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A REVIEW ON COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT
The oral route is considered to be the most preferred route for administration of drugs for systemic effect, but the oral route is not suitable to the administration of drug for lower gastrointestinal (GI) diseases, this happened due to their release at upper GI tract (stomach, small intestine), which further minimizes the accessibility of drugs at the lower GI tract. Colorectal cancer (CCR) is the third most common cancer worldwide in men and women, the second largest cause of death related to cancer, and the main cause of death in gastrointestinal cancer. In this review, we describe the stages, diagnosis, sign & symptoms, risk factors and drug therapy of some antibodies used to treat the colon cancer. Presently, the monoclonal antibodies most frequently used in the treatment of colorectal tumours are bevacizumab, cetuximab, panitumumab, and ramucirumab.zgr

KEYWORDS : *Colonoscopy, Biopsy, Blood Test, Colon Cancer, Colorectal Tumours*

INTRODUCTION

A targeted drug delivery system is highly desirable for the localized treatment of various bowel diseases, including ulcerative colitis, Crohn's disease, amoebiasis, and colon cancer. The colon drug delivery system specifically aims to deliver drugs to the lower gastrointestinal tract, particularly the large intestine. The colon is a suitable site for the absorption of drugs such as proteins and peptides due to: (i) lower diversity and intensity of digestive enzymes, and (ii) reduced proteolytic activity compared to the small intestine. As a result, the colon drug delivery system (CDDS) helps protect peptide drugs from hydrolysis and degradation caused by enzymes in the duodenum and jejunum, allowing for the drug's release in the ileum or colon, leading to improved systemic bioavailability.

The colon drug delivery system is effective for targeting drug release specifically in the colon, ensuring that no drug is released or absorbed in the stomach or small intestine. Colorectal cancer is the third most common cancer in both men and women, with approximately 1.8 million new cases diagnosed in 2018. Various risk factors contribute to the development of this type of cancer, including smoking, poor dietary habits, inflammatory bowel disease, genetic factors, aging, and the presence of polyps. Approximately 90% of patients diagnosed with colorectal cancer are over the age of 50, with a median age of 64.

2.1 Needs of Colon Targeted Drug Delivery System:

- Targeted drug delivery to the colon ensures direct treatment at the disease site (local delivery), allowing for lower doses and reduced systemic side effects.
- A site-specific or targeted drug delivery system enables the oral administration of peptide and protein drugs, while colon-specific formulations can also be used to extend drug delivery.
- A colon-specific drug delivery system is considered advantageous for the treatment of colon-related diseases.
- The colon is a site where both local and systemic drug delivery can be achieved, particularly for the topical treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. These conditions are commonly treated with glucocorticoids and sulfasalazine.
- Several other serious diseases of the colon, such as colorectal cancer, could potentially be treated more effectively through targeted drug delivery to the colon.

2.2Advantages Of Colon Targeted Drug Delivery System

- Reduced dose size
- Enhanced bioavailability
- Flexible design options
- Decreased dosing frequency
- Improved patient compliance
- Delivery of the drug in its intact form as close to the target sites as possible

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2.3 Disadvantages o Of Colon Targeted Drug Delivery System

- Low dose loading
- Increased need for excipients
- Limited manufacturing reproducibility and efficacy
- Multiple formulation steps required
- A large number of process variables

2.4 Limitation of colon targeting drug delivery system

- Accessing the colon can be challenging.
- Successful delivery requires the drug to be in solution before reaching the colon; however, the lower and more viscous fluid content in the colon compared to the upper GI tract limits the effectiveness of poorly soluble drugs.
- The lower surface area and the relative tightness of the tight junctions in the colon can hinder drug transport across the mucosa into the systemic circulation.
- Multiple manufacturing steps.

2.5 Anatomy of Colon

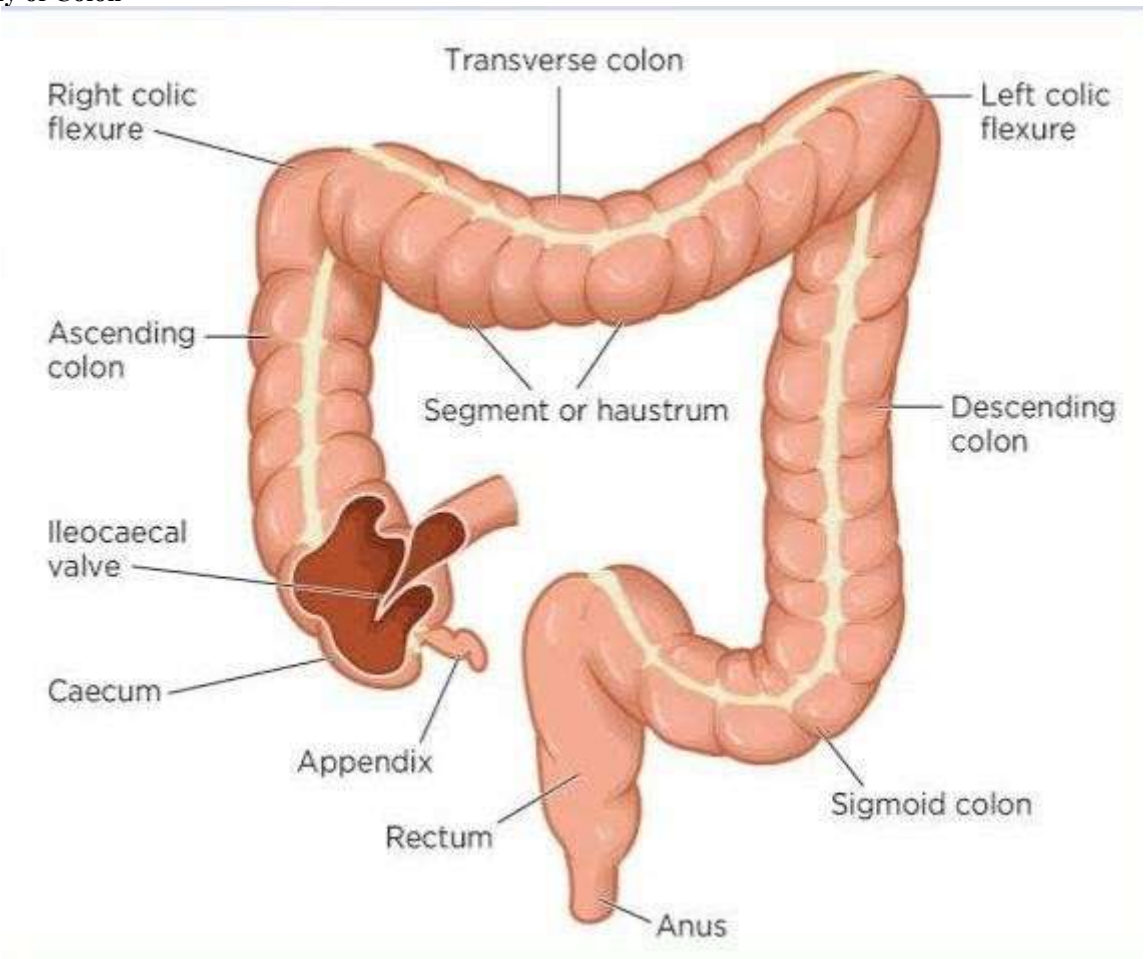

Fig no. 01: Structure Of Colon

3. COLON

The open end of the cecum connects to a long tube called the colon (or food passage), which is divided into the ascending, transverse, descending, and sigmoid sections. The ascending and descending colon are retroperitoneal, while the transverse and sigmoid colon are intraperitoneal.

Anatomical structure: The colon is the lower part of the gastrointestinal tract, extending from the ileocecal junction to the anus. It consists of the ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anus (Figure 1). Although the surface area of the colon is smaller than that of the small intestine, effective absorption occurs due to the presence of villi, microvilli,

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and a long residence time. The colon is a cylindrical tube lined with a moist, soft pink mucosal layer and measures 2 to 3 inches in diameter. Both the colon and rectum have an anatomical blood supply, and lymph nodes are present alongside the blood vessels.
Colonic activity can be categorized into segmenting and propulsive movements. Segmenting movements, which are driven by circular muscles, primarily create the saclike haustra and lead to the mixing of luminal contents. In contrast, significant propulsive activity, associated with defecation and facilitated by longitudinal muscles, is less frequent and occurs approximately three to four times daily.

Anatomical Position

The colon averages 150 cm in length, and can be divided into four parts (proximal to distal):

1) Ascending colon
2) Transverse colon
3) Descending colon
4) Sigmoid colon

1)Ascending colon

The colon starts as the ascending colon, a retroperitoneal structure that extends upward from the cecum. When it reaches the right lobe of the liver, it makes a 90-degree turn to move horizontally. This bend, called the right colic flexure (or hepatic flexure), marks the beginning of the transverse colon.

2)Transverse colon

The transverse colon stretches from the right colic flexure to the spleen, where it makes another 90-degree turn downward. This bend is called the left colic flexure (or splenic flexure). At this point, the colon is connected to the diaphragm by the phrenicocolic ligament.

The transverse colon is the most mobile part of the colon and its position can vary, sometimes dipping into the pelvis in tall, thin individuals. Unlike the ascending and descending colon, the transverse colon is intraperitoneal and is suspended by the transverse mesocolon.

3)Descending colon

After the left colic flexure, the colon descends toward the pelvis and is referred to as the descending colon. In most individuals, it is retroperitoneal but positioned in front of the left kidney, running along its lateral border.

As the colon starts to curve medially, it transitions into the sigmoid colon.

4) Sigmoid colon

The sigmoid colon, approximately 40 cm long, is located in the lower left quadrant of the abdomen, stretching from the left iliac fossa to the level of the S3 vertebra. This path gives the sigmoid colon its distinctive "S" shape.

The sigmoid colon is anchored to the posterior pelvic wall by a mesentery called the sigmoid mesocolon. The length of this mesentery allows for considerable mobility of this section of the colon.

Colon Cancer

Colon cancer is a form of cancer that originates in the large intestine, which is the last section of the digestive system**.** Colorectal cancer ranks as the third most common type of cancer in oncologic pathology.

Colon cancer primarily affects older adults, but it can occur at any age. It often starts as small, noncancerous clumps of cells known as polyps that develop on the inner lining of the colon. Over time, some of these polyps may turn into colon cancer. Polyps can be small and often cause few, if any, symptoms, which is why doctors recommend regular screening tests to detect and remove them before they develop into colon cancer.

Currently, it is one of the leading causes of death in many countries, and its mortality rate is expected to surpass that of heart disease in the coming years. It is most prevalent in individuals aged 65-74, with a higher occurrence in women.

However, this condition is increasingly being diagnosed in younger patients due to risk factors such as obesity, sedentary lifestyles, poor dietary habits (high in fats and proteins), smoking, and the overall aging of the population. In patients with colorectal cancer, the clinical presentation varies based on the tumor's location, size, and the presence or absence of metastases. Common symptoms include abdominal pain, changes in chronic bowel habits, alterations in bowel movements, involuntary weight loss, nausea, vomiting, malaise, anorexia, and abdominal distension.

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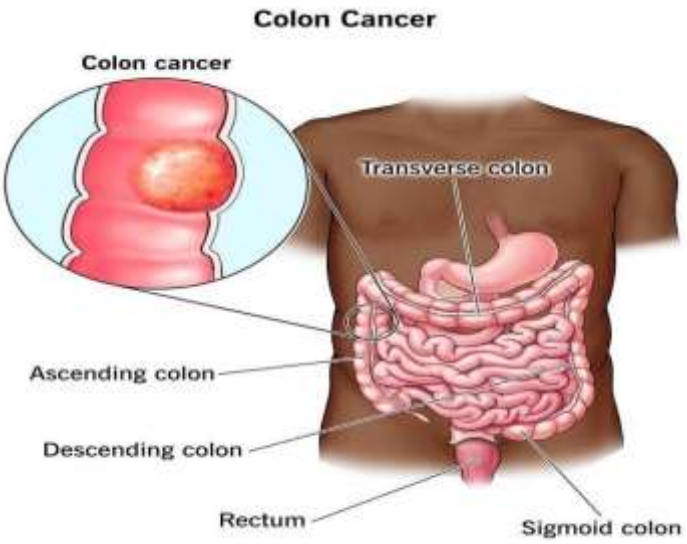
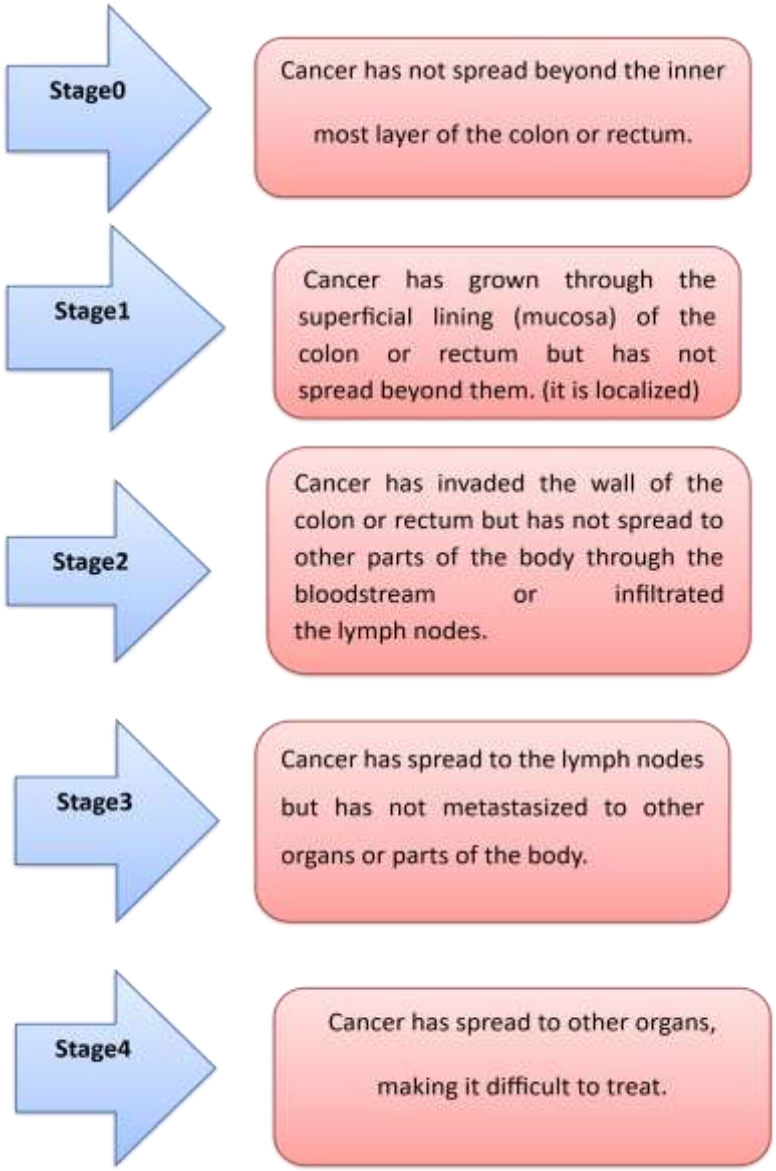


Fig:2 Colon Cancer

3.1 Stages of Colon Cancer



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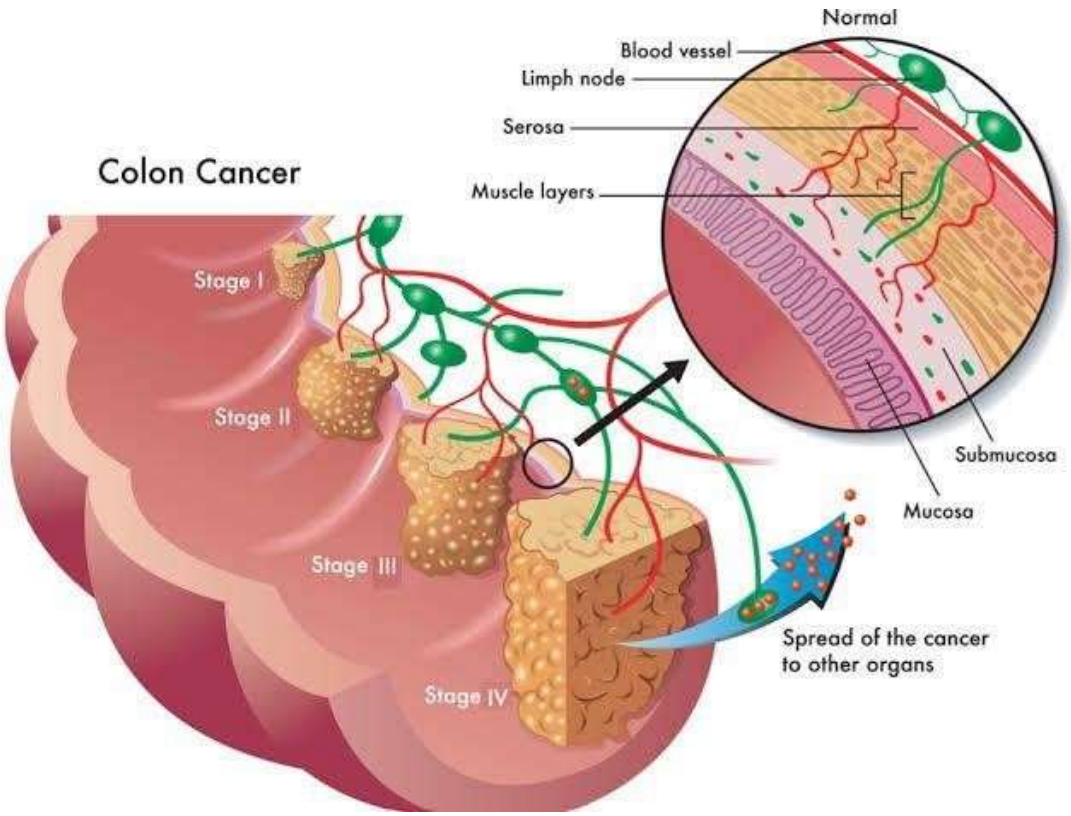

Fig 3: stages colon cancer

3.2 Signs and symptoms

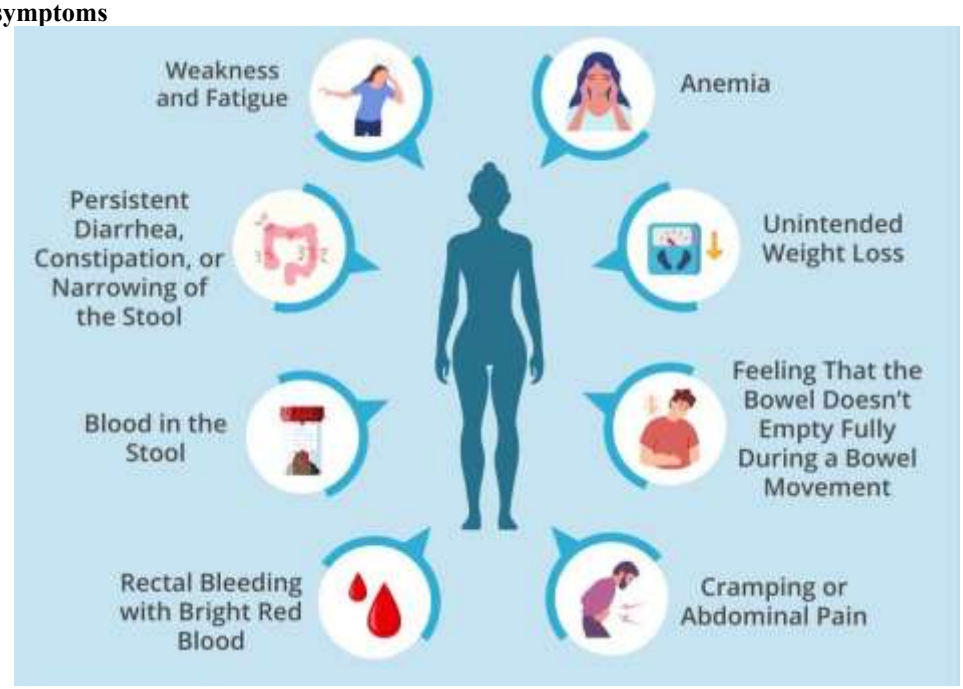

Fig4: Signs & Symptoms

3.3 Risk factor

- **Age :**
  Colon cancer can be diagnosed at any age, but most cases occur in people over 50. While the incidence of colon cancer in individuals under 50 has been rising, the reasons for this trend remain unclear to doctors.
- **Gender**

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- **Family history of colorectal cancer**
  You're more likely to develop colon cancer if you have a blood relative who has had the disease. If more than one family member has colon cancer or rectal cancer, your risk is even greater.
- **Inflammatory intestinal conditionals**
  Chronic inflammatory conditions of the colon, like ulcerative colitis and Crohn's disease, can raise your risk of developing colon cancer**.**
- **Personal history of certain type of cancer**
  Having a history of colon cancer or noncancerous colon polyps increases your risk of developing colon cancer in the future.
- **Low-fiber, high-fat diet:**
  A typical Western diet, low in fiber and high in fat and calories, may be linked to colon and rectal cancer. While research on this connection has produced mixed results, some studies suggest a higher risk of colon cancer in those who consume large amounts of red and processed meats.
- **Diabetes**
  Individuals with diabetes or insulin resistance face a higher risk of developing colon cancer.
- **Obesity**
  People who are obese have an increased risk of colon cancer and an increased risk of dying of colon cancer when compared with people considered normal weight.
- **Smoking:**
  Smokers may be at a higher risk of developing colon cancer.
- **Alcohol:**
  Excessive alcohol consumption increases the risk of colon cancer

3.4 Diagnosis

Your doctor may consider these factors when choosing a diagnostic test:

- The type of cancer suspected
- Your signs and symptoms
- Your age and general health
- Your medical and family history
- The results of earlier medical tests

In addition to a physical examination, the following tests may be used to diagnose colon cancer-

1. Colonoscopy
   A colonoscopy enables the physician to examine the full length of the rectum and colon while the patient is under sedation. A colonoscopist is a medical professional who is trained to conduct this examination. If colorectal cancer is detected, a thorough diagnosis that precisely indicates the tumor's location and extension might not be achievable until the tumor is surgically excised.
2. Biopsy
   A biopsy involves taking a small tissue sample for microscopic analysis. While other tests may indicate the presence of cancer, only a biopsy can provide a conclusive diagnosis of colorectal cancer.
3. Blood test
   Colorectal cancer often causes bleeding in the large intestine or rectum, which can lead to anemia. A complete blood count (CBC) test measuring red blood cell levels may indicate if bleeding is present. Another blood test measures the levels of a protein called carcinoembryonic antigen (CEA). Elevated CEA levels may suggest that cancer has spread to other areas of the body.
   CEA is not a definitive test for colorectal cancer, as elevated levels are found in only about 60% of individuals with colorectal cancer that has metastasized. Additionally, various other medical conditions can also raise CEA levels. The CEA test is primarily used to monitor colorectal cancer in patients undergoing treatment and is not effective as a screening tool. Learn more about cancer tumor markers.
4. Magnetic resonance imaging (MRI).
   An MRI uses magnetic fields instead of x-rays to create detailed images of the body and can be used to measure the size of a tumor. To enhance image clarity, a contrast dye may be administered, either by injection into a vein or as a pill or liquid. MRI is the preferred imaging test for determining the extent of colorectal cancer spread.
5. Ultrasound.
   Ultrasound uses sound waves to create images of internal organs, helping to determine if cancer has spread. Endorectal ultrasound is often used to assess the depth of rectal cancer growth and assists in treatment planning, though it is not as effective at detecting cancer spread to nearby lymph nodes or beyond the pelvis. Ultrasound can also be used to examine the liver, although CT scans or MRIs (mentioned above) are generally more effective for identifying liver tumors.

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6. Chest x-ray.
An X-ray uses a small amount of radiation to create an image of internal body structures. A chest X-ray can help doctors determine if cancer has spread to the lungs.

3.5. Factors To Be Affected In The Design Of Colon - Targeted Drug Delivery System:

1)Anatomy and Physiology of Colon:

The gastrointestinal (GI) tract is composed of the stomach, small intestine, and large intestine. The large intestine, extending from the ileocecal junction to the anus, is divided into three main parts: the colon, rectum, and anal canal. The colon, approximately 5 feet (150 cm) in length, is further divided into five major segments. The right colon includes the cecum, ascending colon, hepatic flexure, and the right half of the transverse colon, as shown in the table. The left colon consists of the left half of the transverse colon, descending colon, splenic flexure, and sigmoid colon. The rectum represents the final anatomical segment before the anus.

1) pH In The Colon :

The pH of the gastrointestinal (GI) tract varies both between individuals and within the same individual. Factors such as diet, disease states, and food intake can influence the pH of gastrointestinal fluids. These pH variations along the GI tract have been utilized for targeted drug delivery to the colon. Radio telemetry studies show that the highest pH (7.5±0.5) is found in the terminal ileum. Upon entering the colon, the pH decreases to
6.4±0.6. In the mid-colon, the pH is 6.6±0.8, while in the left colon, it is 7.0±0.7.

2) Transit of Material in the Colon :

Food intake typically prolongs gastric residence, with some dosage forms staying in the stomach for over 12 hours with regular feeding. Small intestinal transit time is fairly consistent at 3-4 hours and seems unaffected by the type of dosage form or whether the subject is in a fasted or fed state. In comparison to other parts of the gastrointestinal tract, the movement of materials through the colon is much slower. Colonic transit times can vary greatly and are influenced by several factors, including diet (especially fiber content), mobility, stress, illness, and medications. These times typically range from 50 to 70 hours. In cases of active disease, stool weight tends to increase significantly, likely due to the presence of exudates from inflamed epithelium, increased mucus secretion, and reduced reabsorption of fluids and electrolytes.

3) Drug Absorption In The Colon :

Drugs are absorbed passively through either the paracellular or transcellular route. Transcellular absorption involves the passage of drugs through the cells, which is the primary route for lipophilic drugs. In contrast, paracellular absorption occurs through the tight junctions between cells and is the route typically taken by hydrophilic drugs. he limited paracellular absorption of many drugs in the colon is attributed to the tight junctions between epithelial cells. However, the slower transit rate in the colon allows the drug to remain in contact with the mucosa for a longer period compared to the small intestine, partially compensating for the significantly smaller surface area.As water is progressively absorbed along the colon, the colonic contents become more viscous, leading to a reduced dissolution rate and slower diffusion of the dissolved drug through the mucosa. While drug absorption theoretically occurs throughout the entire gastrointestinal tract, most drugs are primarily absorbed in the duodenum and proximal jejunum.

The oral absorption of most peptide and protein drugs is limited due to the following factors:

- Degradation in the acidic environment of the stomach.
- Enzymatic degradation in the small and large intestine.
- Rapid small intestine transit
- Low mucosal permeability.• Extensive first pass metabolism by the absorbing membrane and the liver

4. TREATMENT

4.1 TARGETED DRYG THERAPY OF COLON CANCER:

• How Does Targeted Therapy Work Against Cancer?

Most types of targeted therapy treat cancer by interfering with specific proteins that enable tumors to grow and spread. These therapies work in various ways, including: **Help The Immune System Destroy Cancer Cells**. Cancer cells often thrive by evading the immune system. Some targeted therapies can tag cancer cells, making it easier for the immune system to detect and eliminate them. Other targeted therapies work by enhancing the immune system's ability to combat cancer more effectively. **Stop Cancer Cells From Growing.** n healthy cells, division typically occurs only in response to strong signals that bind to proteins on the cell surface, prompting the cells to divide. This process ensures that new cells are created only when needed. However, some cancer cells have alterations in these surface proteins, causing them to divide uncontrollably, regardless of whether signals are present. Certain targeted therapies block these proteins, stopping them from signaling the cells to divide, which helps slow the uncontrolled growth of cancer.

Stop Signals That Help Form Blood Vessels. Tumors must develop new blood vessels to grow larger, a process known as angiogenesis, driven by signals from the tumor itself. Angiogenesis inhibitors are targeted therapies that block these signals, preventing the formation of a blood supply. Without this blood supply, tumors remain small, and if they already have one, these treatments can cause the blood vessels to die, leading to tumor shrinkage. Learn more about Angiogenesis Inhibitors.

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Deliver Cell-Killing Substances To Cancer Cells. Some monoclonal antibodies are linked to toxins, chemotherapy drugs, or radiation. When these antibodies bind to specific targets on cancer cells, the cells absorb the cell-killing agents, leading to their destruction. Healthy cells without the target remain unaffected.

Cause Cancer Cell Death. Healthy cells undergo a controlled death when damaged or unnecessary, but cancer cells often evade this process. Certain targeted therapies can trigger cancer cells to undergo this programmed cell death.
Starve Cancer Of The Hormones It Needs To Grow. Certain breast and prostate cancers depend on specific hormones to grow. Hormone therapies, a type of targeted treatment, work in two ways: some block the production of these hormones, while others prevent the hormones from affecting your cells, including cancer cells.

- **The Types Of Targeted Therapy :**
  Most targeted therapies are either small-molecule drugs or monoclonal antibodies. 1)Small-molecule drugs are compact enough to penetrate cells easily, making them suitable for targeting intracellular molecules.
  2)Monoclonal antibodies, or therapeutic antibodies, are lab-produced proteins designed to target specific markers on cancer cells. Some mark cancer cells to make them more visible to the immune system, others inhibit cancer cell growth or trigger self-destruction, and some deliver toxins directly to cancer cells.
- **How Is Targeted Therapy Given?**
  Small-molecule drugs are pills or capsules that you can swallow.
  Monoclonal antibodies are usually given through a needle in a blood vein.
- **Treatment Of Colon Cancer, By Stage :**
  Colon cancer treatment primarily depends on the stage of the cancer, though other factors may also play a role. For cancers that haven't spread to distant areas, surgery is typically the main or initial treatment. Chemotherapy may be administered after surgery (known as adjuvant therapy), with most adjuvant treatments lasting around 6 months.
- **Treating Stage 0 Colon Cancer :**
  Stage 0 colon cancers, which are confined to the inner lining of the colon, often require only surgery for treatment. In many cases, this involves removing the polyp or the affected area through a colonoscopy (local excision). However, if the tumor is too large for local excision, partial removal of the colon (partial colectomy) may be necessary.
- **Treating Stage, I Colon Cancer :**
  Stage I colon cancers have extended deeper into the layers of the colon wall but have not spread beyond it or reached nearby lymph nodes.

Stage I includes cancers that originated within a polyp. If the polyp is entirely removed during a colonoscopy, with no cancer cells at the margins of the excised tissue, additional treatment may not be necessary.

If the cancer in the polyp is high grade, or if cancer cells are present at the edges of the removed tissue, further surgery may be recommended. Additional surgery might also be advised if the polyp wasn't entirely removed or if it was removed in multiple pieces, making it difficult to confirm clear margins. For cancers not within a polyp, partial colectomy — the removal of the cancerous section of the colon along with nearby lymph nodes — is the standard treatment, and typically no further treatment is required.

• Treating Stage II Colon Cancer
Many stage II colon cancers have extended through the colon wall and may have invaded nearby tissue, but they have not reached the lymph nodes.

Surgery to remove the part of the colon with cancer (partial colectomy), along with nearby lymph nodes, may be the only required treatment. However, your doctor might recommend adjuvant chemotherapy (chemo after surgery) if certain factors indicate a higher risk of the cancer returning, such as:
The cancer looks very abnormal (is high grade) when viewed under a microscope.
The cancer has grown into nearby blood or lymph vessels.
The surgeon did not remove at least 12 lymph nodes.
Cancer was detected at or near the edge (margin) of the removed tissue, suggesting that some cancer might have been left behind.
The cancer had blocked off (obstructed) the colon.
The cancer caused a perforation (hole) in the wall of the colon.
There is some disagreement among doctors about when chemotherapy should be used for stage II colon cancers. It is essential to have a conversation with your doctor about the benefits and risks of chemotherapy, including its potential to reduce the risk of recurrence and the possible side effects.
If chemotherapy is recommended, the main options include 5-FU and leucovorin, oxaliplatin, or capecitabine, although other drug combinations may also be considered.

• Treating Stage III Colon Cancer
Stage III colon cancers have spread to nearby lymph nodes, but they have not yet spread to other parts of the body.

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The standard treatment for this stage involves surgery to remove the portion of the colon with cancer (partial colectomy) along with nearby lymph nodes, followed by adjuvant chemotherapy.

The most commonly used chemotherapy regimens are FOLFOX (5-FU, leucovorin, and oxaliplatin) or Cape Ox (capecitabine and oxaliplatin), although some patients may receive 5-FU with leucovorin or capecitabine alone, depending on their age and overall health.

For individuals who are not healthy enough for surgery, radiation therapy and/or chemotherapy may be considered as alternative treatment options.

• Treating Stage IV Colon Cancer

Stage IV colon cancers have metastasized from the colon to distant organs and tissues. While colon cancer typically spreads to the liver, it can also affect other areas such as
the lungs, brain, peritoneum (the lining of the abdominal cavity), or distant lymph nodes.

In most instances, surgery alone is not enough to cure stage IV colon cancer. However, if there are only a few small metastatic areas in the liver or lungs that can be surgically removed alongside the colon cancer, surgery may improve survival. This would involve removing the section of the colon with the cancer, along with nearby lymph nodes, as well as excising the metastatic tumors. Chemotherapy is usually administered both before and/or after surgery. In some cases, hepatic artery infusion may be considered if the cancer has spread to the liver.

If the metastases are too large or numerous to be surgically removed, chemotherapy may be given first (neoadjuvant chemotherapy) to shrink the tumors. If the tumors respond to treatment, surgery may then be attempted to remove them. After surgery, chemotherapy would typically be administered again. For liver metastases, alternative options such as ablation or embolization may be considered to destroy the tumors.

If the cancer has spread too extensively for surgery to be curative, chemotherapy is the primary treatment. However, surgery may still be necessary if the cancer is blocking the colon or is expected to do so. In some cases, a stent (a metal or plastic tube) can be inserted during a colonoscopy to keep the colon open, potentially avoiding surgery. Otherwise, procedures like a colectomy or a diverting colostomy (where the colon is cut above the cancer and the end is attached to an opening in the skin for waste to exit) may be performed.

If you have stage IV cancer and surgery is recommended, it's crucial to understand the purpose of the surgery—whether it is aimed at attempting to cure the cancer or to manage symptoms and improve quality of life.

The majority of people with stage IV cancer will receive chemotherapy and/or targeted therapies to manage the cancer.
Some of the most commonly used regimens include: FOLFIRI: leucovorin, 5-FU, and irinotecan (Camptosar)
CAPEOX or CAPOX : capecitabine (Xeloda) and oxaliplatin
FOLFOXIRI: leucovorin, 5-FU, oxaliplatin, and irinotecan
5-FU and leucovorin, with or without a targeted drug
The selection of treatment regimens is influenced by factors such as your previous treatments and your general health.
If a regimen stops being effective, an alternative may be considered. For individuals with specific genetic mutations in their cancer cells, immunotherapy with drugs like pembrolizumab (Keytruda) may be an option after initial chemotherapy.
For advanced cancers, radiation therapy may be used to manage symptoms, such as pain, and potentially shrink tumors temporarily. However, it is unlikely to cure the cancer. If your doctor suggests radiation therapy, it's crucial to understand the intended goal of the treatment.

4.2. DRUGS USED IN THE TREATMENT OF COLON CANCER

Targeted therapy drugs function differently from traditional chemotherapy drugs
They can be effective when standard chemo drugs are not, and they often cause fewer and less severe side effects. These therapies may be used in combination with chemotherapy or on their own if chemotherapy is no longer effective.
A)Drugs that target blood vessel formation (VEGF)
These include:

- Bevacizumab (Avastin)
- Ramucirumab (Cyramza)
- Ziv-aflibercept (Zaltrap)

B) Drugs that target cells with EGFR changes
These include:

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- Cetuximab (Erbitux)
- Panitumumab (Vectibix)

A) Drugs That Target Blood Vessel Formation (VEGF)

Vascular endothelial growth factor (VEGF) is a protein that enables tumors to create new blood vessels through angiogenesis, supplying them with the nutrients required for growth. Medications that inhibit VEGF activity can be used to treat certain colon or rectal cancers.

Vascular Endothelial Growth Factor (VEGF),

Initially referred to as vascular permeability factor (VPF), VEGF is a signaling protein produced by cells that promotes blood vessel formation. It belongs to a sub-family of growth factors within the platelet-derived growth factor family, known for their cysteineknot structure. These proteins play a crucial role in both vasculogenesis, the formation of the embryonic circulatory system, and angiogenesis, the development of new blood vessels from existing ones.

1) Bevacizumab

Avastin (bevacizumab) is a cancer treatment that works by blocking the growth and spread of cancer cells in the body. It is also used to treat cancer in the membrane lining the internal organs of the abdomen and is typically administered as part of a combination therapy.

- **How Is Avastin Given?**

  Avastin is administered through an intravenous (IV) infusion. The initial dose is given over 90 minutes, and if well-tolerated, the infusion time can be reduced to 30 minutes for subsequent doses.

  The dosage of Avastin you receive depends on various factors, including your height, weight, overall health, any existing health conditions, and the specific cancer or condition being treated. Your doctor will decide the appropriate dose and treatment schedule.

- **Mechanism of Action:**

  Bevacizumab consists of human framework regions combined with antigenbinding regions from a humanized murine antibody that specifically targets VEGF. It is produced using recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system, cultured in a nutrient medium containing gentamicin. The purification process includes steps for viral inactivation and removal. By binding to VEGF, bevacizumab blocks its interaction with the VEGF receptors (Flt-1 and KDR) on endothelial cells, thereby inhibiting blood vessel formation and slowing the growth of metastatic tumors.

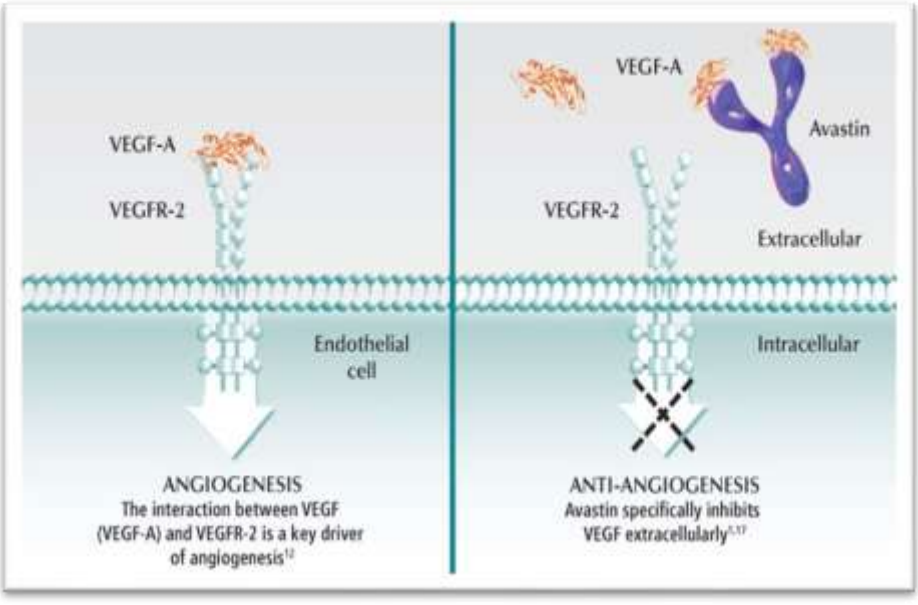

Fig. No. 05 Mechanism of Action Avastin (Bevacizumab)

- **Metastatic Colorectal Cancer**

The recommended dosage of Avastin when given in combination with intravenous fluorouracil-based chemotherapy is:
5 mg/kg intravenously every 2 weeks in combination with bolus-IFL.
10 mg/kg intravenously every 2 weeks in combination with FOLFOX4.
The recommended dosage of Avastin when used with fluoropyrimidine-based
chemotherapy, irinotecan, or oxaliplatin in patients who have progressed on a first-line Avastin-containing regimen is 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks.

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- **Side Effects:**

Common side effects of Avastin include:

- Fatigue and weakness
- High blood pressure
- Diarrhea
- Headache
- Loss of appetite

Serious Side Effects Of Avastin Include: -

- Holes in the colon requiring surgical repair
- Heart attack
- Chest pain
- Kidney damage due to increased protein in the urine
- Decreased ability of wounds to heal (so it shouldn't be used right after surgery)

2) Ramucirumab

Ramucirumab is a human monoclonal antibody (IgG1) that targets vascular endothelial growth factor receptor 2 (VEGFR2), a type II transmembrane tyrosine kinase receptor found on endothelial cells.

How Ramucirumab Is Given :

As an infusion into a vein (intravenous, IV) every 2 weeks.
Medications may be given just before the infusion to reduce the occurrence of infusion-related symptoms.
There is no pill form of ramucirumab.
The dosage of this medication will be based on several factors, including your weight, overall health, and any other existing health conditions. Your doctor will decide the appropriate dosage and treatment schedule.

• Mehanism of Action

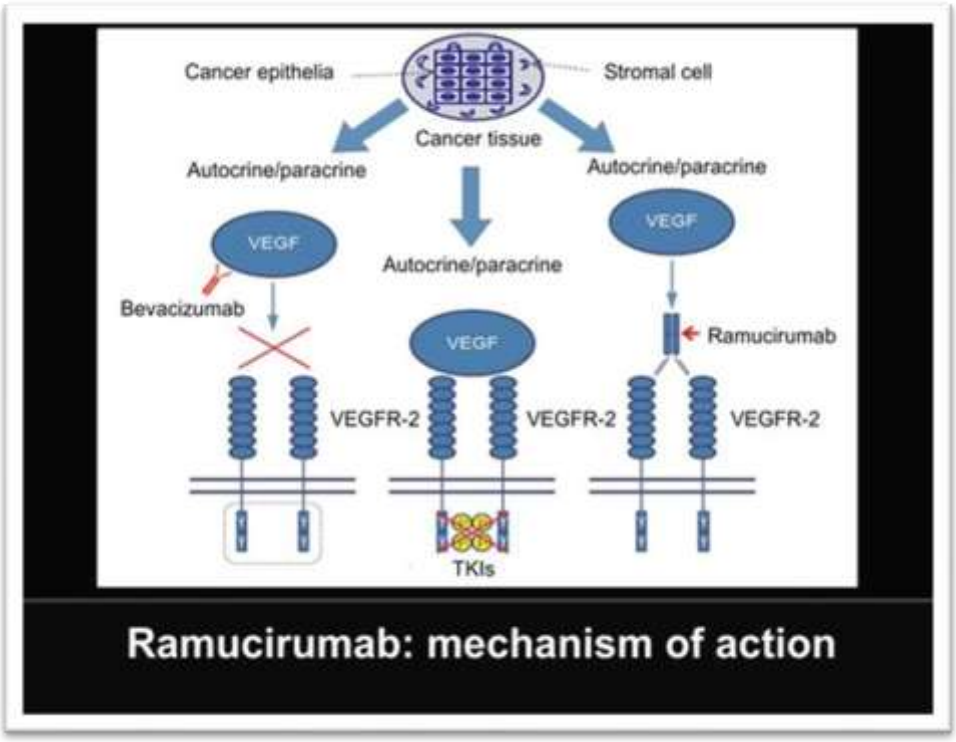

Fig. No. 06 Mechanism of Action of Ramucirumab

Ramucirumab is a human monoclonal antibody (igg1) that targets the vascular endothelial growth factor receptor 2 (VEGFR2), a type II transmembrane tyrosine kinase receptor found on endothelial cells. By binding to VEGFR2, ramucirumab blocks the attachment of its ligands (VEGF-A, VEGF-C, and VEGF-D), thereby inhibiting receptor phosphorylation stimulated by VEGF. This action prevents the ligand-induced proliferation, permeability, and migration of human endothelial cells.

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CYRAMZA binds directly to the ligand-binding pocket of VEGF Receptor 2 to block the binding of VEGF-A, VEGF-C, and VEGF-D*1
VEGF-A, VEGF-C, and VEGF-D have been shown to induce angiogenesis in
preclinical studies.

• **Dose**

Colorectal Cancer

It is indicated for use in combination with FOLFIRI for patients with metastatic colorectal cancer (mCRC) whose disease has progressed after a first-line regimen containing bevacizumab, oxaliplatin, and a fluoropyrimidine.
Ramucirumab 8 mg/kg IV q2wk in combination with FOLFIRI
Continue until disease progression or unacceptable toxicity **Contraindications:**
In Europe, ramucirumab therapy for NSCLC is contraindicated in cases of tumor cavitation or involvement of major vessels.

Adverse Effect

In a study on ramucirumab monotherapy, the most common adverse effects were diarrhea (reported in 14% of patients compared to 9% with placebo), hyponatremia (low blood sodium levels; 6% versus 2%), headache (9% versus 3%), and hypertension (16% versus 8%).

3) Ziv-Aflibercept

Ziv-aflibercept is classified as an antineoplastic (anti-cancer) agent and vascular endothelial growth factor (VEGF) inhibitor.
Administration of ziv-aflibercept:
Ziv-aflibercept is administered intravenously (IV) over one hour and is given before the other chemotherapy agents scheduled for the same treatment day.

Mechanism of Action

Aflibercept is a recombinant fusion protein that functions as a decoy receptor for the ligands vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PIGF). By preventing these ligands from binding to endothelial receptors VEGFR-1 and VEGFR-2, aflibercept suppresses neovascularization and reduces vascular permeability, ultimately slowing vision loss or the progression of metastatic colorectal cancer.
Side effects:
Common side effects of Zaltrap include:

- Diarrhea
- Sores on the mouth and lips
- Low white blood cell count (neutropenia)
- High levels of protein in the urine
- Increased liver enzymes
- Low blood platelet count, and
- Changes in kidney

The following serious adverse reactions are discussed in other sections of the labeling:

- Hemorrhage
- Gastrointestinal Perforation
- Compromised Wound Healing
- Fistula Formation Hypertension
- Arterial Thromboembolic Events

Rare but potentially serious side effects include blood clots, severe bleeding, perforations in the colon, heart issues, kidney problems, and delayed wound healing. If a perforation occurs in the colon, it can lead to a severe infection, possibly requiring surgery to repair. Another rare but serious side effect of these drugs is an infusion-related allergic reaction, which may lead to breathing difficulties and low blood pressure.

Dosage Forms & Strengths

Injectable solution for intravitreal administration:

- 2mg/0.05mL (40mg/mL single-dose vial)
- 2mg/0.05mL (40mg/mL single-dose prefilled syringe)

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B) Drugs That Target Cells With EGFR Changes

1.Cetuximab (Erbitux)

Classes Cetuximab is an antineoplastic, targeted therapy classified as a monoclonal antibody and an Epidermal Growth Factor Receptor (EGFR) inhibitor.

How Cetuximab Is Given

Cetuximab is administered as an intravenous (IV) infusion. The dose you receive depends on several factors, including your height, weight, overall health, other medical conditions, and the type of cancer or condition being treated. Your doctor will determine your specific dose and treatment schedule.

Mechanism of Action

Cetuximab binds to the epidermal growth factor receptor (EGFR) on both normal and tumor cells. EGFR is often overexpressed in many colorectal cancers. Cetuximab competitively inhibits the binding of epidermal growth factor (EGF) and TGF-alpha, thereby reducing their effects on cell growth and metastatic

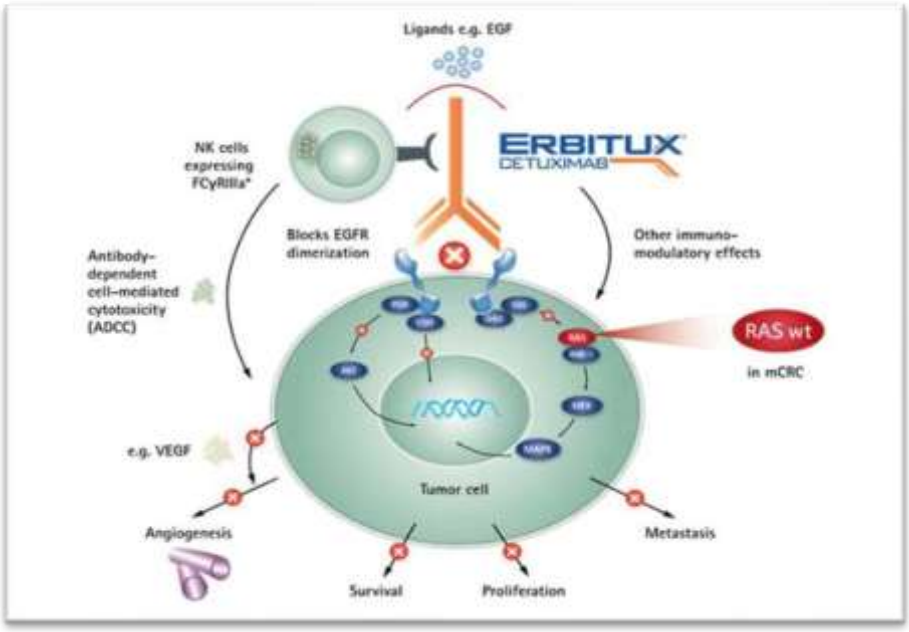

Fig No. 07 Mechanism of Action of Cetuximab

Side Effects

The most frequently occurring side effects of Erbitux include:

- Rash,
- Itching,
- Dry or cracked skin,
- Nail changes,
- Headache,
- Diarrhea,
- Nausea,
- Vomiting,

The following adverse reactions are discussed in more detail in other sections of the label:

- Infusion reactions
- Cardiopulmonary arrest
- Pulmonary toxicity
- Dermatologic toxicity
- Hypomagnesaemia and Electrolyte Abnormalities **Dosage Forms & Strengths:**

The dosage is applicable for either monotherapy or in combination therapy.

- Initial dose: 400 mg/m² IV infusion over 2 hours.

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- Subsequent doses: 250 mg/m² IV infusion over 60 minutes weekly (with a maximum infusion rate of 10 mg/min) until disease progression or unacceptable toxicity occurs.
- Complete cetuximab administration 1 hour before FOLFIRI infusion.
- The infusion rate should not exceed 10 mg/min.

3) Panitumumab (Vectibix)

Panitumumab is a fully human monoclonal antibody that targets the epidermal growth factor receptor.

How Panitumumab Is Given:

Panitumumab is administered through an intravenous (IV) infusion using an infusion pump.
The dose of Panitumumab you receive will depend on several factors, including your height, weight, overall health, other medical conditions, and the type of cancer or condition being treated. Your doctor will determine the appropriate dosage and treatment schedule.

Mechanism of Action

Panitumumab specifically binds to the EGFR on both normal and tumor cells, competitively inhibiting the binding of its ligands. Nonclinical studies have shown that panitumumab's binding to EGFR prevents ligand-induced receptor autophosphorylation and activation of receptor-associated kinases, leading to inhibited cell growth, induction of apoptosis, reduced production of pro-inflammatory cytokines and vascular growth factors, and internalization of the EGFR.

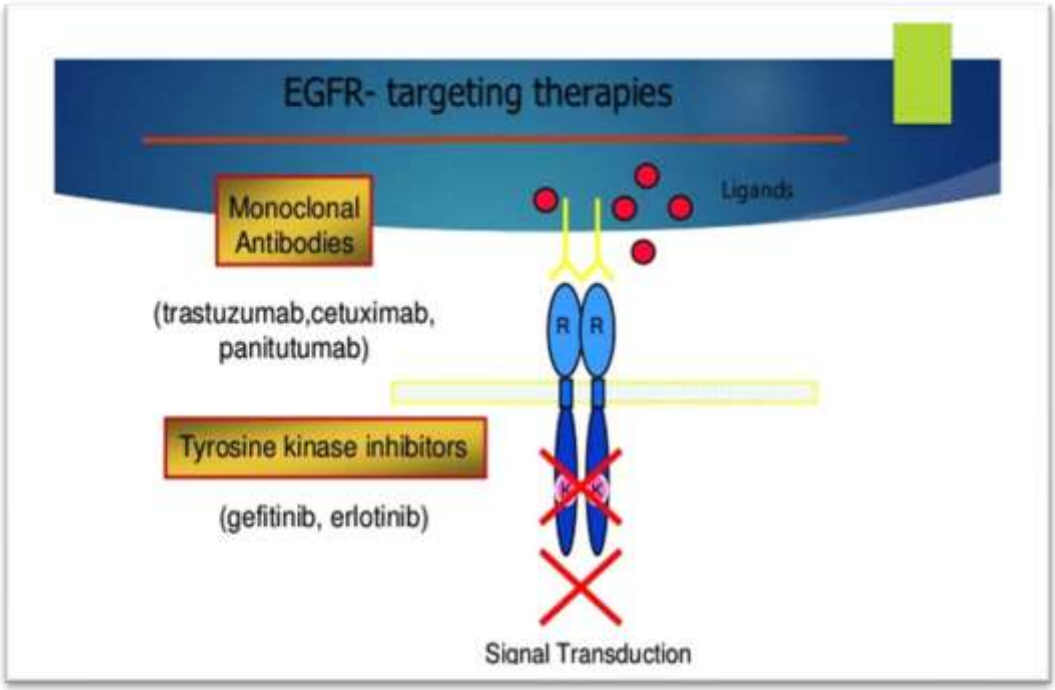

Fig. No. 08 Mechanism of Action of Panitumumab

Dose

6mg/kg infusion over 60 minutes (over 90 minutes if dose>1g) q14 days

Side Effects

Common side effects of Vectibix include:
Skin reactions (redness, acne, itching, or rash)
Diarrhea

- Nausea
- Vomiting
- Tiredness
- Constipation
- Stomach or abdominal pain
- Growth of eyelashes

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The following adverse reactions are described in more detail in other sections of the label:

- Dermatologic and soft tissue toxicity
  -Electrolyte depletion/monitoring
- Infusion reactions
- Acute renal failure when combined with chemotherapy
- Pulmonary fibrosis/interstitial lung disease (ILD)
- Photosensitivity

Dose

6mg/kg infusion over 60 minutes (over 90 minutes if dose>1g) q14 days

Other Targeted Therapy Drugs

Regorafenib (Stivarga) is a targeted therapy classified as a kinase inhibitor. Kinases are proteins located on or near the cell surface that transmit critical signals to the cell's control center. Regorafenib inhibits several kinase proteins involved in tumor cell growth and the formation of new blood vessels to nourish the tumor, thereby helping to slow cancer cell growth.

This medication is used to treat advanced colorectal cancer, usually when other treatments are no longer effective. It is taken orally in pill form. Common side effects include fatigue, loss of appetite, hand-foot syndrome (redness and irritation of the hands and feet), diarrhea, high blood pressure, weight loss, and abdominal pain. Less common, but more serious side effects, may include severe bleeding or perforations (holes) in the stomach or intestines.

6. PREVENTION

Screening colon cancer

Doctors recommend that individuals at average risk for colon cancer begin screening around age 50. However, those with an increased risk, such as a family history of colon cancer, should consider screening earlier.

You can lower your risk of colon cancer by making certain lifestyle changes. Consider taking steps to: Incorporate a variety of fruits, vegetables, and whole grains into your diet. These foods are rich in vitamins, minerals, fiber, and antioxidants, which may help prevent cancer. Aim for a diverse selection of fruits and vegetables to ensure you receive a broad range of vitamins and nutrients. Consume alcohol in moderation, if at all. If you choose to drink, limit your intake to no more than one drink per day for women and two for men. Quit smoking, and consult your doctor for personalized strategies to help you quit.

Aim to exercise most days of the week, targeting at least 30 minutes of activity on most days. If you're new to exercise, start slowly and gradually work up to 30 minutes. Be sure to consult your doctor before beginning any new exercise routine.

Maintain a healthy weight by combining a balanced diet with regular exercise. If you are at a healthy weight, focus on maintaining it. If weight loss is needed, consult your doctor for guidance on healthy ways to reach your goal. Aim for gradual weight loss by increasing physical activity and reducing calorie intake.

7. CONCLUSION

Colon-targeted drug delivery systems provide safe and effective delivery of medications with minimal fluctuations at the target site, including for targeted therapies in colorectal cancer. As the disease often becomes symptomatic at advanced stages, organized screening programs are being implemented worldwide to increase early detection and reduce morbidity and mortality associated with colorectal cancer.

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