancer can develop from many different parts of your body, such as the breast, lungs, stomach, or even from blood. They are mainly categorized into two types: hematologic (blood) cancers and solid tumor cancers.

Solid tumor cancer is the cancer type that will be discussed in this passage. To better understand what sold tumor cancers are, some information about tumors is needed to know. A Tumor is a lump. Lumps are more common, but not all lumps are cancer. The tumors that will spread to other parts of the body are called malignant, which is cancer. For other tumors that will not spread are called benign. [1]

The stomach plays an important role in the process of digestion. Once food has been chewed and swallowed. It passes through the esophagus to the stomach. The connection point at the end of the esophagus is the gastroesophageal junction (shown in Figure 2.), which is located just under the diaphragm (thin muscle used for breathing below the lungs). After food moves down to the stomach, digestive juices known as gastric juice are secreted by the innermost layer called mucosa. Most stomach cancers may also start in this layer. This gastric fluid is acidic and has a pH of 1.5 to 3.5, killing most of the bacteria in the stomach. Food begins to break down in the stomach. After about 4 hours, this mixture of food and gastric juice is transferred to the small intestine. The first part of the small intestine is also known as the duodenum.

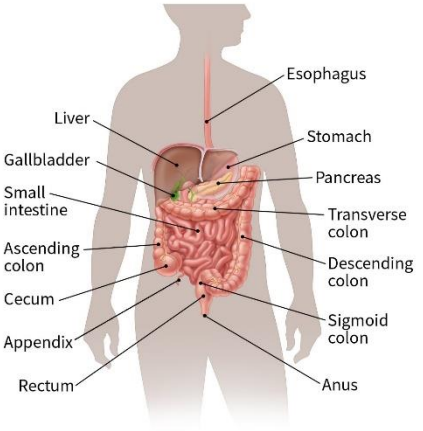

Figure 2. The digestive system of human

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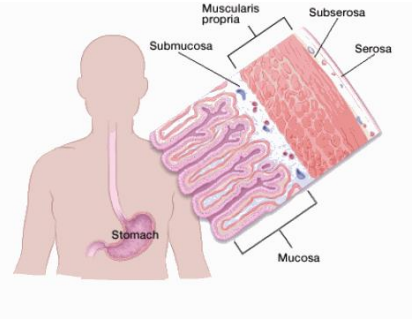

Figure 3. Layers of stomach

2. Overview of Disease

Gastric cancer always develops slowly for many years. There are several different gastric cancers, including Adenocarcinoma, Gastrointestinal stromal tumors, Neuroendocrine tumors, and Lymphomas. The most common type is called **adenocarcinoma (The type of gastric cancer I will focus on)**. Above 90% of gastric cancers are adenocarcinoma. They develop from the gland cells in the inner lining of the stomach, which is mucosa. [2]

Symptoms:

At the most early stage, gastric cancer usually doesn't have symptoms, which makes it hard to detect. The symptoms that can be noticed usually show up after the cancer has spread. However, some symptoms do occur in the early stage of gastric cancer. They may include, indigestion and stomach discomfort, a bloated feeling after eating, mild nausea, or loss of appetite. More severe symptoms will occur in advanced stomach cancer (cancer has been spread to other parts of the body). This may include the most of symptoms in early-stage gastric cancer, and also blood in the stool, vomiting, weight loss, stomach pain, jaundice (yellowing of eyes and skin), or trouble swallowing. [3]

Impact and Number of Mortalities:

According to the data from the World Cancer Research Fund International (WCRF), there were 1,089,103 new cases in 2020, and gastric cancer cases are fifth place in cancer-related diseases. And it ranks as the third leading cause of cancer-related deaths. In 2020, it was responsible for 768,793 deaths, reflecting both its high incidence and low survival rates. The five-year survival rate varies ranging from the lowest 10% to 30% in the highest cases. [4]

Significance in China and Other Countries in the World:

Gastric cancer's impact is global, but especially common in Asia. In 2020, the top six ASR (age-standardized rates)/100,000 were both Asia countries. Tables 1. and 2. below show the detailed case number in different countries. [5]

Risk Factors:

Many factors are closely related to gastric cancer, such as smoking, excessive alcohol consumption, high salt diet, Helicobacter pylori infection, and genetic inheritance. Both of them can increase the chance of mutations. Leading to more formation of tumors. [6]

Helicobacter pylori infection is a significant factor in causing gastric cancer, affecting about 50% of the population in the world. Although most of the infected people remain symptomless, still a small proportion lead to gastric cancer. Studies have shown that treating H. pylori infection can reduce the risk of gastric cancer. The infection can cause inflammation, and oxidative damage, and even lead to the silencing of tumor-suppressing genes.

Other factors like diet and other lifestyle will also contribute to gastric cancer. High ingestion of certain substances like starch, fat, meat, salt, and N-nitroso compounds increases the risk of getting gastric cancer. The digestion process in the stomach can form N-nitroso compounds. Salt-preserved food can also damage the stomach lining, enhancing the risk of H. pylori infection. Increasing the change of gastric cancer. [7]

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Table 1. World cancer cases in 1997 (Female)

	China, Beijing	Algeria, Algiers	UK England	USA, California (Non-Hispanic White)	Brazil, Campinas	Australian Capital Territory
No. Cases	768	155	16,159	669	212	40
Freq.	7.5	4.3	3.1	1.3	6.8	1.9
ASR world (per 100,000)	8.7	3.7	4.9	3.1	10.3	4.5

Table 2. World cancer cases in 1997 (Male)

	China, Beijing	Algeria, Algiers	UK England	USA, California (Non-Hispanic White)	Brazil, Campinas	Australian Capital Territory
No. Cases	1,719	211	27,209	1,120	328	64
Freq.	14.3	6.2	5.2	2.1	11.3	2.6
ASR world (per 100,000)	19.8	5.6	13.1	7.3	21.2	9.1

3. Pathology of the Disease

p53 pathway:

Gene mutations are vital parts of the transformation of normal cells into cancer cells. The TP53 gene, which is encoded for the p53 protein, is mutated in gastric cancer. This protein regulates cell cycles and its inactivity is central to many cancers, including gastric cancer. Mutations or loss of the TP53 gene are more common in gastric cancer, compared to DNA methylation. P53 It's an oncogene. The loss of TP53 and other related genes like p21 can indicate that the p53 pathway has a significant part might developing gastric cancer.

PI3 kinase/Akt pathway:

The PI3 kinase and Akt pathway are crucial in cell metabolism and growth. They are often involved in tumorigenesis. The activation occurs through various processes, including gene mutations. The PIK3CA subunit plays an important role in activating this pathway. It's pretty common in gastric cancer. The PTEN gene is also an oncogene. It usually counteracts this pathway, but changes in PTEN may lead to overactivation during gastric cancer development. Furthermore, the ERBB3 receptor may also increase the change of the overactivation of the PI3 kinase and Akt pathway. Therefore, targeting this pathway might be valuable in treating gastric cancer.

MAPK pathway:

The MAPK pathway includes many kinases, like Ras, Raf, and Mek. It can regulate various cell functions and disrupt gastric cancer. In gastric cancer, oncogenes like KRAS and BRAF often mutate. Some key effectors such as ERK1/2 will activated. Other genes like RASSF1A might be silenced, and activating the MAPK pathway. Thus, blocking cancer cell apoptosis. EGFR is a surface receptor. It can also trigger this pathway. Its overexpression is also linked to the poor survival rate in gastric cancer. Overall, the MAPK pathway might provide a good direction in treating gastric tumorigenesis.

Canonical pathway:

This pathway stabilizes β-catenin and activates gene transcription. It is linked with gastric cancer invasion and metastasis. It can be a key indicator of gastric cancer's situation. A gene called APC (adenomatous polyposis coli) is involved in chromosomal regulation. Its inactivation, or mutations can

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cause the accumulation of β-catenin. Impacting tumor growth in gastric. Another gene called CDH1 gene, is encoded for protein E-cadherin. This protein can maintain normal epithelium construction and interacts with β-catenin. Its inactivation by mutations can lead to tumor metastasis. About 50% of gastric cancer diffusion is related to the loss of the normal functioning CDH1 gene. [8]

Progression Stages:

The American Joint Committee on Cancer (AJCC) has a TNM system. TNM system is the most common method for staging cancer. Table 3. below provides a more detailed explanation of the TNM stage grouping. [9]

Table 3. TNM Stage of gastric cancer

TNM Stage	Stage description
Stage 0	Cancer cells are only limited to the top cell layer of the stomach's innermost lining. Cells in the deeper layer do not contain any cancer cells. Also, do not spread to lymph nodes or other body parts.
Stage IA	The primary tumor already penetrated the top layer of the stomach lining. Cancer cells reach underlying layers but haven't reached lymph nodes or distant parts.
Stage IB	Similar to IA, but already reached 1-2 nearby lymph nodes. The main tumor may grow into a deeper layer, with no distant parts infected.
Stage IIA	Primary tumor growth into deeper layers, and spread to 3-6 nearby lymph nodes. No distant parts were infected.
Stage IIB	Increase the number of layers and lymph nodes with cancer cells involved. No distant parts were infected.
Stage IIIA	Increase the number of layers and nearby lymph nodes with cancer cells involved. No distant parts were infected.
Stage IIIB	Many primary tumors growth into different layers. 7 to 16 or more nearby lymph nodes with cancer cells involved. No distant spread.
Stage IIIC	Cancel cells have penetrated into deeper layers and spread to many nearby lymph nodes, but still no distant spread.
Stage IV	Cancer may grow into stomach wall layers and reach nearby lymph nodes. It has spread to distant organs like the liver, lungs, and peritoneum.

4. Overview of Two Drugs

Fluorouracil (5-FU)

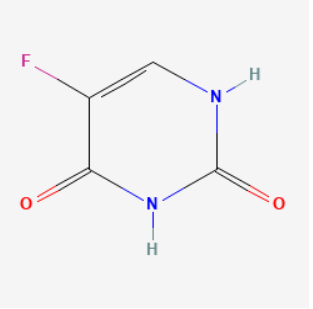

Figure 4. Molecular structure of fluorouracil

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IUPAC name of this molecule is 5-fluoro-1*H*-pyrimidine-2,4-dione, the molecular formula is $C_4H_3FN_2O_2$, and the molecular weight is 130.08 g/mol. 5-FU is a small molecule. It is a nearly white crystalline powder. Its structure includes a fluorine atom and replaces one of the hydrogen atoms in the uracil ring. This structure allows 5-FU to incorporate into RNA and inhibit DNA synthesis. 5-FU is an antineoplastic agent, it can act as an antimetabolite. [10] Fluorouracil is an artificial synthetic compound. It is designed to interfere with the nucleotide metabolism of cancer cells.

In 1954, researchers Abraham Cantarow and Karl Paschkis discovered that tumor cells in the liver will take more radioactive uracil than normal cells. Fluorine in fluoroacetic acid could disrupt the function of an essential enzyme in the cells. Some of the findings showed that 5-fluorouracil blocked tumors in mice. This discovery was originally reported in 1957. One year later, Anthony R. and other researchers published the initial clinical observations of 5-FU on human cancer.

Docetaxel (Taxotere)

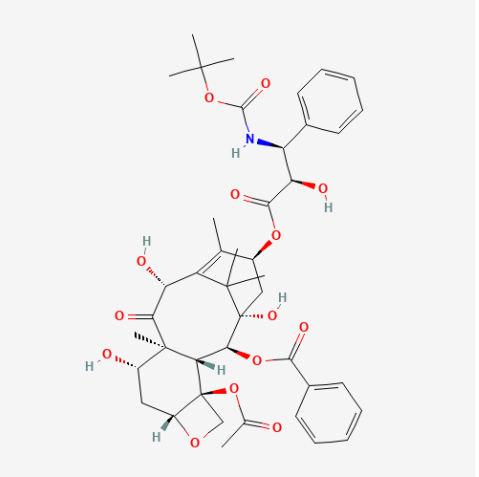

Figure 5. Molecular structure of docetaxel

IUPAC name of this molecule is [(1*S*,2*S*,3*R*,4*S*,7*R*,9*S*,10*S*,12*R*,15*S*)-4-acetyloxy-1,9,12-trihydroxy-15-[(2*R*,3*S*)-2-hydroxy-3-[(2-methylpropan-2-yl)oxycarbonylamino]-3-phenylpropanoyl]oxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.03,10.04,7]heptadec-13-en-2-yl] benzoate, the molecular formula is $C_{43}H_{53}NO_{14}$, and the molecular weight is 807.88 g/mol. Taxotere is also a small molecule. Taxotere is also a white powder but a more complex molecule. Its structure contains a core of taxane ring and other various functional groups. These different functional groups contribute to its ability to stabilize microtubules. It is also an antineoplastic, photosensitizing, or antimalarial agent. [11]

It's a semi-synthetic compound. Originally version of it was paclitaxel (Taxol). Paclitaxel is extracted from the bark of the rare Pacific yew tree (Taxus brevifolia). Due to the limited amount of paclitaxel, more research started to work on the creation of docetaxel. This new compound is extracted from the leaves of the European yew tree, which is more abundant. It is also modified to enhance its solubility and effectiveness in inhibiting cancer cell division.

5. Compare the Pharmacology of Two Drugs

Fluorouracil

The mode of delivery for Fluorouracil includes intravenous administration and ointment. Dosage taken for Fluorouracil is commonly administered weekly, or in cycles every 2, 3, or 4 weeks.

Intravenous Administration:

Fluorouracil can be injected directly into the bloodstream. There are several different methods to inject.

1. Using a short, thin tube called a cannula, insert it into a vein in the arm.
2. Using a long plastic tube that enters a large chest vein for the entire treatment.

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3. Using a portable small pump. Allowing continuous administration.

Ointment:

Fluorouracil also has an ointment form for treating skin cancer. When it is applied to the skin, it doesn't have most of the side effects with injection. Only temporary irritation or inflammation of the skin areas might occur. [12]

Metabolism

In mammals, 5-FU will transfer to fluorodeoxyuridine monophosphate. This compound will combine with thymidylate synthase (TS) to form a complex. This complex can used to inhibit the production of deoxythymidine mono-phosphate (dTMP). Since dTMP is vital for DNA replicating and fixing, so lack of dTMP will cause cell toxicity. 5-FU will convert into dihydrofluorouracil with the control of Dihydropyrimidine dehydrogenase (DPD). It is an important factor in breaking down 5-FU. The liver can break down more than 80% of 5-FU due to the presence of DPD.

TS inhibition:

By facilitating the reaction that converts dUMP into dTMP, TS is an essential enzyme that aids in the creation of thymidylate and is crucial in cell death processes.

In a sequence of processes involving the presence of the complex formed by TS, dUMP, and CH2THF, ch2thf serves as a methyl donor to maintain DNA replication and repair. The reaction has specific steps, involving the formation of a ternary TS–dUMP–CH2THF complex. [13]

The anti-cancer effects of 5-FU are mainly due to inhibition of TS. This inhibition will cause the reduction of dTMP. Leading imbalances in deoxynucleotides, and disrupting DNA synthesis and repair. Finally, it results in lethal DNA damage.

DNA and RNA misincorporation:

Since 5-FU is a pyrimidine analog, it can replace uracil or thymine in DNA and RNA. Disrupting their normal function.

In mammal cells, 5-FU’s combination with DNA is related to cytotoxicity in cells. The misincorporation with RNA plays a vital role in its toxic effects. Genetic analysis has shown that mutations in DNA repairing and nuclear RNA may lead to hypersensitivity to 5-FU.

Research indicates that 5-FU targets rRNA maturation. It will damage the post-transcriptional modification of tRNAs and snRNA protein complexes, just like Figure 6. showed. 5-FU can also inhibit pre-mRNA splicing, and increase the accumulation of polyadenylated rRNA. In addition, 5-FU-containing RNA can block the common modification of noncoding RNA called pseudouridylation. The interaction between pseudouridylation enzyme Cbf5p and 5-FU further increases its cytotoxic of it. [13]

Apoptosis (programmed cell death):

5-FU is used to boost the sensitivity of cancer cells to drug-induced apoptosis. It can cause cancer cell death by activating caspase-6. RSV at higher concentrations can enhance the effect of 5-FU in causing cancer cell apoptosis, without the use of the p53 pathway. Furthermore, 5-FU produces mitochondrial ROS with a p53 pathway. The depletion of BMI-1 will increase NPC cells' sensitivity to chemotherapy. Inducing apoptosis and inhibiting the PI3 kinase and Akt pathway. [13]

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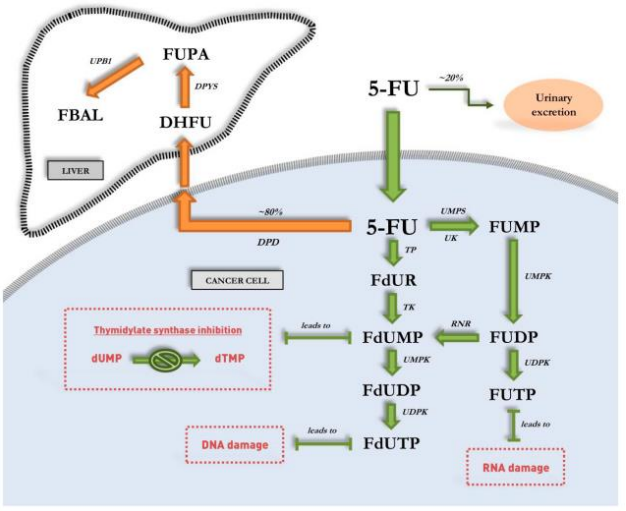

Figure 6. The whole process of fluorouracil's way of action

Docetaxel

The mode of delivery for Docetaxel includes intravenous administration, which is similar to Fluorouracil. Docetaxel is commonly administered once every 3 weeks. Every treatment lasts around an hour. [14]

Metabolism

Docetaxel is mainly metabolized in the liver by CYP3A4 and CYP3A5 isoenzymes. The main metabolic process is oxidation. It happened at the tert-butylpropionate side chain. Forming alcohol docetaxel (M2), and then transformed into three additional metabolites (M1, M3, and M4). Docetaxel's effectiveness is linked to body surface area and the levels of specific hepatic enzymes or alpha1 acid glycoprotein in the plasma.

Binding to β-tubulin:

Docetaxel's interaction with beta-tubulin is demonstrated by nuclear magnetic resonance deconvolution and electron crystallographic density. The three potential hydrogen bonds and the hydrophobic connection between the docetaxel will be formed by the hydrophobic fissures that exist on the surface. The walls will include helices and loops due to the attraction force. The reaction of phenyl and beta-sheets occurs simultaneously when they react with phenyl groups. and the methyl group on the docetaxel will interact with the beta-tubulin. Consequently, it resulted in the binding of beta-tubulin.

Apoptosis (programmed cell death):

Docetaxel uses its cytotoxic effects to promote and stabilize microtubule assembly. Meanwhile, disturbs microtubule disassembly (in Figure 7.). This results in a reduction of free tubulin which is an essential material for microtubule formation. Thus, inhibits cell division in metaphase and anaphase. Preventing the number of cancer cells increases. Due to docetaxel, microtubules do not disassemble. These microtubules accumulate inside the cell, so the cell begins to Apoptosis. This effect is further enhanced by docetaxel blocking the apoptosis-blocking bcl-2 oncoprotein. Studies have demonstrated docetaxel's anti-cancer activity. It also can work with other anti-cancer agents. Its faster intracellular uptake gives it greater cytotoxicity compared to paclitaxel.

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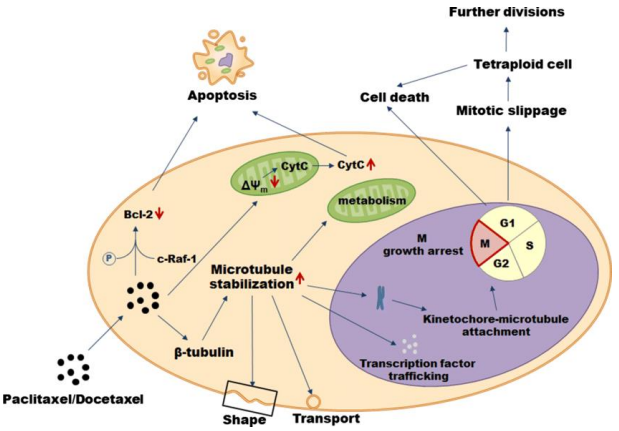

Figure 7. The whole process of Docetaxel's way of action

6. Compare the Resistance and Side Effects of Two Drugs

Fluorouracil

Resistance to 5-FU may have various mechanisms, such as the overexpression of thymidylate synthase (TS), increase the activity of deoxyuridine triphosphatase, methylation of the MLH1 gene, and increased expression of proteins like Bcl-2.

TS Induction and Resistance to 5-FU

TS induction contributes to the resistance against the 5-FU through various mechanisms, including less accumulation of activated substances and pharmacokinetic resistance. A specific pathway may help to save thymidylate. This can eliminate the effect of TS deficiency to some extent. Thus, increasing the 5-FU resistance. When ligands bind to the TS, it can stabilize and change the enzyme's shape. Potentially affecting the cell's response to drugs. The TS over-expression is the main reason that leads to 5-FU resistance. [13] Moreover, other gene changes and mutations may also lead to resistance. The ability to renew thymidylate might also contribute to 5-FU resistance.

DNA and RNA misincorporation

Tajima and his team have discovered that the MMR complex known as hMutS alpha may bind to DNA that has been modified by 5-FU. Research shows that cancer cells with a DNA mismatch repair are more likely to be resistant to 5-FU than normal cancer cells. Even with similar levels of 5-FU misincorporation into the DNA. The specific process of the reaction is that ATP leads the hMutS alpha complex to detach from the 5-FU-modified strand. Compared to the complementary DNA or DNA with a C/T mismatch, the connection between hMutS alpha and 5-FU-modified DNA is stronger. In addition, Qian An and other researchers proposed that Smug1 might remove 5-FU from DNA. It can serve as an indicator of drug response. [13] So helps the tumors to develop resistance.

Anti-apoptosis

The oncogene BMI-1 helps against apoptosis. Reducing the expression of BMI-1 leads to a decrease in the yield of specific proteins. This further affects cell sensitivity to 5-FU. Human Ring-Finger protein also inhibits apoptosis. It is also overexpression and affects proteins like Bcl-2 and Bcl-XL during 5-FU treatment. [13] Furthermore, other pathways involving PI3 kinase are suggested to have vital roles in 5-FU-induced apoptosis. Potentially making therapy less effective.

Docetaxel

Resistance to the anti-cancer drug Docetaxel may also from multiple sources, such as the high expression of βIII-tubulin, leading to decreased tubulin assemble, and changed sensitivity to different classes of tubulin.

β-Tubulin and Resistance to Docetaxel

This medicine increased the number of polymerized tubulins, assembled into microtubules, which can interrupt the mitotic spindle formation. However, the elevation of expression of βIII-tubulin may

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cause a reduction in tubulin polymerization. [15] So further contributes to microtubule construction, leading to resistance to docetaxel.

Anti-apoptosis

FOXM1 is a protein, that serves as a transcription factor. FOXM1 has been found overexpressed in gastric cancer. So it is closely associated with tumor formation.

FOXM1 increases resistance to docetaxel by changing the way microtubule's function. Thus, preventing cell death caused by docetaxel. A specific experiment was conducted to find out the way of FOXM1 functioning. First, the experiment balance between soluble and assembled microtubules after docetaxel was used. In gastric cell lines with FOXM1 either silenced or overexpressed, and either untreated or treated with docetaxol, cells showed similar ratios of tubulin forms. Nevertheless, the difference is when treated with docetaxel, cells with FOXM1 will decrease the number of assembled forms significantly. Although still some FOXM1-expressing cells will be shifted to assembled form, the numbers are much lesser. [16]

This result shows that FOXM1 overexpression in gastric cancer cells can inhibit the anti-cancer effect. Thus, against the apoptosis lead by docetaxel.

Table 4. Side effects of Fluorouracil and Docetaxel

Side effects		
Effects	**Fluorouracil**	**Docetaxel**
Infection Risk	√	√
Pale Appearance and Shortness of Breath	√	√
Bleeding and Bruising	√	√
Diarrhoea	√	√
Nausea and Vomiting	√	√
Breathing Difficulties	√	√
Cardiac Issues	√	×
Mouth and Throat Inflammation	√	√
Appetite Loss	√	√
Hair Loss	√	√
Fatigue	√	√
Hand Foot Syndrome	√	√
Allergic Reactions	×	√
Numbness or Tingling	×	√
Nail Alterations	×	√
Fluid Accumulation	×	√
Muscle Pain	×	√
Taste Alterations	×	√

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7. Conclusion

Gastric cancer is still a big challenge in maintaining global health. Thus, there are many treatments already developed by scientists. Fluorouracil and docetaxel are two drugs that play an important role in chemotherapy. However, their chemical properties, pharmacologies, resistance, and side effects are both different.

Fluorouracil mainly inhibits cancer cells 'DNA synthesis and stops cancer cell proliferation. While docetaxel stabilized microtubules of the cancer cell, leading to apoptosis. The resistance to these drugs is also different. Fluorouracil is mainly due to TS Induction and the presence of other substances, disturbing the normal function of fluorouracil. The resistance to docetaxel is because βIII-tubulin decreases tubulin polymerization or the presence of FOXM1. Two drugs have similar side effects, but the side effect types of docetaxel are more than fluorouracil, including allergic Reactions, etc.

The specific comparison between fluorouracil and docetaxel provides a previous insight into patient treatments. Also showed the significance of continuing research in solving resistance and side effects of the drugs. Understanding the unique characteristics of two drugs is also important in fighting cancer. Leading more personalized treatment strategies. Moreover, provides some potential directions in reducing resistance and side effects of fluorouracil and docetaxel.

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