The Evolution of Fluoropyrimidine Therapy: From Intravenous to Oral

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ABSTRACT

Chemotherapy for advanced colorectal cancer is based on i.v. 5-fluorouracil (5-FU). Numerous attempts have been made to increase the therapeutic benefit of 5-FU through schedule modification and biomodulation, but only modest improvements have been achieved. Capecitabine is an oral fluoropyrimidine that was developed in response to the clinical need for new therapeutic options offering improved efficacy, tolerability, and convenience for patients. Capecitabine was rationally designed to mimic continuous infusion 5-FU. It is rapidly and almost completely absorbed through the gastrointestinal wall and is converted to 5-FU via a three-step enzymatic cascade. 5-FU is generated preferentially in tumor by exploiting the higher activity of thymidine phosphorylase in tumor tissue compared with normal tissue. Results of a randomized, phase II trial led to the selection of a regimen of capecitabine for further clinical development (1,250 mg/m² twice daily for 14 days followed by a 7-day rest period). Subsequently, two large, randomized, phase III trials were conducted to compare capecitabine with i.v. bolus 5-FU/leucovorin ([LV]; Mayo Clinic regimen) in patients with metastatic colorectal cancer. A prospective, integrated analysis of data from the studies showed that capecitabine offers superior activity and an improved safety profile compared with 5-FU/LV. This article summarizes these developments in the treatment of colorectal cancer and assesses the feasibility of replacing i.v. 5-FU-based therapy with oral capecitabine. In addition, retrospective analyses assessing the impact of the dose modification scheme on the efficacy and tolerability of capecitabine are presented, and dose recommendations in special populations are reviewed. The Oncologist 2001;6(suppl 4):3-11

INTRODUCTION

The treatment of advanced colorectal cancer currently involves surgery, radiotherapy, and/or chemotherapy. The principal aims of therapy are to relieve tumor-related symptoms (such as pain, gastrointestinal symptoms, and shortness of breath), to induce remission and halt progression, and ultimately to improve survival, while maintaining or improving patients’ quality of life. Since the introduction of 5-fluorouracil (5-FU), chemotherapeutic options have changed substantially with the development of regimens offering improved efficacy. More recently, advances have included the introduction of new agents, such as irinotecan and oxaliplatin, and the development of more convenient oral alternatives to i.v. therapies. This article traces the evolution of fluoropyrimidine-based chemotherapy for colorectal cancer from 1957 to the present.

The Early Use of 5-FU

Since its synthesis in 1957, the fluoropyrimidine 5-FU has remained the most extensively used chemotherapeutic agent in the treatment of advanced colorectal cancer. Early trials of 5-FU as first-line therapy for colorectal cancer demonstrated response rates ranging from 8% to 85%. Reasons for this wide variation between trials include differences in patient selection, disease-related aspects, variations in regimen, and lack of accurate imaging techniques [1, 2]. In general, response rates tended to fall in the low end of the spectrum and efficacy was limited.
Other chemotherapeutic agents available at the time, such as the nitrosoureas and mitomycin C, offered no improvements in efficacy when used alone or in combination with 5-FU. These compounds were also associated with frequent hematologic and renal toxicities [3-7] and consequently were not incorporated into standard chemotherapy regimens. With such limited therapeutic options, treatment for colorectal cancer tended to be nihilistic, few advances were made, and the outlook for patients with colorectal cancer was poor.

5-FU SCHEDULE MODIFICATION

Following the failure of earlier strategies to increase the therapeutic benefit of 5-FU, studies were conducted in the 1980s to investigate modification of the dosing schedule. A key trial by Lokich et al [8] compared administration of 5-FU by i.v. bolus or continuous infusion, and demonstrated that the latter resulted in improved efficacy. A subsequent meta-analysis of six randomized trials involving 1,219 patients showed that protracted infusion significantly increased the response rate compared with bolus 5-FU (22% versus 14%; p < 0.0002), but was associated with only a modest survival benefit (12.1 versus 11.3 months; p < 0.04) [9]. The meta-analysis also indicated that the method of administration of 5-FU affected the safety profile of the drug [10]. The protracted infusion regimen was associated with a greater incidence of hand-foot syndrome (13% versus 34%), but a substantial reduction in the incidence of grade 3/4 neutropenia (31% versus 4%). The introduction of pumps and implantable catheter systems has since enabled ambulatory continuous 5-FU infusion, thus avoiding lengthy hospitalizations for administration of therapy. Nevertheless, protracted infusion administration is associated with considerable inconvenience and disruption of daily activities for patients.

BIOMODULATION OF 5-FU

Another strategy explored in an attempt to increase the efficacy of 5-FU was biomodulation. A number of biomodulators have been investigated with varying degrees of success. The administration of 5-FU with either N-phosphonacetyl-L-aspartic acid or interferon failed to improve efficacy [11-14], and consequently investigation of these combinations was abandoned. In contrast, several studies and a meta-analysis have shown that sequential administration of methotrexate and 5-FU increases efficacy compared with 5-FU monotherapy [15, 16]. However, this approach was never widely adopted, possibly because of the known schedule dependency of methotrexate and 5-FU, including antagonism if methotrexate is not administered at an appropriate interval prior to 5-FU administration.

The only biomodulator to become widely adopted is leucovorin (LV). A meta-analysis of randomized studies comparing 5-FU alone with 5-FU/LV demonstrated that the addition of LV was associated with a significant improvement in response rate [17]. However, there was no significant improvement in overall survival. Nevertheless, the use of 5-FU/LV therapy has become widespread during the past decade, and a number of 5-FU/LV regimens have been evaluated in an attempt to identify a regimen capable of improving survival. However, no regimen has been shown to significantly improve survival, and no international consensus on the optimal schedule has been established. Consequently, the schedules currently used in each country tend to be those developed in that particular country. Generally, infusion regimens tend to be favored in Europe for their improved safety/efficacy profiles, whereas bolus 5-FU is used in the U.S. because of the ease of administration.

In 1993, a pivotal publication confirmed the utility of fluoropyrimidine-based chemotherapy for metastatic colorectal cancer [18]. Overall survival was almost doubled in patients receiving chemotherapy comprising bolus 5-FU/LV plus cisplatin and supportive care compared with those receiving supportive care alone (11.0 versus 5.0 months; p = 0.006). As cisplatin has little activity in colorectal cancer, the survival benefit observed in this study is most likely due to 5-FU/LV.

NEW AGENTS IN COLORECTAL CANCER THERAPY

The last decade of the 20th century witnessed the introduction of novel agents with mechanisms of action other than thymidylate synthase inhibition. Irinotecan, a topoisomerase I inhibitor, demonstrated a survival benefit over both best supportive care and infused 5-FU as second-line monotherapy in patients whose disease had progressed with prior 5-FU [19, 20] and as first-line treatment when added to 5-FU/LV [21, 22]. Oxaliplatin, a platinum derivative, also demonstrated improved activity as first- and second-line treatment for metastatic colorectal cancer when administered in combination with 5-FU/LV [23-27]. Data for both of these agents are discussed in detail in later articles.

ORAL FLUOROPYRIMIDINES

Another important advance in the treatment of colorectal cancer was the development of novel oral fluoropyrimidines. These agents were designed to overcome the problems seen with i.v. fluoropyrimidine therapies, which are highlighted in the next article and include medical complications and inconvenience associated with (central) venous access. The unpredictable and highly variable
bioavailability of 5-FU makes it unsuitable for oral administration. As a result, two strategies have been explored in the development of oral agents. The first approach is to combine an oral fluoropyrimidine, such as tegafur, with a substrate of dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme in the catabolism of 5-FU. Uracil (a component of UFT), eniluracil, and CDHP (a component of S-1) all inhibit DPD, thus reducing the rate of 5-FU catabolism. UFT (a combination of uracil plus tegafur) in combination with LV is the most extensively evaluated of the DPD-inhibiting therapies: two randomized, phase III trials have compared UFT/LV with i.v. bolus 5-FU/LV in patients with metastatic colorectal cancer, and phase III data are described in the following article. Although UFT/LV had an improved safety profile compared with 5-FU/LV, doubts remain as to the efficacy of this drug. More recently, phase III data for eniluracil have been presented. In one of the two phase III trials, eniluracil resulted in significantly inferior overall survival (hazard ratio 0.770, median overall survival: 10.9 versus 14.6 months with eniluracil/5-FU and 5-FU/LV, respectively) [28]. In the second phase III trial, eniluracil/5-FU failed to achieve statistically equivalent overall survival compared with 5-FU/LV [29]. Consequently, the development of eniluracil has been abandoned. No phase III data for S-1 have been reported. Complete DPD inhibition has in some cases resulted in fatal toxicity when patients are rechallenged with 5-FU before DPD activity has fully recovered. In summary, based on the low antitumor activity observed in clinical trials, it would appear that the DPD inhibitors have not fulfilled their potential.

The second approach, illustrated by capecitabine, is the design of a molecule that precludes activation within the gut, thereby reducing local toxicity. Capecitabine is rapidly and almost completely absorbed in the upper gastrointestinal tract as an intact molecule [30]. Capecitabine is then converted to 5-FU via a three-step enzymatic cascade. The enzyme that mediates the final step in the conversion process, thymidine phosphorylase, is significantly more active in tumor tissue than in normal tissue, resulting in tumor-selective generation of 5-FU [31, 32]. Capecitabine has been evaluated extensively in metastatic colorectal cancer, and data from clinical trials are discussed below.

**Clinical Development of Capecitabine**

The optimal regimen of capecitabine was identified in a randomized, phase II study, which included 109 patients with advanced/metastatic colorectal cancer [33]. The study compared three capecitabine regimens: the intermittent capecitabine monotherapy regimen (1,255 mg/m² twice daily, days 1-14 followed by a 7-day rest period; n = 34), continuous capecitabine monotherapy (666 mg/m² twice daily without interruption; n = 39), or intermittent capecitabine in combination with LV (capecitabine 829 mg/m² twice daily plus LV 30 mg twice daily, both administered on days 1-14 followed by a 7-day rest period).

All three regimens resulted in encouraging response rates of 21%-24%. However, the median time to disease progression was favorable with intermittent capecitabine monotherapy (7.5 months) compared with either continuous capecitabine monotherapy (4.2 months) or capecitabine plus LV (5.4 months). Intermittent monotherapy showed an acceptable safety profile, and had a wider therapeutic index, as determined by a linear regression analysis of dose versus toxicity in the corresponding phase I trials. In addition, the inclusion of a drug-free period in the intermittent schedule was considered more appealing to patients. The addition of LV to capecitabine did not appear to improve efficacy and may compromise an otherwise favorable safety profile. Therefore, the regimen of intermittent capecitabine monotherapy at a dose of 1,250 mg/m² twice daily for 14 days followed by a 7-day rest period was selected by the investigators for further clinical development.

**Efficacy of Oral Capecitabine**

Two large, randomized, phase III trials were conducted to compare intermittent capecitabine monotherapy with bolus i.v. 5-FU/LV (Mayo Clinic regimen) in patients with advanced/metastatic colorectal cancer [34, 35]. These trials were identical in terms of study design, patient selection criteria, conduct, and monitoring, and both were powered to show equivalence in response rates, the primary endpoint. It was predefined in both protocols that the data would be pooled to obtain information on a larger patient population. Therefore, a prospective analysis of the integrated results from the two studies was performed [36], and is reported below.

In total, 1,207 patients were randomized to receive either capecitabine (1,250 mg/m² twice daily for 14 days followed by a 7-day rest period; n = 603), or i.v. 5-FU/LV (LV 20 mg/m² followed by 5-FU 425 mg/m² administered as an i.v. bolus on days 1-5 every 28 days; n = 604). The Mayo Clinic regimen was chosen as the comparator because it is used widely and was required by the Food and Drug Administration in the U.S. as the reference treatment in regulatory trials. The patients’ baseline characteristics (such as gender, age, performance status, predominant metastatic site, and prior adjuvant treatment) were well balanced between the two study arms.
The primary endpoint, tumor response rate, was significantly superior in patients treated with capecitabine compared with patients receiving 5-FU/LV (26% versus 17%; \( p < 0.0002 \)). In addition, when response rates were analyzed by subpopulation, capecitabine therapy resulted in consistently superior response rates compared with 5-FU/LV, as shown in Figure 1. The superior tumor response rate was particularly pronounced among the subpopulation of patients who had received prior adjuvant treatment with 5-FU. Most responses in both treatment arms occurred early in the course of therapy.

Capecitabine was at least equivalent to 5-FU/LV in terms of time to disease progression, with a median of 4.6 months versus 4.7 months, respectively. Furthermore, overall survival was at least equivalent with capecitabine, with a median of 12.9 months in the capecitabine group and 12.8 months in the 5-FU/LV group. The Kaplan-Meier plot of overall survival is shown in Figure 2.

**Figure 1. Subpopulation response rates.**

The oral capecitabine contains less active metabolites than the parent compound, 5-FU, resulting in a lower incidence of nausea and vomiting, and a decreased risk of mucositis. Capecitabine was generally well tolerated, with a safety profile typical of infused fluoropyrimidines. The majority of treatment-related adverse events in patients receiving capecitabine were mild to moderate in intensity and were manageable with treatment interruption or, if necessary, dose reduction. Of the seven treatment-related clinical adverse events most commonly associated with fluoropyrimidine

\[ \text{Capecitabine (n = 603)} \]
\[ \text{5-FU/LV (n = 604)} \]

\( \* p < 0.05 \)
\( \dagger \) Predominant site of metastases; KPS = Karnofsky performance score

**Figure 2. Overall survival curves for capecitabine versus i.v. 5-FU/LV.**
therapy, four (stomatitis, diarrhea, nausea, and alopecia) occurred significantly less frequently with capecitabine than with 5-FU/LV, as shown in Figure 3. Vomiting and fatigue occurred at similar rates in both groups. Only the cutaneous condition, hand-foot syndrome, which affects principally the palms of the hands and the soles of the feet and is characteristic of infused fluoropyrimidine therapy, was more common in patients receiving capecitabine. However, this localized symptom rarely required hospitalization and is per se never life-threatening. As with other adverse events, hand-foot syndrome was effectively managed with treatment interruption and, if necessary, dose modification.

The most frequent grade 3/4 treatment-related adverse events were hand-foot syndrome (17% grade 3) and diarrhea (12% grade 3, 2% grade 4) in the capecitabine group and diarrhea (10% grade 3, 2% grade 4) and stomatitis (14% grade 3, 1% grade 4) in patients receiving 5-FU/LV. The incidence of grade 3/4 stomatitis was significantly lower in patients receiving capecitabine than in those treated with 5-FU/LV, whereas hand-foot syndrome was significantly less common in the 5-FU/LV group.

The analysis of hematologic parameters revealed that neutropenia was significantly less common in patients receiving capecitabine compared with 5-FU/LV (2.2% versus 21.2% respectively; \( p < 0.0001 \)), resulting in a significantly lower incidence of neutropenic fever and sepsis (0.2% versus 3.4%; \( p < 0.0001 \)) and associated hospitalizations. Hyperbilirubinemia, which appears to be a class effect of oral fluoropyrimidines, was more common in patients receiving capecitabine (grade 3/4 \( 1.5-3/3 \times \text{upper limit of normal}; 18.3\% \text{versus} 3.4\% \)), but tended to be an isolated laboratory abnormality affecting almost exclusively the indirect bilirubin, with no concurrent elevation of transaminases or alkaline phosphatase and few, if any, clinical repercussions. In addition, patients with elevated bilirubin at baseline did not experience a higher incidence of adverse events compared with the overall patient population. There was no evidence of renal toxicity with capecitabine.

Consistent with the improved safety profile of capecitabine, the incidence of treatment-related hospitalizations was significantly lower with capecitabine than with 5-FU/LV (12% versus 18%, respectively; \( p < 0.005 \)). Similarly, the number of treatment-related hospitalizations was significantly lower with capecitabine than with 5-FU/LV (76 versus 113, respectively; \( p < 0.005 \)). In the 5-FU/LV group, stomatitis and neutropenic fever/sepsis led to hospitalization in 21 and 17 patients, respectively, compared with only one patient each in the capecitabine arm. In contrast, hand-foot syndrome, the most common adverse event associated with capecitabine, led to hospitalization of only two patients in the capecitabine group, both for <24 hours.

**CAPECITABINE DOSE MODIFICATION**

All phase II/III clinical trials of capecitabine have included a standard capecitabine dose modification scheme, which involves treatment interruption in the event of grade 2 or more severe toxicities, and, if necessary, dose reduction (Table 1). The aim of dose modification is to reduce the risk of development to more serious toxicities and avoid the recurrence of toxicities, while maintaining efficacy at an individually adjusted

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**Figure 3. Most common treatment-related clinical adverse events (all grades).**

![Graph showing treatment-related clinical adverse events](http://theoncologist.alphamedpress.org/Downloaded from)

*\( p < 0.001 \)
dose level. The oral administration of capecitabine enables treatment interruption at the first appearance of a moderate or severe toxicity, and the twice-daily dosing schedule provides numerous opportunities for treatment interruption and, if necessary, dose reduction.

The integrated analysis of the two phase III trials provided an opportunity to assess the impact of the capecitabine dose modification scheme on the efficacy and tolerability of capecitabine in a large, well-characterized patient population. The majority of patients in the capecitabine group did not require dose modification from the standard starting dose, with fewer patients requiring dose reduction in the capecitabine group than in the 5-FU/LV group (34% versus 42%, respectively; \( p = 0.0037 \)) [37]. In addition, dose modification occurred later in the capecitabine group than in the 5-FU/LV group. The median time to dose reduction (to 75% of baseline capecitabine dose or 70%-80% of baseline 5-FU dose) was 2.5 months in the capecitabine group compared with 1.2 months with 5-FU/LV. An important implication of the later dose modification seen with capecitabine is that side effects are avoided in patients who do not ultimately respond.

The adverse events most commonly leading to dose modification were hand-foot syndrome and diarrhea in the capecitabine group and stomatitis and diarrhea in the 5-FU/LV group, reflecting the most common grade 3/4 adverse events in each treatment group. The capecitabine dose modification scheme was effective in avoiding the recurrence of adverse events. For example, following dose reduction for stomatitis, only 20% of patients with grade 2/3 stomatitis experienced a grade 2 recurrence, and there was no further grade 3 stomatitis.

Further analysis demonstrated that the efficacy of capecitabine was maintained in patients requiring dose modification for adverse events. There was no increase in the risk of disease progression or death in patients requiring dose modification compared with those who did not require dose adjustment (hazard ratio = 0.97). However, the corresponding hazard ratio in the 5-FU/LV group was 1.12, meaning that the risk of disease progression was increased by 12% in patients requiring dose reduction compared with those whose dose was not reduced. For patients in the 5-FU/LV group requiring a second-level dose reduction, the risk of disease progression was increased by 30% (both not significant).

These analyses demonstrated that the dose modification scheme is an important facet of capecitabine treatment, enabling adjustment to each patient’s individually tolerable dose, if necessary. To implement the dose modification scheme effectively, patient education is essential. All patients prescribed capecitabine should be educated to recognize its side effects and their severity, and should be fully aware of the consequences of ignoring them. Patients should be instructed to interrupt their treatment if moderate or more severe toxicities develop, and to seek further advice from their oncology team (doctor, nurse, or pharmacist) if necessary. Patients should be reassured that efficacy will not be compromised if their treatment is interrupted or the dose modified. Follow-up procedures, such as telephone calls to remind patients of the appropriate course of action if they experience grade 2 or more severe adverse events, have been effective in improving the safety profile of capecitabine. Current trials are exploring dose reduction at the first occurrence of grade 2 toxicities with the aim of further improving the safety profile of capecitabine.

**Capecitabine in Special Populations**

Retrospective analyses were also performed for special patient populations potentially at higher risk of developing

<table>
<thead>
<tr>
<th>NCIC CTC toxicity grade</th>
<th>Appearance</th>
<th>Adjustment during therapy</th>
<th>Adjustment for next cycle (relative to initial dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1st</td>
<td>Interrupt until resolved to grade 0 or 1</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>Interrupt until resolved to grade 0 or 1</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>3rd</td>
<td>Interrupt until resolved to grade 0 or 1</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>4th</td>
<td>Discontinue drug permanently</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1st</td>
<td>Interrupt until resolved to grade 0 or 1</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>Interrupt until resolved to grade 0 or 1</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>3rd</td>
<td>Discontinue drug permanently</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1st</td>
<td>Discontinue drug permanently or interrupt until resolved to grade 0 or 1*</td>
<td>50% (*)</td>
</tr>
</tbody>
</table>

*At the discretion of the clinician*
side effects. Estimated creatinine clearance is usually calculated using the Cockcroft and Gault formula (given below [38]), in which the principal factors leading to low creatinine clearance are old age, low body weight, and high serum creatinine concentrations.

\[
\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}
\]

*for females, \( \times 0.85 \)

Subpopulation analysis of the safety data, with patients grouped according to their calculated creatinine clearance, revealed that the safety profiles of capecitabine and 5-FU/LV differed quantitatively. In both treatment arms, the incidence of grade 3/4 adverse events was higher in patients with moderate renal impairment (calculated creatinine clearance 30-50 ml/min) than in those with normal (calculated creatinine clearance ≥80 ml/min) or mildly impaired renal function (calculated creatinine clearance 51-80 ml/min). Correspondingly, dose reductions were more frequent in patients with moderate renal impairment, independent of treatment. In patients receiving capecitabine, the response rate was consistently 24%-27% in patients with normal, mildly impaired, or moderately impaired renal function, whereas in the 5-FU/LV group, the response rate fell to 10% in patients with moderate renal impairment.

A separate, pharmacokinetic study demonstrated that the area under the curve of the key capecitabine metabolite and immediate 5-FU precursor, 5′-deoxyfluorouridine (5′-DFUR), was increased by 35% in patients with moderate renal impairment compared with those with normal renal function [39]. These data support a reduction to 75% of the standard starting dose in patients with moderately impaired renal function at baseline, thus aiming for the same systemic exposure in patients with moderate renal impairment as in patients with normal renal function. The renal impairment guidelines for capecitabine administration are summarized in Table 2. Of note, 5-FU/LV did not provide a safer alternative in patients with renal impairment, in whom it also appeared to be less active. There was a trend toward a higher incidence of hand-foot syndrome and grade 4 adverse events in older patients, therefore, renal impairment guidelines, which take age into account, also provide for dose reduction in older, more fragile patients.

### Table 2. Capecitabine renal impairment guidelines

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Calculated creatinine clearance (ml/min)</th>
<th>Starting dose (mg/m² twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>&gt;80</td>
<td>1,250</td>
</tr>
<tr>
<td>Mild</td>
<td>51-80</td>
<td>1,250</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-50</td>
<td>950</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;30</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

Capecitabine offers a superior response rate and at least equivalent time to disease progression and survival compared with i.v. 5-FU/LV as first-line therapy for metastatic colorectal cancer. Oral capecitabine also offers improved convenience and an improved safety profile compared with i.v. 5-FU/LV, with significantly lower incidences of diarrhea, stomatitis, nausea, and alopecia. In addition, capecitabine is associated with a significantly lower incidence of grade 3/4 stomatitis and grade 3/4 neutropenia, leading to significantly less grade 3/4 neutropenic fever/sepsis and fewer associated hospitalizations. Capecitabine is associated with a higher incidence of hand-foot syndrome, but this side effect is never life threatening, rarely leads to hospitalization or treatment withdrawal, and can be effectively managed with treatment interruption and, if necessary, dose reduction. Dose modification to each patient’s individually tolerable dose is possible if patient education programs are implemented effectively and patients are able to recognize the appearance and severity of adverse events, in the knowledge that dose reduction will not compromise the efficacy of capecitabine.

**THE FUTURE OF FLUOROPYRIMIDINE THERAPY**

Current clinical research is focusing on the identification of molecular markers potentially predictive for efficacy and safety, enabling optimal treatment of an individual patient. Researchers are also assessing triple-drug combinations (e.g., fluoropyrimidines, oxaliplatin, and irinotecan). Numerous novel agents directed at new targets, such as endothelial growth factor, vascular endothelial growth factor, and tyrosine kinase are also being explored. The number of treatment options for metastatic colorectal cancer has increased since the synthesis of 5-FU in 1957, and the outlook for patients is more promising, with the concept of effective and well-tolerated, all-oral chemotherapy finally becoming a reality.

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