A Review of the Evolution of Systemic Chemotherapy in the Management of Colorectal Cancer☆

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Abstract

Herein we present a historical review of the development of systemic chemotherapy for colorectal cancer (CRC) in the metastatic and adjuvant treatment settings. We describe the discovery of 5-fluorouracil (5-FU) by Heidelberger and colleagues in 1957, the potentiation of 5-FU cytotoxicity by the reduced folate leucovorin, and the advent of novel cytotoxic agents, including the topoisomerase I inhibitor irinotecan, the platinum-containing agent oxaliplatin, and the 5-FU prodrug capecitabine. The combination therapies, FOLFOX (5-FU/leucovorin and oxaliplatin) and FOLFIRI (5-FU/leucovorin and irinotecan), have become established as efficacious cytotoxic regimens for the treatment of metastatic CRC, resulting in overall survival times of approximately 2 years. When used as adjuvant therapy, FOLFOX also improves survival and is now the gold standard of care in this setting. Biological agents have been discovered that enhance the effect of cytotoxic therapy, including bevacizumab (a humanized monoclonal antibody that targets vascular endothelial growth factor, a central regulator of angiogenesis) and cetuximab/panitumumab (monoclonal antibodies directed against the epidermal growth factor receptor). Despite the ongoing development of novel antitumor agents and therapeutic principles as we enter the era of personalized cancer medicine, systemic chemotherapy involving infusional 5-FU/leucovorin continues to be the cornerstone of treatment for patients with CRC.

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Introduction

The most recent estimates of the worldwide burden of cancer (GLOBOCAN 2012) indicate that colorectal cancer (CRC) is the third most commonly diagnosed cancer (1.36 million cases; 9.7%) after lung (1.83 million; 13.0%) and breast cancer (1.68 million; 11.9%), and the fourth highest cause of cancer death (694,000 deaths; 8.5%) after lung (1.59 million; 19.4%), liver (746,000; 9.1%), and stomach cancer (723,000; 8.8%).[1] Despite these statistics, most patients (70%-80%) newly diagnosed with CRC have localized disease that is amenable to curative (R0) surgical resection.[2] After R0 resection, adjuvant chemotherapy with cytotoxic agents is recommended as standard clinical practice for patients with stage III CRC.[3] This recommendation is supported by a pooled analysis of data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials,[4] which demonstrated significantly improved survival outcomes after surgery and chemotherapy compared with surgery alone ($P < .0001$).

The remaining 20% to 30% of newly diagnosed patients present with unresectable metastatic disease. In addition, a considerable proportion of patients (40%−50%) experience disease recurrence after surgical resection or develop metastatic disease, typically in the liver or lungs.[5] The management of patients with metastatic CRC (mCRC) requires the systemic administration of cytotoxic drugs.[3] Patients with unresectable mCRC who receive supportive care alone have been shown to have a poor prognosis, with a median

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overall survival (OS) of 5 months.[6] In contrast, patients with mCRC who receive chemotherapy have been shown to have a median OS of > 2 years.[7]

Herein, we present a historical review of systemic chemotherapy in the adjuvant and metastatic settings, highlighting the key studies that have driven the development of chemotherapy for patients with CRC (Figure 1).

5-Fluorouracil and Leucovorin

The German chemist Paul Ehrlich was the first person to coin the term 'chemotherapy' during his work on the use of chemical agents to treat infectious diseases in the early 1900s.[8] However, the evolution of chemotherapy for CRC can be said to have begun with the development of 5-fluorouracil (5-FU) in 1957.[9] Charles Heidelberger and colleagues at the University of Wisconsin observed that tumor tissues preferentially used uracil for nucleic acid biosynthesis, and correctly postulated that a fluorouracil analogue would inhibit tumor cell division by blocking the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (thymidylate). Biochemical studies demonstrated that the main route of 5-FU activation proceeds via complex metabolic pathways that result in the formation of 5-fluorodeoxyuridine monophosphate (FdUMP), a potent inhibitor of thymidylate synthase (Figure 2).[10-14] The level of inhibition of thymidylate synthase achieved with FdUMP in patient tumors was shown to correlate with the clinical response to 5-FU treatment.[15,16] Studies of the molecular mechanism of thymidylate formation identified the transient formation of a ternary complex consisting of the substrate dUMP, the folate cofactor 5,10-methylenetetrahydrofolate (MTHF), and thymidylate synthase.[17,18]

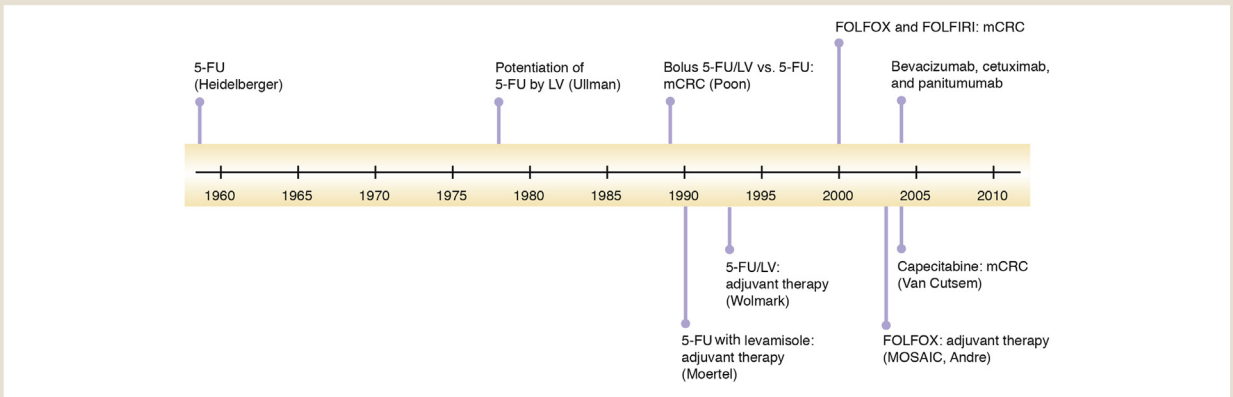
The next key advance in the development of 5-FU-based chemotherapy was the finding that inhibition of thymidylate synthase by 5-FU could be potentiated by increased intracellular levels of reduced folates.[12,19-22] At this juncture, it is interesting to note that the antitumor activity of folic acid analogues, including aminopterin and amethopterin (methotrexate), was first demonstrated in 1948 by Sidney Farber and Louis Diamond in children with leukemia.[23] The potentiation of 5-FU activity was shown to be mediated by the formation of a stable ternary complex consisting of FdUMP, MTHF, and thymidylate synthase.[10,13,24] Polyglutamate derivatives of MTHF were shown to substantially increase the efficiency of binding of FdUMP to thymidylate synthase compared with monoglutamate derivatives, in a human colon adenocarcinoma xenograft[25] and human Michigan Cancer Foundation-7 breast cancer cells.[26] In a pivotal in vitro study of the biomodulation of 5-FU activity by the reduced folate leucovorin (5-formyl tetrahydrofolate [THF]), Ullman et al[19] reported that 20 μM leucovorin enhanced 5-FU cytotoxicity approximately fivefold in cultured leukemia cells. Following on from this study, the antitumor activity of 5-FU/leucovorin and 5-FU/methyl THF was established in a number of studies of tumor cell lines, including those of human origin.[20,22,27-31]

The preclinical data on the biomodulation of 5-FU cytotoxicity by leucovorin led to a large number of phase I and II clinical studies in the 1980s.[32] In a pooled analysis of 21 phase II studies of patients with advanced CRC, conducted by Poon et al in 1989, the response rate (RR) of tumors to 5-FU/leucovorin was reported to be 23%.[33] The 2 most commonly used 5-FU/leucovorin treatment regimens in these early studies were those described by Machover et al[34] and Madajewicz et al.[35] Machover et al administered 200 mg/m^2 leucovorin using intravenous (I.V.) bolus and 370 mg/m^2 5-FU in a 15-minute I.V. infusion daily for 5 days to patients with gastric cancer and mCRC, with courses repeated at 28-day intervals.[34] Madajewicz et al administered 500 mg/m^2 leucovorin as a 2-hour infusion to patients with mCRC, with escalating bolus doses of 5-FU up to a maximum of 750 mg/m^2 given 1 hour after the leucovorin infusion; this schedule was repeated weekly for 6 weeks, followed by a 2-week rest period.[35]

Treatment of mCRC

In 1989, the seminal study of Michael Poon and colleagues[33] showed that there was only a trend toward increased OS with I.V. bolus 5-FU/leucovorin, but RR and progression-free survival (PFS) were significantly increased, compared with 5-FU alone in

Figure 1 Landmark Advances in the Evolution of Systemic Chemotherapy for Patients With CRC



Abbreviations: 5-FU = 5-Fluorouracil; FOLFIRI = Infusional 5-FU/LV With Irinotecan; FOLFOX = 5-FU/LV With Oxaliplatin; LV = Leucovorin; mCRC = Metastatic Colorectal Cancer; MOSAIC = Multicenter International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer.