Drug Treatment of Colorectal Cancer
Current Status

Leonard Saltz
Gastrointestinal Oncology Service, Section of Medical Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

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Summary

Drug therapy is most often used in colorectal cancer for palliation of metastatic disease. Current data also support the use of adjuvant chemotherapy following complete surgical resection in patients with locoregional lymph node metastases. The agent most widely used in the treatment of colorectal cancer is the antimetabolite fluorouracil (5-fluorouracil; 5-FU). This fluoridated pyrimidine has been available for over 30 years, yet to date no other single agent has proven to be more efficacious.

Controversy exists about the most desirable schedule for administration of fluorouracil. Efforts have been made to improve upon its therapeutic index and efficacy by using the concept of biomodulation, in which chemicals which are not themselves active antineoplastic agents against colorectal cancer are administered with fluorouracil in an attempt to enhance the sensitivity of the cancer cell to fluorouracil. Biomodulation agents currently in use in clinical practice include leucovorin (calcium folinate), methotrexate, and interferon-α. Other biomodulation strategies are currently under investigation.

Adding putatively active antineoplastic agents to fluorouracil to form combination chemotherapy regimens has not yielded convincingly superior results to treatment with fluorouracil alone, and the toxicities of many of these combination regimens have been formidable. Secondary therapies following failure of fluorouracil-based regimens have been similarly disappointing. Cur-
rent areas of investigation into the chemotherapy of colorectal cancer include development of new agents, locoregional administration of chemotherapy, and manipulation of intrinsic drug resistance mechanisms of the cancer cells.

Colorectal cancer represents a major source of morbidity and mortality throughout the world. The disease is most prevalent in the industrialised nations, with an annual incidence in the United States alone of approximately 150 000 cases per year. Although early detection and complete surgical resection can lead to cure in many cases, and aggressive surgical management may salvage some patients with advanced tumours, roughly half of all patients will ultimately develop unresectable and therefore incurable disease (Cohen et al. 1989).

The most common indication for chemotherapy in the treatment of colorectal cancer is the presence of metastatic or otherwise surgically incurable disease (section I). The other regular indication is in the adjuvant setting following complete surgical resection of locally advanced disease (see section 2). The overall multidisciplinary management of colorectal cancer is far too large a topic to be encompassed in this brief article, and as such only the issue of chemotherapy is dealt with.

1. Chemotherapeutic Agents in the Treatment of Metastatic Disease

1.1 Fluorouracil

The antimetabolite fluorouracil (5-fluorouracil; 5-FU) [fig. 1] has been available since the late 1950s, and to date no other single agent has proven as efficacious in the treatment of colorectal cancer. Fluorouracil is a fluoridated pyrimidine which has several putative mechanisms of action. One major mechanism of activity appears to result from the conversion of fluorouracil to the active metabolite 5-fluoro-2'-deoxyuridylate (FdUMP) [fig. 2]. FdUMP inhibits the function of the enzyme thymidylate synthetase, which is necessary for the production of the thymidine nucleotides required for DNA synthesis. In addition, fluorouracil can also exert a cytotoxic effect through its direct incorporation into RNA as a fluoridated nucleotide. There is also some evidence for direct incorporation of fluorouracil into DNA (Major et al. 1982).

Numerous studies have been performed in an attempt to define the optimum schedule for fluorouracil administration. Schedules involving bolus administration on a weekly basis, bolus on 5 consecutive days, and continuous infusions of anything from 24 hours to 5 days to as long as several months have been attempted. To date there is no clear agreement as to which administration schedule of fluorouracil is best; data from various different studies are conflicting and often inconclusive. For example, a study which claimed to demonstrate a benefit in terms of improved response rate for a 5-day continuous infusion of fluorouracil compared to daily bolus injections for 5 successive days (Seifert et al. 1975) failed to take into account and stratify certain prognostic variables which tended to favour the group which received infusional therapy. As such, firm conclusions cannot be drawn on the basis of this study.

Others (Lokich et al. 1989) have attempted to maximise the length of fluorouracil exposure through continuous intravenous infusion at a fluorouracil dose of 300 mg/m²/day for 12 weeks. This was compared in a randomised trial to a conventional 5-day bolus administration schedule of 500 mg/m²/day for 5 consecutive days repeated every 5 weeks. The 30% response rate seen with the pro-

![Fig. 1. Structural formula of fluorouracil.](image-url)