Original Article

Role Of Nanoparticles In Colorectal Cancer

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Abstract

The growth of cancer from the colon or rectum is referred to as colorectal cancer (CRC), sometimes known as bowel cancer, colon cancer, or rectal cancer. It is the third most prevalent disease in women and the fourth most common cancer in men worldwide. Colorectal Cancer (CRC) is one of the leading causes of cancer-related deaths worldwide. More recently, nanomedicine has emerged as an attractive modality to overcome issues of therapeutic resistance, improper delivery, or suboptimal targeting of tumor cells. Around 50 nano-formulations have so far been approved as diagnostic and therapeutic agents in humans. One of the most promising methods for cancer treatment is the use of nanoparticles as a drug delivery mechanism. Targeted nanoparticles could take use of chemicals that are differentially expressed on the surface of tumour cells to deliver deadly medicines effectively. Recent research has shown that different compounds can act as ligands on nanoparticle surfaces to engage with tumour cells and facilitate the delivery of anticancer medicines. Here, we examine the intriguing utilisation of ligands and cellular targets in potential CRC therapeutic options and show recent developments in targeted nanoparticles against CRC.

Keywords: Nanoparticles, colorectal cancer, etiology

INTRODUCTION

The growth of cancer from the colon or rectum is referred to as colorectal cancer (CRC), sometimes known as bowel cancer, colon cancer, or rectal cancer (parts of the large intestine). There are notable international variations in the distribution of colorectal cancer, which is the third most prevalent disease in women and the fourth most common cancer in men worldwide [(1)]. Although colorectal cancer still primarily affects industrialized nations, incidence rates have been climbing there recently. Moreover, the population expansion, ageing, and adoption of westernised behaviours and lifestyles are all likely to contribute to a rise in the worldwide burden. It has been demonstrated that colorectal cancer screening significantly lowers mortality rates, which have fallen in many long-established as well as recently economically developed nations. To create focused initiatives that could lessen the burden of the disease, statistics on colorectal cancer incidence are crucial. This study aims to analyse colorectal cancer incidence, death, and survival rates as well as geographic differences and historical trends..The National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) provided mortality data from 1930 to 2010. (NCHS). The National Cancer Institute's (NCI's) Surveillance, Epidemiology and End Results (SEER) programme and the CDC's National Program of Cancer Registries both gather population-based data on cancer incidence in the United States. Based on data from the nine oldest SEER areas (Connecticut, Iowa, Hawaii, New Mexico, Utah, and the metropolitan areas of Atlanta, Detroit, San Francisco-Oakland, and Seattle-Puget Sound), which together account for about 10% of the US population, long-term incidence and survival trends (1975–2010) for both blacks and whites were calculated. Because more cases of Alaska Natives have been registered in the SEER 13 data, allowing for segmentation by race and ethnicity [(2,3)].

Etiology

The World Health Organization estimates that 900,000 instances of colorectal malignancies were discovered globally in 1996, making up 8.5% of all new cancer cases. Crude incidence rates reveal significant differences between nations, ranging from 50-70/100,000 in North America, Western Europe, Australia, and New Zealand to 0.6-5.0% new cases/lOO,OOO each year in numerous Third World countries (such as Senegal, Mexico, and India). The majority of the time, dietary disparities have been blamed for these variations, although other environmental (or genetic) influences cannot be completely ruled out. In India, the rich and westernised Parsi population experiences colorectal cancers far more frequently than the Hindu and strictly vegetarian Janists [(4)].

Diet and micronutrients:

Similar to other digestive organ tumour, various investigations looked into whether there might be a connection between certain dietary components and colon cancers.
The findings of these analyses were generally at odds with one another, the relative hazards that were reported were typically small and barely significant, and no clear causative element could be found. Given the long biological progression of colorectal neoplasms (from adenomatous polyps to infiltrating carcinoma), the dietary habits of 20 or 30 years prior to the occurrence of cancer may be more significant than the diet at the time. The effect of individual dietary components is difficult to evaluate, especially in case control studies, in which individuals should try to remember type, frequency, and amount of food regularly consumed in previous years [(5)].

Hormonal influences

Gastrin is thought to be a possible promoter of colorectal tumorigenesis because it enhances the replication of healthy colonic epithelial cellsj6. Additionally, people with Zollinger-Ellison syndrome do not appear to be at elevated risk for colorectal neoplasms. Several case-control studies have failed to consistently link serum gastrin to colorectal cancer. However, a recent prospective study found an odds ratio (OR) of 3.9 for the association between serum gastrin levels above normal and an increased risk for colorectal cancer [(6)]. The authors hypothesized that if this association is coincidental, then 8 to 9% of all colorectal malignancies may be related to high gastrin levels. The etiology of colorectal tumour may include both endogenous and exogenous sexual hormones. Therefore, it appears that nuns and nulliparous women are more likely to acquire colorectal cancer, whereas higher parity, a younger age at first delivery, and regular use of oral contraceptives may be linked to a lower risk. The results of further examinations, however, fell short of being conclusive. When examining the potential link between hormone replacement treatment and colorectal cancer risk, similar conflicting findings were made [(7)].

Smoking and beverages

The vast list of tobacco-related neoplasms does not typically include colorectal cancers; nonetheless, studies have shown that those who smoke cigarettes, cigars, or pipes have an increased chance of developing colon cancer. Giovannucci's two large cohort studies also revealed a positive relationship between recent cigarette smoking and the prevalence of adenomatous polyps in the large intestine for both sexes. The researchers came to the conclusion that, after allowing for an induction period of at least 30–40 years, tobacco use was associated with a higher risk of colorectal cancer.A risk factor for colorectal cancer has been identified as excessive alcohol use. As a result, Stocks 47 was the first to document a marginally increased incidence of colorectal cancer among beer drinkers compared to abstainers. Since then, other cohort and case-control studies have investigated the link between alcohol use and the likelihood of developing colorectal adenoma or carcinoma, although the findings are debatable. The World Cancer Research Fund came to the conclusion in 1997 that increased alcohol consumption likely raises the risk of colorectal cancer, and that this link is likely caused more by overall ethanol intake than by the specific alcohol beverage [(8)].

Lipid oxidation:

ROS are capable of oxidising polyunsaturated fatty acids (PUFAs), which are involved in the construction of cell membranes. As a result of this reaction, lipid peroxidation begins, which sets off a series of processes that result in the production of various free radicals and chemicals including malondialdehyde (MDA), conjugated dienes, hydroperoxides, lipoperoxides, and deadly aldehydes [(9)]. Cell membrane fluidity is altered by lipid peroxidation, which also decreases the ability to maintain an equilibrium gradient of concentration and promotes membrane permeability and inflammation. Neutrophils and other inflammatory cells are attracted to the site of injury via chemotaxis, which is caused by the escape of normal intracellular enzymes into extracellular fluids. Additionally, the byproducts of lipid peroxidation, in particular MDA and 4-hydroxy-2-nonenal (HNE), may behave as signal transducers and, at low concentrations, affect a number of cellular processes, including gene expression and cell proliferation. Additionally, they react strongly with DNA bases. It was discovered that MDA, one of the most well-known lipid peroxide breakdown products, reacts with DNA bases G, A, and C to create M1G, M1A, and M1C DNA adducts, respectively. Evidence suggests that these mutagenic etheno-DNA adducts may contribute to cancer, especially CRC [(10)].

Symptoms:

Patients often experienced three symptoms when they were diagnosed (range 1–10). Rectal bleeding (58%), stomach pain (52%), and a change in bowel habits (51%) were the most prevalent symptoms. 77% of individuals with positive faecal occult blood tests were also anaemic and had a majority of anaemia (57%) as well. In addition, all patients had at least one of the typical reasons for a colonoscopy by the time of diagnosis.The findings of the factor analysis revealed that there were three underlying clusters in the symptoms. Anorexia, nausea, vomiting, abdominal pain, or weariness made up the first cluster; constipation or obstructive symptoms made up the second; and diarrhoea, mucus in the stools, rectal discomfort, or tenesmus made up the third. These symptoms were mathematically intercorrelated, which suggests that they may have a shared aetiology. For example, all of the symptoms in the third cluster point to a rectal motility issue [(11)].

Diagnosis:

Although there are various ways to test for colon cancer, none of them is the best. Fecal occult blood tests, flexible sigmoidoscopy, CT colonography, capsule endoscopy, and double contrast barium enema are only a few of the screening

techniques available. To identify persons at risk of developing advanced adenomas or colorectal cancer who might benefit from colonoscopy, a simple, inexpensive, noninvasive, and relatively sensitive screening test is needed [12].

Approach through nanoparticles:

There are currently several different treatments available for CRC, including surgery, chemotherapy, and radiation therapy. The medication only reaches the target site in non-effective concentrations, making these operations ineffective. However, a higher dose might have unfavourable effects (13). The field of nanotechnology in biomedicine is one that is rapidly developing.Between the science and technology of various NPs and nanophases, nanotechnology serves as a bridge. In terms of drug delivery and clinical therapies, nanoparticles with at least one dimension less than 100 nm have a lot of potential and are crucial for applications in the delivery of cancer drugs. Longer circulation half-lives, enhanced pharmacokinetics, carrying huge amounts of medications, reducing adverse effects, and directing the drug to a specific area of the body are some of the primary benefits of nanoparticle drug delivery (14).

Liposomes: Bangham identified liposomes as the first nanoparticle platform used in medicine in 1961. The first drug delivery system authorised for clinical use was liposomes. Liposomes, in particular nanoliposomes, are one of the most often utilised delivery vehicles for proteins, peptides, tiny and long nucleic acids, and small compounds. Natural non-toxic liposomes are tiny, spherical artificial carriers with an aqueous centre [15]. Liposomes are the most efficient drug delivery vehicles into cells because of their phospholipid bilayer, size, and capacity to incorporate a variety of chemicals. They have qualities such as slow-releasing, targeting, and the potential to reduce adverse effects (16). Since the middle of the 1990s, FDA has approved liposome formulations that contain chemotherapy drugs including daunorubicin (DaunoXome®) and doxorubicin (Doxil®). Doxil is roughly 100 nm in size and exhibits significantly less cardiac and gastrointestinal toxicity, but it still has a number of undesirable side effects, including severe skin peeling, redness, and discomfort. Marqibo® is the most latest liposomal medication, and it has been FDA-approved since 2012. Marqibo is a cell cycle-dependent anticancer medication that is roughly 100 nm in size. Drug resistance has been combated in some ways, as seen by Doxorubicin's administration in liposome form [17] .

Polymeric nanoparticles: Synthetic polymers or polymeric nanoparticles (PNPs) are objects with a diameter of 10 to 100 nm. To reduce immunological interactions, nonionic surfactants cover the majority of the PNPs (e.g. opsonization). Two prominent PNPs that have received USFDA approval are poly lacticco-glycolic acid (PLGA) and polycaprolactone (PCL). The first-line treatment for CRC is 5 fluorouracil (5-FU), although in reality, this treatment also affects healthy cells when given, and the colon region has poor drug availability. Citrus pectin and Eudragit S100 (a pH-responsive enteric polymer) have been chosen by Subudhi et al. as nanoparticle drug delivery systems for the efficient treatment of CRC. They came to the conclusion that Pectin was an effective drug delivery mechanism for the colon. Studies conducted in vitro and in vivo have demonstrated the efficacy and safety of Eudragit S100 coated CPNs (E-CPNs) for the delivery of 5-FU to CRC [18] .

Combined anticancer therapies loaded in NP’s for colon cancer: Combining drug loaded nanostructures with chemotherapy has the potential to improve tumour targeting and local medication concentration in the treatment of CRC. Curcumin/5-fluorouracil loaded thiolated chitosan nanoparticles (Cur-TCS/5-FU-TCS Nanoparticles) were studied for their potential ability to combat colon cancer by Anita et al (HT29). Additionally, pH-sensitive nanostructures of Cur-TCS (size = 150 nm, zeta potential = + 35 mV) and 5-FU-TCS (size = 150 nm, zeta potential = + 48 mV) were compared and shown to have 2- and 3-fold higher anticancer effects. Additionally, the dose that was required to see a particular cytotoxic impact was decreased. pH-sensitive polymer nanostructures that carry curcumin were created by Payjakata et al. The drug encapsulation efficiency in this technique was 72%, and the particle size was smaller than 130 nm. By using these nanostructures, the amount of curcumin needed to prevent colon cancer might be reduced, and curcumin's ability to enter cells would be improved [19].

Examples:

Drugs	Nanoparticles	Advantages	Reference
5-FU and BEZ-235	LDH NPs	NPs enhance BEZ-235's ability to target the PI3K/Akt inhibitor.	[20]
5-FU	Hyaluronan/chitosan NPs	NP amplifies the effects of 5-FU on MUC1-producing cells.	[21]
5-FU	Mesoporous silica, magnetic nanocapsules	Nanoformulations are efficient at lengthening the drug's half-life and reducing tumour development.	[22]
Oxaliplatin	Nanoemulsion, chitosan NPs, polymeric micelles	improved tumour regression, longer medication half-life, and greater drug penetration into the tissue	[23]

Capecitabine	Solid lipid NPs and PAMAM dendrimers	Nanostructures promote apoptosis and increase bioavailability in cancer cells.	(24)

CONCLUSION

Targeted nanoparticles have a bright future because various potential formulations are now being developed for CRC in preclinical and clinical settings. These formulations may soon reach the market after meeting the FDA's strict requirements for patient safety and efficacy. Implementing methods or processes to identify the molecular expression profile of tumours from CRC patients and categorize them in accordance with the genetic profile, stage of tumour development, and putative targeted molecules will be a future challenge. The sensible administration of precisely targeted nano formulations carrying the most potent drug combination will be supported by everything mentioned above.

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