



DOSTRALIMAB IN RECTAL CANCER:A COMPREHENSIVE REVIEW

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ABSTRACT:

Cancer is a large group of diseases that can start in almost any organ or tissue of the body. Rectal wall is made up of layers of tissue. Cancer begins in the innermost layer that comes in touch with food. Dostarlimab is a humanized monoclonal antibody that is developed for the treatment of various cancers. Brand name of Dostarlimab is jemperli. Dosage of Dostarlimab in adults include Dose 1 through 4 of jemperli is 500mg every 3weeks. Common side effects of Dostarlimab may include abnormal liver function tests, nausea, diarrhoea, constipation, low white blood cell counts, anaemia, or feeling weak or tired. Dostarlimab belong to class of drugs called anti-programmed cell death-1 (PD-1) monoclonal antibodies, immune checkpoint inhibitors, programmed death-ligand 1 (PD-L1) blocking antibodies. This drug was initially tried in treating uterine cancer and it was found to be effective. The recent study by the memorial Sloan Kettering cancer centre, New York, is the first clinical investigation that shown its effectiveness against rectal cancer. In the trial patients had stage II or III cancer and drug was given every three weeks for six months. The trial shown dramatic results that there are no apparent signs of tumour after at least follow-up for six months in rectal cancer patients. Locally advanced rectal cancer is usually managed by neoadjuvant chemotherapy and radiation followed by surgical resection of the rectum. Recent evidence suggests that use of neoadjuvant therapy in which induction chemotherapy with a fluoropyrimidine in combination with oxaliplatin followed by chemotherapy and then surgery. In recent clinical trial Dostarlimab is used for rectal cancer and it shown prominent result. But longer follow-up is needed to assess the drug whether disease cautious to be uncontrolled or whether the drug is safe.

KEYWORDS:

Rectal Cancer, Dostarlimab, Jemperi, Chemotherapy, Immune checkpoint inhibitors.

INTRODUCTION

Cancer is a large group of diseases that can start in almost any organ or tissue of the body (1). It can start almost anywhere in human body which is made up of trillions of cells. Normally human cells grow and multiple to form a new cell. Sometimes, this process breaks down and leads to damaged cells which grow and multiply these cells may form as tumors. These tumors can be benign and malignant. (2)

There are hundred types of cancers in this article will discuss about rectal cancer.

ANATOMY OF RECTUM

The rectum is last part of large intestine between the sigmoid colon and the anal canal. Its starts from rectosigmoid junction at the level of third sacral vertebra or the sacral promontory and terminates at the level of the anorectal ring. It is about 12-15cm in length with an internal calibre is much like to sigmoid colon (3). Rectum is typically divided into three parts upper, middle, and lower described their distance most commonly from the AV or, rarely from the dentate line (DL) which was measured by MRI (4). The lower limit of rectum is generally defined through the anorectal ring, an anatomical landmark palpable on physical examination or visible radiography because the upper border of anal sphincter and puborectalis muscle tissue. The upper limit of rectum has been variably defined by the splaying of taniae coli, the sacral promontory, the proximal value of Houston or the extent of the peritoneal reflection. A recent consensus conference described the factor of the sigmoid take off (i.e., the junction of the sigmoid mesocolon and mesorectum). As visible on MRI given the correlation among those landmarks is imperfect and the presence of all 3 values of Houston is inconsistent, the upper limit of the rectum, from a clinical perspective, may be truly elusive. In practice, the region of a rectal cancer is most commonly assessed by distance from its distal margin to the anal verge. Tumors within 15cm of the anal verge are usually classified as rectal cancer, despite the fact that the overall length of the rectum can range by body habitus and sex (5).

RECTAL CANCER STAGES:

Rectal wall is made up of layers of tissue. Cancer begins in the innermost layer that comes in touch with food. This layer is referred to as mucosa. The next layer is the submucosa. It is made up of connective tissue and contains mucous glands, blood and lymph vessels and nerves. The submucosa followed by a layer of muscle called the muscularis propria. While the colon has a fourth layer called serosa a whole lot of the rectum does no longer have this outer layer. This can make it easier for rectal cancer to spread to nearby areas in the pelvis. If left untreated cancer cells develop through the rectal wall, in the direction of interior of the pelvis. The cancer can then invade to organs and other structures or outside the rectum, and it can also travel through lymph or blood to nearby lymph nodes.

The American joint committee on cancer (AJCC) tumor, node, metastasis (TNM) system is used to stage rectal cancer. In the AJCC system, the subsequent key pieces of information about the cancer are used to present it a level.

T: How far the tumor has grown into or through the rectal wall

N: Whether any lymph nodes have cancer in them.

M: Whether the cancer has spread to areas or organs outside the rectum.

The T, N, and M scores are combined to assign the cancer a stage. There are five stages of rectal cancer. (6)

Stages- 0: In this stage abnormal cells are found in the mucosa of rectum wall. These cells may become cancer and spread to nearby tissue. This stage is also known as carcinoma insitu.

Stage-1: In stage -1 cancer has formed in the mucosa (Inner most layer) of the rectal wall and spread to submucosa or muscle layer of rectal wall.

Stage-2: Stage-2 cancer is divided into stages IIA, IIB, IIC.

Stage IIA: Cancer has spread through the muscle layer of rectal wall to the serosa (outer layer) of rectal wall.

Stage IIB: Cancer has spread through the serosa of the rectal wall to the tissue that lines the organs in the abdomen (Visceral peritoneum).

Stage IIC: Cancer has spread through the serosa of the rectal wall to nearby organs.

Stage-3: It is divided into three stages i.e., stage IIIA, IIIB, IIIC.

Stage IIIA: Cancer has spread through mucosa to submucosa and four to six nearby lymph nodes.

Stage IIIB: Cancer has spread through the mucosa to submucosa and may spread to rectal wall, and cancer has spread to seven or more nearby lymph nodes.

Stage IIIC: Cancer has spread through the serosa to nearby organs and to one or more nearby lymph nodes or to tissue nearby lymph nodes.

Stage-4: Cancer is divided into three stages i.e., IVA, IVB, IVC

Stage-IVA: Cancer has spread to one area or organ that is not near the rectum, such as the liver, lung, ovary, or a distant lymph node.

Stage-IVB: Cancer has spread to more than one area or organ that is not near the rectum.

Stage-IVC: Cancer has spread to the tissue that lines the wall of the abdomen and may have spread to other areas or organs. (7)

DIAGNOSIS:

Diagnosis of rectal cancer is based on digital rectal examination (DRE) and endoscopy with biopsy for histopathological confirmation.

Tumors with distal extension ≤ 15 cm from anal margin is classified as rectal

Cancer is divided into three types i.e., low, middle, high. Low is up to 5cm, Middle is of from > 5 to 10cm, High is from >10 to 15cm. (8)

TREATMENT:

Stage 0: In this stage as cancer have not grown beyond the rectum lining, so removing or destroying of cells is needed. You can usually treat with polypectomy, local excision, or transanal resection.

Stage-1: cancer have gone to deeper wall of rectum but not spread outside the rectum

This stage includes cancer that were part of polyp. If polyp is removed completely no other treatment is required. If polyp is present at the edges of cancer cells you might advise for surgery.

For other stage-1 cancer main treatment is surgery, cancer can be removed by performing transanal resection. In some cases, low anterior resection (LAR), proctectomy may be done. This procedure is selected based on where the cancer is located in rectum. After performing surgery additional treatment is not required. But if physician find that cancer is more advanced then they will prefer combination drugs before the surgery the drug is 5-FU and capecitabine are most commonly used.

Stage-2: This stage is usually treated with chemotherapy, radiation therapy, and surgery, although the order of treatment may vary from person to person. Most people get both chemo and radiation therapy as their first treatment. Usual drug of choice is either 5-FU or Capecitabine.

Followed by surgery i.e., low anterior resection, proctectomy with colo-anal panastomosis or abdominoperineal resection (APR), this performed depending upon where the cancer is located in rectum. If chemo-radiation therapy shrink the tumor then transanal resection is performed.

Chemotherapy is given after performing the surgery for a period of six months i.e., either FOLFOX regimen (oxaliplatin, 5-FU, and Leucovorin), or 5-FU and Leucovorin, or CAPEOX (Capecitabine, oxaliplatin) or capecitabine alone. These drugs are preferred based on patient need.

Stage-3: This stage is usually treated with chemotherapy, radiation and surgery. Most often, chemo is given first this may shrink the cancer and easier to take large tumours. It lowers the chance that cancer will come back to pelvis. Giving radiation before surgery which leads to fewer problems then giving after surgery.

Followed by surgery here remove the rectal cancer and nearby lymph nodes by using either LAR or APR, if cancer is reached to nearby organs, then pelvic exenteration may be needed. Followed by chemo the drugs which are used in stage-2 those drugs are used in stage-3 also.

Stage-4: Rectal cancer has spread through distant organs and tissue such as liver or lungs. If there are tumours in liver or lungs most common treatment options are

- Surgery followed by chemo
- chemo followed by surgery to remove rectal cancer and followed by chemoradiation
- Chemo followed by chemoradiation followed by surgery and might be followed by chemotherapy.
- Chemoradiation followed by surgery and might be followed by chemotherapy.

Most commonly performed surgery is LAR or APR. If cancer is more widespread and it can't be treated with surgery in this case it is treated with chemo or targeted therapy drugs some of them are

FOLFOX regimen, CAPEOX FOLFIRI (Leucovorin, 5-FU, oxaliplatin, and irinotecan with any of these combination plus either a drug that targets VEGF(Bevacizumab) or ramucirumab(Cyramza) or a drug that targets EGFR(cetuximab) or Panitumumab(vectibix) the choice can be depend on patient condition and the location of cancer in rectum. (9)

Dostarlimab is a humanized monoclonal antibody that is developed for the treatment of various cancers (10) Dostarlimab is an anti-programmed death receptor -1 (PD-1) monoclonal antibody used for treatment of adult patients with mismatch pair deficient (dMMR) recurrent or advanced endometrial cancers. Brand name of Dostarlimab is jemperli. (11)

Dosage of Dostarlimab in adults include Dose 1 through 4 of jemperli is 500mg every 3weeks. Subsequent dosing beginning 3 weeks after dose 4 i.e., dose 5 onwards of jemperli is 1000mg every 6weeks. The safety and efficacy of jemperli have not been established in paediatric patients. In pregnant women jemperli may harm foetus so in females of reproductive potential are advised to use effective contraception during treatment with jemperli and for 4 months after last dose.it is unknown that drug may pass into breast milk as it causes serious adverse effects breastfeeding is not recommended during treatment. (12)

Common side effects of dostarlimab may include abnormal liver function tests, nausea, diarrhoea, constipation, low white blood cell counts, anemia, or feeling weak or tired.

Dostarlimab may also cause serious side effects like cough, shortness of breath, chest pain, irregular heartbeats, confusion, hallucinations, eye pain or redness, vision problems, severe stomach pain, nausea, vomiting, diarrhoea, bloody or tarry stools, low red blood cells (anaemia)--pale skin, tiredness, cold hands and feet; low white blood cell counts--fever, mouth sores, skin sores, sore throat, cough; kidney problems--swelling in your ankles, blood in your urine, little or no urination; liver problems--right-sided upper stomach pain, loss of appetite, bruising or bleeding, dark urine, jaundice , signs of a hormonal disorder--frequent or unusual headaches, dizziness, feeling very weak, mood or behaviour

changes, hoarse or deepened voice, increased hunger or thirst, increased urination, constipation, hair loss, sweating, feeling cold, weight gain or loss.(13)

Contraindications of jemperli includes overactive thyroid gland, a condition with low thyroid hormone levels, type 1 diabetes mellitus, severely decreased function of cortex of adrenal gland, interstitial pneumonitis, inflammation of the large intestine, inflammation of the liver called hepatitis, kidney inflammation, high blood sugar, pregnancy, a patient who is producing milk and breastfeeding, inflammation of the pituitary gland. (14)

Dostarlimab belong to class of drugs called anti-programmed cell death-1 (PD-1) monoclonal antibodies, immune checkpoint inhibitors, programmed death-ligand 1 (PD-L1) blocking antibodies. It works by recruiting the body's natural immune mechanism to fight against cancer. This drug was initially tried in treating uterine cancer and it was found to be effective. The recent study by the memorial Sloan Kettering cancer centre, New York, is the first clinical investigation that shown its effectiveness against rectal cancer. In the trial patients had stage II or III cancer and drug was given every three weeks for six months. The trial shown dramatic results that there are no apparent signs of tumour after at least follow-up for six months in rectal cancer patients. (15)

Locally advanced rectal cancer is usually managed by neoadjuvant chemotherapy and radiation followed by surgical resection of the rectum. Recent evidence suggests that use of neoadjuvant therapy in which induction chemotherapy with a fluoropyrimidine in combination with oxaliplatin followed by chemotherapy and then surgery.

This treatment results in complete pathological response in patients, but it is related with certain complications and harmful effects including bowel, urinary, and sexual dysfunction, infertility and altered quality of life in substantial portion patients.

5-10% of rectal adenocarcinomas are mismatch repair deficient and these tumours are poorly responded to standard chemotherapy regimens including neoadjuvant chemotherapy in rectal cancer patients.

We hypothesized that single agent programmed death 1(PD-1) blockade might be useful in locally advanced rectal cancer. To test this theory, we initiated a phase 2 study to explore the overall frequency and response of neoadjuvant treatment with Dostarlimab a PD-1 inhibitor in patient population.(16)

Dostarlimab is a humanized anti-programmed death (PD)-1 monoclonal antibody that binds with high affinity to the PD-1 receptor and effectively blocks its interaction with the ligands PD-L1 and PD-L2. Jemperli is a novel accuracy cancer immunotherapy tranquilizes that assists with restoring the body's immune system in fighting malignant growth by releasing checkpoints that cancer uses to close down the immune system. PD-1 and PD -L1 are proteins that inhibit certain types of immune responses, permitting cancer cells to evade an attack by the body's immune cells. Dostarlimab works similar to other checkpoint inhibitors.

Mismatch Repair Genes work like genetic "spell checkers." When issues occur in these spell-checking MMR genes, it implies that areas of DNA begin to become unstable and the body is unable to correct the errors that happens during DNA replication and consequently accumulate errors. The accumulation of errors causes the production of novel microsatellite fragments that can be estimated. The presence of MSI represents evidence that the MMR capability is not working normally and predisposition to developing cancer exists. Because Mismatch repair-deficient tumours are known to be sensitive to checkpoint inhibitor immunotherapy treatment researchers evaluated Jemperli in patients with early stage rectal cancer to check whether it could replace radiation and surgery. Fourteen patients with mismatch repair-deficient stage II and stage III rectal adenocarcinoma were treated with Jemperli every 3 weeks for 6 months, followed by standard chemoradiation and surgery. In any case, the people who accomplished a complete response to therapy could exclude chemo radiation and medical procedure. (17)

CONCLUSION:

In recent clinical trial dostarlimab is used for rectal cancer and it shown prominent result. But longer follow-up is needed to assess the drug whether disease cautious to be uncontrolled or whether the drug is safe.

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