REVIEW ARTICLE

Chemotherapy in Colorectal Cancer - Past, Present and Future

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Introduction:

Colorectal cancer (CRC) ranks fourth among the most commonly diagnosed cancers worldwide and second most frequent cause of cancer related deaths in USA. Every year about 1,023,000 new cases and 5,29,000 deaths are estimated to occur[1]. In 2005, USA alone will have 1, 45,290 new cases and 56,290 deaths.[2]

Pathological stage at presentation is the most important prognostic indicator in CRC. The TNM system of staging (by AJCC-American Joint Committee on Cancer) has now mostly replaced the original and modified Dukes' staging system. Five-year survival based on this TNM staging is reflected in Table-I. About 30% of patients with this malignancy present in advanced stage and 50% of those who present in early stage develop advanced recurrence during their life time.[3] Early stage disease can be managed with satisfactory long term results by surgery alone. Advanced stage disease poses particular problems and is incurable. It is the advanced disease which is responsible for most morbidity and mortalities related to CRC. In advanced disease, chemotherapy along with palliative radiotherapy constitute mainstay of management. Chemotherapy in CRC has undergone revolutionary changes during last 10 years or so after long domination of 5-FU in adjuvant and palliative setting. Systemic chemotherapy is the treatment of choice for patients with metastatic CRC to prolong survival, and to improve symptoms and quality of life. This holds true for middle aged and elderly people equally, contrary to the common belief resulting in older patients often being inadequately staged and fewer elective operations are performed[4], and they are less likely to receive adjuvant chemotherapy and/or radiotherapy. [5-8] Recently published meta-analysis [9]and population based analysis [6,8,10] showed that elderly patients with colon and rectal cancer benefit from adjuvant chemotherapy or radio-chemotherapy to the same extent as younger patients. 5-FU based treatment is generally offered to these patients.

Table-I

TNM staging system for colorectal cancer

Stage	TNM classification	Five-Year Survival%
I	T1-2, NO, MO	>90
IIA	T3, NO, MO	60-85
IIB	T4, NO, MO	
IIIA	T1-2, N1, MO	
IIIB	T3-4, N1, MO	25-65
IIIC	T (any), N2, MO	
IV	T (any), N (any), M1	5-7

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Chemotherapeutic drugs:

In the era of evidence based medicine, results of trials with agents used in advanced disease is applied to neo-adjuvant and adjuvant settings. It implies that the drugs in neo-adjuvant, adjuvant and advanced disease settings are almost similar. In neo-adjuvant setting the drugs utilized should be effective in reducing the bulk of the tumour and render inoperable tumour to be operable or undertake organ sparing surgery or allow radiotherapy to take care of the disease where inoperable. In adjuvant treatment the drug must prove its efficacy in extending overall or disease free survival. On the other hand, in advanced disease, the goal of therapy is palliation of symptom or prolongation of life, if possible. 5 FU/ LV, Xeloda[11,12,13], Irinotecan, Oxaliplatin all have efficacy in neo-adjuvant and adjuvant setting and in advanced CRC. Various combinations of these drugs are more effective in each of these settings. Even many of these combinations are effective as second line therapy after 5 FU/ LV failure.

5- Fluorouracil (5-FU), an antimetabolite, acts by inhibiting DNA synthesis. Until mid-90s 5-FU with its various schedule and biomodulated forms have been used as adjuvant therapy, and in metastatic CRC with prolongation of medium survival from approximately six months (without treatment) to about 11 months[14-18]. Biochemical modulation of 5-FU and/or administration as continuous infusion are achievements of the 1980s and have resulted in increased response rate and prolonged progression free survival (PFS), while the influence on overall survival (OS) has been limited[19-22].

Despite controversies about efficacy of 5-FU in adjuvant setting, recent meta-analysis demonstrated probability of remaining free of tumour recurrence after five years in stage-III disease from 42 percent to 58 percent and likelihood of five year overall survival from 51 percent to 64 percent.[23] Role of adjuvant therapy in stage-II disease is still controversial and is recommended only in high risk cases – tumour adhesion to adjacent organ, bowel perforation or obstruction[24-26]. Different regimens of 5-FU varies in doses and schedule. Mayo clinic regimen uses bolus administration of 5-FU and Leucovorin whereas de Gramont regimen utilizes continuous infusion of 5-FU. Though absolute gain in efficacy of one regimen over the other of these gamut of schedules has not been observed, toxicity profile varies considerably. de Gramonts one produces more hand-foot syndrome but less gastrointestinal and haematologic toxicity compared to bolus schedules, and is claimed to be moderately more effective than a rapid bolus approach[22]. Single agent activity of Irinotecan[15,27,28] and Oxaliplatin [29] in metastatic CRC led to their use in combination with 5-FU/LV for treatment of patients in advanced disease as well as in adjuvant setting.

Oral fluorinated pyrimidines, UFT, Eniluracil, S-1 and Capecitabine (Xeloda) have the advantage of avoiding hospital visits and admissions for administration. UFT, Eniluracil and S-1 have not been very popular but Capecitabine, a pro-drug of 5-FU, which is tumour activated, has shown promising response, at least as good as 5-FU, but impact on median overall survival is not significant.[13] In fact, it has replaced 5-FU as the backbone of many combinations in recent past because of its favorable safety profile, convenience and cost-effectiveness. Capecitabine's unique mechanism of tumour activation results in the generation of 5-FU preferentially in tumor tissues, minimizing systemic exposure to this drug[30], Moreover, its chemical structure prevents direct release of 5-FU in gastrointestinal tract and its associated toxicities. Capecitabine mono-therapy is an established treatment option for patients with anthracycline and taxane pretreated metastatic breast cancer [31,32] and is active in patients with metastatic CRC[11,13,33]. Two large phase-III trials have demonstrated that, as first line therapy for metastatic CRC, Capecitabine achieves significantly superior response rates, equivalent time to disease progression and equivalent survival compared with 5- FU/ LV[13,33,34]. Drugs approved by FDA for treatment of CRC is shown in Table-II.

Table-II

Glossary of treatments for colorectal cancer

***FDA-approved drugs:**

Fluorouracil

Capecitabine (Xeloda)

Irinotecan (Camptosar)

Oxaliplatin (Eloxatin)

Cetuximab (Erbitux)

Bevacizumab (Avastin)

FDA-approved combination regimens:

IFL: Irinotecan, bolus fluorouracil, and leucovorin – first-line therapy

FOLFIRI: Irinotecan, infusional fluorouracil, and leucovorin – first-line therapy.

FOLFOX: Oxaliplatin, infusional fluorouracil, and leucovorin – first-and second-line therapy

Intravenous fluorouracil and bevacizumab – first-line therapy.

Cetuximab and irinotecan – therapy for **EGFR-positive, irinotecan-refractory disease

*FDA - Food and Drug Administration, and **EGFR- epidermal growth factor.

Newer agents and combinations:

Irinotecan plus 5-FU/ LV (FOLFIRI or IFL) and Oxaliplatin plus 5-FU/ LV (FOLFOX) have demonstrated increased anti-tumour activity and efficacy compared with 5-FU / LV alone in phase-III randomized studies[35-38]. FOLFOX 4: Recent evidence suggest better disease free survival of stage II & III CRC patients with FOLFOX4 (Folic acid, 5-FU, Oxaliplatin) compared to 5-FU/LV (de Gramont regimen) administered as adjuvant therapy and reduced the risk of recurrence by 32%; probability of disease free survival at three years is 78.2% vs 72.9% (p= .002) [39]. This regimen had already doubled the response rates and prolonged progression free survival among patients with metastatic CRC[38] and is superior to IFL[40]. Furthermore, studies with Oxaliplatin plus 5-FU / LV have indicated that a highly active first line chemotherapy regimen may permit, in a small sub group of initially unresectable metastatic CRC patients, a radical approach to metastases after response to chemotherapy, and that approximately 30-40% of operated patients will survive without evidence of disease for greater than five years.[41,42] Therefore, these data indicate that, in metastatic CRC, a more active first line treatment can be more effective, and a meta-analysis of 15 randomized trials of first line treatment with standard bolus intravenous fluoropyrimidines versus experimental treatments (5-FU plus LV, 5-FU plus Methotrexate, 5-FU –CI) also support the relationship between tumour response to first line chemotherapy and survival[40]. The GERCOR study[43] compared FOLFIRI and FOLFOX in sequential order, FOLFIRI followed by FOLFOX vs. FOLFOX followed by FOLFIRI and found median survival of 20.6 months vs. 21.5 months, the highest survival times reported up to now in any randomized study of metastatic CRC. This study suggests that exposure of metastatic CRC patients to all these most active agents 5 FU/LV, Irinotecan and Oxaliplatin, is associated with promising survival which is also supported by study of Goldberg et al[40]. Another recent phase-III trial demonstrated that survival in MCRC is correlated with the proportion of patients who received all the three active drugs in the course of their disease, but not with the proportion of patients who received any second line therapy[44]. That is why upfront administration of all these three drugs in 100% patients, if feasible and tolerable, should be attempted. Moreover, no data is available supporting the hypothesis that patients progressing rapidly on a two drug combination (FOLFOX or FOLFIRI) will respond to a triplet (FOLFOXIRI) or any currently available chemotherapy. The initial FOLFOXIRI[45] and its better tolerable version[46] have demonstrated maximum efficacy of median progression free survival of 10.4 and 10.8 months and median overall survival of 26.5 months and 28.4 months respectively.

Targeted therapy:

Angiogenesis plays central role in growth and spread of many solid tumours. Attempt to inhibit these factors constitutes rational approach in causing tumour shrinkage and prevention of its spread. Of the different factors VEGF (vascular endothelial growth factor) and EGFR (epithelial growth factor receptor) received much attention**.** Bevacizumab (Avastin), a recombinant humanized monoclonal antibody against VEGF, was tried in combination with chemo-therapeutic agents in trials[47-49]. The study by Hurwitz and colleagues[44], who added Bevacizumab with IFL, revealed an impressive, statistically significant increase in median overall survival and a 4.7 months prolongation in median overall survival (to 20.3 months vs 15.6 months with IFL and placebo). A recent study, adding Bevacizumab to FOLFOX as compared to FOLFOX alone, in patients who previously received Irinotecan based therapy, demonstrated a statistically significant prolongation in median survival[50]. Of late, Bevacizumab received FDA approval for treatment of advanced CRC patients with any Fluorouracil containing regimen.[51] Thalidomide, as an angiogenesis inhibitor, has been in use for multiple myeloma and other solid tumours. Recent evidence suggests its role in CRC along with chemotherapeutic agents.[52] Cetuximab (Erbitux), a monoclonal antibody against EGFR, is approved in USA for treatment of metastatic CRC. Saltz and colleagues studied combination of Cetuximab and Irinotecan in advanced CRC unresponsive to Irinotecan alone , and found radiological objective tumour regression in 19% of patients.[53] Study by Cunningham and colleagues confirmed the above experience who found 23% disease regression in patients who received Irinotecan and Cetuximab compared to 11% in those who received cetuximab alone.[54] The FDA approved drugs/ regimens are shown in Table-II and impact of these agents on median survival, particularly in advanced disease, over the last decade, is reflected in Table-III.

Table-III

Trends in the median survival of patients with advanced colorectal cancer

Reference	Treatment Status	Median survival
Scheithauer et al[14]	Before any active chemotherapy	6 mo
Cochrane Database[55]	Fluoropyrimidine only	10-12 mo
Saltz et al[36] and	Fluoropyrimidine and one other active	14-16 mo
de Gramont et al[38]	cytotoxic chemotherapeutic agent (irinotecan or oxaloplatin)	
Goldberg et al[40]	Fluoropyrimidine, irinotecan, and oxaliplatin (in combination as sequential therapy) or	
Hurwitz et al[52]	Cytotoxic chemotherapy and targeted therapy	>20 mo

Adapted from Grothey et al[44].

Future:

Last decade has witnessed profound improvement in chemotherapy of CRC after long plateau in survival curve. Many ongoing trials are attempting to achieve further gain in treatment outcome. Along with currently available reasonably effective agents, greater focus is now directed towards targeted therapy either alone or in combination with chemotherapeutic agents. ZD1839(Irresa), OSI-774(Tarceva), COX-2 inhibitors, farnesyltransferase inhibitors (e.g Zarnestra), to name only few, among the novel agents which are being incorporated in therapy, with hope of and aspiration to increase survival and relieve symptoms in advanced disease as well as early and locally advanced disease.

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