Oral Chemotherapeutic Agents for Colorectal Cancer

SUNIL SHARMA, a LEONARD B. SALTZ a,b

a Gastrointestinal Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, USA; b Department of Medicine, Weil Medical College, Cornell University, New York, New York, USA

Key Words. Oral chemotherapy · Colon cancer · Rectal cancer · Economic analysis · Patient compliance

ABSTRACT

A number of novel oral chemotherapeutic agents are entering practice or are under development in the United States. Many of these agents display significant clinical activity against colorectal cancer. Many classes of compounds, including fluoropyrimidine analogs, dihydropyrimidine dehydrogenase (DPD) inhibitors, topoisomerase inhibitors, farnesyl transferase inhibitors, and others, are being developed for oral administration. This manuscript describes the progress of clinical development of these agents and also explores the relative merits and challenges of these approaches. Economic issues, patient preference, and patient selection issues surrounding oral chemotherapy for colorectal cancer will also be discussed. The Oncologist 2000;5:2:99-107

INTRODUCTION

Colorectal cancer is the second most common cause of cancer mortality in the United States. It has been estimated that 129,400 new cases will be diagnosed in 1999 [1]. Colorectal cancer can be cured in the early stages and in selected patients with advanced disease by definitive resection, however, chemotherapy for advanced and metastatic disease remains disappointing. Treatment of metastatic colorectal cancer with chemotherapy is a palliative approach. Complete responses to front-line chemotherapy are rarely observed, and partial responses are observed in less than 25% of patients [2]. With the recent introductions of irinotecan and oxaliplatin, there has been an extension of the repertoire available to the clinician. However, all of these agents can have significant toxicity (gastrointestinal toxicity, myelosuppression, and neurotoxicity) and require repeated clinical visits and/or infusion pumps for administration on a long-term basis.

RATIONALE FOR ORAL CHEMOTHERAPY IN COLORECTAL CANCER

There has been interest in development of oral chemotherapy agents for cancer therapeutics for a long period of time, beginning with the development of agents such as busulfan and hydroxyurea. Administration of oral chemotherapy has several potential advantages. These include the potential for greater patient convenience and acceptance and significant cost savings, both in terms of treatment costs and lost wages incurred by patients and family during physician visits [3]. There is evidence that with regular patient education and monitoring, adequate patient compliance to oral medications can be achieved, although issues of compliance and safety remain a concern [4]. Recently, there has been a surge in the development of oral therapies for colorectal cancer. We present an overview of several such drugs in various stages of clinical development.

NOVEL FLUOROPYRIMIDINES AND DIHYDROPYRIMIDINE DEHYDROGENASE (DPD) INHIBITORS

Fluoropyrimidines, for example, 5-fluorouracil (5-FU) and fluorodeoxyuridine (FUDR), have been successfully used in the treatment of colorectal cancer for more than four decades. Currently, there are several oral fluoropyrimidines in clinical practice or in advanced stages of development.

Capecitabine

Capecitabine (XelodaTM, Roche Pharmaceuticals; Nutley, NJ) is an oral fluoropyrimidine that is now commercially available. It is a prodrug of 5-FU and is absorbed intact from the intestine. It is converted to doxifluridine by the sequential action of acylamidase isoenzyme A and cytidine deaminase in the liver. The latter enzyme is also present in tumor tissue. Doxifluridine, in turn, is converted to 5-FU in normal and tumor tissue by thymidine phosphorylase (TP) [5], and levels...
of TP are higher in some tumor tissues than in normal tissues. In some human tumor xenograft models, capecitabine seemed to be more effective as compared to 5-FU [6]. Antitumor activity was reported in a fluorouracil-resistant xenograft model [7]. There seemed to be a higher degree of 5-FU in the tumor as compared to healthy tissue after capecitabine administration to colorectal cancer patients [8]. This may also be due to higher levels of TP present in tumor tissues [9]. Major toxicities in phase I trials have included diarrhea, palmar-plantar erythrodysesthesia (hand-foot syndrome), nausea, vomiting, dizziness, and stomatitis [10, 11]. Myelosuppression was not seen in these phase I trials to any appreciable degree. In pharmacokinetic studies, capecitabine displayed linear pharmacokinetics with good gastrointestinal absorption [12]. Recently, preliminary results of a three-arm, randomized phase II trial of capecitabine on continuous and intermittent schedules and, as a third arm, in combination with leucovorin were reported [13]. The study demonstrated comparable efficacy in all arms with several complete responses. Moderate toxicity was observed in all arms, with hand-foot syndrome, stomatitis, and diarrhea being the most commonly observed toxicities. Based on these studies, the intermittent schedule (14 of 21 days) without leucovorin was taken into phase III trials. The recommended phase II dose of 2,500 mg/m²/day in twice-a-day divided doses, for two of three weeks has been developed for therapeutic use. In the European phase III trial [14], 602 untreated colorectal patients with metastatic disease were randomized to receive either capecitabine or 5-FU/leucovorin on the daily × 5 (one tablet a day for five consecutive days) Mayo regimen. There was a higher response rate in the capecitabine arm (26.6% versus 17.9%, p = .013), although the response duration and progression-free survival were comparable in both arms. In addition, the complete response (CR) rate was also similar in both arms (2.3%). While hand-foot syndrome and diarrhea were more common with capecitabine, neutropenia and its attendant complications were more common in the 5-FU/leucovorin control arm. In the United States, phase III trial [15], 605 patients were randomized to the identical arms as above. Again, the response rates were higher in the capecitabine arm (23.2% versus 15.5%, p = .02) but this did not translate into higher CR rates, duration of response, or progression-free survival. Similar toxicity data were obtained as in the European trial. Capecitabine has been approved for treatment of metastatic breast cancer by the Food and Drug Administration, and combination trials of capecitabine are planned. It seems from the above data that use of capecitabine as a single agent in the first-line treatment of colorectal cancer could be a consideration, although the final word will have to be postponed until broader experience has been obtained and peer review publications are examined.

**UFT**

UFT (Orzel™, Bristol Myers Squibb; Princeton, NJ) is a combination of tegafur, a prodrug of 5-FU, and uracil in a molar ratio of 1:4. Tegafur is converted to 5-FU by hepatic cytochrome P450 pathway [16], whereas uracil enhances the half-life of converted 5-FU by competing for its degradation by DPD, which is the rate-limiting enzyme in the catabolism of 5-FU. This leads to higher intracellular concentrations of 5-FU with increased antitumor activity in preclinical models [17] and in tumor tissues when given to humans [18].

Tegafur has been approved for clinical use in Japan, and it had a response rate of 10% in advanced gastrointestinal malignancies [19]. Clinical utility of tegafur has been limited because of the neurologic toxicity observed. This can manifest as depression, anosmia, headache, and dizziness. This neurotoxicity is due to an inactive metabolite generated during conversion of tegafur to 5-FU. Since uracil greatly reduces the amount of tegafur used, the amount of this metabolite becomes negligible.

Phase I trials of UFT were initially conducted in Japan and subsequently in the United States. In the United States trials, UFT was evaluated most commonly as a three times daily dose given for 5 of 21 or 28 of 35 to 42 days [20-22]. The most common toxicities were myelosuppression on the five-day schedule and diarrhea on the 28-day schedule. No neurotoxicity was observed. When administered on a 28-day schedule, plasma concentrations of 5-FU were comparable to those achieved with continuous intravenous administration. No neurotoxicity was seen.

Because of enhancement of antitumor activity of 5-FU with simultaneous administration of leucovorin and similar enhancement of UFT activity in animal models [23], UFT was next evaluated in combination with oral leucovorin in phase I trials. In two trials using the 28-day UFT regimen, diarrhea was dose limiting. Several phase II trials of UFT have now been reported in colorectal cancer and are summarized in Table 1. As seen from the table, UFT was well tolerated in combination with calcium folinate, and toxicity was proportional to administered dose. In addition, there was evidence of moderate activity in each of these schedules [24]. Based on these trials, a combination of 300 mg/day of UFT with 75-90 mg/day of leucovorin was selected for further clinical development. Results of two phase III trials have now been reported for the UFT/oral leucovorin combination. In the first study [25], 816 patients were randomized between Orzel (UFT at 300 mg/m²/day with 75-90 mg/day of leucovorin) and intravenous 5-FU
and leucovorin arms (5-FU 425 mg/m²/day and leucovorin 20 mg/m²/day for five days every 28 days). The overall response rates in both arms were comparable (12% for UFT/leucovorin and 15% for intravenous 5-FU and leucovorin). The UFT/leucovorin arm had reduced incidence of febrile neutropenia and hand-foot syndrome. UFT-leucovorin combinations are also being explored for development in adjuvant therapy of colon and rectal cancer [26-29].

The National Surgical Adjuvant Breast and Bowel Project (NSABP) has conducted a randomized phase III trial in resected stage II and III colon cancer between 5-FU/leucovorin and UFT/leucovorin (NSABP C-06). This trial is now closed to accrual. A postoperative oral UFT/leucovorin and radiotherapy trial is currently open for rectal cancer at Memorial Sloan-Kettering Cancer Center and a preoperative trial in the same disease is ongoing at M.D. Anderson Cancer Center [27].

S-1

S-1 (Taiho Pharmaceutical Ltd.; Tokyo, Japan) combines tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and oxonic acid in a molar ratio of 1:0.4:1. CDHP inhibits activity of DPD and oxonic acid prevents intestinal phosphorylation of 5-FU by pyrimidine-phosphoribosyl-transferase. The development of S-1 in colorectal cancer is primarily being pursued at this time by the European Organisation for Research and Treatment of Cancer (EORTC) Early Clinical Studies Group (ECSG). In their first reported experience [30], 36 patients were treated with S-1 at a dose of 35 mg/m² twice daily after meals (the first four patients at a dose of 40 mg/m² twice daily had gastrointestinal toxicity). The most common side effects at this dose were diarrhea, nausea, fatigue, and anorexia. Four patients had a partial response and further development work is underway.

Eniluracil (5-Ethynyluracil)

Eniluracil (Glaxo Wellcome; Research Triangle Park, NC; 776C85, GW776) is an extremely potent noncompetitive inhibitor of DPD. Eniluracil is not a prodrug of 5-FU or an anticancer agent, rather, it potentiates the effects of 5-FU by causing virtually complete inhibition of DPD. Since DPD is the major inactivator of 5-FU, eniluracil greatly increases the bioavailability of 5-FU in animal models [31]. In a single-agent study, eniluracil was administered at a dose of 10 mg/m² twice daily for three days prior to surgery [32]. In tumor samples collected at surgery, there was complete suppression of the tumor DPD catalytic activity. There was also complete suppression of systemic DPD activity in mononuclear cells. Since erratic bioavailability of oral 5-FU is thought to be a reflection of intestinal and hepatic DPD activity [33], a combination of oral 5-FU and eniluracil has been developed. In the phase I trial [34], eniluracil therapy caused a sustained decrease in DPD activity by at least 90% in mononuclear cells for 24 h or longer. The recommended phase II doses for combination of eniluracil and oral 5-FU in the study were 50 mg/day and 15 mg/m²/day, respectively, when given on a daily 5 schedule every four weeks. The major toxicities in this study were myelosuppression, diarrhea, and mucositis. However, small increases in the doses of oral 5-FU above the acceptable dose level led to substantial increases in the incidence of toxicities in this study. In the pharmacokinetic analysis, complete bioavailability (100%) of 5-FU with a half-life of 4.5 h was observed, and interpatient variability was reduced as compared to intravenous 5-FU administration [35]. In addition, a strong correlation between 5-FU clearance, calculated creatinine clearance, and serum creatinine levels was observed. Thus, eniluracil should be used with extreme caution in patients with renal dysfunction.

### Table 1. Representative phase II trials of UFT in colorectal carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>UFT dose</th>
<th>Calcium folinate dose</th>
<th>Response rate</th>
<th>Toxicities (Gr 3 or Gr 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sultz et al. [66]</td>
<td>350 mg/m²/day × 28/35 days</td>
<td>15 mg/day × 28/35 days</td>
<td>5/21 (23%)</td>
<td>Diarrhea (18%)</td>
</tr>
<tr>
<td>Sanchiz et al. [67]</td>
<td>600 mg/m²/day × 14/28 days</td>
<td>90 mg/m²/day × 14/28 days</td>
<td>21/52 (59%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Pazdur et al. [24]</td>
<td>300-350 mg/m²/day × 28/35 days</td>
<td>150 mg/day × 28/35 days</td>
<td>19/45 (42%)</td>
<td>Diarrhea (11%-71%)*</td>
</tr>
<tr>
<td>Gonzalez-Baron et al. [68]</td>
<td>195 mg/m² day 1 then every 12 h × days 2-14</td>
<td>500 mg/m² IV day 1 then 15 mg every 12 h orally × days 2-14</td>
<td>29/75 (39%)</td>
<td>Diarrhea (3.5%)</td>
</tr>
</tbody>
</table>

*Patients treated with 350 mg/m² of UFT experienced higher incidence of side effects as compared to patients treated with 300 mg/m² of UFT.
In a recently reported phase II trial, eniluracil in combination with oral 5-FU was administered on a twice daily schedule for 28 days of a five-week course [36]. In untreated patients with metastatic colorectal cancer this regimen had a 24% response rate. Diarrhea (13%), stomatitis (3%), and myelosuppression (3%) were the major dose-limiting toxicities. This combination has also been tested with oral leucovorin [37]. A similar response rate (33%) was observed in this trial. The Eastern Cooperative Oncology Group (ECOG) has initiated a randomized phase III trial comparing a combination of oral 5-FU and eniluracil versus continuous infusion 5-FU in patients with advanced colorectal cancer.

Other Agents

Other agents, including BOF-A2 (Emetifur), which combines 1-ethoxymethyl 5-fluorouracil (EM-FU), which is a slow-release form of 5-FU with 3-cyano-2,6-dihydropyrimidine (CNDP), which inhibits DPD, are also in development [38].

Topoisomerase I Inhibitors

Topoisomerase I (topo-I) is an enzyme used by dividing cells to relax DNA supercoiling. Camptothecins are a class of recently characterized compounds that stabilize the DNA-topoisomerase I cleavable complex, thereby inhibiting the normal repair of the nicks introduced by topo-I. This, in turn, leads to more lethal DNA damage in the presence of high rates of ongoing DNA synthesis [39]. Irinotecan (CPT-11) is a highly active topo-I inhibitor and is approved for treatment of metastatic colorectal cancer in the United States by parenteral administration. Several newer camptothecin analogs and an oral formulation of CPT-11 are under development.

Irinotecan

Irinotecan (Camptosar™, Pharmacia & Upjohn; Kalamazoo, MI), administered intravenously, has demonstrated considerable clinical activity in colorectal cancer. In animal models, protracted oral administration of camptothecins had superior tumor response rates compared to intermittent intravenous treatment and also demonstrated reduced toxicity [40]. Also, liver has high levels of carboxylesterase, the enzyme that converts CPT-11 to its active form, SN-38. Since oral agents are preferentially taken up by the portal circulation, oral administration could lead to more efficient activation of CPT-11 to SN-38. Thus, theoretically, this could be advantageous for treatment of liver metastases from colon cancer. In a phase I trial of intravenous formulation of irinotecan administered in fruit juice orally, the toxicity profile was similar to intravenous administration. Cholinergic symptoms were less commonly observed and there was evidence of antitumor activity in metastatic colorectal cancer [41]. Delayed diarrhea was the major toxicity and myelosuppression was seen at higher dose levels. Equivalent biological activity, when compared to the intravenous dosing, was observed at tolerable dose levels even with substantially lower areas under the curve for CPT-11 lactone. A new powder-filled capsular formulation of irinotecan is in phase I trials in the United States and Europe on two different schedules: a 5 of 21-day schedule in Europe and a 14 of 21-day schedule at Memorial Sloan-Kettering Cancer Center. An additional five-day administration schedule is being developed at the Mayo Clinic. Future combination trials with oral fluoropyrimidines are also planned.

9-Aminocamptothecin

A colloidal dispersion formulation of 9-aminocamptothecin (9-AC) was tested in phase I trials recently. Marked interpatient variability was reported with poor correlation to the dose administered [42]. In another trial, using a different formulation, rapid drug absorption and bioavailability in the range of 27% to 49% were observed [43]. In several different intravenous schedules, 9-AC was found to lack activity in metastatic colorectal cancer [43-46]. The oral formulation may be developed for further study after the initial evaluation is completed. Given the lack of activity of this agent in the parenteral form in colorectal cancer, however, it is unlikely that this agent will play a major role in this disease.

9-Nitrocamptothecin

Since 9-nitrocamptothecin (9-NC) has broad antitumor activity in animal models, it has been evaluated as an oral formulation in adult cancers. A maximum tolerated dose of 1.5 mg/m²/day on a five-consecutive-day, every-week schedule was observed [47]. Significant toxicities were observed, notably nausea, neutropenia, thrombocytopenia, and cystitis. Several antitumor responses were observed, and phase II trials in colon cancer are ongoing.

Farnesyltransferase Inhibitors

Ras proteins are normally associated with the inner surface of plasma membrane and act as intermediates in transmitting a wide variety of extracellular signals to the cytoplasm and the nucleus. Ras oncogenes are mutated in more than 40% of colonic adenocarcinomas and mutation leads to constitutive activation of ras [48]. Association of ras with the inner surface of plasma membrane is facilitated by farnesyl protein transferase (FPT), which modifies the cysteine residues on the protein. A variety of farnesyl transferase
inhibitors is in clinical development and a selection of these oral agents are discussed below.

SCH66336

SCH66336 (Schering-Plough Research; Kenilworth, NJ) is a nonpeptidic small molecule with a tricyclic nucleus and is a potent and selective inhibitor of FPT. In preclinical studies, this compound inhibits growth of cell lines expressing mutated K-ras. In vivo studies have demonstrated that SCH66336 has potent antitumor activity against colon xenografts among many other types of implanted tumors in nude mice [49]. In two phase I trials [50, 51], SCH66336 was given orally twice daily as continuous administration or on a two of four-week schedule. The recommended phase II dose in both trials was 200 mg twice a day. The primary toxicities were diarrhea, anorexia, fatigue, and nausea. These toxicities were described as being mild and reversible on discontinuation of therapy. In the intermittent administration trial, two patients with colon cancer exhibited stable disease for four months. Recently, a continuous once-daily dosing trial was also reported [52]. An equivalent dose of SCH66336 (400 mg/day) was well tolerated on this schedule. Phase II trials are ongoing with SCH66336 as a single agent in chemotherapy-resistant colorectal cancers, and phase I trials in combination with 5-FU are in progress.

R115777

R115777 (Janssen Research Foundation; Titusville, NJ) is an oral quinolone analog that inhibits farnesylation with consequent inhibition of growth of a variety of human tumor cell lines at nanomolar concentrations [53]. In human tumor xenografts of colon cancer, R115777 inhibited tumor growth without any overt toxicity [53]. Two phase I trials have been reported with this compound. In the first trial [54], R115777 was administered orally twice a day for 21 of 28 days. The recommended phase II dose on this schedule was 240 mg/m² as a twice daily dose. The principal toxicities were myelosuppression (neutopenia and thrombocytopenia), fatigue, and confusion. Plasma levels at the well-tolerated dose were equivalent to concentrations required for in vitro activity. In the second trial, R115777 was administered twice daily for five days every two weeks [55]. This regimen was not very myelosuppressive, but nausea, vomiting, headache, fatigue, and neutropathy were observed. A phase I trial combining chronic daily administration of R115777 along with bimonthly 5-FU and leucovorin administration has also been reported in patients with colorectal or pancreatic cancer [56]. Myelosuppression was the principal toxicity and final results are awaited regarding a recommended phase II dose in these patients.

CHALLENGES IN DEVELOPMENT OF ORAL CHEMOTHERAPY FOR COLORECTAL CANCER

There are several challenges facing the development of oral chemotherapy for colorectal cancer. In phase I and II trials of oral chemotherapy, our experience has been that patients have needed considerable supervision at home. This means that patients enrolled in these trials (not unlike other trial candidates) need to have a high degree of motivation and reliability. Patients have self-modulated drug dosages in our experience. In clinical trials, a requirement has been that meticulous records be kept by the patient and regular reviews of these records along with other drug audits (including pill counting and intermittent telephone verifications) be carried out by the research staff. Often, research nurses make regular phone calls to patients to inquire about compliance and toxicity, or to make recommendations regarding continuing or delaying toxicity. Sponsors have been generally willing to bear the higher costs associated with this intense monitoring and follow-up of patients enrolled in these trials. There are several unresolved questions regarding issues of administration of these drugs in the community setting. It may not be possible to monitor patients as closely as in standard practice. It may then be difficult to observe similar safety profiles seen in the research studies. Optimal follow-up strategies including patient visits, hematologic monitoring, etc., have not been defined for "real world" settings and may have to await larger trials and, possibly, postmarketing data collection. No published data have evaluated postmarketing "real-life" compliance issues surrounding the administration of oral chemotherapy with agents like capecitabine and UFT, although this would be of great interest.

A major issue in development of the oral chemotherapy is a strict evaluation of concomitant medications. For instance, 18 Japanese patients were reported to have died because of coadministration of tegafur with sorivudine, a new antiviral therapy for herpes zoster. The mechanism of action appears to be DPD inhibition by a metabolite of sorivudine [57]. Other drugs, for example, antacids, salicylates, antibiotics, anticonvulsants, etc., can sometimes have significant interactions associated with oral chemotherapy. Some of these agents administered orally can interfere with the absorption and also compete for the first-pass elimination of chemotherapy from the hepatic parenchyma. In one report, for example, acute phenytoin intoxication was observed in patients on tegafur, presumably because of interference of phenytoin metabolism by tegafur [58]. Some of these medications may lead to large inter- and intrapatient variability in toxicity and efficacy, depending on concomitant medications being taken by the patients.
**COMBINATION CHEMOTHERAPY WITH ORAL AGENTS**

Combination therapies with oral agents utilize similar rationales as traditional combination chemotherapy trials. Primarily, there is hope of synergy with nonoverlapping toxicities when two or more agents are combined. Preliminary results from some trials combining parenteral 5-FU and irinotecan [59, 60] or oxaliplatin and 5-FU [61] seem promising, with higher overall response rates in metastatic disease and suggestive trends toward improved survival.

Combination therapies with oral agents are in the planning stages and will generate new challenges. These will involve issues of scheduling two or more oral drugs, and the potential for complex pharmacokinetic interactions. The various combinations that are of interest include intravenous irinotecan and oral fluoropyrimidines, oral irinotecan and oral fluoropyrimidines, oxaliplatin and oral fluoropyrimidines, oxaliplatin and oral irinotecan, etc. In addition, there are ongoing trials to evaluate oral chemotherapy agents with radiation in rectal carcinoma. Preliminary results from Europe are promising for neoadjuvant treatment with UFT/folinic acid in rectal cancer [62]. Other agents will likely be evaluated with radiation in the future. Further information about open clinical trials can be obtained from the National Cancer Institute website: http://cancernet.nci.nih.gov/trialsrch.shtml

**ECONOMIC CONSIDERATIONS FOR DEVELOPMENT OF ORAL CHEMOTHERAPY**

Intravenous chemotherapy for colon cancer can be expensive. In a study comparing the relative costs of bolus and infusional 5-FU for colon cancer therapy, the average cost of administration was related to length of infusion and bolus schedule [63]. In this retrospective analysis done in 1996, the authors estimated that infusion schedules of 28-day and five-day durations incurred an average cost of $2,360 and $1,338 per month, respectively. On the other hand, the five-day or weekly bolus schedules incurred a cost of $1,250 or $2,081, respectively. This analysis incorporated cost of doctor visits, laboratory monitoring, and pharmacy costs. The actual cost of administering this chemotherapy is, in reality, higher when other considerations, for example, time lost at work for visits and hospitalizations, are taken into account [64].

Oral chemotherapy has been widely thought to have a potential for cost savings when compared to intravenous chemotherapy. However, cost of chemotherapy is dependent on a variety of factors, including clinic visits, cost of laboratory tests, costs incurred due to loss of productivity, etc. The Red Book estimates the average wholesale price for chemotherapy agents and is widely utilized by pharmacists. Table 2 indicates the wholesale cost of some chemotherapy agents published in the Red Book in 1999. As can be seen from this analysis, newer oral chemotherapy may be more expensive than the older intravenous counterparts. There is no reason to believe that oral chemotherapy is less toxic and would require less close monitoring than intravenous chemotherapy. Thus, a monthly cost comparison of the cost of capecitabine as compared to 5-FU by a protracted 28-day infusion indicates equivalent charges generated by both regimens (Table 3). Thus, although, oral chemotherapy has the potential of generating substantial savings in the long term, higher drug costs associated with newer and recently approved oral therapies may negate this potential in the initial years after drug approval. In the initial years after approval, there are also challenges facing providers and patients to convince insurance companies and prescription plans to pay for the oral agents. This may be difficult if the newer agents are substantially more expensive and do not replicate research results in the community setting.

| Table 2. Representative costs of several oral and intravenous drugs in the United States |
|---------------------------------|---------|---------|
| **Chemotherapy Agent**         | **Oral Drug** | **IV Drug** |
| Cyclophosphamide                | $147    | $105    |
| Etoposide                       | $840    | $612    |
| Capecitabine                    | $1,073  | NA      |
| 5-Fluorouracil                  | NA      | $20     |
| **Cost per month**              |         |         |

These costs are based on average wholesale prices (Source: Red Book [69]). The calculations of monthly costs are based on common regimens employed in treatment for patients with cancer for a period of one month. The calculation is based on a body surface area of 1.8 and a weight of 70 kg for the patient.

<table>
<thead>
<tr>
<th>Table 3. Comparative monthly cost of administering 5-fluorouracil (5-FU) as a 28-day infusion or capecitabine as oral therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>28-day 5-FU infusion</strong></td>
</tr>
<tr>
<td>Physician visit</td>
</tr>
<tr>
<td>Clinic visit</td>
</tr>
<tr>
<td>Laboratory CBC</td>
</tr>
<tr>
<td>Drug cost</td>
</tr>
<tr>
<td>Disposables</td>
</tr>
<tr>
<td>Pump rental</td>
</tr>
<tr>
<td>Total charges</td>
</tr>
</tbody>
</table>

*The charges are derived from a 1996 analysis reported by Lokich et al. [63].†The cost of capecitabine is the average wholesale price (see text for explanation).
PATIENT PREFERENCES FOR ORAL CHEMOTHERAPY

In an elegant study by Liu et al. [65], 103 patients with cancer were questioned about their preference for oral or intravenous chemotherapy. Patients were told initially that clinic visits, laboratory evaluations, and toxicities of oral or intravenous regimens were comparable. Ninety-two of 103 patients expressed a preference for oral chemotherapy. The predominant reason for this appeared to be problems with intravenous access or convenience of administration outside a clinic setting. Interestingly, most patients would not prefer oral chemotherapy if it was slightly inferior to intravenous chemotherapy. This study did not distinguish between patients receiving adjuvant or palliative chemotherapy or the performance status of patients participating in the study.

Practical experience has shown that many patients assume that oral chemotherapy is less toxic and “less serious.” As more extensive experience is gained with oral chemotherapy, patient and physician perception may be altered. However, this will require ongoing education and will be a long-term process.

CONCLUSIONS

Oral chemotherapy is in a stage of rapid development for treatment of colorectal cancer. Various new oral agents are in advanced stages of development for treatment of these cancers around the world, but several challenges are being encountered by investigators in the development of these agents. In surveys, patients have expressed preference for these agents only if they are at least equivalent in efficacy to the traditional intravenous chemotherapy. Economic issues surrounding oral chemotherapy are complex and need to be evaluated prospectively in controlled trials. In the future, combination trials of these agents with each other, or with intravenous chemotherapy, are likely to advance the development and clarify a place for these compounds in the clinician’s armamentarium.

REFERENCES


19 Futatsuki K, Komita T, Kamano T. Clinical results of treatment with the UFT fine granule preparation under coopera-
Oral Chemotherapeutic Agents for Colorectal Cancer


Saltz LB, Kemeny NE, Tong W et al. 9-Aminocamptothecin administered as a 72-hour continuous intravenous infusion is inactive in the treatment of patients with 5-fluorouracil-refractory colorectal cancer. Cancer 1997;80:1727-1732.


