Oral Adjuvant Therapy for Colorectal Cancer: Recent Developments and Future Targets

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Abstract:

Colorectal cancer (CRC) is considered the third most frequent malignant neoplasm occurring in both men and women worldwide. Most approaches that have been used to fight and treat this type of malignancy are either invasive or non-selective. Non-invasive therapy using oral route can increase patient compliance and reduce treatment costs. Innovative measures such as use of nanotechnology and theranostic systems have been initiated in the oral therapy, which has been proven to be greatly advantageous in decreasing side effects, improving detection and diagnoses. This manuscript investigates recent innovative and novel therapeutic approaches through oral route and potential targets in the treatment of CRC.

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1. Introduction

Cells in our body receive different information signals and process them, these signals may allow them to either grow, divide, differentiate or undergo apoptosis. However, when these signals reaching the cells are not followed and get out of control, then these cells become known as cancer cells. Cancer cells are cells that keep on growing, replicating and spreading although they are located near non-stimulated cells [1].

There are more than one hundred different types of cancer which are unique from one another by their behavior and response to treatment [2]. Cancer incidents and mortality rates are keep on increasing globally. It was estimated that in 2018 the new cancer incidents will increase up to 18.1 million in addition to that the death rates are predicted to reach up to 9.6 million [3]. Among different types of cancer, CRC is ranked as a third common cancer occurring in both genders worldwide. In addition to that, it is second cancer leading to mortality after lung cancer in both men and women according to the 2018 cancer statistics [3]. According to recent statistics conducted in 2019 for the ten leading cancer types for the estimated new cancer cases and deaths by sex in the United States, CRC ranked 3rd in terms of deaths and incidents after prostate and lung cancer in males, and breast and lung cancer in females. The statistics show that there are

about 78,500 new estimated cases and 27,640 estimated deaths in males. On the other hand, there are 67,100 new estimated cases and 23,380 estimated deaths in females [4].

CRC is caused by the abnormal division of cells taking place in rectum as well as in colon region. The earliest phase of CRC starts with the appearance of clusters of enlarged crypts that proliferate abnormally, known as polyps. The majority of CRCs develop from abnormal polyps that later become malignant due to the infiltration to the submucosa [5]. CRCs have many symptoms associated with it, the main symptoms include rectal bleeding, diarrhea or constipation which are better known as changing bowel habits, and other symptoms include weight loss, abdominal discomfort and anemia [6]. There are number of risk factors associated with CRC. The CRC is more likely in people who had inflammatory bowel diseases and family history of CRC since the factors disposing CRC such as Lynch Syndrome is caused by a germline mutation in MMR gene [7]. Approximately half of the families that had Lynch Syndrome carrygermline mutation in MMR genes. Diseases and gut flora disturbance are also predisposing factors to CRC as the disturbance in the microbiota is able to induce diseases such as IBD or cancers. The following bacteria were found to impact cancer development such as *Escherichia coli* *Helicobacter pylori*, *Enterococcus faecalis*, *Clostridium septicum*, *Streptococcus bovis*,*Fusobacterium* spp., and *Bacteroides fragilis* [8]. Sedentary lifestyle, smoking, age, increased BMI, poor diet that lacks vegetables and fruits while being high in red meat were also major risk factors associated with the disease [9,10].

Luckily, nowadays there are various approaches to treatment options available for CRC such as surgery, chemotherapy, radiotherapy and targeted therapies. However, these treatment options differ depending on the stage of CRC (Table 1). The most common treatment for CRC is usually surgery or chemotherapy, most of the patients of the metastatic phase or CRC are candidates for systemic chemotherapy to increase the quality of life and decrease the symptoms [11]. Currently available adjuvant therapies are depicted in **Figure 1**.

Intravenous (IV) 5-Fluorouracil (5-FU) is the main drug of choice used for CRC. Moreover, new advances in the field of oncology have been developed [12] and recently scientists have introduced new treatment methods such as laparoscopic surgery, resection of metastatic disease, neoadjuvant and palliative chemotherapy. Nevertheless, long-term survival and cure rates were found to give only minimal results [13].

Although IV route is most commonly used, patients were seen to prefer oral chemotherapy in comparison to IV chemotherapy that was observed in the study which was comparing patient preference between oral UFT versus IV 5-FU and leucovorin [14]. The patient choice was influenced by compliance and drug toxicity. That being said, patients try to avoid traditional invasive therapy and that was a factor that spiked the scientists' interest to develop new drug delivery systems that can be given to the patient orally as an oral cancer treatment is having many advantages such as patient compliance and acceptance as well as cost saving [15].

Innovative measures have been initiated with the oral therapy as there were previous limitations with the bioavailability primarily because of cytochrome P450 (CYP) activity and drug transporters, such as P-glycoprotein (P-gp) in gut wall and liver [16]. The use specific, low-toxicity inhibitors of CYP3A4, (P-gp), and other drug metabolizing enzymes such as dihydropyrimidine dehydrogenase was initiated as a solution to this problem that lead to the success of the oral chemotherapy formulations [17]. Other notable innovations that helped oral cancer therapy was the use of nanotechnology and advanced targeted drug delivery systems [18] that were either encapsulating chemotherapeutic drugs [19] or being coated with cell surface specific antigens such as monoclonal antibodies [20]. Theranostic nanomedicine is a recent technology to fight against cancers in addition to providing diagnoses and scanning applications as an all in one treatment. This system includes nanoshells, plasmonicnanobubbles, quantum dots etc. Such new advances in nanoimaging and nanotherapy open doors to the development of effective cancer treatment [21].

The purpose of this review is to provide the reader with complete up-to-date information related to oral adjuvant therapy options that are available for CRC. This review further examines innovative measures such as use of nanotechnology and theranostic systems along with an overview of potential targets in the treatment of CRC.

Oral Route of Administration

Currently, the adjuvant therapy of colorectal cancer mostly requires IV administration, necessitates regular visits to clinics. IV route of administration further leads to discomfort, infection and chances of extravasation. Oral route of administration offers significant advantages like flexibility in the design of dosage form, ease of manufacturing with least sterility constraints, patient convenience, self-administration, cost-effectiveness. However, oral bioavailability of

many anticancer drugs are low and highly variable, low solubility and low permeability, instability, and metabolism by intestinal and hepatic enzymes. Therefore, only few oral therapies are available in market and are presented in **Table 2**.

After oral administration, there are two main pathways through which drug act on colon cancer as depicted in **Figure 2**. The first pathway follow absorption of drugs into systemic circulation, while second pathway allows local targeting to colon site. Several strategies for enhancing oral bioavailability are being pursued including the development of pro-drugs, the co-administration of inhibitors of enzyme and transporter activity, and various formulation approaches, such as excipient enhancement, and polymeric- and lipid-based nanocarriers that deliver the medicine through the lymphatic system. Local delivery at colonic site such as prodrugs, covalent linkage of a drug with a carrier, pressure dependent systems, pH-sensitive systems, timed released systems, microbially triggered systems, bioadhesive systems, osmotic controlled drug delivery systems can also be utilized to deliver high drug payload to the colonic site. The benefit of this approach can be demonstrated by the fact if 5-FU delivered specifically to the colon, its distribution and thus side effects to other organs and tissues can be minimized. In addition, 5-FU get converted to active metabolite 5-fluoro-2′-deoxyuridine by the colon tumor, the benefits of the 5-FU therapy can be maximized [22]. Therefore, this approach for local colon delivery for colon cancer is well investigated and very well reviewed [23] and hence are not discussed further.

Capecitabine

An oral fluoropyrimidine drug that has been developed, it acts as a prodrug of 5-FU and is absorbed intact from the intestine which later undergoes a series of conversions until it yields Doxifluridine that gets converted to 5-FU. Capecitabine showed better results than 5-FU as it was showed to elevate the levels of 5-FU up to three times in the tumor as compared to healthy tissue after its administration to cancer patients [24].

A randomized phase III study was conducted by Hoff PM et al. to compare capecitabine with bolus 5FU/LV treatment regimen. It was found the tumor response rate to be significantly higher in the capecitabine group (24.8%) than in the 5-FU/LV group (15.5%; P =.005). In addition to that capecitabine produced significantly lower incidence of diarrhea, stomatitis, nausea, and alopecia, as well as grade 3/4 stomatitis and grade 3/4 neutropenia thus significantly less

neutropenic fever/sepsis. However, only grade 3 hand-foot syndrome and grade 3/4 hyperbilirubinemia toxicities were more frequent in capecitabine than with 5-FU/LV treatment [25].

Oral Irinotecan (CPT-11)

Irinotecan is a topoisomerase inhibitor [26], that is usually given via IV route to treat cancer, recent studies and clinical trials are testing irinitecan when given via oral route. One of these studies showed a phase I dose-escalation trial of irinotecan being administered orally by mixing CPT-11 IV solution with cran-grape juice to measure its maximum tolerated dose and its dose-limiting toxicities in cancer patients with solid tumors. The results have shown Grade 4 delayed diarrhea was the dose-limiting toxicities at the 80 mg/m2/d dosage in patients younger than 65 years of age and at the 66 mg/m2/d dosage in patients 65 or older. As neutropenia was found to be the major toxicity or oral irinotecan and one patient with previously treated CRC and liver metastases succeeded in getting a partial response. The findings have led to the conclusion that dose-limiting toxicities of diarrhea are similar to that observed with IV administration of CPT-11, as well as the need for further clinical development [27].

Another phase I oral irinotecan study was made by giving it daily for 14 days every 3 weeks in 45 patients with solid tumors to study its pharmacokinetic profile. This time the drug was given via oral route in a powder-filled capsule at doses ranging from 7.5 to 40 mg/m2 per day. The dose-limiting toxicities found were grade 3 nausea, grade 3/4 vomiting and diarrhea as well as one occurrence of grade 3 asthenia, as for the maximum tolerated dose it was found at 30 mg/m2 per day, and two partial responses were documented [28].

Oxaliplatin

New studies that are aiming to transfer chemotherapeutic agents to oral treatments have developed Oxaliplatin as an oral formulation to be tested against CRC. This preparation method included the encapsulation of the chemotherapeutic agent in pH-sensitive alginate microsphere that has been coated with the mucoadhesive chitosan. The aim behind such formulation was to protect the drug and make sure that it gets released after passing the acidic GIT media thus targeting the intestines. This formulation was studied on an orthotopic mouse model of CRC and was able to reduce the tumor in addition to the mortality[29]. In another study, scientists test the

synergistic activity of combining the oral formulation of TAS-102 (Lonsurf) along with intravenous Oxaliplatin against colorectal and gastric cancer cells using a mouse model. TAS-102 (Lonsurf) is a new antitumor agent that consists of trifluridine (FTD) along with tipiracil hydrochloride, a thymidine phosphorylase inhibitor approved to be used in the treatment of CRC that is either unresectable advanced or recurrent. Results have shown that the tumor growth-inhibitory activity and RTV5 in the animal mouse model given TAS-102 with oxaliplatin were showing significantly better results than those given monotherapy. Overall the results indicated that such a synergistic combination give promising results for either CRC or gastric cancer and can be used against tumors that have not received chemotherapy before as well as those that have been treated with 5-FU and showed 5-FU resistance [30]. Based on the results of these two studies, we suggest studying the synergistic effect of oral TAS-102 and oral oxaliplatin on CRC.

Nanotechnology and advanced drug delivery systems

CRC treatment effectiveness is getting limited recently due to the chemotherapy resistance [31]. This resistance is either intrinsic or acquired and it lowers the effectiveness of the chemotherapeutic drugs leading to poor patient response, its mechanism is mainly by reducing drug accumulation and elevating drug export in addition to changing drug targets, and repairing the DNA damaged by chemotherapy. Other factors include stroma and cancer stem cells [32]. Thus this slow growth in the cancer treatments calls for the need for new therapeutic approaches such as nanosystems or nanotechnology to solve drug delivery problems[33]. Nanoparticles were showing great potential for therapeutic molecule protection, transport and loading with various physiological properties [34–36] as well are targeting and having multiple functions [37,38]. Nanocarrier based drugs which are also known as nanomedicines have shown great benefits in fighting cancer stem cells (CSC) that were having significant effects on tumor progression and drug resistance as well as cancer metastasis. These nanomedicines were able to deliver an adequate amount of the drug to the tumor-targeted cells especially the CSC's niches and this was not seen in other drug delivery systems since it was considered as a limitation in the conventional treatment methods [39]. Nanomedicines have shown great therapeutic effectiveness against pump-mediated drug resistance as well as reducing the harmful effects on normal stem cells due to its selectivity [40]. The in-vivo mechanisim at which such nano-particles work falls into a four-step process which includes: the transport through blood circulation to tumor regions via

blood vessels; transport across vasculature walls into surrounding tumor tissues; penetrate through the interstitial space to target cells; and cellular uptake by endocytosis and intracellular delivery. Cellular uptake by endocytosis was found to be achieved through five main different mechanisms, including phagocytosis, clathrin-mediated endocytosis, caveolin-mediated endocytosis, clathrin/caveolae-independent endocytosis and micropinocytosis [41].

The newly developed nanomedicine treatments of diseases such as intestinal cancer are showing promising opportunities in clinical trials [42]. A recent study used a squaline based nanoparticle filled with cisplatin (SQ-CDDP NP) [43]. The effect of this new formulation was measured by using a mouse model having intestinal cancer. The results have shown a difference of 10 folds greater with the new nano-formulation in comparison to un-complexed cisplatin, further investigation showed that the nano-formulation SQ-CDDP NP stimulated the reactive oxygen species as well as heavy metal and stress-induced gene expressions and finally apoptosis. It is also demonstrated that ferulic acid from plant sources can be chemically modified to form poly(ferulic acid) (PFA) to prepare nanoparticles. Both PFA blank and loaded with paclitaxel showed colon tumor inhibition suggesting PFA itself has an anticancer effect in vivo [44] and thus not only enhance drug delivery, but also provide additional anticancer benefits to the patients. Same group also prepared doxorubicin loaded PFA nanoparticles that where shown to released drug continuously under slightly acidic conditions in vitro mimicking the conditions of acidic tumor microenvironments suggested effective drug delivery at tumor site. These nanoparticles showed enhanced permeability and retention at tumor site in vivo while reducing the toxicity of free doxorubicin and improving its safety [45].

Nanoemulsion systems have been also used in the treatment of CRC, a recent study used a cisplatin third generation analogue known as oxaplatin that is used as first-line therapy in combination with 5-FU in the treatment of CRC. Since both drugs have a low bioavailability due to bad membrane permeability a new invention was needed to increase their efficacy. An ion pairing complex was created between oxaplatin and a deoxycholic acid derivative to increase permeability followed by the preparation of water-in-oil-in-water nano-emulsions including oxaplatin/deoxycholic acid and 5-FU to increase the drug absorption when taken orally.The study also tested the membrane permeability by using Caco-2 cell monolayer and an artificial intestinal membrane. Then by using the mouse animal model bioavailability testing and CRC cell

growth inhibition was conducted after administering the formulation orally and the results have shown greater in vivo permeability and a significant increase in oral absorption and bioavailability, as well as better tumor growth inhibition. Thus all these findings gave a better understanding of the importance of using nanomedicine and its development in treating cancer as well as using it in oral combination therapies for CRC[46].

Another advanced targeted drug delivery system that has been introduced to be used against CRC is the use of liposomes when combined with a chemotherapeutic drug. In a recent study[47], two anti-cancer drugs have been used in the treatment of CRC the first one being Apatinibmesylate, a new and selective VEGFR-2 inhibitor that can be used to treat a variety of tumors and the second one being docetaxel (Taxotere), a traditional anticancer drug that is a semisynthetic taxoid in solid tumors. The drug delivery systems used were a liposome and methoxypoly(ethylene glycol)-poly(ε-caprolactone) (MPEG-PCL) to deliver apatinib (Lipo-Apa) and docetaxel, correspondingly. The Co-administration of the two systems showed synergistic effects on stopping the cell proliferation and inducing cell programmed death of CT26 cells in vitro. Moreover, when the treatment was given to the animal model a significant improvement was shown in the anti-tumor activity in a subcutaneous xenograft model in addition to the abdominal metastasis model of CRC. thus leading to the conclusion that these two formulations have the potential to be used clinically in CRC therapy[47].In another study, liposomes were conjugated with folic acid enclosing Oxaliplatin a monoclonal antibody and entrapped in alginate beads coated with Eudragit-S-100 to be administered orally to the animal mouse model have CRC tumors[48]. The study showed positive results with the ability of these beads to be used as a potential carrier in CRC.

Furthermore, newer advanced targeting techniques were introduced such as formulating folic acid conjugated liposomes containing Oxiplatin and entrapping them inside aliginate beads that were coated with Eudragit-S-100 to achieve effective drug delivery to CRC site [48]. Oral aliginate microcapsules have also been formulated to successfully deliver curcumin-loaded micelles to the CRC and promote the concept of chemotherapy at home [49].

Scientists have also succeeded in the development of a targeted large intestinal oral nanoparticle vaccine that is consisting of pH-dependent microparticles to induce colorectal immunity. This study was done on a mouse animal model in order to see the efficacy of such a vaccine in the

protection against rectal or vaginal viral changes to the mucosa. The study has also stated the potential application of this new delivery technology to be used in different forms of vaccines such as DNA, recombinant proteins, peptides as well as others. Furthermore, it suggested a new approach to formulate vaccines fighting against mucosal malignancies such as colorectal as well as cervical cancer [50].

Immunotherapy

Immunotherapy treatments function by overcoming or relieving tumour-induced immunosuppression, thereby enabling immune-mediated tumour clearance[51]. Recently cancer immunotherapy has become a validated clinical treatment for various types of cancers. This kind of treatment has many approaches to the cancer treatment such as the use of cancer vaccines, adoptive transfer of *ex vivo* activated T and natural killer cells, oncolytic viruses, and the use of antibodies or recombinant proteins that may co-stimulate cells or cause blockage to the immune checkpoint pathways [52].

Angiogenesis has always been a concern with tumor formation and metastasis, thus antiangiogenic treatments are available these days. The use of monoclonal antibodies (mAbs) is promising treatment option and receiving remarkable clinical success for lymphomas and solid tumors [53].

A recently developed small-molecule inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2) which is better known as Apatinib has shown to possess oral bioavailability when treating various cancers yet it's still being studied under clinical trials [54]. A recent case report that was published on the use of Apatinib as a third line therapy given to two Chinese patients having metastatic CRC displayed promising benefits after the drug treatment the chance of prolonged survival of mCRC patients along with good safety and tolerability profile. The first patient who was a 52-year-old female achieved progression-free survival period of four months and an overall survival of eleven months however she did not continue the treatment due to abdominal distension and loss of appetite. On the other, hand the second patient who was a 59-year-old man, achieved progression-free survival period of more than ten months later on due to PD is shown on frequent CT scans the drug administration was stopped. This case report suggested further investigation on the drug to be given as a single drug or in combinations, as well as it raised the question of the use of this drug in other ethnic groups due to regional

differences. Finally report recommended further research on the mechanisms of drug resistance, alternative triggers of angiogenesis, and the potential predictive biomarkers that aid in patient selection [55].

Regorafenib is another orally administered monoclonal antibody that is the first small-molecule multi-kinase inhibitor used for metastatic CRC. Regorafenib has undergone a phase 3 trial and showed an overall survival benefit in comparison to the placebo that shows its potential to be used with patients who didn't respond to standard treatments[56].

Theranostic Systems and new developments for CRC treatment

Nowadays researchers are looking for methods to monitor and treat the human body by noninvasive means. Nanotechnology was the gate to develop a noninvasive detection method and targeted treatments. The development of such nanoscale products is vital because it will lead to early detection as well as a prompt localized treatment only to the affected body tissues such as cancer cells. The idea of a carrier to target, detect and treat a non-healthy cell is better known as Theranostics. This system combines detection agents used in diagnosis as well as the drugs used for treatment leading to an all-in-one, localized, diagnostic and treatment system. Nowadays researchers are studying nano-theranostic systems that use imaging nanoparticles able to use therapeutic systems [57].

Theranostic nanoparticles were also having the advantage over normal radiation as radiation may produce some damages to healthy tissue in contrast to the radio-sensitized nanoparticles that only affect the diseased cells while limiting the dose to healthy organs [58]. A very recent study conducted was using all in one Theranostic system nano-agent with ROS generation, PDT and CTD. These researchers have developed a Biocompatible copper ferrite nano-sphere (CFNs) that was used to intensify the ROS production by laser creating direct electron transfer and photo enhanced Fenton reaction in addition to increasing the photothermal conversion creating a synergistic action on the treatment. By using the oxygen generation properties while depleting the copper ferrite nano-spheres from glutathione they were able to come up with better photodynamic therapy and photodynamic therapy for cancer eradication in general [59].

Future Perspectives:

The overall goal of adjuvant therapy is patient survival and should be based on toxicity, ease of administration, and cost since it is for longer duration generally for 6 months. Therefore, better strategies that provides not only improved adjuvants but also that allows self-administration with minimum side effects. The oral route offers significant advantages over other routes of administration like flexibility in the design of dosage form, ease of manufacturing with least sterility constraints, patient convenience, self-administration, cost-effectiveness. However, oral bioavailability of many anticancer drugs are low and highly variable, low solubility and low permeability, instability, and metabolism by intestinal and hepatic enzymes. Therefore as of now, only few drugs have reached the market. Many pharmaceutical approaches have been identified for colon drug delivery following oral administration such as prodrugs, covalent linkage of a drug with a carrier, pressure dependent systems, pH-sensitive systems, timed released systems, microbially triggered systems, bioadhesive systems, osmotic controlled drug delivery systems. Nanoparticle formulations such as nanoparticles, nanoemulsions, liposomes are also developed to deliver adequate amounts of the drug to the tumor-targeted cells especially the CSC's niches, have shown great therapeutic effectiveness against pump-mediated drug resistance as well as reducing the harmful effects on normal cells due to its selectivity. In this era of precision oncology as more specific and cost effective techniques for molecular profiling of colorectal tumors are evolving, more specific adjuvant therapies based on molecular subtypes of colorectal tumors will emerge. Advances in bioinformatics and availability of high-throughput gene expression and other functional genomics data sets such as Gene Expression Omnibus (GEO) database had led to identification of potential biomarkers for the management of CRC [60,61]. New therapeutic targets including *PD-1/PD-L1* [62], *NEK2* [63], *COL1A1* [63], *BCL9* [64], *miR-124* [65], *9p21 locus* [66] and many others associated with progression and prognosis of colorectal cancers were identified by integrating protein-protein interactions (PPIs) network and gene expression data and co-expression analysis. In earlier study, combination of NEK2 siRNA and chemotherapeutic agent cisplatin showed improved antitumor activity in colorectal cancer suggesting the benefits of combined treatment using potential therapeutic targets with traditional chemotherapeutic agents [67]. In near future, combining these gene targets along with other therapies will be a viable approach for treatment of CRC. It is hoped that these innovations, particularly those in nanotechnology, will facilitate effective and safe oral chemotherapy at home, without introducing further cost for healthcare systems in near future. However,

adherence to oral therapy needs to address properly. Overall, authors believe that oral route is a promising approach especially for colorectal cancer.

Executive summary

Overview on colorectal cancer (CRC)

- Colorectal Cancer ranks third in terms of deaths and incidents in both genders.
- Nowadays there are many treatment options available for CRC such as surgery, chemotherapy, radiotherapy and targeted therapies that differ depending on the stage of the cancer.
- Patients prefer oral non-invasive chemotherapy in comparison to IV chemotherapy.
- The site of action as well as mode of action of the chemotherapeutic and chemopreventive agents influence the rationale for colon-targeted oral drug delivery.

Non-invasive treatment approaches for colorectal cancer (CRC)

- New studies that are aiming to transfer chemotherapeutic agents to oral treatments to increase patient compliance such as the development of TAS-102 (Lonsurf), Capecitabine (Xeloda), oral irinotecan and Oxiplatin.
- Since CRC treatments are being limited due to cancer chemo- resistance scientists have started incorporating drugs in nanocarriers such as liposomes to fight resistance and solve drug delivery problems.
- Recent studies focus on using immunotherapy treatment for CRC as they function by overcoming or relieving tumour-induced immunosuppression, and enable immune-mediated tumour clearance. Regorafenib (Stivarga) is an example of such oral immunotherapy.
- A new technology that combines detection agents used in diagnosis as well as the drugs used for treatment leading to what's known as an all-in-one, localized, diagnostic and treatment system.
- In this era of precision oncology as more specific and cost effective techniques for molecular profiling of colorectal tumors are evolving, more specific adjuvant therapies based on molecular subtypes of colorectal tumors will emerge. It is hoped that these innovations, particularly those in nanotechnology, will facilitate effective and safe oral chemotherapy at home, without introducing further cost for healthcare systems.

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Table 1: Different stages of colorectal cancer and their treatment options [68]

Stage	Definition	Treatment Options
Stage 0	Localized; didn't grow beyond the colon inner lining.	Polyps are removed during colonoscopy (also known as polypectomy)
Stage I	Cancer grown deeper through the colon wall layers, however, it has not spread yet.	Removal of affected area through local excision (resection surgery)
Stage II	Cancer grown outside the colon wall and possibly spread to nearby tissue but not yet spread through the lymph nodes. Further divided into 3 types, IIA, IIB and IIC.	Resection surgery with or without adjuvant chemotherapy
Stage III	Cancer spread to close by lymph nodes. Further divided into 3 types, IIIA, IIIB and IIIC.	Surgical resection with adjuvant chemotherapy and other therapies if necessary, Radiation and/or chemotherapy
Stage IV	Cancer spread all over the body and reached the metastatic stage. Further divided into 2 types; IVA and IVB	Surgical resection of colon along with surgical removal of other affected parts of the body, chemotherapy Combinations of chemo and/or targeted therapies before or after surgery, Radiation therapy for symptomatic relief

Table 2: Oral chemotherapy Drugs used in Colorectral Cancer in the Market

Chemotherapy	Trade name	Class
Capecitabine	Xeloda®	Antineoplastics, Antimetabolite
Regorafenib	Stivarga®	Receptor tyrosine kinase inhibitor
Trifluridine-tipiracil hydrochloride	Lonsurf®	Trifluridine: thymidine-based nucleoside analogues. Tipiracil: thymidine phosphorylase inhibitors.
Tegafur/Uracil	Uracel ™	Dihydropyrimidine dehydrogenase inhibitory fluoropyrimidines

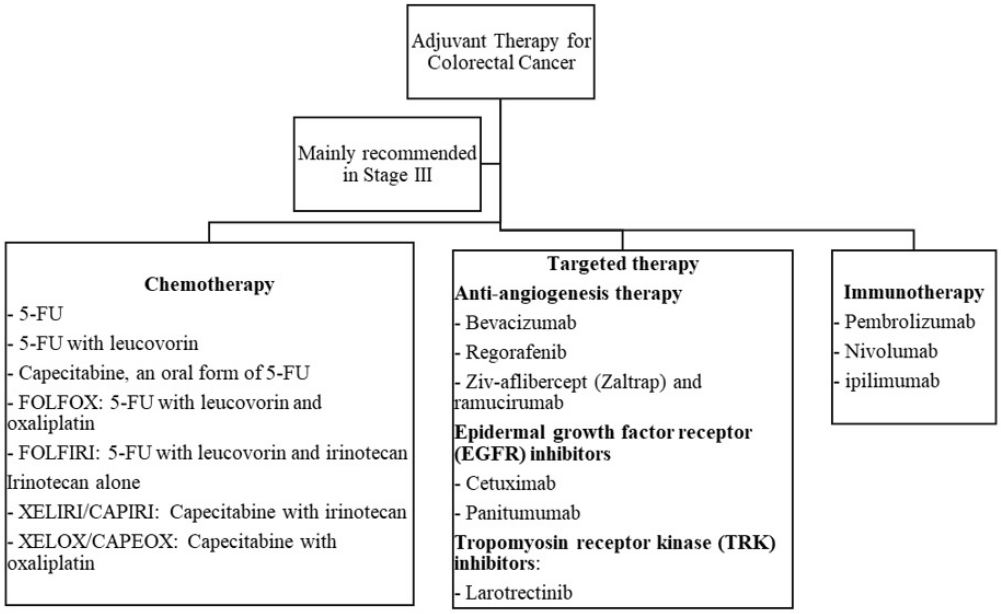

Figure 1: Currently Available Adjuvant Therapy for Colorectal Cancer

241x148mm (96 x 96 DPI)

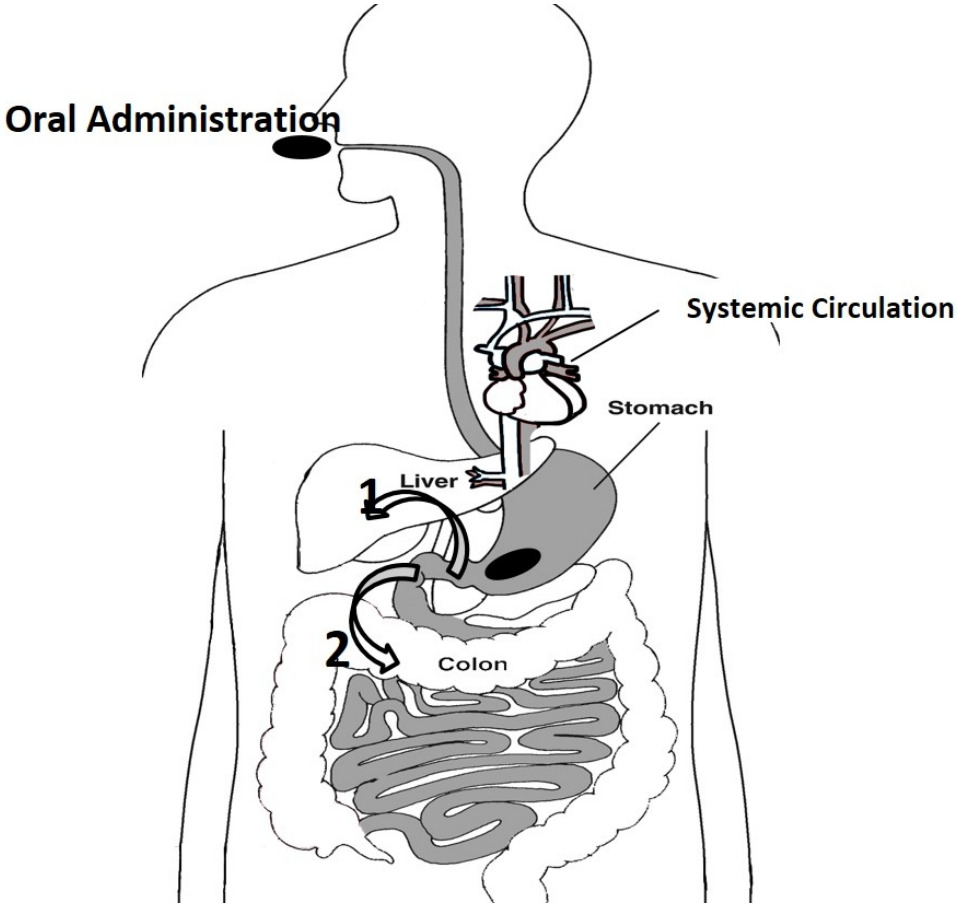

Figure 2: Main pathways through which drug act on colon cancer following oral administration. The first pathway (1) follow absorption of drugs into systemic circulation, while second pathway (2) allows local targeting to colon site

154x139mm (150 x 150 DPI)