Dean&Francis
ISSN 2959-409X

MS003682

A Comprehensive Overview of Cardia Cancer: Exploring a Chemotherapeutic Agent and Two Targeted Therapeutics

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Abstract:

Cardia cancer, a subtype of gastric cancer occurring at the gastroesophageal junction, poses significant challenges due to its high malignancy, rapid progression, and tendency for metastasis and recurrence. Its development is linked to chronic gastric diseases, gastroesophageal reflux disease, and Helicobacter pylori infection. HER2 status is crucial in cardia cancer, with HER2-positive tumors benefiting from targeted therapies like Herceptin. Diagnosis relies on endoscopy, biopsy, and imaging techniques. Treatment involves chemotherapy and targeted therapies. Capecitabine, a chemotherapeutic agent, mimics continuous 5-FU infusion but with reduced gastrointestinal toxicity. It selectively accumulates in tumor tissue, inhibiting cell division by disrupting DNA and RNA synthesis. Two synthetic routes for capecitabine are described, both starting from D-ribose and utilizing distinct chemical transformations. Herceptin, a targeted therapy, binds to the HER2 receptor, inhibiting its downstream signaling pathways and promoting cell-cycle arrest and apoptosis in HER2-positive cardia cancers. However, resistance mechanisms may limit its efficacy over time. Bevacizumab targets vascular endothelial growth factor (VEGF), inhibiting angiogenesis and reducing tumor blood supply, nutrition, and metastasis. By normalizing tumor vasculature, bevacizumab enhances chemotherapy efficacy. Its use with chemotherapy regimens has shown improved survival outcomes in clinical trials. Adverse effects include hypertension, proteinuria, and gastrointestinal perforation, necessitating careful patient monitoring. In conclusion, the paper provides an overview of cardia cancer, discussing its epidemiology, diagnosis, and treatment with a focus on capecitabine as a chemotherapeutic agent and Herceptin and Bevacizumab as targeted therapies. These approaches aim to improve outcomes for patients with this aggressive subtype of gastric cancer.

Keywords: cardia cancer; chemotherapeutic agents; targeted therapies; pharmacology

ISSN 2959-409X

1. Introduction

Gastric cancer is one of the most common malignant tumors worldwide [1]. Based on data released by the National Cancer Center, there were over 4.064 million new cancer cases reported nationwide in 2023, with the number of deaths reaching 2.4135 million.

Cardia cancer, a subtype of gastric cancer, occurs at the gastroesophageal junction (as shown in Figure 1). Due to its unique anatomical location, the symptoms of cardia cancer frequently resemble those of esophageal and gastric cancers, posing challenges for clinical diagnosis. It is characterized by a relatively high malignancy rate, rapid progression, and a higher propensity for metastasis and recurrence, which makes its treatment more challenging. Cardia cancer follows a multistep histopathologic pathway known as the Correa cascade, which involves the following steps: chronic active gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and, ultimately, cancer [2]. Research indicates that the development of cardia cancer is closely associated with chronic gastric diseases, gastroesophageal reflux disease (GERD), and Helicobacter pylori infection.

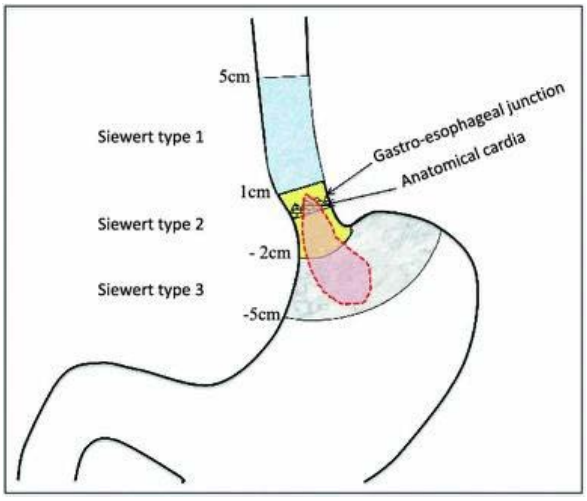

Figure 1. Anatomy of the gastroesophageal junction for tumor staging.

HER2 (human epidermal growth factor receptor 2) has emerged as a significant concept in the realm of cardia cancer, a subtype of gastric cancer originating at the gastroesophageal junction. This transmembrane tyrosine-kinase receptor plays a pivotal role in modulating cell proliferation, differentiation, and survival [3]. Gastric carcinomas are classified as HER2-positive when the immunohistochemical intensity score is 3+ or exhibits a 2+ score accompanied by positive fluorescence in-situ hybridization, as depicted in in Figure 2. The advent of HER2-targeted therapies, notably Herceptin, has demonstrated potential in enhancing outcomes for patients with advanced cardia cancer that is HER2-positive.

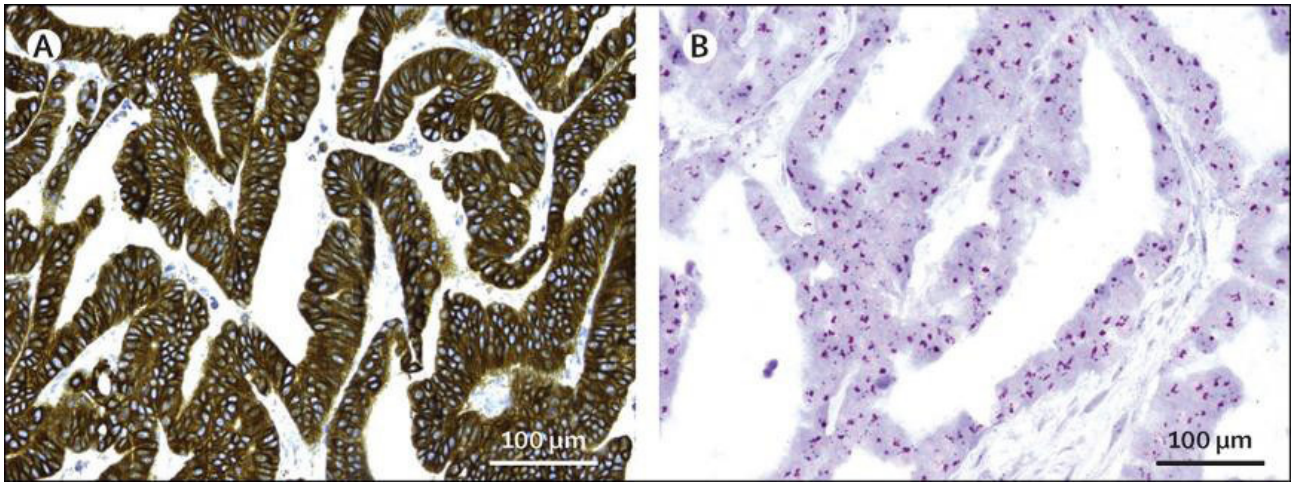

Figure 2. The histological appearance of an HER2-positive tumour is exemplified by: (A) an immunohistochemistry intensity score of 3+, and (B) amplification of the HER2 gene, which is evident through a chromogenic in-situ hybridisation test indicated by a red HER2 probe.

Early-stage cardia cancer is often asymptomatic in most patients, leading to frequent diagnoses at advanced stages. The most prevalent symptoms observed at diagnosis encompass dysphagia, anorexia, dyspepsia, weight loss, and abdominal pain.

The diagnosis of cardia cancer primarily involves en-

doscopy and biopsy to confirm the presence of cancer. Staging of the disease is typically achieved through endoscopic ultrasonography and CT scans of the chest and abdomen, with endoscopic ultrasonography demonstrating high sensitivity and specificity for distinguishing between superficial and advanced cardia gastric carcinomas. Laparoscopy is employed to rule out small-volume peritoneal metastases. Although PET-CT and MRI are not routinely used for staging, PET-CT can improve the detection of involved lymph nodes and metastatic disease, and MRI is emerging as useful for identifying peritoneal metastases.

Chemotherapeutic agents and targeted therapies both play crucial roles in the treatment of cardia cancer. Chemotherapeutic agents primarily exert their effects by directly interfering with the mechanisms of cancer cell division and proliferation. In contrast, targeted therapies function by specifically targeting molecules or signaling pathways unique to cancer cells. These drugs often exhibit high selectivity, allowing for a more precise impact on cancer cells while minimizing damage to normal cells. The following sections will provide a detailed introduction to one chemotherapeutic agent and two targeted therapies used in the treatment of cardia cancer.

2. Methods

The primary data source for this review was the Web of Science database, which was chosen for its comprehensive coverage of scientific literature across multiple disciplines. A structured search query was designed to identify relevant studies published in peer-reviewed journals focusing on cardia cancer, its epidemiology, diagnosis, and treatment. The search strategy was designed to be as inclusive as possible while maintaining specificity to the topics of interest.

3. Chemotherapeutic Agent- Capecitabine

3.1 Introduction

Cardia cancer, a subtype of gastric cancer occurring at the gastroesophageal junction, poses significant challenges due to its aggressive nature and tendency for rapid progression, metastasis, and recurrence. In the pursuit of more effective treatment options, chemotherapeutic agents play a crucial role in inhibiting cancer cell growth. Among these agents, capecitabine stands out as a promising alternative to traditional chemotherapeutics due to its tumor-selective accumulation and reduced gastrointestinal toxicity. This section delves into the mechanism of action and synthetic routes, highlighting its potential in the treatment of cardia cancer.

3.2 The mechanism of action

Chemotherapeutic agents primarily exert their effect by inhibiting cell division (Figure 3). These drugs target rapidly dividing cells, which encompass both normal tissues such as hair, gastrointestinal epithelium, and bone marrow, as well as cancer cells.

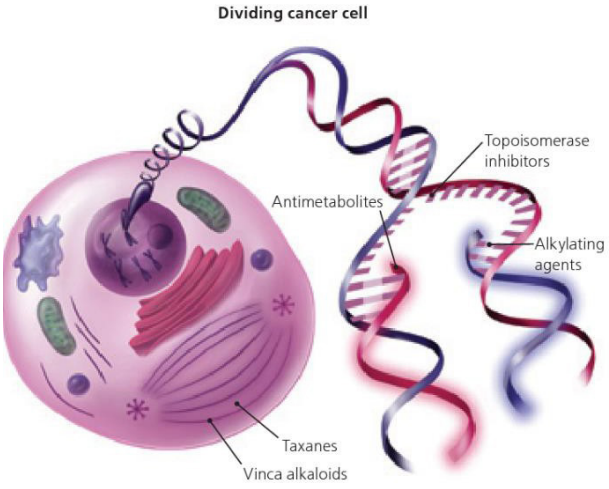

Figure 3. Mechanisms of traditional chemotherapy [4]

Capecitabine stands as a prototypical chemotherapeutic agent. It was developed to mimic the continuous infusion of 5-FU, specifically N4-pentyloxycarbonyl-5′-deoxy-5-fluorocytidine. An earlier oral form of 5-FU, known as 5’-deoxy-5-fluorouridine (5’-DFUR), was associated with severe gastrointestinal (GI) toxicities due to the high expression of the enzyme converting 5’-DFUR to 5-FU in both normal GI tissue and tumor tissue. Conversely, capecitabine can traverse the intestinal mucosa intact, thereby mitigating GI toxicities. Upon entering the body, capecitabine undergoes a three-step conversion process to become 5-FU. Initially, it is converted into 5’-deoxy-5-fluorocytidine (5’-DFCR) by carboxylesterase in the liver. Subsequently, 5’-DFCR is hydrolyzed into 5’-DFUR by cytidine deaminase present in the liver and/or tumor tissue. Finally, 5’-DFUR is transformed into 5-FU by thymidine phosphorylase (TP). Notably, cytidine deaminase and TP are found at higher concentrations in tumor tissue compared to normal tissue, resulting in selective accumulation of 5-FU in tumors and minimal exposure to normal tissue [5].

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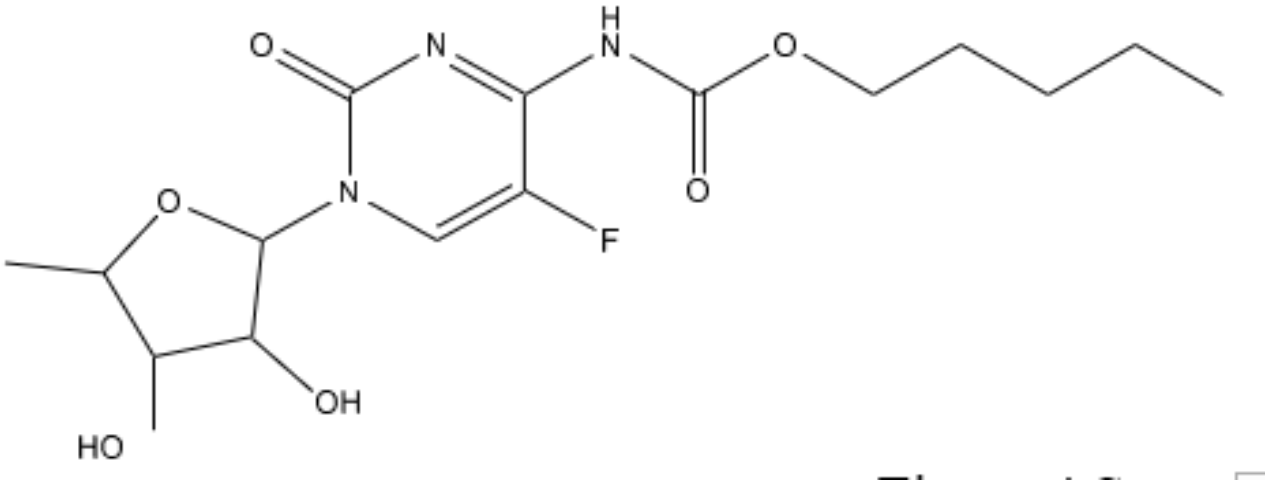

Figure 4 Structure of capecitabine.

Both normal and tumor cells metabolize 5-FU into 5-fluoro-2′-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP), which induce cellular damage through two distinct mechanisms. Firstly, FdUMP forms a covalently bound ternary complex with thymidylate synthase (TS) and the folate cofactor N5,10-methylenetetrahydrofolate. This binding inhibits the conversion of 2'- deoxyuridine monophosphate into thymidine monophosphate, a crucial precursor for thymidine triphosphate, which is essential for DNA synthesis. Consequently, this inhibition halts cell division. Secondly, during RNA synthesis, RNA polymerase may mistakenly incorporate FUTP instead of uridine triphosphate (UTP), leading to disruptions in RNA processing and protein synthesis.

3.3 Synthetic routes

Regarding the synthesis of capecitabine, two synthetic routes have been reported in the literature, each starting with different raw materials:

Synthetic route one [6], as shown in Figure 5, can be divided into two parts: the main ring and the side chain. The main ring starts with D-ribose as the raw material. Through ketalization protection, p- toluenesulfonylation under pyridine catalysis, sodium borohydride reduction, and hydrolytic deprotection under acidic conditions, the hydroxyl groups at positions 1, 2, and 3 on the furan ring are acetylated to obtain Cape-5. Cape-5 then undergoes a silylation reaction to produce Cape-6.

For the side chain, n-pentyl chloroformate is used as the starting material. Under pyridine catalysis, n-pentyl chloroformate is added dropwise to a dichloromethane solution of Cape-6 at low temperature to obtain Cape-7, which is finally hydrolyzed under lithium hydroxide catalysis to yield capecitabine. Additionally, Cape-7 can also be obtained via another route: n-pentyl chloroformate reacts with 5-FC under pyridine catalysis at low temperatures to produce Cape-b, which then undergoes a silylation reaction with Cape-5 to yield Cape-7.

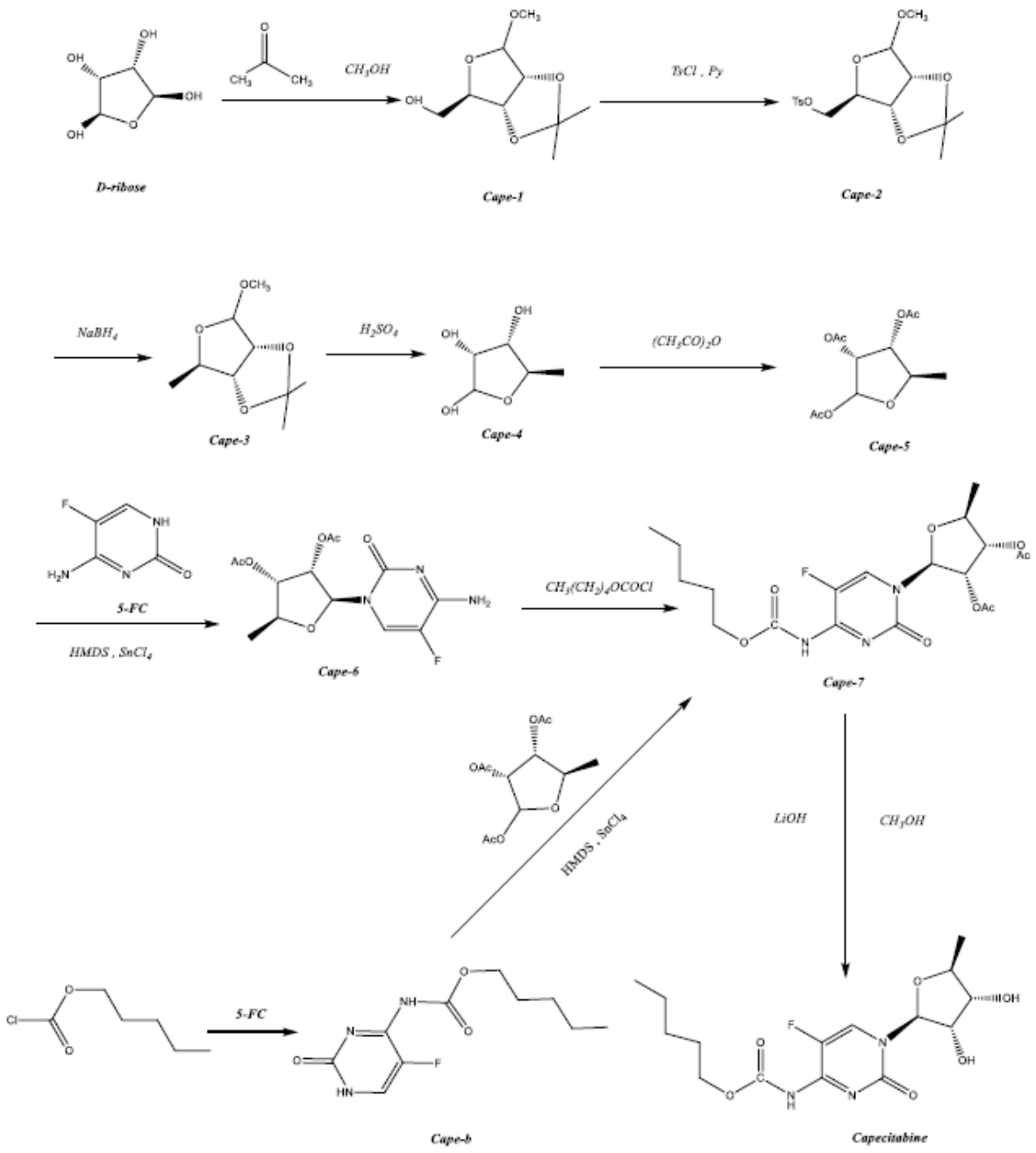

Figure 5. The first synthetic route of Capecitabine.

Synthetic route two [7], as shown in Figure 6, also starts with D-ribose as the raw material. Initially, under pyridine catalysis, D-ribose is converted to 1,2,3,5-O-tetra-benzoyl-β-D-ribose. Subsequently, acetylation at the 1-position in an acidic environment yields 1-acetyl-2,3,5-tri-benzoyl-β-D-ribose.

Next, this compound undergoes a silylation reaction with 5-FC, followed by hydrolysis catalyzed by sodium methoxide to produce 5-fluorocytidine. The 2′,3′ positions of 5-fluorocytidine are then protected with a propylene group, followed by iodination at the 5′ position, catalytic hydrogenation, and acidic deprotection at the 2′,3′ positions to yield 5′-deoxy-5-fluorocytidine. Finally, 5′-deoxy-5- fluorocytidine undergoes direct condensation with n-pentyl chloroformate under microwave conditions to form capecitabine.

ISSN 2959-409X

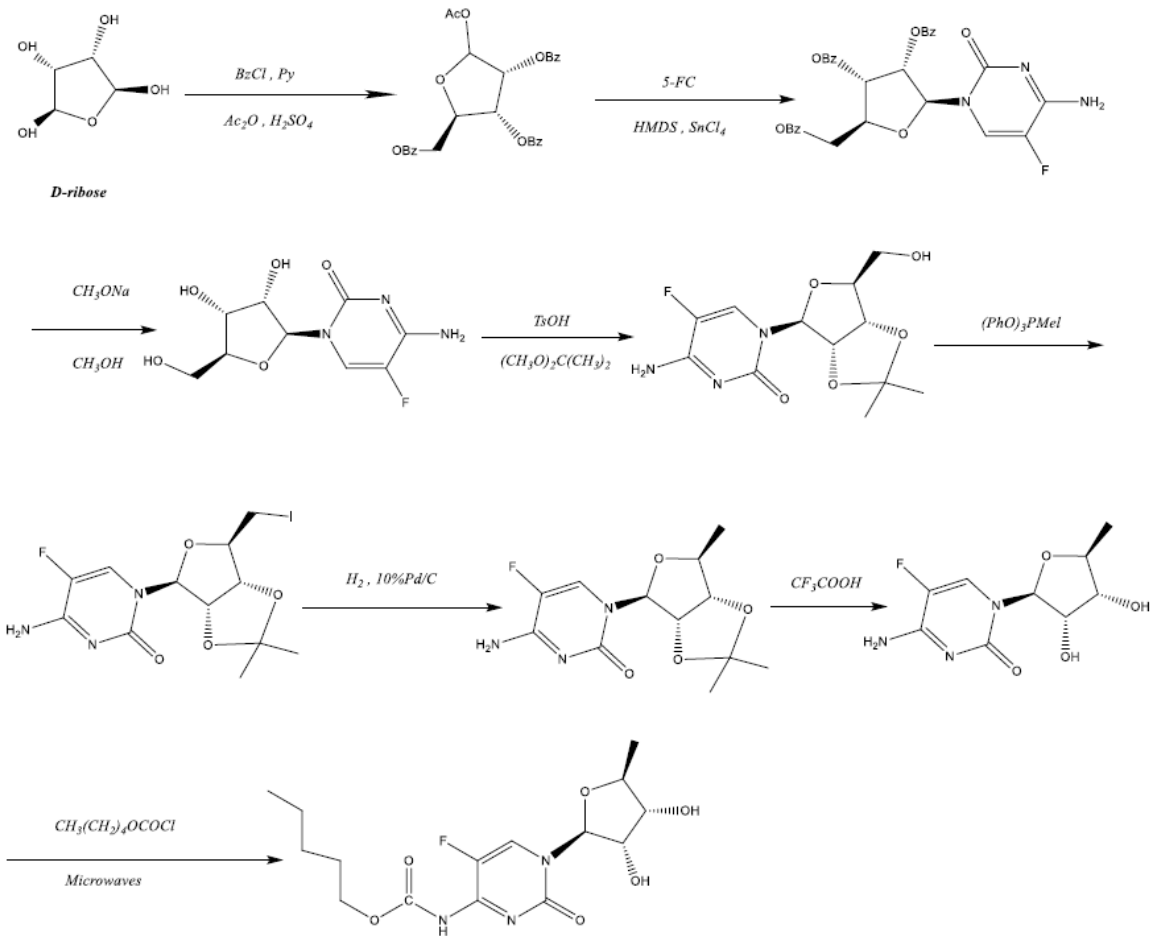

Figure 6. The second synthetic route of Capecitabine.

Both synthetic routes start with inexpensive D-ribose (220 RMB/kg). Despite the complexity of the synthetic steps, the overall production cost is relatively low. In route two, the strategy involves attaching 5-FC first and then removing the 5′-hydroxyl group. This approach eliminates the need for additional processing and allows the reaction progress to be controlled almost entirely in the liquid phase. However, attaching 5-FC at an early stage inadvertently increases the cost of raw materials. Additionally, the use of microwave technology in the final step complicates the industrial-scale production of capecitabine via route two.

4. Targeted Drugs

Targeted therapies impede the proliferation of cancer cells by specifically inhibiting molecules essential for tumor growth and development (Figure 7). In contrast to conventional chemotherapy, which indiscriminately impacts both healthy and malignant cells, targeted therapies are designed to selectively modulate specific molecular targets. This precision approach aims to limit collateral damage to normal cells, thereby mitigating adverse effects and enhancing therapeutic efficacy and patient outcomes.

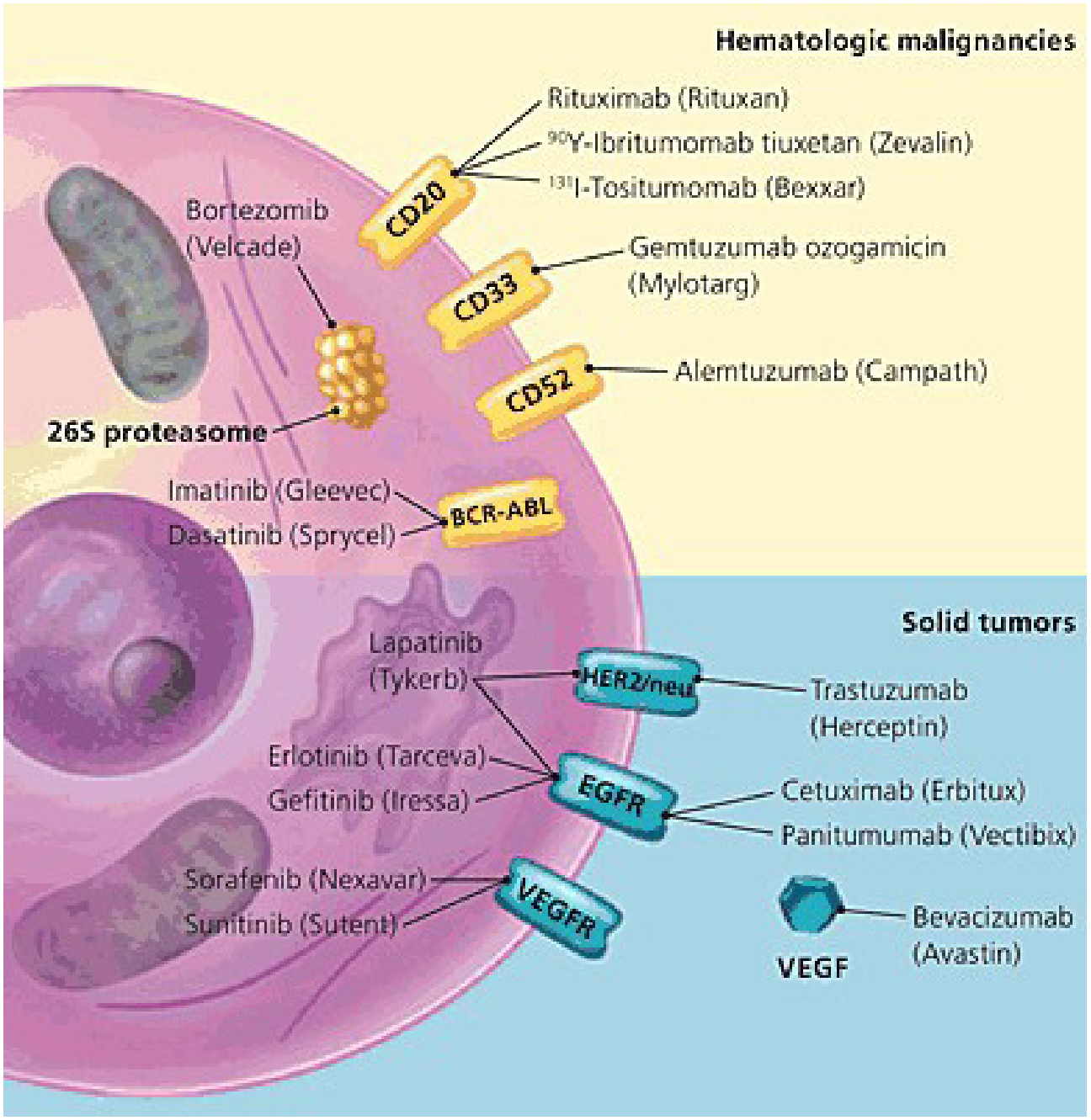

Figure 7. Mechanisms of targeted therapies.

4.1 Herceptin

4.1.1 Introduction

Targeted therapies have revolutionized cancer treatment by selectively inhibiting molecular pathways critical for tumor growth and survival. Among these targeted agents, Herceptin (trastuzumab) has emerged as a vital tool in the management of HER2-positive cancers, including cardia cancer. By specifically binding to the HER2 receptor, Herceptin inhibits downstream signaling pathways, leading to cell-cycle arrest and apoptosis in cancer cells. This section explores the molecular mechanisms of Herceptin, challenges associated with resistance development, and mode of delivery, providing insights into its role in improving outcomes for patients with HER2-positive cardia cancer.

4.1.2 The molecular mechanisms of Herceptin

Herceptin (trastuzumab) is used as a targeted therapy for patients with gastric cancer, including those with cancer at the gastroesophageal junction (such as the cardia), because

ISSN 2959-409X

it specifically targets the HER2 receptor. In some gastric cancers, including cardia cancer, the HER2 receptor is overexpressed, leading to aggressive tumor growth. Trastuzumab binds to this receptor, inhibiting its activity and slowing down the growth and spread of the cancer cells [8]. This targeted approach helps to improve the effectiveness of treatment while minimizing damage to healthy cells.

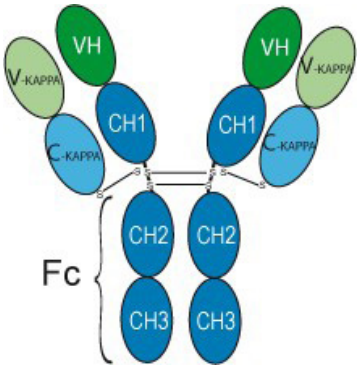

Figure 8. The protein structure of Herceptin.

To attenuate signaling mediated by HER2, Herceptin acts through the phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) cascades. By reducing downstream signaling, it induces the cyclin-dependent kinase inhibitor p27kip1, which promotes cell-cycle arrest and apoptosis [9,10].

Herceptin swiftly dissociates the non-receptor tyrosine kinase Src from HER2, leading to a diminution of Src activity. As a result, phosphatase and tensin homolog deleted on chromosome ten (PTEN) undergo dephosphorylation and relocate to the plasma membrane, becoming activated in this location [11]. This activation subsequently inhibits the PI3K downstream effectors, Akt and mammalian target of rapamycin (mTOR).

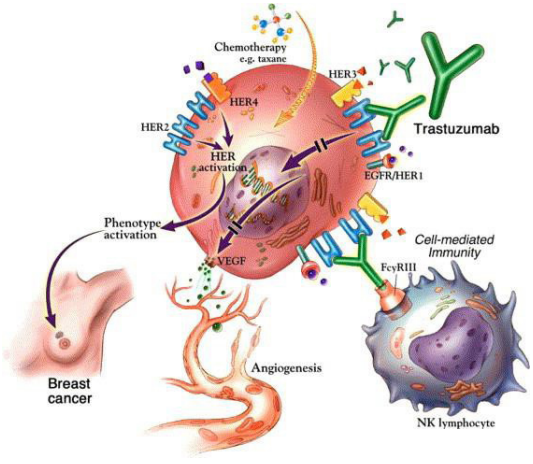

Figure 9. Proposed mechanisms of action of Herceptin (trastuzumab). The illustrated mechanisms are described in detail in the text.

4.1.3 Challenges associated with resistance development

However, in the treatment of gastroesophageal junction cancer, resistance to Herceptin can develop due to various mechanisms. Primary resistance may arise from an initial lack of HER2 overexpression or mutation, limiting the drug's efficacy from the start. Acquired resistance often occurs through HER2 pathway alterations, such as downstream signaling pathway activation or HER2 gene amplification, reducing trastuzumab's ability to inhibit tumor growth effectively over time. To address these resistance mechanisms and improve patient outcomes, combination therapies, and alternative treatment strategies are being explored.

4.1.4 Mode of delivery

In the treatment of gastroesophageal junction cancer, the recommended dosing regimen for Herceptin begins with an initial loading dose of 8 mg/kg, followed by a maintenance dose of 6 mg/kg administered every three weeks. The initial infusion duration is approximately 90 minutes to ensure patient tolerance. Subsequent infusions may be shortened to 30 minutes if the patient exhibits good tolerance during the initial infusion, aiming to enhance treatment convenience and patient comfort. This therapeutic approach continues until disease progression occurs.

4.2 Bevacizumab

4.2.1 Introduction

The aggressive nature of cardia cancer is often fueled by unchecked angiogenesis, the formation of new blood vessels that nourish and support tumor growth. Vascular endothelial growth factor (VEGF) plays a pivotal role in this process, making it an attractive target for therapeutic intervention. Bevacizumab (Avastin), a humanized monoclonal antibody, specifically targets VEGF, inhibiting angiogenesis and thereby starving the tumor of essential nutrients and oxygen. This section outlines the mechanism of action of bevacizumab, its clinical applications in combination with chemotherapy, and potential adverse effects, emphasizing its potential to enhance treatment outcomes in patients with cardia cancer.

4.2.2 The mechanism of action

Cardia cancer presents significant challenges in oncology, marked by its aggressive growth and poor prognosis [12]. Among the recent therapeutic advancements, bevacizumab (Avastin) has emerged as a pivotal agent targeting vascular endothelial growth factor (VEGF), a key regulator in tumor angiogenesis and progression.

Vascular endothelial growth factor (VEGF) plays a crit-

ical role in promoting angiogenesis, a process essential for tumor growth and metastasis, including in esophageal cancer [13]. In the hypoxic conditions of the tumor microenvironment, hypoxia-inducible factor (HIF) stimulates the upregulation of VEGF expression. Elevated VEGF levels bind primarily to VEGFR-1 and VEGFR-2 receptors on endothelial cells, initiating signaling pathways that promote the formation of new blood vessels. This dysregulated angiogenesis in cardia cancer contributes to the development of an abnormal vascular network that sustains tumor progression and metastasis.

Bevacizumab, a humanized monoclonal IgG antibody, specifically neutralizes VEGF-A, a major isoform crucial for angiogenesis. By binding with high affinity to VEGF-A, bevacizumab prevents its interaction with endothelial cell receptors, thereby inhibiting downstream pro-angiogenic signaling pathways. This blockade disrupts the formation of new blood vessels necessary for tumor growth, leading to a normalization of tumor vasculature. Consequently, the tumor's blood supply is reduced, potentially enhancing the effectiveness of concurrent chemotherapy regimens.

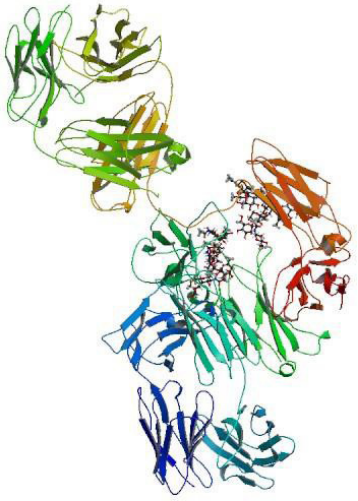

Figure 10. The protein structure of bevacizumab.

The inhibition of VEGF-A by bevacizumab yields several critical effects. Firstly, it reduces microvessel density within tumors by impeding new blood vessel formation [14]. This reduction starves the tumor of essential nutrients and oxygen, thereby hindering its growth and metastatic potential. Secondly, bevacizumab contributes to the normalization of tumor vasculature, which is often characterized by leakiness and inefficiency. Normalization facilitates improved delivery of chemotherapeutic agents into the tumor, thereby enhancing treatment efficacy. Thirdly, bevacizumab decreases interstitial fluid pressure within tumors [15]. High interstitial fluid pressure, a consequence of abnormal vessel formation, typically hinders effective drug penetration into tumor tissues. By lowering this pressure, bevacizumab enhances drug distribution within the tumor, further augmenting therapeutic outcomes.

4.2.3 Clinical applications

In recent studies, the combination of bevacizumab with conventional chemotherapy has shown promising results in clinical trials for various cancers, including cardia cancer. This combination therapy exploits bevacizumab's ability to normalize tumor vasculature and enhance drug delivery, thereby maximizing the cytotoxic effects of chemotherapy agents on cancer cells. Clinical evidence suggests that patients receiving bevacizumab in combination with chemotherapy experience prolonged progression-free survival and improved overall survival rates compared to those receiving chemotherapy alone.

Moreover, the use of bevacizumab has not been without challenges. Adverse effects such as hypertension, proteinuria, and gastrointestinal perforation have been observed, necessitating careful patient monitoring and management. Strategies to mitigate these side effects include pre-treatment assessment of cardiovascular risk factors and vigilant monitoring during therapy.

In conclusion, bevacizumab represents a significant advancement in the treatment of cardia cancer by targeting VEGF-mediated angiogenesis. Its ability to normalize tumor vasculature, reduce micro vessel density, and lower interstitial fluid pressure enhances the efficacy of concurrent chemotherapy regimens. Future research efforts should focus on optimizing patient selection criteria, exploring combination therapies, and further elucidating the molecular mechanisms underlying resistance to anti-angiogenic therapies. These endeavors promise to refine treatment strategies and improve outcomes for patients with cardia cancer and other malignancies.

In clinical practice, the use of bevacizumab for cardia cancer patients typically involves its administration alongside standard chemotherapy regimens. Initial treatment plans may include combination therapies such as FOLFOX (folinic acid, fluorouracil, and oxaliplatin) or FOLFIRI (folinic acid, fluorouracil, and irinotecan), tailored to the patient's disease stage and overall health status. Bevacizumab is administered intravenously, often on a biweekly or three-weekly schedule, to optimize its anti-angiogenic effects. Regular monitoring for treatment response and adverse effects is essential to adjust dosages and ensure patient safety while maximizing therapeutic outcomes.

4.3 Different mechanisms between the two drugs

Herceptin and Bevacizumab are both targeted therapies

ISSN 2959-409X

employed in the treatment of cardiac cancers, yet they operate via distinct mechanisms. Herceptin specifically targets the HER2/neu receptor, which is overexpressed in certain cardiac malignancies. By binding to HER2, Herceptin inhibits downstream signaling pathways that facilitate cancer cell proliferation and survival, thereby decelerating tumor progression. Additionally, Herceptin may induce antibody-dependent cellular cytotoxicity (ADCC), enabling immune cells to recognize and eradicate cancer cells. This therapeutic is typically utilized in HER2-overexpressing cancers, such as specific subtypes of breast and gastric cancer. In cardiac cancers, Herceptin targets HER2/neu-positive tumors, assisting in the retardation of tumor progression by blocking HER2 signaling pathways. Conversely, Bevacizumab targets vascular endothelial growth factor (VEGF), a protein that stimulates angiogenesis, which is crucial for tumor growth and metastasis. By binding to VEGF, Bevacizumab prevents its interaction with receptors on vascular endothelial cells, thereby inhibiting the formation of new blood vessels within the tumor. This mechanism starves the tumor of oxygen and nutrients, curtailing its growth. Bevacizumab is broadly employed across various malignancies, including cardiac cancers, where angiogenesis plays a pivotal role in tumor development.

5. Conclusion

Cardia cancer, a malignant gastric cancer subtype at the gastroesophageal junction, poses significant challenges due to its high malignancy and tendency for rapid progression, metastasis, and recurrence. This thesis explored the epidemiology, diagnosis, and treatment options for cardia cancer, focusing on capecitabine, Herceptin, and Bevacizumab. Capecitabine, a prodrug of 5-FU, selectively accumulates in tumor tissue, minimizing gastrointestinal toxicity. Herceptin targets HER2 receptors, inhibiting cell growth in HER2-positive cancers, though resistance can develop. Bevacizumab blocks VEGF, inhibiting angiogenesis and improving chemotherapy efficacy. However, adverse effects require careful monitoring. In conclusion, the combined use of chemotherapeutic agents like capecitabine and targeted therapies like Herceptin and Bevacizumab holds promise for improving outcomes in cardia cancer patients. Ongoing research should focus on optimizing dosing, exploring combination therapies, and understanding resistance mechanisms to these treatments.

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