How to optimize the effect of 5-fluorouracil modulated therapy in advanced colorectal cancer

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Keywords: 5-fluorouracil; colorectal carcinoma

INTRODUCTION

Colorectal adenocarcinoma is one of the most common tumor types in the industrialized western countries. At the time of diagnosis, approximately 20% of the patients display clinically detectable spread of the disease to distant sites and 40% to locoregional lymph nodes [1]. More than half of the patients who undergo surgical procedures with the intent to cure eventually relapse and die from their disease [2]. Radiation therapy may significantly diminish the local recurrence rate, but there is no consensus that it prevents development of distant metastases or prolongs survival [3,4].

A number of chemotherapeutic drugs have been examined for clinical activity in patients with advanced colorectal cancer. The most effective single agent seems to be 5-fluorouracil (5-FU) [5]. The objective response rate of systemic parenteral 5-FU monotherapy in advanced colorectal cancer ranges from 8 to 25%. The response durations are short, and there are no or only marginal effects on survival [6-8]. Several factors may explain the wide range of objective responses reported in different series of colorectal cancer patients receiving 5-FU monotherapy. These may include age, performance status, tumor burden, differentiation of the tumor cells, doses and dose intensities of 5-FU and modes of administration.

During recent years a number of articles have been published showing that the clinical activity of 5-FU in advanced colorectal cancer may be augmented, or modulated; by other agents which exhibit little if any antitumor activity by themselves. This rapidly progressive research field is important since it may yield meaningful chemotherapy schedules for patients with advanced colorectal cancer. More importantly, such schedules may be used also in adjuvant settings to prevent relapses following surgery in high risk cases for primary disease. In fact, there are already some reports showing that 5-FU based modulated chemotherapy may palliate and prolong life of patients with advanced colorectal cancer [9,10], decrease the relapse rate, and increase survival when given as an adjunct following surgery [11].

The principal aim here is to present a critical review on the clinical effectiveness of 5-FU with particular emphasis on comparisons between long-term infusions and bolus injections, and on drugs considered to modulate the cytotoxic activity of 5-FU. Treatment of liver metastases by hepatic arterial or portal vein infusion of 5-FU, oral 5-FU treatment and regimen containing cytotoxic drugs which are not known to modulate the activity of 5-FU fall outside the scope of this review.

MECHANISMS OF ACTION OF 5-FU

Most 5-FU is catabolized to inactive metabolites or excreted in the urine. The initial enzyme in the catabolic pathway is termed dihydropyrimidine-dehydrogenase. The level of this enzyme may vary in different individuals and may even be lacking, which may cause severe side effects of 5-FU therapy. The proportion of 5-FU which is anabolized to cytotoxic metabolites usually ranges
188
5FU MODULATED THERAPY IN ADVANCED COLORECTAL CANCER

Fig. 1. metabolic pathways and site of action of 5-FU.
Abbreviations: dUMP = deoxyuridine monophosphate; dTMP = deoxythymidine monophosphate; dTDP = deoxythymidine diphosphate; dTTP = deoxythymidine triphosphate; DNA = deoxyribonucleic acid; FdUrd = 5-fluoro-2'-deoxyuride; FdUMP = 5-fluoro-2'-deoxyuridine monophosphate; FdUDP = 5-fluoro-2'-deoxyuridine diphosphate; FdUTP = 5-fluoro-2'-deoxyuridine triphosphate; FUMP = 5-fluorouridine monophosphate; FUDP = 5-fluorouridine diphosphate; FUTP = 5-fluorouridine triphosphate; RNA = ribonucleic acid.

between 1 and 5%. There are three main metabolites considered to exert antitumor activity: (i) 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP); (ii) 5-fluorouridine-5'-triphosphate (FUTP) and 5-fluoro-2'-deoxyuridine-5'-triphosphate (FdUTP) (Fig. 1). The latter may be incorporated into the DNA of cells whereas FUTP may be incorporated into cellular RNA. From the clinical point of view FdUMP is considered to be the most important. This metabolite inhibits the enzyme thymidylate synthase (TS), which catalyses the conversion of 2'-deoxyuridine-5'-monophosphate (dUMP) to 2'-deoxythymidine-5'-monophosphate (dTMP) which is required for biosynthesis of DNA. During this reaction N⁵, N¹⁰ methylene tetrahydrofolate (N⁵, N¹⁰-CH₂-FH₄) serves as a cofactor as the methylene group of folate is added to dUMP and after reduction dTMP is formed. FdUMP binds to TS and competes with dUMP. FdUMP-TS thus forms a bivalent complex which, however, is relatively unstable. In the presence of N⁵, N¹⁰-CH₂-FH₄, especially its polyglutamated forms, a ternary complex is formed which is far more stable. FdUMP thus inactivates TS leading to a DNA-synthetic block of cells. (For reviews see [8] and [12].)

Continuous infusion versus bolus injection of 5-FU
Assuming that the main tumoricidal effect of 5-FU is mediated by FdUMP one would expect a rather limited clinical activity following bolus injections. This is because in colorectal cancer the frequency of cells in S-phase at a given time is usually less than 3%, and the plasma half life of 5-FU is of the order of 5–20 minutes with a dissociation half life of the FdUMP-TS-N⁵, N¹⁰-CH₂-FH₄ complex of about 6 hours [12]. Therefore, prolonged continuous infusion of 5-FU may be clinically superior to bolus injections in the treatment of colorectal cancer. This issue has been the subject of at least four randomized clinical trials in patients with advanced colorectal cancer [13–16]. The results are summarized in Table 1.

In each trial the control arm contained daily pushes of 5-FU for five consecutive days, repeated at 4 to 5 week intervals. This treatment strategy was compared with protracted continuous infusions of 5-FU over several days (5–70 days). As can be seen in Table 1 the objective response rates (complete and partial) was in all the studies numerically higher among patients who received continuous infusions than in patients treated by bolus injections. However, the difference reached statistical significance in only one of the trials [14]. Survival of the patients was not linked to treatment schedule.

Taken together, these results indicate that continuous infusion of 5-FU may be superior to i.v. injections with respect to induction of objective responses in patients with colorectal cancer.

Combination of folinic acid and 5-FU
As mentioned above, N⁵, N¹⁰-CH₂-FH₄ serves as a donor of methyl groups and a reducing agent in the biosynthesis of dTMP. In the presence of this reduced folate binding of FdUMP to the catalysing enzyme, TS becomes firm and its enzyme activity is blocked for a prolonged time period. Thus, on