The Use of Thymidylate Synthase Inhibitors in the Treatment of Advanced Colorectal Cancer: Current Status

D. Papamichael
Cyprus Oncology Centre, Strovolos, Nicosia, Cyprus

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ABSTRACT

The combination of 5-fluorouracil (5-FU) and leucovorin has been the unofficial “standard” therapy for patients with colorectal cancer for over a decade. Recently, however, a number of new agents targeted against the enzyme thymidylate synthase have been synthesized and are in various stages of development. The currently available thymidylate synthase inhibitors are discussed.

Enormous efforts have been made over the years to improve the efficacy of 5-FU, the most popular of these agents. Biochemical modulation by leucovorin has been the most successful so far. Continuous infusion schedules also appear to be advantageous over bolus administration. However, marked intra- and interpatient variability, combined with nonlinear elimination kinetics and erratic oral bioavailability are relative limitations to further development of 5-FU. New oral 5-FU prodrugs such as UFT, S-1, and Capecitabine may help to overcome some of these difficulties. Eniluracil, a potent inhibitor of the enzyme dihydropyrimidine dehydrogenase, may also help by overcoming potential 5-FU resistance mechanisms, in addition to increasing its bioavailability. Of the antifolate-based inhibitors, Tomudex is in the most advanced stage of development. Similar efficacy with 5-FU and a convenient schedule may suggest a role in future combination regimens.

It is quite likely that even the most optimal thymidylate synthase inhibition will have limitations in terms of clinical efficacy. Novel combinations of 5-FU or its analogs with agents that have different mechanisms of action (e.g., oxaliplatin, irinotecan) could provide important new opportunities for improving the outlook of patients with colorectal cancer. The Oncologist 1999;4:478-487

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common malignancy globally and the second leading cause of cancer deaths in Western countries, with approximately 300,000 new cases per annum diagnosed in the USA and Europe. The three major types of therapy in CRC are surgery, chemotherapy, and radiation therapy, each one of them applied differently, depending on whether the aim of treatment is curative or palliative. Approximately 50% of patients will ultimately die of locally advanced or metastatic disease [1]. Only a minority of patients with metastases qualify for surgical resection. Consequently, the most widely used approach for this group is systemic or locoregional chemotherapy combined with, where appropriate, palliative radiotherapy. Randomized trials have shown that chemotherapy improves both survival and quality of life (QOL) in advanced CRC [2-5]. Treatment with 5-Fluourouracil (5-FU) and calcium leucovorin (LV) has been the “standard” therapy for patients with CRC for over a decade. Recently however, a number of new agents targeted against thymidylate synthase (TS) have been synthesized and are in various stages of development. The purpose of this article is to review the currently available TS inhibitors used in the treatment of advanced CRC.

THYMIDYLATE SYNTHASE INHIBITION

An important feature of nucleotide metabolism is the duplication of pathways; inhibition of any one enzyme can be circumvented by one or more alternative routes. One notable exception to this is TS, a “bottleneck” enzyme which provides the only means of adding a methyl group to the 5-position of...
the pyrimidine ring in the de novo synthesis of thymidine. Thymidylate synthase is also the one enzyme in the nucleotide synthesis pathway which, instead of metabolizing the 5-FU derivative to its natural substrate, is instead inhibited by it.

Since thymidine is the only nucleotide precursor specific to DNA, TS is an obvious target for cytotoxic agents. The enzyme’s activity is a two-stage process. First, deoxyuridine monophosphate (dUMP) binds to a receptor site; this induces a configurational change which opens an adjacent binding site for N-5,10-methylene-tetrahydrofolate (CH2FH4). The folate’s one-carbon group is then transferred to the uridine ring, yielding deoxythymidine monophosphate (dTMP) and dihydrofolate [6, 7]. dTMP is subsequently phosphorylated by a kinase to dTTP and dTTP, one of the bases for DNA synthesis (Fig. 1).

It has long been known that fluorodeoxyuridine monophosphate (FdUMP), a 5-FU metabolite, potently inhibits TS, and that this is one of the main mechanisms underlying 5-FU action [7]. It binds at the same site and with the same affinity as dUMP (KS 1-2×10⁻⁶ M), but unlike hydrogen, the fluorine atom at the 5’ position cannot be displaced. Subsequently, FdUMP and the reduced folate become covalently bound with TS, to form a ternary complex (Fig. 2), where a cysteine thiol of TS is attached to the 6’ position of FdUMP, with the one-carbon group of the folate adjacent to F at the 5’ position (Fig. 3).

5-FU AND ITS PRODRUGS

Since its introduction over 40 years ago by Heidelberger [8], 5-FU has been the drug of choice for systemic therapy in CRC, although it can be argued that the optimum treatment strategy for its use has not been fully established. Enormous efforts have been made to improve the efficacy of 5-FU, either by changing its biochemical modulation and/or the method of administration. These efforts have been inspired by new insights into the biochemical pharmacology of 5-FU and the identification of agents that effectively enhance the anti-tumor activity of 5-FU in preclinical models. The three potential ways of modifying its activity are: A) through manipulation of dose or schedule; B) by the addition of other agents to modulate the activity of 5-FU and thus

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**Figure 1.** In the thymidylate synthesis cycle, dietary folate is reduced to dihydrofolate, which is further reduced by the enzyme dihydrofolate reductase to tetrahydrofolate, using dihydronicotinamide adenine dinucleotide phosphate as a hydrogen source. Tetrahydrofolate is then converted to mehtyltetrahydrofolate by the enzyme serine transhydroxymethylase, which uses vitamin B6 as a cofactor. The methylene-group-carrying cofactor, methylene tetrahydrofolate, then provides both a methylene group and reducing activity, to convert dUMP to dTMP by the action of the enzyme thymidylate synthase (U = uridine; C = cytidine; PP1 = pala pyrazofurin; A = adenosine; G = guanosine; d = deoxy-; DP = diphosphate; MP = monophosphate; TP = triphosphate).
producing metabolic or functional interactions, and C) by the use of analogs/prodrugs.

**5-FU SCHEDULING**

5-FU is characterized by marked schedule dependency in both the quality and quantity of its effects. This has been demonstrated in numerous studies, in vitro, in animal models, and in clinical practice, where bolus and infusional regimens have been compared and contrasted in terms of their activity and toxicity profiles [9]. Bolus 5-FU is more likely to exert its effect through an action on RNA, whereas infusional 5-FU is more likely to work through TS. Differences in the two schedules can be seen in diverse settings; e.g., an improvement in survival was reported in an adjuvant randomized chemoradiotherapy rectal cancer trial, when a protracted infusional 5-FU regimen was used, as compared with bolus [10]. Unmodulated bolus 5-FU appears to have a threshold dose intensity (500-600 mg/m²/wk) [11]. A similar dose-response relationship also appears to exist with 5-FU continuous-infusion (CI) regimens [12]. The threshold dose

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**Figure 2. FdUMP/folate binding to TS.**

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**Figure 3. Interaction of FdUMP with thymidylate synthase.**
for clinical activity for CI regimens is likely to be in the range of 1,500 mg/m²/wk; on the other hand, there is probably no therapeutic gain in giving more than 2,600 mg/m²/wk [13, 14]. It should be noted that dose intensity achieved with CI regimens is three to four times higher than that of bolus 5-FU. In 1998, a meta-analysis of all randomized trials comparing infusional and bolus administration of 5-FU was published [15]. A database of just over 1,200 patients was covered. Tumor response was significantly higher in the CI arm (22% versus 19%, p = 0.002). Furthermore, although median survival times were close, overall survival was significantly higher for patients on infusional 5-FU (hazard ratio = 0.88, p = 0.04).

5-FU Modulation

The use of modulating agents to enhance the activity of 5-FU is currently widely employed. To date, the most successful and commonly used biochemical modulator of 5-FU is LV. Many clinical trials have now been performed with the combination, including several phase III trials comparing 5-FU plus LV with 5-FU alone. The meta-analysis of 1,381 patients in nine randomized clinical trials confirmed the advantage of treatment with the combination in terms of objective response [16]. The response rate of the combination, as compared with 5-FU alone, was 23% versus 11% (p < 10⁻⁷). This benefit was documented in trials involving weekly and daily schedules of administration with both high-dose LV (>200 mg/m²/day) and low-dose LV (<25 mg/m²/day). The meta-analysis, however, did not reveal an advantage in terms of survival.

One disappointing aspect of the clinical experience with 5-FU and LV is that toxicity to normal tissues is increased, necessitating a reduction in the dose of 5-FU administered. This is contrary to the hope and expectation that normal tissues, having adequate baseline folate pools, would be unaffected by the addition of LV. The clinical toxicity profile of 5-FU modulated by LV seems to be more dependent on the schedule of 5-FU rather than on the dose of LV [17]. Study of the 5-FU/LV combination continues both in the advanced as well as the adjuvant settings, so that questions relating to the optimum use of LV (e.g., high versus low dose) can be resolved.

The use of methotrexate (MTX) as a modulating agent has also been investigated, although its use has not been so widespread. This is despite a meta-analysis showing a survival advantage for the use of MTX in combination over 5-FU alone [18]. The use of other agents such as interferon (IFN) and hydroxyurea has so far been less promising. In the case of interferon, a number of randomized phase III clinical trials conducted to assess the addition of IFN to a number of different “popular” 5-FU/LV regimens, proved very disappointing [19-22]. In all of the above studies, it became evident that while toxicity was increased by the addition of IFN, there was no enhanced efficacy. The initial phase II data, on which the enthusiasm for the use of IFN was based [23], were therefore not confirmed.

The clinical pharmacology of 5-FU is characterized by marked intra- and interpatient variability, non-linear elimination kinetics, and erratic oral availability. As the administered dose increases, 5-FU displays saturable pharmacokinetics, i.e., the plasma half-life increases, plasma clearance decreases, hepatic extraction decreases, and the area under the concentration-time curve (AUC) increases disproportionately. As a result, the plasma concentration achieved with any given dose is dependent both on the dose administered and the rate of the infusion. Whether 5-FU plasma concentrations can be used to individualize dosing remains controversial [24]. In view of the above limitations, a number of agents were developed in an effort to overcome some of these problems.

Eniluracil

Eniluracil is a potent inactivator of dihydropyrimidine dehydrogenase (DPD). The recent recognition of the clinical importance of DPD—the first enzyme in a degradation pathway that rapidly catabolizes more than 80% of orally administered 5-FU—has led to new potential strategies for improving the efficacy and safety of 5-FU administration. The importance of DPD on 5-FU pharmacology has been further emphasized by results of studies suggesting the influence of DPD on pharmacokinetics, bioavailability, toxicity, and efficacy of 5-FU. DPD follows a circadian pattern in animals and humans [25]. Also, there is DPD interpatient variability (enzyme activity), taking a gaussian pattern, in some instances responsible for severe toxicity in patients with low DPD who are exposed to 5-FU for the first time [26].

In animal models, pretreatment with eniluracil significantly increased the bioavailability and reduced the variability of oral 5-FU, giving a pharmacokinetic pattern similar to that produced when the drug is administered i.v. [27, 28]. It has also been demonstrated in vitro that DPD activity was an independent factor significantly related to 5-FU sensitivity. It is possible, therefore, that the inhibition of DPD by eniluracil in colorectal tumors may eliminate a potential mechanism of 5-FU resistance [29].

In a phase I trial of oral eniluracil plus i.v. 5-FU with or without oral leucovorin, the dose-limiting toxicities (DLT) were neutropenia and diarrhea [30]. Clinical responses in CRC patients were noted. Pharmacokinetic data showed that eniluracil decreases the clearance of 5-FU and prolongs its half-life. Another phase I trial assessed several different regimens of oral eniluracil plus oral 5-FU [31]. It was noted from that study that the bioavailability of oral 5-FU was greatly increased, and that there was a marked decrease in interpatient variability. Renal excretion appeared to be the principal
mechanism for 5-FU elimination. The DLT for the combination was neutropenia, and this precluded escalation of 5-FU to doses >25mg/m²/day for five days in combination with eniluracil given at 3.7 mg/m²/day on days 1-7 every four weeks. With this oral 5-FU dose, the systemic exposure achieved was comparable to that observed using 5-FU doses of 1,000 mg/m²/day for five days as a CI. Mani et al. reported preliminary results from a phase II study in CRC, where response rates of 25% and 29% were observed for 1.0 and 1.15 mg/m²/day for five days as a CI.

On the basis of the above promising results, two large phase III trials (FUMA308 and FUMB3002) are currently under way in the USA and Europe. The toxicity pattern in these trials will be of great interest. If side effects such as hand-foot syndrome, cardiotoxicity, and neurotoxicity are related to 5-FU catabolism, one might expect these to be less pronounced in patients receiving a DPD inhibitor.

5-FU ANALOGS/PRODRUGS

5′-deoxy-5-fluorouridine

A number of other fluoropyrimidines have been synthesized, most of which act as prodrugs for 5-FU. For example, the 5′-deoxynucleoside, 5′-deoxy-5-fluorouridine (doxifluridine) must have its ribosyl group removed by the enzyme uridine phosphorylase to produce 5-FU [33]. This enzyme is reported to be more active in some tumor cells than in normal tissues, resulting in an improved therapeutic ratio in tumor-bearing mice [34]; however, very high activity is found in normal human liver, casting doubt on doxifluridine’s claimed sensitivity [35]. Unfortunately, clinical trials have been marked by severe neurotoxicity, and there is as yet no evidence that it gives any clinical benefit over 5-FU, except that it may be used orally.

UFT

Another prodrug, fltorafur (1-tetrahydrofuranyl-5-fluorouracil) is metabolized to 5-FU either by hepatic P-450 microsomal enzymes or by ubiquitous cytosolic enzymes [36]. It has the advantage of 100% bioavailability. Its activity is improved by the coadministration of uracil in a 4:1 molar ratio (“UFT”), which blocks its degradation by DPD and gives more prolonged concentration of 5-FU in tumor tissues [37, 38].

The toxicities observed with UFT, which is orally administered, are typical of the fluoropyrimidines. Phase II studies with oral UFT in a variety of cancers showed comparable activity to single-agent i.v. 5-FU [39]. Randomized studies to date, comparing either 5-FU/cisplatin versus fltorafur/cisplatin in patients with head and neck cancer [40] or UFT and 5-FU in combination with cyclophosphamide and doxorubicin in advanced breast cancer [41] showed no significant differences in terms of activity or toxicity. Furthermore, in a study comparing the pharmacokinetic profile of oral UFT to that of protracted i.v. 5-FU, it was concluded that the AUC of 5-FU generated was equal in both treatments [42]. In addition, UFT peak and disappearance curves followed the same pattern as for 5-FU. Already, phase III trials in advanced CRC are well under way, comparing UFT in combination with LV versus “standard” 5-FU/LV regimens. Early results from two phase III trials, giving a combined experience from just under 1,200 patients, reported similar efficacy for the two treatment arms. However, the combination of UFT/LV was thought to be safer in terms of toxicity and a more convenient oral alternative to 5-FU [43, 44].

The potential for combining UFT with other agents may have a wider application [45]. Also, the ease of oral administration of UFT eliminates the need for long-term indwelling catheters and their accompanying complications.

Capecitabine

Capecitabine (Xeloda), is a new orally administered, tumor-activated, and tumor-selective fluoropyrimidine carbamate. After absorption through the intestinal mucosa as the intact molecule, due to its carbamate structure and thus potentially causing less diarrhea, it is converted to 5′-deoxy-5-fluorouridine by a sequential triple enzyme pathway. The last tumor-selective enzyme reaction is mediated by the tumor-associated angiogenic factor thymidine phosphorylase, when it is further metabolized to 5-FU. Theoretically, therefore, it has two major advantages, which may translate into an improved therapeutic index: first, enhanced drug concentration at the cancer site and therefore greater anti-tumor activity, and second, reduced drug levels in non-tumor tissues, with a consequent reduction in systemic toxicity.

Preclinical data have suggested an improved efficacy profile over 5-FU and oral UFT, with tumor selectivity for Capecitabine’s activation [46]. In xenograft models, concentrations of 5-FU were found to be higher in tumor than in plasma or healthy tissue (127-fold higher than in plasma, and 22-fold higher than in muscle). In contrast, selective distribution of 5-FU was not observed following 5-FU administration.

Side effects in early clinical trials were similar to those observed with infusional 5-FU, including hand-foot syndrome. Results from a randomized phase II clinical trial carried out with three dosage schedules were somewhat less encouraging, at least in terms of response rates [47]. Two phase III trials enrolling patients with advanced colorectal carcinoma are comparing an intermittent capecitabine schedule with i.v. 5FU/LV (“Mayo”), in terms of efficacy as well as quality of life and pharmacoeconomic resource parameters. Early results,
reported so far only in abstract form, show higher response rates (26.6% versus 17.9%, \( p = 0.013 \) [48], and 23.2% versus 15.5%, \( p = 0.02 \) [49]) and a more favorable toxicity profile than modulated bolus 5-FU [48, 49]. The same regimen of capecitabine is also being evaluated in a large-scale adjuvant trial, which is expected to recruit approximately 1,700 Duke’s C colon cancer patients (X-ACT study).

**S-1 (BMS-247616)**

Another potentially very interesting orally bioavailable 5-FU prodrug is S-1. It consists of tegafur and two modulators: a 5-chloro-2,4-dihydroxypyridine (CDHP)—an inactivator of DPD—200 times more potent than uracil), and potassium oxonate (inactivator of normal gastrointestinal tissue phosphoribosyl pyrophosphate transferase, thereby reducing diarrhea), causing decreased drug incorporation into cellular RNA. As with UFT, the aim of S-1 is to mimic 5-FU prolonged CI. Preclinical as well as early clinical data point to encouraging activity particularly in advanced gastric cancer (49% complete and partial response rate) with a mild toxicity profile [50], and possible synergistic activity when combined with cisplatin [51]. Preliminary data from a phase I study show effective inhibition of DPD, with diarrhea as the main toxicity. In this study, the maximum tolerated dose was 45 mg/m\(^2\) given in two daily doses for four weeks, followed by a one-week rest. In a phase II study that used a schedule of 100 mg/m\(^2\)/day for four weeks, the response rate was 17% in 30 patients with CRC [51].

**DIRECT TS INHIBITORS**

Currently, four folate-based agents that have been designed to interact with the folate-binding site of TS by using binding side-structure analysis, are either available as licensed products or in clinical trials at various stages. These are: raltitrexed (Tomudex); nolatrexed, LY231514, a multi-targeted antifolate (MTA), and ZD9331. As well as displaying interesting clinical activity, these new drugs also illustrate the principles of rational drug design being used to explore and exploit the features of folate metabolism.

Although 5-FU inhibits TS, it also has major effects in other pathways, as well—in particular, RNA metabolism. Specific TS blockade is therefore not achieved. Also, as TS inhibition causes an increase in intracellular dUMP pools, dUMP will eventually compete with 5-FU for binding to TS. In contrast, folate-based inhibitors have distinct advantages; they can inhibit TS without significantly influencing other folate-dependent enzymes. Additionally, dUMP enhances the binding of folate analogs to TS.

**Raltitrexed (TOM)**

Raltitrexed, a water-soluble antifolate agent, is a specific inhibitor for TS. Being a classical antifolate, it possesses a terminal glutamate residue which is converted to a polyglutamate form in the cell. Polyglutamates tend to be significantly more potent than monoglutamates as enzyme inhibitors and are also retained in the cell for long periods. Potential causes of resistance to the drug would arise from the fact that it requires a specific transport protein to cross the cell membrane, as well as the fact that it functions as a prodrug for its polyglutamate form [52]. Pharmacokinetic studies indicate a triphasic elimination with a wide range in the mean terminal half-life (8.2-105 h). There is a linear relationship between the dose and both the AUC and the maximum concentration, although there is no clear association between these parameters and either clinical response or toxicity.

In the clinical setting, a reasonable side-effect profile from phase I [53] and a promising overall response rate (26%) in patients with advanced colorectal cancer in phase II studies, led to the initiation of three randomized phase III trials [54-56]. The European trial [54] compared TOM with 5-FU/LV administered using the “Mayo” schedule. In 439 patients, this study showed no significant difference between the two treatments in terms of response rate (19% versus 17%), median survival (10.3 months), or time to progression (4.7 versus 3.6 months). The North American trial made the same comparison in 459 patients [55]. The response rate for the two treatments at 12 months’ follow-up was comparable (14% and 15% respectively), although the median survival time was significantly shorter for the TOM treatment group (9.7 versus 12.7 months). The international trial that compared TOM with 5-FU/LV (“Machover schedule”) in 495 patients reported comparable response rates (19% versus 18% respectively) and median survival times (10.7 versus 11.8 months) for the two treatments [56]. Raltitrexed appears to have an advantage in terms of less myelotoxicity and mucositis, but a disadvantage in terms of transaminitis (reversible), nausea and sometimes prolonged asthenia, as compared with 5-FU. The use of alternative doses and schedules (apart from the 3 mg/m\(^2\) bolus every three weeks) has not been widely explored, although the 4 mg/m\(^2\) bolus every three weeks schedule was found to be too toxic in one of the phase III trials reported above [55].

A Pan-European Intergroup Trial (PETACC-1) has been launched to compare 5-FU/LV (“Mayo”) versus TOM in an adjuvant setting for stage Duke’s C colon cancer. In the meantime, the Medical Research Council of the United Kingdom is conducting a study comparing TOM with two different 5-FU schedules (“de Gramont”—a bi-monthly bolus and CI 5-FU/LV 48-h regimen [57] and Protracted Venous Infusion-PVI 5-FU [58]) in the advanced disease setting. The recruitment of just over 900 patients, which is now complete, will hopefully provide firmer conclusions in relation to TOM’s place in the management of advanced CRC. However, preliminary results from the above study
suggest that TOM may be inferior to infusional 5-FU in terms of treatment-related deaths, progression-free survival, and QOL [59].

Nolatrexed (Thymitaq, AG337)

Nolatrexed is a water-soluble lipophilic inhibitor of TS which does not have glutamate side chains and can enter the cell by passive diffusion. This makes it different from other antifolates such as TOM or MTA (see below). It has a short plasma half-life, and since it cannot form polyglutamates and thus be retained in cells, this necessitates a prolonged (5-day) infusion. Its spectrum of toxicities is more similar to 5-FU than TOM, with myelosuppression and mucosal toxicity being dose-limiting [60]. Limited activity in colorectal and pancreatic cancer has been observed [61, 62], deserving further evaluation. More recently, while in phase II evaluation, nolatrexed was withdrawn from further clinical study; the reasons for this are not as yet clear.

LY231514—MTA

MTA has multiple targets in the folate pathway. It causes inhibition of a range of enzymes involved in folate metabolism, the most important being TS, dihydrofolate reductase (DHFR), human monofunctional glycaminide ribonucleotide formyltransferase (hGARFT), and aminomimidazole carboxamide ribonucleotide formyltransferase (AICARFT). MTA is transported across the cell membrane using the reduced folate carrier system (like TOM) and has low affinity to folate receptors, as well as being an excellent substrate for the enzyme FPGS.

In phase I studies its DLT were neutropenia and thrombocytopenia for all schedules tested [63]. Other side effects included mucositis, rashes, and transient elevation of transaminases. The three-weekly schedule (minor responses seen in six patients with colorectal cancer) was chosen for phase II evaluation in breast and colorectal cancer. Early results indicate encouraging activity in colorectal cancer, with responses in the range of 15%-17% in a total of just over 70 patients [64, 65].

ZD9331

This molecule is of particular interest because of its unique preclinical profile. It is a potent TS inhibitor, while neither being lipophilic nor polyglutamated [66]. It is currently undergoing phase I studies, displaying an extremely long half-life in the range of 70 to 120 hours. No phase II data are as yet available.

CONCLUSION

Until recently, 5-FU was the only available drug with moderate but nevertheless consistent activity in CRC. Biochemical modulation and new administration schedules have occasionally led to improved response rates and a more favorable side-effect profile, but have not really had a significant impact on survival. Several new drugs have now become available and are in various stages of development. The 5-FU prodrugs may be used either A) to allow a more convenient schedule (e.g., oral therapy), or B) to exploit a tumor-specific prodrug-activating enzyme. Of these, UFT, capecitabine, and S-1 have shown interesting response rates in phase II studies, and early results from ongoing phase III studies (for the first two agents) are encouraging. Their potential advantages in terms of ease of administration and possible improved therapeutic index may have a significant impact on their future use. At the very least, the above agents offer an alternative simplified strategy for achieving protracted exposure to fluoropyrimidine chemotherapy, eliminating the need for indwelling catheters and special infuser pumps. This would make outpatient treatment much more feasible and might have a significant impact on the patient’s QOL as well as healthcare costs. The biochemical modulator ethinyluracil, also allows the oral administration of 5-FU and has the potential to overcome one of 5-FU’s resistance mechanisms; however, results of phase III clinical trials are not yet available. Among the new antifolates, raltitrexed is in the most advanced stage of development. It does not appear to be more effective than 5-FU/LV as first-line treatment, although its convenient schedule may suggest a possible role in future combination treatments.

All of the agents described above have TS as their primary target. It is quite likely that even the most optimal TS inhibition will have its limitations in terms of clinical efficacy. A combination of TS inhibitors with agents that have a different mechanism of action seems a logical approach. Two drugs that may well fulfill this role are irinotecan (CPT-11)—a topoisomerase-1 inhibitor [67], and oxaliplatin—a new DACH platinum compound with a favorable side-effect profile [68]. Both agents have shown activity in first- and second-line treatment either by themselves or in combination with various schedules of 5-FU/LV [69, 70]. Preliminary phase III data are already available, indicating the superiority of both agents in combination with 5-FU over 5-FU alone [71, 72]. It is quite clear that we are entering a new era in the treatment of colorectal cancer, with new agents likely to change the so far standard 5-FU/LV combinations that have dominated the landscape of CRC treatment for the past decade. The use of these new cytotoxic agents together with the advent of novel biologic therapies will hopefully translate into a significant and meaningful survival advantage for this group of patients.
REFERENCES

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