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New Chemotherapy Approaches In Colorectal Cancer: A Review

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Colorectal Cancer is a common type of cancer encountered in medical oncology practice. Many patients are presenting in advance stage of disease and the rest are requiring adjuvant therapy after surgery. The results of the current standard therapy so far are not encouraging. This review is addressing the issue related to the new chemotherapy agents has been recently introduced to clinical practice. Those recently published studies utilizing these chemotherapeutic agents are highlighted in this review.

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Colorectal cancer is one of the leading causes of cancer deaths in the western world. It ranks third in cancer deaths for men and women in the United States, with more than 130,000 new cases diagnosed and approximately 58,000 fatalities annually (Around 50%)[1]. Approximately 50% of all patients with colorectal cancer develop metastatic disease and are thus candidates for systemic therapy.

Most patients with distant metastases will die of their disease, with less than 10% alive after 5 years[2]. In the past 2 years, several cytotoxic agents with promising activity in colorectal cancer have been developed that have substantially widened the spectrum of therapeutic options for this fatal disease[3].

This review focuses on the emerging role of these new agents in the treatment of advanced colorectal cancer.

New aspects of treatment with 5-Fluorouracil/ Leucovorin:

At the end of 1999, standard first –line therapy for metastatic colorectal cancer consisted of 5-Fluorouracil plus leucovorin as a bolus regimen (eg. Mayo clinic protocol).

Infusion 5-Fuorouracil (with or without leucovorin) regimens were known to yield significantly higher response rate, but conferred only modest increase in the median overall survival[4].

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In a large study, 497 patients with advanced colorectal cancer were randomly assigned to three different treatment arms (Mayo clinic protocol, high dose 5FU protracted infusion or standard 5FU with high dose LV). The regimen with 5FU 24h/LV demonstrated higher but not significantly different remission rate and significantly progression free survival (6.4 vs. 4.1 vs. 4.4 months). However, no significant difference in overall survival was observed between the three treatment groups.

In conclusion, the infusion versus bolus 5FU protocol was found to be superior and also the role of biochemical modulation with leucovorin became quite evident[5].

New agents in palliative chemotherapy in colorectal cancer:

Oral Fluoropyrimidines:

Two oral Fluoropyrimidines; **UFT** and **Capecitabine**, have recently been introduced into clinical practice in the treatment of colorectal caner. **UFT** is a combination of Uracil and Tegafur in a fixed molar ratio of 4:1. Tegafur is a 5FU prodrug while Uracil can compete for binding to DPD (Dihydropyrimidine Dehydrogenase), the most important enzyme in the degradation of 5FU, thus reducing the 5FU clearance. Two randomized trials enrolling 816 & 380 patients with metastatic colorectal cancer, demonstrated equal efficacy (Remission rates 12,11% UFT/Leucovorin vs. 15, 9% 5FU/Leucovorin) and less toxicity of UFT/LV compared with conventional 5FU/lv bolus regimen[6]. Currently, several studies are assessing the feasibility of UFT as a substitute for IV 5FU in combination protocols with new drugs like Irinotecan and Oxaliplatin[7].

Capecitabine (Xeloda = Roche) is an oral fluoropyrimidine carbamate that must undergo a three-step enzymatic conversion to 5FU. Two randomized phase III trials demonstrated that capecitabine is at least as effective & less toxic than conventional modulated 5FU bolus regimen[8].

Therefore, Capecitabine will be introduced into combination protocols with new chemotherapy agents such as Irinotecan and Oxaliplatin.

Trimetrexate:

Trimetrexate (TM TX), a 2,4-diaminoquinazoline is a synthetic inhibitor of the enzyme dihydrofolate reductase (DHFR) and is approved for treatment of pneumocystis Carinii pneumonia. Several phase II studies in colorectal cancer suggest that TM TX provides added activity when combined with 5FU /LV[9].

Raltitrexed (Tomudex):

This is a specific Thymidylate Synthetase (TS) inhibitor which has been investigated in three phase III trials including 1361 patients that compared raltitrexed monotherapy with 5FU/LV regimens, demonstrating equal response rates (14.3-19.3% vs. 15.2-18.1 %)[10]. Excess treatment-related mortality and impaired quality of life (QoL) were noted in the raltitrexed arm of a randomized MRC study conducted in UK, which

compared raltitrexed with two infusional 5-FU regimens[11]. Therefore, raltitrexed cannot be considered standard of care in advanced colorectal cancer.

Irinotecan:

This is a semi synthetic derivative of captothecin, a natural alkaloid. Based on positive results of studies using irinotecan as second-line therapy, two phase III trials were initiated to assess the role of irinotecan in the first-line treatment of advanced colorectal cancer. Saltz et al[12] compared the Mayo clinic protocol as standard therapy with an irinotecan monotherapy and weekly 5FU/LV bolus (Roswell park protocol) plus irinotecan combination.

The irinotecan monotherapy was equally effective in terms of remission rate, time to progression, and overall survival but were more toxic than the Mayo clinic protocol, the irinotecan/weekly bolus 5FU/LV combination was found to be superior to the standard therapy in terms of efficacy and had comparable and tolerable toxicity. The most important was survival advantage in the combination arm compared to Mayo arm (14.8 vs. 12.6 months).

Oxaliplatin:

This is the first cisplatin derivative with activity in colorectal cancer, in particular in combination with 5FU.

Two-phase III trials have recently been reported investigating the role of 5FU/LV plus oxaliplatin as first-line therapy for advanced colorectal cancer. The addition of oxaliplatin to 5FU?LV resulted in a significant increased response rate (53% vs. 16%) & prolonged progression-free survival (8.7 vs. 6.1 months)[13].

In summary, the addition of irinotecan or oxaliplatin to 5FU/LV substantially increases the anti-tumor activity of first-line protocols in advanced colorectal cancer.

New aspects of adjuvant therapy for colorectal cancer:

Adjuvant treatment for colorectal cancer has not seen dramatic changes during the past decade. Still 6 months of bolus 5FU/LV (Mayo Clinic or Roswell Park Protocols) are considered standard therapy for Dukes C and high risk Dukes B colorectal cancer[14].

Studies addressing the efficacy and side effects of novel therapies such as Capecitabine, UFT/Leucovorin, Irinotecan, or Oxaliplatin combinations are ongoing or have recently closed. Results of these trials are not yet available.

CONCLUSION

The introduction of new therapeutic agents and combination in first- or second – line therapy has already resulted in substantially increased remission rate, prolonged progression-free and overall survival, and positive effects on quality of life. It is likely that oral fluoropyrimidines will replace intravenous 5FU in

combination regimens and that new agents directed against molecular targets will find their way into current combination protocols.

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