Is More Not Better?

Combination Therapies in Colorectal Cancer Treatment

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KEYWORDS

• Combination chemotherapy • Adjuvant therapy • Targeted therapy
• First-line therapy • Metastatic colorectal cancer • Systemic therapy
• Optimal sequence

KEY POINTS

- The availability of new chemotherapeutic agents (oxaliplatin, irinotecan, capecitabine) as well as vascular endothelial growth factor and epidermal growth factor receptor inhibitors has translated into improved outcomes in colorectal cancer (CRC).
- With respect to combination therapy for CRC, more is often better, but at the expense of increased toxicity and cost. It also has the potential to lead to worse outcomes, underscoring the importance of randomized clinical trials and appropriate patient selection.
- The addition of oxaliplatin improves outcomes in stage III colon cancer, but the data do not support its use in stage II colon cancer, patients older than 70 years, or as a radiosensitizer in rectal cancer. Furthermore, targeted agents have no role in adjuvant therapy for colon cancer.
- Choice of therapy for metastatic disease is governed by several factors, including previous therapy, comorbidities, goals of therapy, tumor mutational status, and personal preference.
- The small incremental benefits observed with individual lines of therapy will hopefully be enhanced by better patient selection (ie, avoiding unnecessary toxicity in patients who are unlikely to benefit and accepting toxicity in patients who stand to benefit the most from combination therapy).

INTRODUCTION

The treatment of colorectal cancer has evolved dramatically over the last decade, as shown by the availability of additional chemotherapeutic agents as well as agents targeting the vascular endothelial growth factor (VEGF)–signaling and epidermal

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growth factor receptor (EGFR)-signaling pathways. The most striking impact has been in patients with metastatic disease, in whom access to these new therapeutic strategies has been associated with a more than doubling of overall survival (OS). Although more has often translated into better (eg, higher response rates [RRs] with combination chemotherapy), more has also typically come at a price, both literally and figuratively, leading one to question if more is always better, and if some patients stand to benefit more than others. This issue is perhaps best exemplified by the lack of incremental benefit of greater than 6 months of adjuvant chemotherapy for stage III colon cancer, the lack of benefit from targeted agents in the adjuvant setting, and the potential for harm when EGFR inhibitors are used in patients with RAS mutant tumors or when combining targeted agents for first-line treatment of metastatic disease. Furthermore, less may be acceptable in the setting of maintenance therapy for advanced disease, but giving something may be better than nothing. Additional information is needed to optimize patient selection and choice of therapy in treating colorectal cancer.

ADJUVANT COMBINATION THERAPY FOR RESECTABLE COLON CANCER

Stage III Colon Cancer

Given a significant risk of recurrence, the use of adjuvant fluoropyrimidine (FP)-based treatment is standard in stage III colon cancer.[1,2] This treatment was initially given for 12 months, and subsequent studies proved that more was not superior to less. The optimal duration of therapy is unknown, but the data suggest that adjuvant therapy should not be given for more than 6 months.[3] Most of the current phase 3 trials in adjuvant therapy are focused on the optimal duration of therapy (**Table 1**), many of which are encompassed by the IDEA (International Duration Evaluation of Adjuvant Chemotherapy) collaboration.[4] In terms of combination chemotherapy (**Table 2**), the addition of oxaliplatin (OX) (eg, FOLFOX [infusional/bolus 5-fluorouracil, leucovorin, OX], XELOX [capecitabine (CAPE)/OX], FLOX [OX, bolus 5-fluorouracil, leucovorin]) improves disease-free survival (DFS) in patients with stage III disease.[5–7] In addition, in the Multicenter International Study of Oxaliplatin, 5-Fluorouracil, Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) study, treatment with FOLFOX

Table 1
Adjuvant therapy for colon cancer: selected ongoing phase III trials[a]

Study ID	Stage	Study Arms	Location
CALGB/SWOG 80702	III	FOLFOX (3 vs 6 mo) with or without celecoxib	United States
ICOG-CC01	IIIA/B	UFT/LV with or without polysaccharide-K	Japan
2007-000354-31	II/III	FOLFOX (3 vs 6 mo) with or without bevacizumab	Italy
CDR0000613042	II/III	12 vs 6 cycles OxMdG or XELOX	UK
CDR0000647466	III	3 vs 6 mo FOLFOX or XELOX	France
2009-11-008	II/III	3 vs 6 mo of oxaliplatin in patients receiving 6 mo adjuvant FOLFOX/CAPOX	Korea
CT/09.12	II/III	3 vs 6 mo FOLFOX/CAPOX	Greece
NeoCol	T3,4	Neoadjuvant chemo × 3 followed by surgery vs surgery + adjuvant chemo × 8	Denmark

Abbreviations: CAPOX/XELOX, capecitabine/oxaliplatin; FOLFOX/OxMdG, infusional/bolus 5-fluorouracil, leucovorin, oxaliplatin; LV, leucovorin; UFT, tegafur-uracil.

[a] http://www.clinicaltrials.gov.