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Review

A Review On Colorectal Cancer And Its Chemotherapeutic Management

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Abstract

Colorectal Cancer (CRC) is one of the main causes of cancer-related death. Almost 64% of patients are affecting with CRC in the next 20 years in India and China. Nearly 60,800 deaths happening worldwide with CRC. Gender wise epidemiological data of CRC reveals that 1 in 23 males and 1 in 25 females are affecting, making it the third most common cancer, with. CRC accounts for 8% of all cancer-related deaths, making it the second most common cause of death due to cancer. In order to achieve improved survival rates, chemotherapy in conjunction with surgery is the cornerstone of treatment for colorectal cancer. The patients at the early stage of CRC (stage-1 and 2), survival rate for 5 years' time is recorded above 60%. Although 5 years survival rate for patients at the early stage of CRC (stage-1 and 2) is above 60%. More than 50% of patients are diagnosed at or beyond stage-3, when distant metastasis has already occurred. In which case, 5 years survival rate drops to 10%. Chemotherapy for colorectal cancer patients has seen significant change in the last several years. Recent clinical trials data suggests that chemotherapy may increase a patient`s chances of survival for some individuals who have had colorectal cancer surgically unconcerned. 5-fluorouracil (5-FU) is used as a first line of drug in systemic chemotherapy in both adjuvant and palliative therapy. The combination of 5-FU/Leucovorin & oxaliplatin and 5-FU/leucovorin and irinotecan is used as an effective combination therapy for the treatment of metastatic CRC. However, the 5-FU may show drug resistance in some cases after surgery. The 5-FU is more effective when they give in combination with drugs like Oxaliplatin, Irinotecan… The treatment for chemoresistance in CRC is briefly discussed.

Keywords: Colorectal cancer, Chemotherapy, 5-FU, oxaliplatin, Chemoresistance.

INTRODUCTION

Colorectal cancer is the type of cancer that appears in the rectum, which is final few inches of large intestine before the anus, or the colon, which is the longest section of the large intestine. It is a type of cancer that appears near the bottom of the digestive tract. Colorectal polyps, a development of tissues or cells from a bodily surface that is often a mucous membrane, are the cause of about 95% of incident occurrences of colorectal cancer.

Gastrointestinal polyps most frequently occur in colorectal cancer. The formation of adenomatous polyps (precancerous polyps) due to hyperplastic and hypotonic nature of the normal intestinal leads to colorectal cancer.[1] CRC is the third most common cancer globally (8%) after breast cancer in women (16%) and prostate (15%) lung cancer (12%). CRC is the second most leading cause of death due to cancer accounting for (9.2%) of all cases (9% male and 8% female)[2] Estimates have shown that by the year 2035, there will be an increment in the cases of colon and rectal cancer by 71.5% and 60.0% respectively. [3]

Mostly CRC are adenocarcinomas showing different degrees of differentiation and variable amount of mucinous expression, high heterogeneity is molecularly seen between different cancers at different parts of large intestine.[4] The choice of treatment for CRC is estimated on the bases of multiple approaches such as tumor related characteristics those are the number and location of metastases, tumor progression, presence or absence of the biochemical markers and etc.[5] Presently several types of procedures are performed to cure colorectal cancer. Majorly through surgery which follows by chemotherapy, immunotherapy, radiotherapy, and targeted therapy, biological therapy, as well as palliative treatment which acts as an extra layer of support during cancer treatment. However these therapies may have certain limitations such as non-specific and cytotoxic to normal cells, which may lead to the several complications. The death rate for CRC patients is relatively high after the surgical resection, and adjuvant treatment. So, there is a need to develop novel CRC therapies that have the ability to render resistant tumors more sensitive to chemotherapeutic drugs. (Wen Chen et al, 2024)$_1$ In which, chemotherapy is most widely used at various stages of CRC treatment.

Chemotherapy is defined as cytotoxic therapy that is directly towards rapidly dividing cells. The era of chemotherapy can be traced to world war-2, when an explosion of mustard gas led to bone marrow and lymphoid hypoplasia in those exposed to the gas. This incident led to the use of alkylating agents (derivatives of mustard gas) in the treatment of Hodgkin lymphoma and lymphomas. Sometimes, chemotherapy is given prior to surgery to shrink a tumor and reduce the extent of surgery, which is called as neoadjuvant therapy.

Stages of colorectal cancer

The Tumor Node Metastasis (TNM) categorization serves as the staging approach for colorectal cancer. In line with this classification, TNM is described as; T stands for tumor invasion depth in the several layers of colon wall (T1 submucosa, T2 muscularis propria, T3 mesocolic or mesorectal fat and T4 perforation of serosa or ingrowth in other organs). The N stands for the number of lymph nodes involved, which can be classified as (N0, no lymph nodes involved, N1, 1-3 nodes involved, N2 4 or more nodes involved). Recently, the unique nodal category N1c was established which denotes the existence of tumor deposits where there are no lymph nodes present. The M denotes existence of distant metastases (M0, no distant metastases; M1, metastases beyond local lymph nodes).

CRC is diagnosed as either stage-0, stage-I, stage-II, stage-III, and stage-IV. The higher the number, the more the cancer has spread to other areas in the body through nearby tissue, the blood and the lymph system. Stage-0 is categorized as either intramuscular or in situ carcinoma. Tis, this condition is known as carcinoma in situ, is better understood as high grade neoplasia rather than cancer. Early-stage cancer classified as stage-I is limited to the bowel wall (T1, T2) and does not have lymph node metastases; stage-II is characterized by the absence of lymph node metastases and T3-T4 tumors; stage-III is typified by the absence of distant metastases but the presence of lymph node metastases; and stage-IV is typified by the presence of distant metastases (M1) at the time of diagnosis. The stages T, N, and M are not self-contained. The likelihood of lymph node metastases and distant metastases rises with rising T stage, while likelihood of distant metastases rises with increasing N stage.[6]

Clinical staging, the term used to describe the current method of CRC staging, is based on the findings of imaging tests (such as MRI scans, X-RAYS, CT scans, PET scans, and physical examinations) as well as biopsies. The most frequently used staging system of CRC is the AJCC cancer staging manual developed by American Joint Committee on Cancer (AJCC), based on the guidelines of TNM.[7] According to AJCC based clinical staging of CRC, it is mainly divided into early stage and stage-I to stage-IV.

Pathogenesis involved in colorectal cancer

When oncogenes and tumor suppressor genes are altered genetically, the adenocarcinoma process advancements from normal to dysplastic epithelium, which leads to the development of CRC.[8] According to the Nurses` health survey, there is a correlation between periodontal disease and CRC. Women who suffer from severe or moderate periodontal disease may have a little elevated chance of acquiring CRC.[9] In contrast to oral pathogens, which are a major cause of CRC, gut microbia plays a significant role in the bacteria-driven pathogenesis of CRC. The connection between oral infections and colorectal cancer has been the subject of numerous research discussions during the last thirteen years. The majority of them concentrated on the mechanism of prophyromonas gingivalis & fusobacterium nucleatum. The key to the pathogenesis of CRC is the altered immunity and the micro environment of the tumor of these pathogens.[10] Gastrointestinal physiology is greatly influenced by the circadian system, and alterations in the molecular circadian clock may have a role in the development of colorectal cancer

tumors. The phenotypic of colon cancer, patient survival, and the response to chemotherapy are all impacted by the circadian genes, which are frequently altered in colorectal malignancies.[11]

The role of oncogenes and tumor markers in crc

The identification of protooncogenes has led to progressions in our knowledge of the molecular genetics of polyp growth.[12] Reliability for protooncogenes to have a role in the pathophysiology of human and animal cell. Oncoprotein results in altered regulation, higher concentration, or enhanced protein activity as compared to normal proteins. Protooncogenes are normal genes that have potential to become oncogenes due to mutation.[13] Ras protein, a protooncogene which is most often metamorphosed in human cancer. Oncogenes with a proven role in CRC are Ras, EGFR (Erb-B1), Erb-B2, TGFalfa, TGF-Beta 1.

Tumor markers are bio chemical substances expounded by tumor cells due to the cause of malignant process. Tumor markers are produced at higher rate in melanoma cells. The tumor markers are produced by the tumor and present in particular amounts indicates the presence of tumor. They exist as intracellular substance in tumor surrounded tissue and may be discharged into bloodstream and may show up in serum investigations. The neoplastic cells can synthesize wide variety of macromolecules at higher concentrations having broad range. The presence of malignant tumors in patients with CRC is indicated by the emergence of tumor markers at increased concentrations.[14] Cancer patients may benefit clinically from tumor markers, which are often proteins linked to a malignancy.[15] Tumor markers are used to identify CRC. Tumor markers including carcinoembryonic antigen (CEA) is a oncoferal tumor marker, carbohydrate antigen (CA 19.9, CA 242- Salicylated lewis carbohydrates), Tumor associated glycoproteins-72 (TAC-72), Tissue polypeptide specific antigens (TPS), have outstanding investigative accuracy. Information helpful in the treatment can be obtained through analysis of circulating cancer cells, which are either related to or accountable for metastasis. The utilization of hematopoietic growth factors (HGF) and different enzymes such as intrleukin-3, interleukin-6, macrophage-colony stimulating factors (M-CSF), granulocyte macrophage-colony stimulating factors (GM-CSF), and enzymes (alcohol dehydrogenase & lysomal exoglycosidases) are finding markers that would enable early diagnosis of malignant tumors is crucial since the prognosis for patients with CRC is connected with the clinical stage at which the tumor is found or detected. The ranging of CRC is primarily essential for management. [16,17]

Chemotherapy in crc

The adjuvant chemotherapy with cytotoxic drugs is the typical medical practice for patients with colorectal cancer. According to the trails conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), they recommended this adjuvant chemotherapy with cytotoxic drugs for CRC patients is highly reactive.[18] The word chemotherapy was first described by Paul Erlich, the German chemist in the early 1900`s during his work on the use of chemical agents to treat infectious diseases.

In 1957, the chemotherapy for CRC has been evolved which is begun with the development of 5-floro uracil. The patients who are suffering with stage-I and stage-II CRC mostly have five years of survival rate, But the ones who are diagnosed with metastatic cancer has very low rate of survival than the stage-I and stage-II respectively. As per the data provided by American Joint committee on Cancer, patients who are suffering with stage-I & II have 30% chance of recurrence after surgical treatment while the patients with stage-III CRC have 50-60% chance of recurrence.[19] Hence, chemotherapy is followed by surgical treatment in CRC. The chemotherapy is either given before or after surgical treatment. If the chemotherapy is used before treatment to shrink the cancer cells which helps to easily remove the tumors during surgery. The chemotherapy is given after surgery to reduce chances of recurrence. In some cases, such as where tumor biopsy shows deficiency in DNA mismatch repair (MMR-D) or high microsatellite instability (MSI-H) the adjuvant chemotherapy is suggested.[20] The combination of 5-FU/Leucovorin & oxaliplatin and 5-FU/leucovorin and irinotecan is used as an effective combination therapy for the treatment of metastatic CRC. This is used to improve survival rates when used as an adjuvant therapy. The infusional 5-FU/Leucovorin is act as an cornerstone of treatment for patients with CRC.[18]

5-fluorouracil and it`s drug resistance

In colorectal cancer patients, the 5-fluorouracil (5-FU) is used as a first line of drug in systemic chemotherapy in both adjuvant and palliative therapy. 5-FU is an anti-metabolite and first chemotherapeutic drug having anti-neoplastic activity. It was first discovered by Heidelberger in 1957. 5-FU is used to treat more than 2 million cancer patients each year worldwide. The 5-FU is used in the treatment of different types of malignant tumors such as breast, prostate, liver, pancreatic, skin, stomach, brain, neck cancers. The intravenous or oral 5-FU or some other fluoropyrimidines are used in systemic chemotherapy for CRC.[21] In the administered dose of 5-FU only 1-3% is converted into fluorodeoxyuridine monophosphate (FdUMP) and the remaining 80% of the drug is degraded swiftly. The FdUMP obstructs the thymidylate synthetase and blocks the deoxy thymidine triphosphate synthesis (DTTS) which acts as a potential prognostic factor in CRC patients.[22] When a 5-FU is given as single agent in first line treatment of metastatic CRC, it only shows 10% of objective response but when it is given in a combination with leucovorin or directed as intravenous infusion it shows improved response to 40-50%.[23]

Even through the 5-FU has numerous advantages the clinical use of 5-FU is limited due the development of drug resistance after chemotherapy. Due to the alteration of binding of cytoplasmic p53 some CRC cells become resistant to 5-FU.[24] Thymidylate synthase (TS) is an essential enzyme in the metabolism of 5-FU which is one of the most important pathways of 5-FU anabolism. The TS may involve in either 5-FU anabolism or catabolism. The alteration of this enzyme may encourage 5-FU resistance. The significant factors involved in Multidrug Resistance (MDR) is drug transporters. The vital 5-FU resistance mechanisms are mainly created by 5-FU facilitated microRNA (miR) dysregulations and epigenic changes as well as Epithelial-mesenchymal transition (EMT).[24]

Oxaliplatin and it`s drug resistance

Oxaliplatin is a water-soluble platinum compound that origins intrastrand cross-links in DNA which results in the inhibition of DNA synthesis. This inhibition of DNA synthesis by oxaliplatin is caused by the induced formation of platinated intrastrand DNA adducts. The oxaliplatin is used in first and second-line advanced treatment because it is categorized by a diamino cyclohexane (DACH) platinum carrier ligand, has proven its efficacy.[25] The oxaliplatin is used in the treatment of first line advanced CRC shows low hepatotoxicity, and well measured gastrointestinal toxicity but with moderate peripheral neurological symptoms. It does not cause toxic deaths and it is well tolerated.[26] The oxaliplatin by intravenous administration (iv oxaliplatin) is either used as monotherapy or in combination with other agents in patients with metastatic colorectal cancer. The combination of oxaliplatin with 5-floro uracil is highly reactive in the treatment of advanced CRC.[27] The oxaliplatin may shows drug resistance in some cases. The resistance mechanism of oxaliplatin is associated with copper transporter proteins, nucleotide excision repair (NER), glutathione metabolism, drug efflux protein. The diminished drug accumulation results in decrease in the sensitivity of drugs and promotes resistance.[28] Oxaliplatin is described to be intricate in AKT pathway/phosphatidylinositol 3-kinase pathway, p38 kinase activation and caspase cascade activation mainly through the apoptotic intrinsic pathway. The origins of oxaliplatin drug resistance are ill understood. Oxaliplatin resistance is a multifactor process that has been characterized by boosted tolerance to damage, apoptosis inactivation, improved detoxification and repair, modification in pathways involved in cell cycle kinetics, and diminished drug accumulation.[39]

Treatment for chemoresistant of crc

Even after massive research exertion, the patients who are examined with CRC still have low prognosis level after chemotherapy. The development of chemoresistance to frontline chemotherapeutic drugs such as 5-FU and oxaliplatin in CRC treatment is the chief drawback. But the main cause of chemoresistance to 5-FU and oxaliplatin is still unknown.[30] The chemoresistance occurred in monotherapy of CRC is reversed by using the known chemical drugs, combined with similar medical drugs, and some herbal medicine monomers. This may enhance the chemosensitivity of tumors to chemotherapeutic drugs. Along with those, numerous drugs are combined with Nanocarriers, Exosomes, Hydrogels, Liposomes as drug delivery systems. These directly transport the drugs to the targeted tumor site thereby enhances the drug effect by control the drug release. For the treatment of chemoresistance in CRC Gene therapy and protein inhibitors are also introduced which become a hot spot in the treatment of cancer and chemoresistance.[31] The expression of REV7 is the major component in translation synthesis (TLS) polymerase which is suggestively boosted in both 5-FU and oxaliplatin resistant CRC cells. REV7 is recognized as a proficient goal for chemoresistant CRC treatment for its inhibitory effects on CRC.

Abbrevations

Colorectal Cancer (CRC), Tumor Node Metastasis (TNM), American Joint Committee on Cancer (AJCC), National Surgical Adjuvant Breast and Bowel Project (NSABP), DNA Mismatch Repair (MMR-D), High Microsatellite Instability (MSI-H), 5-Fluorouracil (5-FU), Fluorodeoxyuridine Monophosphate (FdUMP), Deoxy Thymidine Triphosphate Synthesis (DTTS), Thymidylate Synthase (TS), Multidrug Resistance (MDR), MicroRNA (miR), Epithelial-Mesenchymal Transition (EMT), Diamino Cyclohexane (DACH), Nucleotide Excision Repair (NER).

CONCLUSION

The colorectal cancer is the third most commonly diagnosed cancer across the globe. The therapeutic management of patients with metastatic CRC requires the systemic administration of cytotoxic drugs. The chemotherapy is the cornerstone in the therapeutic management of CRC. The adjuvant chemotherapy in metastatic CRC shown very effective improvement in the treatment of CRC. It also enhances the survival rates in the colorectal cancer. The recurrence of CRC after surgery is minimized by chemotherapeutic agents. The 5-fu is the most effective drug in the treatment of CRC in 1957. However, the 5-FU may show drug resistance in some cases after surgery. The 5-FU is more effective when they give in combination with drugs like Oxaliplatin, Irinotecan… In this review we conclude that there is a chance of development of chemoresistance to frontline chemotherapeutic

drugs such as 5-FU and Oxaliplatin. The chemoresistance of CRC is reversed by different chemical drugs, combined with known clinical drugs, herbal drugs, gene therapy, protein inhibitors and by using Nanocarriers, exosomes, liposomes, hydrogels as drug delivery system. The resistance of 5-fu and oxaliplatin is inhibited by the expression of REV7. The extensive and consistent literature review and research works on 5-FU and its various combinations in chemotherapy will reduce the incidence of development of drug resistance in CRC.

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