REVIEW ARTICLE

# Oral Chemotherapy: Rationale and Future Directions

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***Purpose and Methods:*** **The expanding role of oral chemotherapy in oncology is suggested by the abundance of orally formulated agents currently in development. The pharmacoeconomic principles that drive oral drug formulation are discussed. Patient preference for oral therapy is identified as a second major impetus for the design of oral cytotoxics. While the rationale for oral formulations is apparent, substantial patient compliance and pharmacokinetic limitations have been identified for this route of administration. Specific aspects of bioavailability limitations and patient compliance are discussed. Relevant pharmacokinetic data for each orally formulated chemotherapy agent are compared and selected novel oral cytotoxics and cytotoxic modulators are discussed.**

***Results:*** **A review of pharmacokinetic literature suggests substantial variability in bioavailability for many orally formulated cancer cytotoxics. While these findings are observed for all classes of oral drugs, the issue is especially critical for cancer chemotherapy, in which a narrow therapeutic index is frequently observed. Improved bioavailability and reduced interpatient biovariability are therefore desirable for new cytotoxic formulations. Pharmacologic manipulations to improve bioavailability and reduce costs are examined.**

***Conclusion:*** **Oral chemotherapy represents a fundamental change in contemporary oncology practice, driven by pharmacoeconomic issues, patient convenience, and the potential for improved patient quality of life. Novel cytostatic therapies that require protracted drug administration periods will also favor an oral formulation. While the use of oral chemotherapy may initially be limited to metastatic disease palliation, demonstration of equivalent efficacy would allow for its subsequent use in adjuvant settings. This efficacy is contingent on circumventing bioavailability limitations and patient noncompliance. The development of specific, low-toxicity inhibitors of CYP3A4, P-glycoprotein (P-gp), and other drug metabolizing enzymes such as dihydropyrimidine dehydrogenase represents a major innovative step in the successful formulation of oral chemotherapy.**

***J Clin Oncol 16:2557-2567.*** 

AS WITH VIRTUALLY ALL office-based and academic medicine, the issue of cost-effectiveness must be addressed by the medical oncologist. Cost may no longer be considered as an aside, but will likely become a central issue in therapeutic decision-making, particularly in the limitations of the palliative setting. At the beginning of the next century, it is estimated that health care expenses will amount to $1.5 trillion dollars or 15% of the projected Gross National Product.[1] In 1990, an estimated $35 billion was spent on direct costs for cancer care.[2] The direct cost of chemotherapy agents represented only a small fraction of this sum. A cost survey of one outpatient cancer center noted direct chemotherapy charges accounted for only 5.4% of total Medicare cost claims.[2] In an analysis of adjuvant and metastatic breast cancer settings, direct drug charges accounted for only 19% to 36% of total care costs.[3] These examples of the relatively small contribution of chemotherapy agents to the overall cost of oncology care are representative of national health care expenditures as a whole. In 1991, prescription drugs represented only 6.4% of total health care expenditures.[4]

While cost-effectiveness has been substantiated for both adjuvant and palliative chemotherapy,[5-8] it is likely these therapies will continue to be scrutinized in terms of their component charges, primarily direct drug costs and administration costs. Administration costs traditionally have incorporated some or all of the following charges: hospitalization, physician fees, salaries of nursing and technical support personnel, infusion equipment supply costs, administration supply product fees, and overhead charges (capital equipment, regulatory compliance costs, and liability insurance costs). In the evolving era of managed care, the impact of cost-effective strategies on these charges is evident to many in practice-based oncology. From 1991 to 1996, the average Medicare reimbursement for a chemotherapy administration declined 57% from $155.51 to $67.01.[9] Additionally, the Health Care Finance Administration (HCFA) formally eliminated payment for all supplies used to administer chemotherapy in 1992. In a recent appraisal of cost and reimbursement patterns for commonly used infusional and bolus lymphoma,

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*Submitted August 12, 1997; accepted March 24, 1998.*

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*0732-183X/98/1607-0002$3.00/0*

breast, and colon regimens, Lokich et al[10] noted Medicare endorsement averaged just 21% to 36 % of total charge claims. The larger implications for reimbursement denials of novel, off-label, or investigational infusional regimens are obvious. Pharmacoeconomics, heralded by Medicare, and, increasingly, private-payer capitation constraints will promote increasingly cost-effective treatment regimens. From the pharmacoeconomic viewpoint, the rapid emergence of orally available oncologic agents might be as readily anticipated as the transition from hospital- to outpatient-based chemotherapy administration.

An administrative cost analysis of ganciclovir therapy provides an illustration of the economic issues for orally formulated agents.[11,12] A late complication of AIDS, cytomegalovirus retinitis requires a protracted ganciclovir treatment course. Sullivan et al[12] have examined cost issues of ganciclovir administered over an 80-day schedule. While the direct drug costs of oral ganciclovir were nearly 170% those of the intravenous formulation, mean oral total therapy costs averaged just 58% those of intravenous therapy ($4,938 *v* $8,583). Cost variables examined include administration and nursing, central intravenous catheter, and infusion pump costs, and costs related to adverse effects of intravenous ganciclovir administration, such as line sepsis. A significant cost differential was noted for induction, adverse-event treatment, and combined home care, nursing administration, and monitoring charges, for which oral therapy costs represented only 54%, 36%, and 14% of intravenous therapy costs, respectively.[12] Thus, prescription of oral ganciclovir results in increased revenues for its manufacturer and decreased revenues to health care providers and hospitals.

Aside from economic considerations, it seems intuitive that patient preferences and quality-of-life issues will be another major impetus for the development of orally formulated chemotherapy. Recognizing the limitations of cytotoxic therapy in many metastatic cancers, patient quality of life is increasingly becoming a central consideration in palliative treatment regimens. The issue of patients' preferences regarding chemotherapy administration has recently been examined by Liu et al.[13] Patients with advanced malignancies were asked about their preferred method of treatment before initiation of chemotherapy. Of 103 patients, more than 90% indicated a preference for orally administered agents, provided significant reductions in efficacy or duration of response would not result from this mode of treatment. The reasons for patients' preferences included convenience (57%), current concerns or previous difficulties with intravenous access lines (55%), or preference to control the chemotherapy administration environment (33%). If equivalent safety and efficacy are demonstrated, an all oral regimen would likely first be realized in the palliative setting, for example, an oral fluoropyrimidine replacing intravenous fluorouracil (5-FU) in the treatment of metastatic colorectal carcinoma.

## DRUG ADMINISTRATION CONSIDERATIONS

To have efficacy in an oral formulation, a chemotherapeutic drug must be sufficiently bioavailable. Bioavailability concerns the rate and extent to which a drug is absorbed into the systemic circulation. The bioavailability of oral agents is contingent on adequate intestinal absorption and the circumvention of intestinal and, subsequently, hepatic metabolic systems. In considering absorption, the limitations of saturability and structural stability in gastric and intestinal pH must be addressed. The importance of saturable absorption is exemplified by oral etoposide and oral leucovorin. The large bioavailability variation between low- and high-dose oral etoposide suggests a saturable absorption system. Hande et al[14] noted a 76% ± 22% bioavailability of 100 mg etoposide, while a 400-mg dose was only 48% ± 18% bioavailable. A linear increase of etoposide bioavailability at doses up to 200 mg has been demonstrated by other investigators, which confirms the saturable absorptive kinetics.[15] Leucovorin represents a second agent for which limited oral bioavailability is clinically relevant. While leucovorin's relative bioavailability is 78% in a 40-mg oral dose, bioavailability is reduced to only 31% in a 200-mg dose.[16] These constraints would limit the use of oral leucovorin in some commonly used adjuvant regimens for colon carcinoma.

The importance of structural stability in gastric and intestinal pH is also demonstrated by the etoposide model. Etoposide stability is optimal at pH 5. Joel et al[17] attempted to improve oral etoposide bioavailability through coadministration of agents that improve stability of etoposide in intestinal fluid (ethanol or bile salts) or increase pH (cimetidine).[17] Although the bioavailability and area under the concentration-time curve (AUC) of etoposide were not significantly enhanced with the modifications imposed in this study, it is nevertheless valuable to consider pH manipulations for structural stability in etoposide and, potentially, other oral chemotherapeutic drugs.

An ideal chemotherapeutic drug would have little interpatient variability (in absorption and AUC) and, more importantly, little intrapatient variability with successive doses. Comparing bioavailability from 143 studies in several drug classes (including antineoplastics), Hellriegel et al[18] noted a significant inverse correlation between decreasing absolute bioavailability and intersubject variability in absolute bioavailability. It follows that caution must be taken in prescribing an oral chemotherapy drug with low bioavailability. The generally narrow therapeutic index of these agents means significant interpatient variability would predispose some

individuals to excessive toxicity, or, conversely, inadequate efficacy.

There are numerous examples of clinically significant variability in bioavailability for orally formulated chemotherapeutic agents. While etoposide bioavailability averages 50%, significant interpatient and intrapatient biovariability produces a bioavailability range of 25% to 75%.[19] For busulfan, Hassan et al[20] have noted up to a twofold and sixfold variability in bioavailability in adult and young pediatric populations, respectively. Similarly, Lebbe et al[21] observed a greater than fivefold range of AUC in patients who received low-dose oral methotrexate. Noting a fivefold interpatient variability in mercaptopurine AUC following oral administration, Zimm et al[22] questioned the efficacy of the standardized oral dose used as maintenance therapy for acute lymphoblastic leukemia.

*Other Bioavailability Limitations Specific for Oral Drugs*

*Intestinal CYP3A4.* As mentioned previously, intestinal metabolic systems represent a "first-pass" bioavailability limitation unique to oral drugs. Principal among these is enterocyte CYP3A4. CYP3A4 is an enzyme subtype of CYP3, itself one of three major subclasses of cytochrome P-450 enzymes (CYP1, CYP2, and CYP3). The P-450 enzymes are primarily responsible for phase I metabolism, facilitating drug excretion through nonconjugation reactions. CYP3A represents the major P-450 subclass, which accounts for as much as 25% of phase I drug metabolism in humans.[23] While hepatocytes contain the highest concentrations of P-450, these enzymes have been isolated from the endoplasmic reticulum of several cell types. Four distinct intestinal CYP3A P-450s have been characterized in humans, CYP3A3, CYP3A4, CYP3A5, and CYP3A7. These enterocyte P-450s lie below the surface of the jejunal microvillus. In humans, CYP3A4 is the major intestinal P-450.[24]

While it is difficult to distinguish between the activity of enteric and hepatic CYP3A4, the importance of this enterocyte enzyme in oral bioavailability limitations is suggested by clinical studies of cyclosporine metabolism. The brief anhepatic phase of orthotopic liver transplantation provides a system to analyze isolated metabolic activity of enterocyte CYP3A4. Measuring cyclosporine M1 and M2 metabolites following jejunal drug delivery, Kolars et al[25] concluded that as much as 50% of cyclosporine is metabolized by enterocyte P-450 3A4.

Table 1 lists representative chemotherapeutic substrates of CYP3A4. Orally formulated etoposide and cyclophosphamide are subject to substantial first-pass metabolism by enterocyte CYP3A4. The exact contribution of enterocyte CYP3A4 in the metabolism of oral etoposide is not known; however, inhibition studies discussed below suggest the possibility for a substantial role.[34] Further investigation will be required to elucidate the role of enterocyte CYP3A4 in the first-pass metabolism of other orally available cytotoxic agents.

**Table 1. Investigational and Available Oral Chemotherapeutic Agents That Are Substrates of CYP3A4 and P-gp**

| Agent | CYP3A4 | P-gp | References |
|---|---|---|---|
| Cyclophosphamide | x | | 26 |
| Etoposide | x | x | 27, 28 |
| Idarubicin | | x | 29 |
| Paclitaxel* | x | x | 28, 30 |
| Topotecan* | | x | 31 |
| Vinorelbine | x | x | 32, 33 |

*Investigational agents.

In determining the potential pharmacokinetic significance of enterocyte CYP3A4 for a given oral agent, it is necessary to consider the significant interpatient variability in CYP3A4 expression. It is known that hepatic CYP3A4 concentrations and catalytic activity vary at least 10-fold among individuals.[35] This has practical implications in the metabolism of many drugs, including cyclosporine. Likewise, Lown et al[36] have reported a greater than sixfold interpatient variability in *enterocyte* CYP3A4 metabolic activity. This substantial heterogeneity may also have important clinical implications in oral drug metabolism. While hepatic CYP3A4 catalytic activity may be quantified by the erythromycin breath test (ERMBT), this test is not useful for enterocyte CYP3A4.[36] Developing a noninvasive, quantitative probe for enterocyte CYP3A4 will be necessary to further our understanding of this enzyme's contribution in oral drug metabolism.

Perhaps the most important reason for fully elucidating CYP3A4 metabolism is that bioavailability may be substantially enhanced through pharmacologic manipulations of this system. CYP3A4 has numerous inducers, principally rifampin, phenobarbital, and dexamethasone.[23,37] Conversely, erythromycin, quinidine, ketoconazole, and cyclosporine serve as inhibitors of CYP3A4.[38-40] An appreciation of the utility of these agents may be gained by examining the cyclosporine model. Herbert et al[41] demonstrated a significant reduction in cyclosporine oral bioavailability with the concomitant administration of rifampin, whereas Gupta et al[42] markedly increased oral cyclosporine bioavailability with the coadministration of erythromycin. Similarly, Gomez et al[43] noted coadministration of ketoconazole increased oral cyclosporine bioavailability from 22% to 56%. The cost implications of increasing cyclosporine bioavailability through CYP3A4 inhibition have been examined. Keogh et al[44] noted an annual savings of $5,200 per patient for cardiac transplant patients who received cyclosporine coadministered with ketoconazole.

Kobayashi et al[34] have recently examined the effect of ketoconazole modulation on the metabolism of etoposide.

Etoposide is known to be metabolized by CYP3A4-mediated O-demethylation.[27] With coadministration of the potent CYP3A4 inhibitor ketoconazole, a 44% increase in plasma etoposide AUC was noted.[34] This model suggests CYP3A4 modulation may be of great value in improving the oral bioavailability of chemotherapeutic agents that are its substrates.

*Intestinal P-glycoprotein.* P-glycoprotein (P-gp) is a drug efflux pump well known to confer chemotherapy resistance. Orally formulated cytotoxic drugs known to be P-gp substrates include etoposide, idarubicin, and topotecan (investigational formulation).[29,31] Encoded by MDR1, P-gp has been isolated in several human tissues, including the intestinal mucosa.[45] There are preclinical data that suggest P-gp limits the intestinal absorption of paclitaxel, docetaxel, and vinblastine.[46,47] Moreover, Leu et al[48] reported a significant increase in etoposide bioavailability in rat jejunal and ileal loops first exposed to intravenous quinidine, a known P-gp inhibitor. The effect was realized at quinidine concentrations at or below the therapeutic range. A monoclonal antibody against P-gp similarly produced a marked decrease in etoposide efflux from this rat jejunal system. Two preclinical studies of oral paclitaxel have demonstrated the significant bioavailability limitations imposed by P-gp. Sparreboom et al[47] noted a sixfold increase in paclitaxel AUC in mdr 1a (-/-) mice, which lack intestinal P-gp. Using a murine model, Van Asperen et al[49] have recently examined the effects of the P-gp blocker SDZ PSC 833 on the oral bioavailability of paclitaxel. The effect of this potent P-gp blocker was substantial; SDZ PSC 833 pretreatment resulted in a 10-fold increase in paclitaxel AUC. The bioavailability limitations imposed by P-gp must therefore be considered in the development of orally formulated chemotherapy. Trials that use P-gp inhibitors such as quinidine, verapamil, or SDZ PSC 833 may be anticipated in the successful formulation of oral paclitaxel or other agents.

Table 1 lists representative chemotherapeutic substrates of P-gp.[28]

### *Patient Compliance Issues*

Aside from bioavailability limitations, patient noncompliance represents a second potential major obstacle for orally formulated chemotherapy. Bonadonna and Valagussa[50] underscored the implications of an incomplete treatment course in the adjuvant breast setting; markedly inferior disease-free survival was experienced in patients who received less than 65% of planned therapy. Various studies have examined noncompliance in patient self-administered chemotherapy regimens. Lebovits et al[51] noted a noncompliance rate of 43% in 51 breast cancer patients treated over 26 weeks with an outpatient, oral cyclophosphamide regimen. Factors associated with higher rates of noncompliance included lower socioeconomic status or treatment in a community-based setting. Levine et al[52] examined outpatient allopurinol and prednisone compliance in a cohort of patients who received concomitant chemotherapy for hematologic malignancies. With no interventions, a full allopurinol compliance rate of only 17% was noted in patients responsible for one component of a potentially curative treatment regimen.[52] Moreover, pharmacokinetic analysis showed actual compliance was less than half that suggested by patient self-report. Importantly, measures designed to increase compliance, including patient education, home psychologic support, and exercises in pill taking, were able to increase compliance nearly threefold. The impact of side effects, complexity of treatment regimen, and age on compliance rates has subsequently been investigated.[53] The occurrence, frequency of occurrence, or severity of physical side effects correlated with clinic appointment noncompliance, but not with compliance of self-administered chemotherapy medications.

For self-administered oral regimens, quantifying compliance rates will be essential for the accurate determination of regimen efficacy. In this regard, a novel electronic model has been suggested by Lee et al.[54] An electronically activated tablet bottle scored opening to indicate daily outpatient compliance with an oral chemotherapy agent. A compliance rate of 110.6% ± 20.6% was demonstrated in a cohort of 21 patients responsible for a self-administered component of an outpatient lymphoma chemotherapy regimen. It is also encouraging that, using the identical electronic model, these investigators were able to demonstrate a 93.2% ± 12% compliance rate in a cohort of small-cell lung carcinoma patients receiving low-dose oral etoposide.[55] The high compliance rate was maintained despite the cohort's generally poor overall prognosis.

## ORALLY AVAILABLE AGENTS AND OVERVIEW OF SELECTED NOVEL CYTOTOXICS

Table 2 lists relevant pharmacokinetic and cost data for the orally formulated chemotherapeutic agents. For several of these agents, bioavailability varies substantially between patients, with increasing drug dose, or with food. Given the narrow therapeutic index for many of these agents, it is desirable to improve bioavailability and reduce intrapatient biovariability through mechanisms discussed earlier. Where applicable, an oral/intravenous cost ratio is given for equivalent milligram doses of drug at average wholesale prices. These ratios do not consider the extensive costs of intravenous drug administration. While price data for the investigational oral agents are not currently available, it is likely their price will be considerably greater than that of the intravenous preparation, as in the previously discussed case of

**Table 2. Comparison of Oral Chemotherapeutic Agents**

| Class | Agent | Oral Bioavailability (%) | Terminal Half-life (hrs) | Cost Ratio (oral/ intravenous) | Comments | References |
|---|---|---|---|---|---|---|
| Pyrimidine antimetabolites | 5-FU | 0-80 | 0.22 | | 122% mean bioavailability and 4.5-hour half-life reflect 5-FU modulation with 5-ethynyluracil | 56-61 |
| | | 122 | 4.5 | | | |
| | UFT | 100 | 6-16 | | | 62-65 |
| | Capecitabine | 61 | 0.80 | | | 66 |
| Other antimetabolites | Mercaptopurine | 16-50 | 1.5 | | Extensive first-pass gut metabolism to thiouric acid | 22, 67, 68 |
| | Thioguanine | 14-46 | 11 | | | 69-71 |
| | Methotrexate | 20-90 | 3-15 | 4.56 | Bioavailability substantially limited over 30 mg/m² | 72, 73 |
| | Hydroxyurea | 100 | 2.0-3.0 | | | 70 |
| Epipodophyllotoxins | Etoposide | 48-76 | 6.6 | 0.46 | Bioavailability reduced at doses >100 mg | 14 |
| Alkylating agents | Cyclophosphamide | 85 | 2.8 | 1.53 | | 74 |
| | Procarbazine | 100 | 0.16 | | | 70, 75 |
| | Lomustine | 100 | 1.3-2.9 | | Half-lifes are of *cis*- and *trans*-4-OH CCNU metabolites, respectively | 76 |
| | | | 1.3-2.5 | | | |
| | Melphalan | 58-95 | 0.95-1.8 | 0.15 | | 77, 78 |
| | Busulfan | 100 | 2.3-3.4 | | | 71, 79, 80 |
| | Chlorambucil | 70-80 | 2.0 | | | 78 |
| Platinum derivatives | JM-216 | | 6.0-7.7 | | Half-life of platinum in ultra-filtrate with 120 mg/m²/d × 5 JM216 schedule | 81, 82, 83 |
| Vinca alkaloids | Vinorelbine | 26-45 | 24-56 | | | 84, 85 |
| Camptothecins | Topotecan | 30 | 2.82 | | Undergoes reversible pH-dependent conversion to hydroxy acid | 86-88 |
| | 9-aminocamptothecin | 27-49 | 7.5-24.3 | | A colloidal dispersion is poorly bioavailable | 89, 90 |

ganciclovir. Selected novel oral cytotoxic agents are now discussed.

### *Novel Oral Fluoropyrimidines and Modulators*

*UFT.* UFT is an oral preparation of 1-(2-tetrahydrofuryl)-5-FU (tegafur) and uracil admixed in a 1:4 molar ratio. UFT is a unique oral prodrug that undergoes both hepatic P-450 and target tissue metabolism to 5-FU.[91] The 1:4 tegafur-to-uracil ratio was noted to provide the highest intratumoral levels of 5-FU.[92] The oral bioavailability of UFT is excellent; Antilla et al[62] noted a comparative oral/intravenous AUC of 115% ± 8%. Phase I investigations of 28-consecutive-day administration with concomitant high- or low-dose leucovorin have suggested feasibility and acceptable toxicity at doses less than 350 mg/m²/d.[93,94] UFT has been used extensively in Japan. Examining pooled phase II of more than 400 patients with cholangiocarcinoma, colorectal, gastric, and breast cancers, Ota et al[95] noted single-agent UFT response rates that ranged from 25% to 32%.[95] More recently, Pazdur et al[96] noted a 42% response rate in therapy-naive colon carcinoma patients. Comparing oral ftorafur and intravenous 5-FU in a small cohort of patients with advanced colorectal cancer, Andersen et al[97] noted equivalent gastrointestinal toxicity with significantly lower hematologic toxicity in ftorafur-treated patients. There was no significant difference in median or overall survival in UFT- or 5-FU–treated patients.[97] Confirmatory phase III trials will be necessary to justify UFT in a metastatic or, ultimately, adjuvant colorectal setting. The ability to administer UFT over protracted schedules may allow for the simulation of continuous infusion 5-FU kinetics, which suggests a role as a radiosensitizing agent.

*Capecitabine.* Capecitabine represents an orally bioavailable fluoropyrimidine designed with unique tumor selectivity. An oral 5′-deoxy-5-fluorocytidine derivative, it is absorbed unchanged from intestinal mucosa and converted to 5′ deoxy-5-fluorocytidine ribonucleotide (5′-DFCR) via hepatic acylamidases. The drug is subsequently converted to 5′-DFUR by cytidine deaminase, an enzyme preferentially located in hepatic and tumor tissues. Finally, the conversion of 5′ deoxy-5-fluorouridine ribonucleotide. (5′-DFUR) to 5-FU occurs intratumorally via pyrimidine nucleoside phosphorylases (PyNPases), uridine phosphorylase, and thymidine phosphorylase.[98,99] Specificity is achieved with PyNPase, which is constitutively expressed at high levels within tumors.

Capecitabine phase I data have been determined for 6-week continuous and intermittent administration schedules.[100] A maximum-tolerated dose (MTD) of 1,657 mg/m²/d was determined for capecitabine on a 6-week daily

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