Narrative Review Article

Advances and Challenges in Gastric Cancer Management: Chemotherapy, Radiation, and Targeted Therapy

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ABSTRACT

Gastric cancer continues to rank as one of the most prevalent and deadly cancers globally. There is an overall five-year survival rate of less than 40% with worse outcomes in advanced stages. Gastric Cancer (GC) has poor prognosis indicators due to late diagnosis and therapy resistance. Standard treatment for gastric cancers includes surgery with systemic or localized therapies. Chemotherapy, which is often administered in neoadjuvant and adjuvant settings, employs combinations of drugs to shrink tumors, decrease the risk of recurrence, and improve survival. These therapies are successful but have some challenges, like toxicity and resistance remaining huge. Radiation therapy can be delivered as three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy (IMRT), as a means to offer enhanced local tumor control. When combined with chemotherapy, radiotherapy has shown greater survival benefits, like in clinical trials such as INT-0116. Targeted therapies like trastuzumab for HER2-positive disease and claudin 18.2 antibodies represent a change towards precision by offering improved selectivity, but this is restricted to groups with specific biomarkers. This paper reviews current treatments, chemotherapy, radiation, and targeted therapies, while highlighting their benefits, weaknesses, and the growth of individualized treatment in improving outcomes for patients.

Keywords: Gastric Cancer; Chemotherapy; Radiation Therapy; Targeted Therapy; Treatments

INTRODUCTION

Gastric cancer (GC) begins when cells in the stomach lining grow out of control. It is one of the most common cancers in the world while also being one of the deadliest. Only about 40% of patients survive five years after diagnosis, and for advanced cases, it can fall below 10% (1). Early symptoms like indigestion or mild stomach pain are easy to dismiss, so by the time it is found, the cancer has already spread (2). Treating it is not simple either, as tumors are different for each patient because some tumors respond differently to therapy, and some become resistant over time. This is due to genetic and genomic variations; each tumor can have a distinct set of genetic mutations in genes. The standard treatment combines surgery with other therapies, like chemotherapy and radiation. For some patients, targeted therapy is a better approach.

This paper reviews research on the three most common forms of treatment for GC: 1) chemotherapy, 2) radiation, and 3) targeted therapy. It highlights their

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treatment process, benefits, and weaknesses while also talking about the emergence of individualized treatment and the growing body of literature documenting its potential for improving outcomes for patients.

CHEMOTHERAPY AND ITS MECHANISM OF ACTION

Chemotherapy is the systemic administration of a drug that uses powerful chemicals to kill fast-growing cells in the body. It is most commonly used to treat cancer because cancer cells grow and multiply much more quickly than other cells in the body. In gastric cancer, it is used in neoadjuvant (pre-surgery), adjuvant (post-surgery), and palliative settings to reduce tumor burden and improve survival.

Chemotherapeutic medicine can be given through a vein (intravenous infusion, IV) or in pill form. Pill form options are less common and typically used with regimens or when patients prefer at-home treatment. In some stages of stomach cancer, neoadjuvant chemotherapy is one of the standard treatments. If chemotherapy is given before surgery, it is also administered after to eliminate residual microscopic disease (3).

Neoadjuvant therapy is received before surgery to remove a cancerous tumor. This can be referred to as perioperative therapy or induction therapy. In stages 2 and 3 of GC, neoadjuvant chemotherapy is often part of the standard treatment approach to shrink tumors so they are easier to remove. In rare cases, if neoadjuvant therapy eliminates the tumor, surgery will no longer be needed (4).

Adjuvant therapy is given after primary treatments like surgery. It is used to lower the chance of cancer recurrence because even if all visible cancer is removed during surgery, there may still be some remaining in the body that are not visible. It helps destroy the invisible remnants and lowers the chance of the tumor returning. In chemotherapy, medicine can be given through a vein (intravenous infusion, IV) or in pill form. Pill form options are less common and usually used with regimens or when patients prefer at-home treatment (4).

Chemotherapy is often used in a regimen to kill or inhibit the growth of cancer cells. One of the most common cancer regimens is the combination of fluorouracil, folinic acid, oxaliplatin, and docetaxel (FLOT). Fluorouracil disrupts DNA and RNA synthesis, which prevents cancer cells from dividing and growing; folinic acid enhances the effect of Fluorouracil by stabilizing the binding to the target protein; oxaliplatin causes DNA cross-linking and cell death, which damages the DNA of cancer cells to inhibit their growth; docetaxel disrupts cell division by affecting microtubules that are essential for cell structure and division. If the cancer is too advanced, some other chemotherapy drugs can be used, such as cisplatin (5).

Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) destroy quickly dividing cancer cells. FLOT is given through a long plastic tube (central line, PICC line, or portacath) that goes into a large vein in the chest. The tube stays in place throughout the treatment. If a central line is not available, treatment can also be given through a thin, short tube (a cannula) that goes into a vein in your arm. FLOT is used in cycles, and each cycle lasts 2 weeks. A patient typically has 8 cycles altogether, and surgery is used to remove the cancer after cycle 4. The 5th cycle is usually initiated 6 to 12 weeks post-surgery. Steroid tablets are normally taken for 3 days before chemotherapy (4) (Figure 1). The overall survival rate of FLOT is a median of 39 months (11). FLOT is typically recommended for patients with resectable tumors (localized or locally advanced, stages T2 or higher) where surgery is feasible (12).

Another type of chemotherapy, cisplatin, also works by quickly destroying cancer cells. Cisplatin is dripped into the bloodstream (intravenously) for about 6 to 8 hours. Extra fluid is added into the drip before the cisplatin and for about 6 to 12 hours after cisplatin to avoid kidney damage. The more liquids a patient drinks, the less likely kidney damage is to occur. Like FLOT, treatment is given through a long plastic tube (central line, PICC line, or portacath) that goes into the large vein in the chest. The tube stays in place throughout the treatment, and if a central line is unavailable, a cannula will go into the vein in the arm. Though when cisplatin is used with a cannula, damage to the tissue is a possibility, as the cisplatin might leak out of the veins (extravasation). This might happen because cisplatin is an irritant and can be vesicant at higher concentrations. It can also irritate the veins, leading to inflammation and damage to the vein walls. Cisplatin is used in cycles that vary depending on cancer type. Cycles may take place every 3 or 4 weeks, once a week for 6 weeks, or every day for 5 days for every 3-4 weeks (7). Cisplatin is commonly used for GC, and it is also common to have it combined with other chemotherapies. The median survival for cisplatin combined with 5-fluoropyrimidines was 9 months (13)

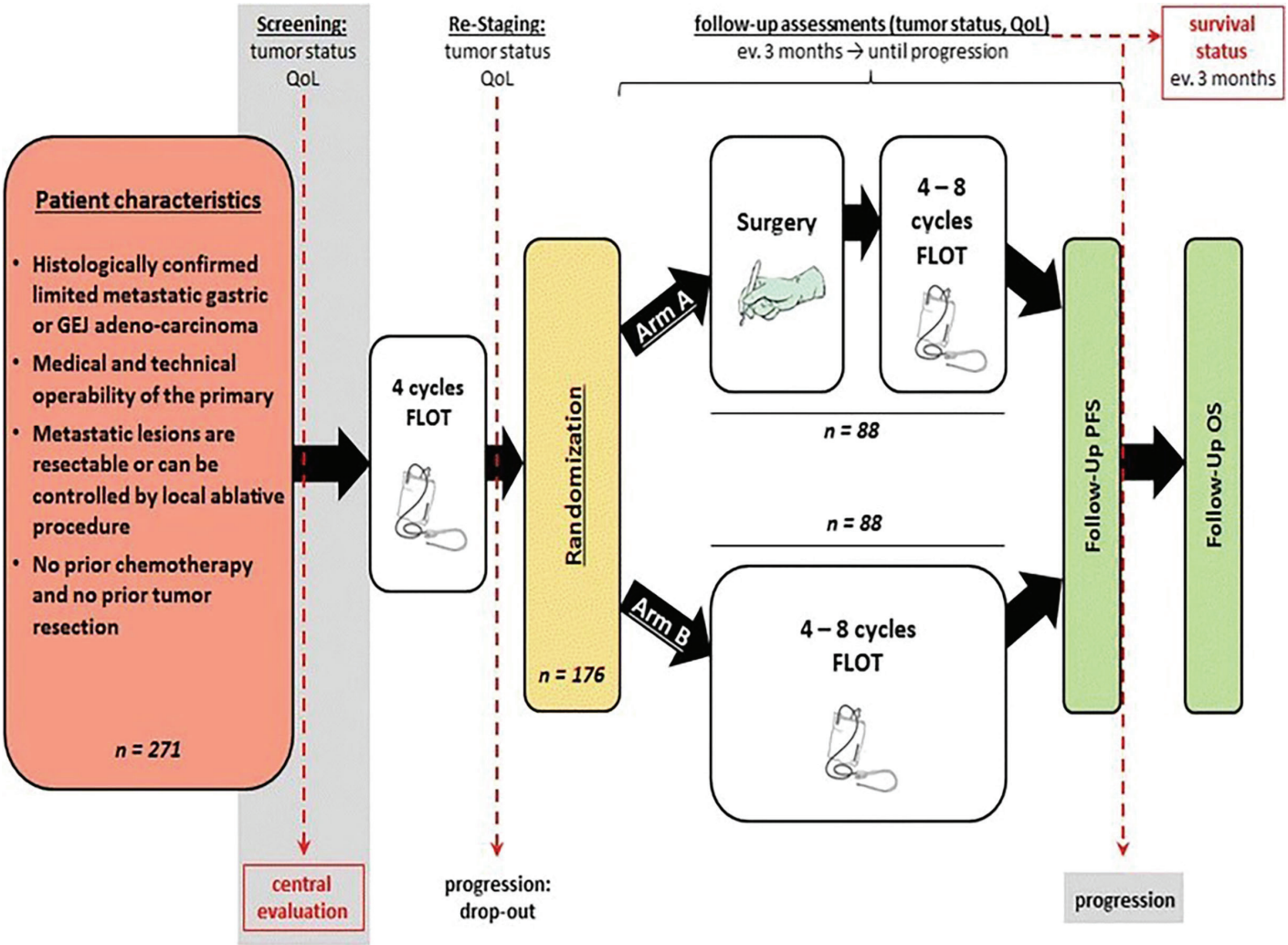

Figure 1. Arm A is an example of a patient's FLOT cycle that involves prior surgery. Arm A: Surgery is scheduled 4-6 weeks after d1 (1 cycle) of the last cycle of preoperative chemotherapy (d1 + 4 to 6 weeks). The protocol provides recommendations on surgical intervention for the different types of limited metastatic disease (types 1 to 2, VII). Post-operatively, an additional 4 to 8 cycles of FLOT can be administered starting 4 to 12 weeks after the surgery. Arm B is an example of a patient's FLOT cycle that doesn't require surgery. Arm B: Patients are treated with an additional 4 to 8 weeks of FLOT (10).

BENEFITS, RISKS, AND EFFECTIVENESS OF CHEMOTHERAPY

Chemotherapy can help shrink tumors to potentially make surgery more successful. When given after surgery, it can help destroy any remaining cancer cells and lower the chance of recurrence. In stages of advanced or metastatic cancer, chemotherapy is useful in targeting cancer cells throughout the body, slowing their spread, and relieving symptoms. Some potential side effects are nausea, vomiting, fatigue, and loss of appetite. Some more serious risks involve damaging the heart, kidneys, and nervous system (8). Chemotherapy is not specific to cancer cells, as it also targets healthy cells, but this is still an effective treatment because the healthy cells have a mechanism that repairs themselves and regenerates, while the cancer cells are unable to repair themselves.

While FLOT chemotherapy is a powerful treatment option for GC, there are many risks involved. Some risks associated with FLOT chemotherapy are hematological toxicity, which can increase the risk of infection, fatigue, and bleeding, and neuropathy, i.e., numbness or tingling in the hands and feet (especially with oxaliplatin). Cisplatin also has numerous risks, including kidney

problems (nephrotoxicity) and myelosuppression (bone marrow suppression). Nephrotoxicity can lead to acute renal failure, and damage can be cumulative depending on the dose amount. Myelosuppression can lead to low blood cell counts, increasing the risk of infections, anemia, and bleeding and bruising (9, 10)

Chemotherapy offers benefits across various stages of GC, from shrinking tumors preoperatively to reducing recurrence and alleviating symptoms in advanced cases. While its effectiveness has been evident, challenges like vomiting, heart damage, and fatigue show the need for advancements.

RADIATION THERAPY AND ITS MECHANISM OF ACTION

Radiation therapy is a type of cancer treatment that uses high-energy rays or particles, generally X-rays, to destroy cancer cells. For GC, radiation therapy is normally used after surgery and is often combined with chemotherapy to kill any remaining cancer cells. There are different types of radiation therapy, such as three-dimensional conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT) (17, 19).

General radiation therapy works by damaging the DNA inside cancer cells, which prevents them from continuous growth and division. High-energy radiation creates breaks within the DNA strands that healthy cells can repair, but cancer cells generally cannot. Ionizing radiation causes the formation of ROS (reactive oxygen species) that are indirectly involved in DNA damage. ROS generates apurinic/apyrimidinic (abasic) areas in DNA (Figure 2). When DNA is damaged, the repair machinery of the cell is activated and stops the cell cycle at control checkpoints to repair DNA damage and prevent the continuation of the cycle. Cancer cells frequently have mutations in genes involved with this DNA repair pathway, which weakens their ability to fix damaged DNA, making them more vulnerable (13). This type of radiation directly damages DNA by splitting chemical bonds on the helical backbone, creating single-strand breaks (SSBs) and double-strand breaks (DSBs) with any amount of exposure. CDKs are common checkpoint proteins expressed in radioresistant phases. In G1, cells are expanding, and the CDK inhibitors are expressed to safeguard progression into the DNA synthesis phases (S phase). Once the cell enters S phase, the CDK inhibitors are relatively overexpressed to ensure that the DNA synthesis is accurate and complete. In G2, cells are considered radioresistant because of lingering enzymes and CDK complexes from S phase. P13 family kinases activated by ATM and other proteins lead to CDK inhibition and cell cycle arrest when DNA damage is detected. During early M phase (prophase), when chromosomes condense, the DNA becomes highly susceptible to radiation damage. In the M phase, generally, no major checkpoints to prevent progression to cell division, and thick, bulky, condensed DNA provides the perfect target for ionizing radiation. This is the basis of fractionated radiation treatments, which aim to catch dividing cells at this phase of the cell cycle (14). Cells in the S phase are more radioresistant because the genes and enzymes responsible for accurate genomic replication and repair are overexpressed in the S phase (14) (Figure 3).

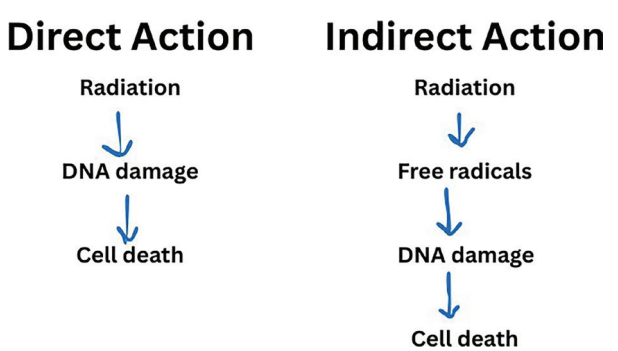

Figure 2. The pathway of direct action uses radiation therapy, which causes DNA damage to cancer cells which leads to cell apoptosis. Indirect action uses radiation that interacts with water molecules and creates free radicals. These radicals damage the DNA indirectly, and if the damage is not repairable, it leads to cell apoptosis.

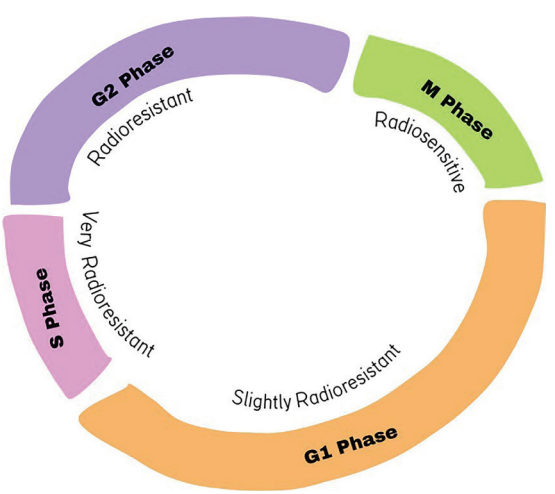

Figure 3. The stages of the cell cycle for radioresistance.

Intensity-modulated radiotherapy (IMRT) delivers precise radiation to a tumor while minimizing the dose to the surrounding healthy tissue by using linear accelerators. IMRT delivers precise radiation doses to malignant tumors or specific areas within the tumor. This treatment is planned using 3-D computed tomography (CT) or magnetic resonance (MRI) images of a patient, along with computerized doses to determine the dose intensity pattern that best fits the tumor shape (18). When IMRT is not applicable, three-dimensional conformal radiation therapy (3D-CRT) is used. 3D-CRT employs beams that are specifically shaped to match the shape of the cancer. 3D-CRT is particularly useful for cancers that are close to sensitive structures and organs (14).

The efficacy of IMRT and 3D-CRT in gastric cancer remains controversial. A meta-analysis investigated the efficacy and safety of IMRT with 3D-CRT in treating patients with GC by comparing 3-year survival rates, local control rates, and toxic event rates across 9 controlled clinical studies with 516 GC patients. Overall, the authors found that IMRT might be superior to 3D-CRT in treating patients with GC due to? local control rates, with increasing toxicity (14).

BENEFITS, RISKS, AND EFFECTIVENESS

Radiation therapy is highly effective at killing the majority of cancer cells inside a tumor. Several clinical trials have evaluated clinical outcomes and toxicity in patients with gastric cancer who were treated with IMRT and 3D-CRT. The 1 and 2-year overall survival rates for IMRT were 94.7% and 77.1% respectively, while the rates for 3D-CRT were 76.7% and 52.5%. The differences in these two groups were not statistically significant (P = 0.072). Both of these groups have survival rates of above 50% (21, 22).

One advantage of using 3D-CRT is that it targets cancerous tumors while limiting the radiation damage to nearby healthy tissue (25). While 3D-CRT is effective, there are potential side effects like fatigue, skin irritation, and nausea; though these are less severe than older methods of treatment (21). Despite limitations on damages to nearby healthy tissue, 3D-CRT is not as precise as IMRT. IMRT has the same potential side effects as 3D-CRT, but there are higher risks of radiation hitting healthy tissue with 3D-CRT than with IMRT, especially with complex tumor shapes (20).

Radiation therapy combined with chemotherapy has been shown to improve survival rates in gastric cancer patients. The INT-0116 trial, a clinical study of patients who received chemotherapy after surgery, had a median survival of 36 months, while those who had surgery by itself had a median survival of 27 months. This is due to the radiation's ability to destroy the cancer cells left behind after surgery (23).

Notwithstanding, its effectiveness depends on the stage of cancer and location. Radiation therapy alone is generally not effective as a main type of treatment for gastric cancer because it cannot treat cancer that has spread past the stomach.

TARGETED THERAPIES AND THEIR MECHANISM OF ACTION

Targeted therapy is a type of cancer treatment that acts on the proteins that regulate how cancer cells grow, divide, and spread. There are many types of targeted therapies, either small-molecule drugs or monoclonal antibodies. Small-molecule drugs enter cells easily, so they are used for targets that are inside cells. Monoclonal antibodies are also known as therapeutic antibodies, which are designed to target proteins on the cell surface. Unlike small-molecule drugs, antibodies are produced by the body normally, and so this is relatively safe. These proteins are designed to attach to specific targets found on cancer cells. Some monoclonal antibodies mark cancer cells so they can be better seen and destroyed by the immune system. Monoclonal antibodies trigger the immune system by acting like targeted flags that attract immune cells to destroy specific cells or molecules, or by directly interfering with the disease processes. Others directly stop cancer cells from growing and cause them to self-destruct (25).

A protein that plays a role in the structure and function of epithelial cells, particularly in the stomach, is Claudin 18.2 (CLDN 18.2). CLDN 18.2 dysregulation in GC exposes the proteins on tumor cell surfaces, where frequent overexpression promotes tumor growth and makes it a highly specific target for antibody-based therapies. CLDN 18.2 is a target for new therapies, specifically monoclonal antibodies like zolbetuximab, which bind to CLDN 18.2 and trigger the body's immune system to attack cancer cells. CLDN 18.2 is used as a target in GC treatment because it is abnormally expressed in a significant portion of gastric cancer cells, while being limited in healthy gastric tissue. Anti-CLDN18.2 is administered intravenously after chemotherapy. The selective expression makes it a good target for therapies like monoclonal antibodies, which bind to and destroy cells expressing CLDN 18.2 while minimizing harm to healthy tissue (26) (Figure 4).

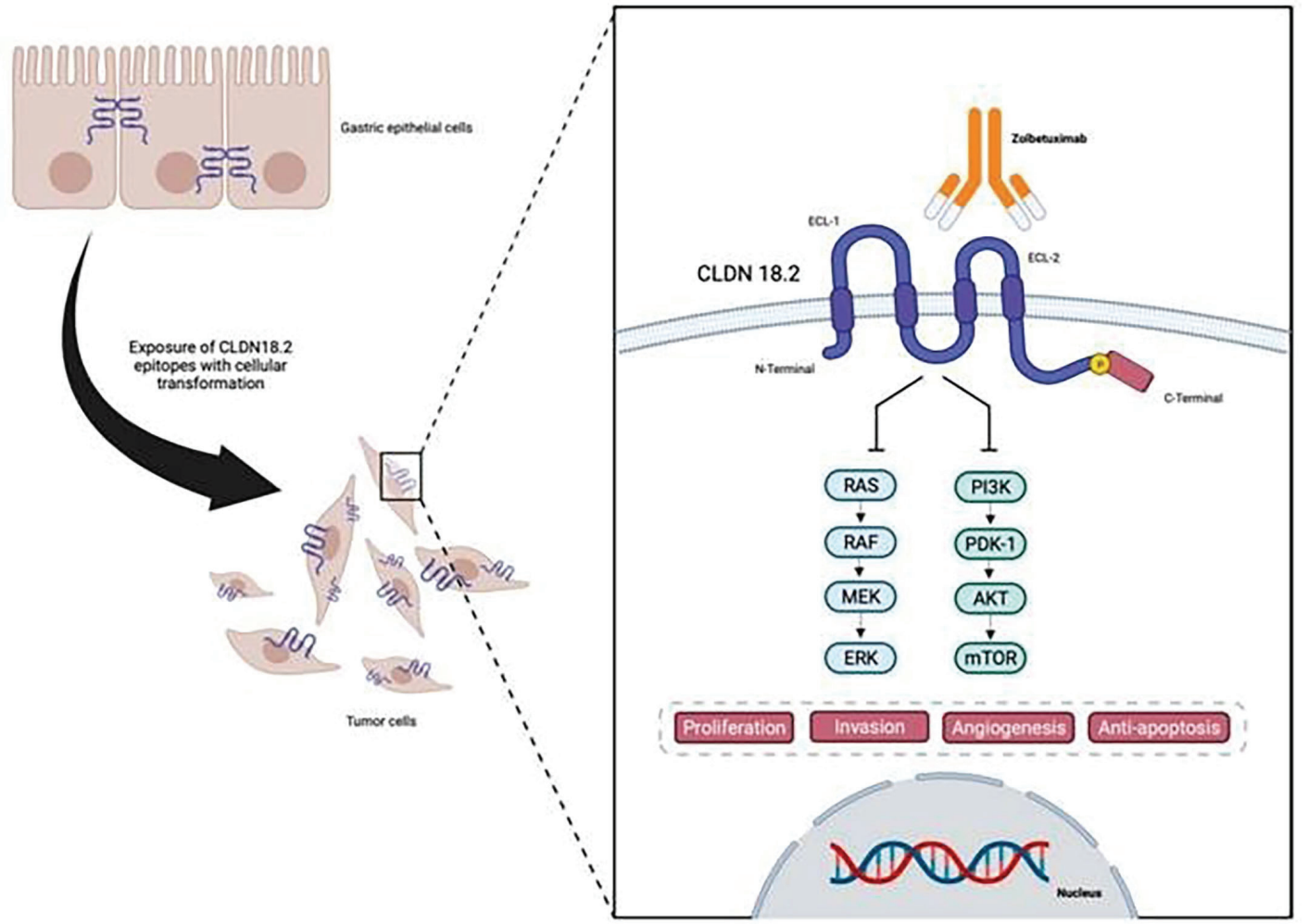

Figure 4. A representation of CLDN18.2 in gastric cancer cells and structure and interaction with anti-CLDN18.2 (29).

Trastuzumab is a monoclonal antibody that targets human epidermal growth factor receptor 2 (HER-2). When HER2 is activated, it can signal the cell to grow and divide. Adding trastuzumab to chemotherapy can help some people with advanced HER-2 positive stomach cancer live longer than just chemotherapy alone. In the ToGA trial, the addition of trastuzumab to chemotherapy improved median overall survival by about 2.7 months (26% reduction in risk of death) (27). However, its clinical impact applies to only around 20-22% of patients whose tumors overexpress HER2. Trastuzumab is infused into a vein through an IV or central venous catheter. This works by binding to the HER2 protein found on the surface of some cancer cells. HER2 is a protein that helps regulate cell growth and repair. It is typically given once every 2 or 3 weeks along with chemotherapy. This differs from the anti-CLDN18.2 because the anti-CLDN18.2 triggers the immune system, while trastuzumab primarily functions by blocking the signalling pathways within the tumor cell itself to trigger the tumor cells' dysfunction and thereby their death (25).

BENEFITS, RISKS, AND EFFECTIVENESS

While targeted therapy is designed to be more precise than traditional chemotherapy, it still carries the risk of side effects like fatigue, skin rashes, and even increases the risk of infection or second cancers. Increased susceptibility to infections is a significant concern, which emerges as a result of weakened immune responses stemming from damage to the bone marrow. Recurrence of GC is rare but may still happen

with long-term use of targeted therapies (31).

Despite this, trastuzumab carries several potential risks, like cardiotoxicity and infusion reactions. Trastuzumab can cause cardiomyopathy, a weakening of the heart muscle, which may result in a left ventricular ejection fraction. The risk of cardiotoxicity is higher when trastuzumab is combined with certain chemotherapy drugs like anthracyclines. Symptoms of cardiotoxicity (cardiomyopathy) are swelling of the ankles or legs, cough, and unexplained weight gain. Severe infusion reactions can occur during or shortly after trastuzumab is administered. Some symptoms are fever, chills, skin rash, and breathing difficulties (25, 28).

Studies evaluating the role of CLDN18.2 in GC locate an overall survival rate of 19.8% (27). Clinical trials like FAST have explored zolbetuximab, an anti-CLDN18.2 monoclonal antibody in combination with chemotherapy. This study showed moderate improvements in median overall survival compared to chemotherapy alone. However, these benefits vary based on CLDN18.2 expression thresholds and geographic populations. Overexpression of CLDN18.2 has been linked to an increased risk of metastasis, poor prognosis, and heightened interaction with cancer-associated fibroblasts, which can promote cancer cells' adhesion and spread. While CLDN 18.2 represents a promising target for therapy, its expression can also be linked to worse outcomes in some cases (30). Further clinical trials are required to clarify these effects and determine which patient subgroups will benefit the most from CLDN18.2.

CONCLUSION

A variety of therapies and treatments are used to address GC. Among the most common are chemotherapy, radiation therapy, and targeted therapies. Firstly, Chemotherapy is typically administered in two ways: intravenously or orally. Once in the body, the medicine travels through the bloodstream, finding and attacking cells that grow and divide quickly. That is why it can shrink tumors before surgery, lower the risk of cancer coming back, and help manage symptoms in later stages. Though it is non-specific and cannot always differentiate between healthy cells and cancer cells. Secondly, radiation therapy uses powerful beams of energy from a machine outside the body to find and destroy cancer cells in the stomach or nearby areas. It is often combined with chemotherapy, and research like the INT-0116 trial has shown that together, they can boost survival rates. Newer techniques, like intensity-modulated radiation therapy (IMRT), make the radiation safer by shaping the beams so they fit the tumor and miss more of the healthy tissue around it. Finally, unlike chemotherapy and radiation therapy, targeted therapies work in a more focused way. Instead of attacking all the fast-growing cells, they go after cancer cells with specific features. Trastuzumab, for example, is given through an IV and blocks the HER2-positive protein. Anti-CLDN18.2 antibodies latch onto the CLDN18.2 protein found on some gastric cancer cells, flagging them for the immune system to destroy. These treatments leave most healthy cells alone, but they only work for patients whose tumors have the right markers. Every treatment has pros and cons, but radiation therapy's accuracy, especially when paired with chemotherapy, makes it one of the most effective treatments for fighting gastric cancer.

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CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article.

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