



Treatment Strategies for Metastatic Colorectal Carcinoma - A Mini Review

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ABSTRACT

Colorectal cancer is the second most common cause of cancer related death worldwide and is implicated with a rising incidence rate in many parts of the world. Treatment for colorectal cancer diagnosed at an earlier stage may involve surgical colectomy, resection and microsurgical procedures. Over the last few decades remarkable progress has been made in advances of surgical techniques and chemotherapy for colorectal cancer with metastases and advanced disease stage. This review focuses on the conventional, standard as well as novel treatment approaches towards progression free and ideally disease free survival in patients clinically diagnosed with colorectal carcinoma. We have discussed the therapeutic attribute of novel platinum compound Oxaliplatin in combination of 5Fluorouracil and Leucovorin, which is the mainstay of colorectal cancer treatment in both adjuvant and neoadjuvant settings with optimal objective regression.

Keywords: Colorectal cancer, metastases, surgery, cytotoxic agents.

INTRODUCTION

The management of colorectal cancer has evolved in the last three decades. The challenges in the management of colorectal cancer today is to improve surgical techniques to improve organ preservation, selective use of adjuvant and neoadjuvant chemotherapy and tailored individual therapy¹. Colorectal cancer can be effectively prevented as 85% cancers arise in a premalignant polyp by effective screening of individuals with presymptomatic neoplastic lesions who require treatment with surgery and/or chemotherapy². Mortality rates in colorectal carcinoma patients has been lowered over the last three decades, however heterogeneity in survival rates is mainly governed by patient and tumor characteristics, treatment modalities and host response factors^{3,4}. The induced toxicity of cytotoxic agents is a huge challenge which interferes with the treatment modalities.

Surgical treatments for colon and rectal cancer

Before any apparent clinical symptoms, fecal blood can be detected in patients of by stool test, occult blood tests and fecal DNA tests. Endoscopic screening e.g. flexible sigmoidoscopy, colonoscopy helps in the detection, removal and biopsy of the polyps and thus referred to as Gold standard diagnostic procedures⁵. The earlier stage colon cancer can be treated mainly by surgery.

Open colectomy also referred to as partial colectomy or hemicolectomy is the resection of parts of the colon (usually 1/3 or ¼ of colon) and surrounding lymphnodes (at least 12 nodes). Open colectomy is used to refer the surgeries which are by a single incision⁶.

Laparoscopic-assisted colectomy is the newer approach to remove parts of the colon which requires several small

incisions rather than a large single incision. The laparoscope is the long surgical camera bedded instrument which gives an insight of the abdomen to help remove the affected colon part and lymph nodes which are removed through a larger incision made. The surgery requires special skills and results in less post surgical pain and comparatively early healing than open colectomy⁶.

Polypectomy of the colon requires cutting the polyp (cancer) from the stalk and removed whereas local excision is used to remove superficial cancer. polypectomy and local incision of the rectum does not require abdominal incision and can be done by instruments administered from anal opening⁷.

Local Transanal resection is the full thickness resection also referred to as transanal excision which cuts through all the layers of the rectum to remove the cancer and surrounding normal rectal tissues which are removed to seal the hole in the rectal wall, employed during stage I CRC with T1 N0 M0 which comprise of small cancer near anus⁸.

Transanal endoscopic microsurgery (TEM) is employed for stage I CRC with T1 N0 M0 which comprises of cancer located higher in the rectum with the help of magnifying scope and requires skilled and specialized expertise⁹.

Low anterior resection is employed mainly in stage II or III and sometimes stage I cancers in the upper third of the rectum which is located at the junction of the colon and is removed to attach the colon with the remaining part of the rectum to facilitate normal bowel movement¹⁰.

Proctectomy with colo-anal anastomosis is a rather difficult procedure involving the removal of the whole rectum and attachment of the colon to the anus (colo-anal anastomosis). Colonic J pouch or coloplasty which



may function as the rectum can also be made. It is employed in stage II and III rectal cancers which are located in the middle and lower third of rectum. The colon is then connected to the anus. The total mesorectal excision (TME) is required to remove all the lymph nodes in the rectum¹¹.

Abdominoperineal (AP) resection requires a permanent colostomy. This operation is employed treat stage II or III rectal cancers located in the lower third of the rectum (including cancer that grows into the sphincter muscle). The surgery involves two incisions, one at the abdomen and another in the perianal area to remove the anus¹².

Pelvic exenteration is an extensive surgical operation which involves the removal of bladder, prostate/uterus if the cancer has metastasized into these organs in addition to the rectum¹³.

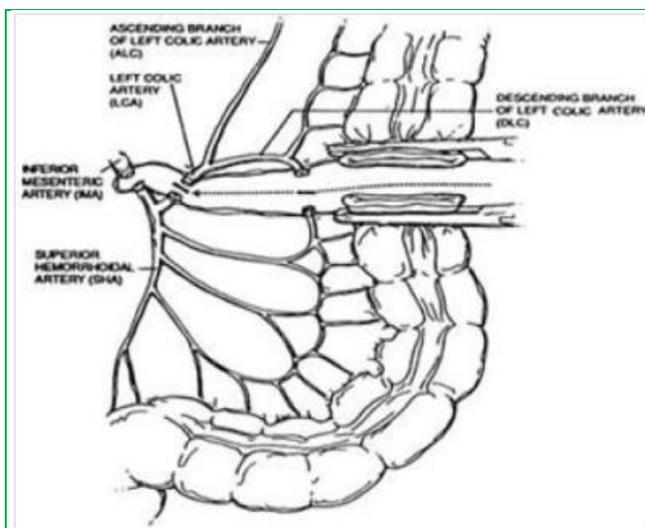


Figure 1: Colon resection

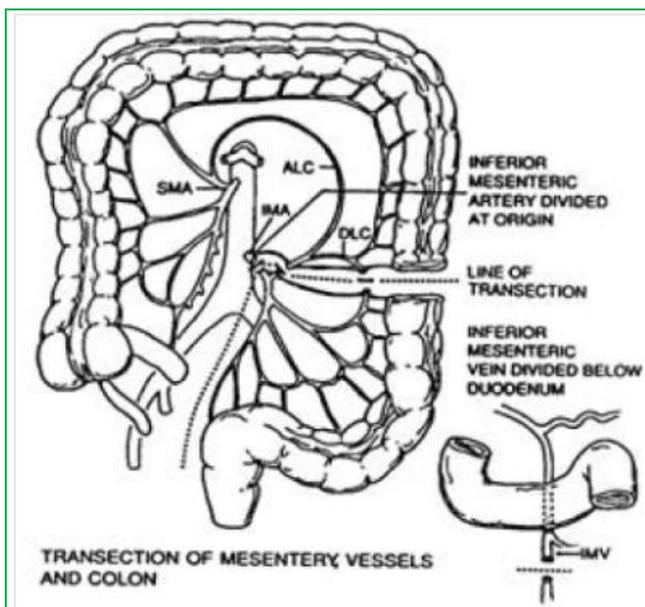


Figure 2: Transection of mesentery vessels and colon

Chemotherapy for colorectal carcinoma

Although surgery is rendered the most effective method for treatment of colorectal cancer, but only 15-20% patients are able to undergo surgery and metastases recurs eventually on follow up. Chemotherapy especially in neoadjuvant settings with combination of 5FU and Oxaliplatin has been the focus of research in the last decade to effectively treat colorectal carcinoma¹⁴.

Systemic and regional chemotherapy

Because of the high incidence rate of colorectal carcinoma, nearly every chemotherapeutic drug has been tested in various combinations¹⁵. Chemotherapy to treat colorectal carcinoma may comprise of systemic or regional chemotherapy. Systemic chemotherapy is the administration of the cytotoxic agent through IV route or oral, which ensures the systemic bioavailability of the drug and hence is effective in distant metastases of the disease. The systemic chemotherapy of colorectal carcinoma can be dated back with the introduction of fluorinated pyrimidines (fluoracil and the deoxyriboside complex of fluorouracil–floxuridine)¹⁵. The chemotherapeutic agent can also be administered in the artery replenishing the part of the body with the cancer with a concentrated dose. This therapy is referred to as regional chemotherapy (e.g. intra hepatic arterial infusion) which limits the cumulative adverse effects of the therapy. Hepatic arterial infusion of floxuridine ensures high concentration of the drug in the liver with higher frequency of tumor shrinkage^{16,17}. Hepatic arterial infusion is done by an abdominal surgery to adjust an arterial catheter with the implantation of an infusion pump¹⁸.

Adjuvant chemotherapy

Chemotherapy is most of the time the standard second line treatment after surgery which prevents the relapse of the cancer and adds survival benefit in patients of stage II and Stage III cancer patients. The chemotherapy given after surgery is referred to as adjuvant chemotherapy. Different combinations with Fluorouracil were designed and studied in the past to serve as the most effective postoperative adjuvant regimen for CRC. 5FU in combination with Semustine and Vincristine were evaluated for effective therapy but the no significant survival benefit was noted in these combinations despite long term leukemogenic effect of Semustine^{19,20}. Taylor *et al.*, (1985)²¹ tested the adjuvant efficacy of fluorouracil by infusion in the portal vein with no significant survival benefit. Levamisole which is an anthelmintic agent with immunostimulation was combined with 5FU in 1989 which reduced the relapse rate of the disease with elevation of liver enzymes and neurotoxicity²².

Neo Adjuvant chemotherapy

The chemotherapy with and without radiation treatment before surgery to shrink and contain the tumor and facilitate the surgical procedure is referred to as neoadjuvant chemotherapy, it is employed more often in

rectal cancer. Chemotherapy for advanced carcinoma may not treat the cancer completely, as at the advanced stage the cancer tends to undergo metastases but it adds to progression free disease and overall survival of the patients. The mainstay in treatment of colorectal carcinoma is 5FU in combination with leucovorin. The biological and biochemical modulation of fluorinated-pyrimidine therapy has been constantly investigated. Substances had been extensively studied in the past that could add to the antineoplastic activity of Fluorouracil such as Thymidine, Interferon and Leucovorin¹⁵. Capecitabine is the precursor of 5FU and can be given orally, changes to the active form at the tumor site. Irinotecan and Oxaliplatin are novel agents used in many combinations for the effective chemotherapy of CRC.

Targeted gene and protein therapy

The targeted therapy for colorectal cancer is by monoclonal antibodies like Bevacizumab (targeting the VEGF to stop angiogenesis), Cetuximab (targeting the EGFR to stop tumor growth) and Panitumumab (targets EGFR). The latter is used when the patients fails to respond to the rest of the therapy.

Tailored approach is needed to select the optimal chemotherapeutic agent with tolerable adverse effects. The patients who cannot sustain the adverse effects of FOLFOX are treated with 5FU/LV which is otherwise considered less effective than FOLFOX. A fifty percent reduction in the tumor mass, referred to as objective regression is a determinant of the therapeutic efficacy of a chemotherapeutic regimen¹⁵.

Cytotoxic agents for CRC chemotherapy

The cornerstone of chemotherapy for colorectal carcinoma is 5-Fluorouracil. 5FU based chemotherapy represents the gold standard for CRC treatment in adjuvant and metastatic settings²³. The therapeutic ratio is shifted in different 5FU/LV regimens and none of them serve as the internationally accepted optimal schedule. FOLFOX regimen is considered the best chemotherapeutic regimen with appropriate safety/efficacy ratio for treatment of advanced colorectal carcinoma²⁴. The aims of any therapy in patients with advanced colorectal cancer are to control symptoms, maintain or improve quality of life and ultimately to prolong survival²⁵. 5-FU synthesized in 1957 by Heidelberger, remains to be the most effective drug administered in different schedules, dosages and routes for the treatment of colorectal carcinoma. The clinical oncologists used it earlier as a single treatment agent bearing low response rate and no significant effect on survival²⁶, however, the therapeutic outcome and the toxicity of 5-FU differs markedly in different doses, combinations, schedules of administration and routes of administration. Folinic Acid/Leucovorin incorporated in a 5-FU based regimen, enhances the cytotoxicity of 5-FU. Improved tumor response rate and overall survival rate has been demonstrated in many controlled clinical trials when the combination of 5-FU and Folinic Acid/Leucovorin was

given in different doses and schedules of administration²⁷. Today, the standard therapy following resection of high-risk colon cancer is intravenous bolus 5-Fluorouracil (5-FU) with Folinic Acid, but there is no consensus on the optimum regimen of these drugs²⁸. Credible studies which have been designed to compare the therapeutic ratio of a monthly schedule of low-dose Leucovorin and 5-Fluorouracil (5-FU) bolus with a bimonthly schedule of high-dose LV and 5-FU bolus plus continuous infusion in patients with advanced colorectal cancer have shown that the bimonthly regimen is more effective and less toxic than the monthly regimen and has increased the therapeutic ratio²⁹.

The success of biochemical modulation of 5FU is attributed to the remarkable therapeutic efficacy of 5FU in combination with Leucovorin¹⁵. *In vitro* studies show that leucovorin has the capability to stabilize the ternary complex of fluorodeoxyuridine monophosphate, 5, 10, methylenetetrahydrofolate and thymidylate synthase thus boosting the cytotoxicity of 5FU and also adding to the intensity of the adverse effect most sufficiently by the same mechanism³⁰. Higher rate of objective regression was seen with high dose leucovorin (with higher toxicity as well e.g. severe diarrhea) whereas low dose leucovorin was not better than 5FU alone^{19,27}. Some of the studies have implied that the toxicity, benefit and survival rate of elderly colorectal patients subjected to chemotherapy is not different from young patients³¹. However comorbidities, advanced age and poor general status should be taken in account as these factors may alter the therapeutic response and the frequency of toxic events; whereas, higher mortality rate has also been reported in elderly women diagnosed with colorectal carcinoma as the proportion of cancer related death tends to increase with higher age³². The standard chemotherapeutic regimen for colorectal carcinoma is 5-FU in combination with Leucovorin whereas incorporation of Oxaliplatin to this regimen enhances the therapeutic efficacy especially for metastatic colorectal carcinoma. The addition of Oxaliplatin to 5FU/LV has doubled the response rate and increased the progression free survival in patients of metastatic disease³³. Cetuximab in combination with irinotecan is the standard treatment for Irinotecan refractory and treatment naïve settings³⁴. Vascular endothelial growth factor and epidermal growth factor receptors are utilized to expand treatment options and validate individualized treatment protocols.³⁵ Drug development in CRC treatment was considered stagnant within spans of various large trials with approved cytotoxic agents however, multiple new agents are currently in development.³⁶

CONCLUSION

Advances in pharmaceutical research for the quest of novel cytotoxic agents have resulted in design of optimal regimens and development of targeted agents which have entered the clinical trial in a fast pace and are rendered effective in metastatic colorectal carcinoma.



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