A Pharmacoeconomic Comparison of UFT and 5-FU Chemotherapy for Colorectal Cancer in South America

By Andre Marcio Murad, MD, PhD [2], Carlos Augusto De Andrade, MD [3], Carlos Delfino, MD [4], Steven Arikian, MD [5], and Neeta Sinha, MA [6]

The escalating role played by managed care organizations in the health-care system is reflected in the increased demand for cost-effectiveness analyses (CEAs) to assess the balance between economic impact

Introduction

Health-care systems worldwide are in a state of transition as a result of many influences, including evolving technologies, demographic changes, new diseases, and globalization of markets. Given the limits on available resources, new health-care technologies should be evaluated for both their economic impact and clinical efficacy. Health economics analysis in general and cost-effectiveness analysis (CEA) in particular can be conducted from a number of research perspectives, such as those of the payor, insurer, patient, or provider. For example, the United States Department of Health and Human Services sponsored a recent conference for health economists on newly published cost-effectiveness analysis guidelines. In it a call was issued for studies that adopted a "societal" perspective, to consider the widest possible range of influencing factors. More than 130 million Americans—approximately half the present population—are now enrolled in managed care organizations. Managed care organizations dominate employer health plans (controlling about 70% of this sector) and the government actively promotes managed care among its Medicaid and Medicare populations. The increasing role of managed care organizations in the health-care system has heightened the demand for cost-effectiveness analysis in a wide variety of therapeutic areas. It may appear that all analyses of this kind are simply about "dollars and cents." However, it is impossible to conduct meaningful health economics studies without a thorough evaluation of the clinical process as applied in the disease area under investigation. Even the most basic cost-effectiveness analysis can yield markers for clinical efficiency and effectiveness. Although studies based on society's perspective are often not feasible, as clinicians seek to increase their control over the decision-making process in managed care, it is certain that more studies will be done that include patient and provider perspectives. The following is a discussion of an economic analysis performed to achieve optimal allocation of resources in the treatment of colorectal cancer.

Economic Comparison of Chemotherapeutic Approaches to Colorectal Cancer

This study provides examples of the types of clinical modeling and provider validation that take place in a relatively straightforward economic comparison of two chemotherapy regimens used in the treatment of colorectal cancer. Although elements of the study are specific to two South American nations, the basic architecture can be applied to many different clinical and geographic settings. As demand for broad-perspective analyses increases, such studies will provide a valuable foundation for further work. The high incidence of colorectal cancer in Latin America (Brazil: 0.0025),[1] coupled with significant costs associated with its treatment, stipulates comprehensive economic evaluation in order to ensure efficient allocation of limited health-care funds. The introduction of oral tegafur and uracil (UFT) to this market provides a research opportunity to determine the comparative pharmacoeconomic advantage of this new agent vs fluorouracil (5-FU), the current treatment standard for colorectal cancer. UFT is an antineoplastic agent composed of tegafur and uracil at a molar ratio of 1:4. It has demonstrated activity in colorectal, gastric, breast, and head and neck carcinomas.[2-4] In vivo, tegafur is converted to 5-FU.[5] Coadministration of uracil increases the
intratumor concentration of 5-FU, resulting in greater antitumor activity.[6] In terms of clinical outcome, UFT has demonstrated therapeutic equivalence to 5-FU. It has the advantage of oral administration (vs continuous intravenous infusion for 5-FU) and a mild toxicity profile. Thus, the objective of the study is to evaluate the potential pharmacoeconomic benefits of oral UFT over 5-FU chemotherapy in the treatment of colorectal cancer in South America. The perspective of this economic analysis was that of the health-care payor. Hence, a reimbursement analysis for the treatment of colorectal cancer was conducted based on the South American health-care system.

This research study was designed as a cost-minimization analysis. The end point of this evaluation was a total average cost per treatment per patient, stratified by treatment agent, by treatment type (adjuvant or metastatic), and by two major South American countries (Brazil and Argentina). The regimen used in the study was 5-FU with either levamisole (Ergamisol) or leucovorin as a modulator vs a modeled oral UFT/leucovorin regimen. A pharmacoeconomic model was developed for both Brazil and Argentina. Clinical practice patterns associated with chemotherapy administration and adverse-event management practices were identified with the help of a panel of physicians assembled from each country. Practice patterns and clinical events were then evaluated for resource utilization. Country-specific charge data were applied to the identified resources to arrive at an average cost per patient for the respective treatments.

**Methodology**

The primary objective of a study that evaluates medical care technologies is to conduct an explicit examination of the resources used and to incorporate the results into decisions regarding their use. Since the objective of the study was to estimate and compare the total average cost of oral UFT vs 5-FU-based chemotherapy for adjuvant and metastatic colorectal cancer in Brazil and Argentina, a cost-minimization analysis was performed. The analytic time frame was approximately 18 months, spanning from the time of oncologist referral to 6-month follow-up. Treatment was observed primarily in the outpatient setting, unless high-grade adverse events required hospitalization. A modified Delphi technique was used to construct the country-specific treatment algorithms. This technique systematically incorporates informed opinions on specific issues from a group of experts. The Delphi panel in the current study was composed of three physicians from Brazil and three from Argentina. The following treatment modules delineated the total cost of chemotherapy:

- Prechemotherapy care, including staging procedures, physician visits, and initial premedications for the first chemotherapy session only
- Chemotherapy cycles 1 through 6, including diagnostic procedures, physician visits, premedications, and laboratory procedures
- Chemotherapy follow-up, including physician visits and laboratory procedures
- Adverse-event management, including procedures, hospitalizations, and drug therapy.

Certain clinical assumptions were required to provide for reasonable comparisons between agents. These laboratory and diagnostic tests were assumed to be equivalent between agents and oral UFT was assumed to require oral rather than intravenous premedication. As a first step toward development of a total-cost-of-treatment model, a treatment algorithm for the management of colorectal cancer was developed for each country for both adjuvant and metastatic chemotherapy. Expert physician panels were assembled to define each country’s treatment behavior.[7] Treatment algorithms, based on the information and insights obtained from these physician panels, incorporated the physicians’ choice of chemotherapeutic agent as well as the preferred dosage and administration method. A median duration of therapy of six cycles was chosen as the standard duration for these treatment algorithms. Treatment algorithms developed in this manner (based on practicing physicians’ input) are intended to represent community or “real world” practice. They can typically be used to account for differences in local, regional, or national practice patterns. Valuation of such patterns is consistent with the prescribed methodology in published pharmacoeconomic guidelines.[8]

The expert panel was interviewed to identify preferences in the treatment of grade-specific adverse events. Adverse events typically observed with both treatment regimens included diarrhea, nausea/vomiting and mucositis. The 5-FU combination regimen yielded greater hematologic toxicities, such as leukopenia and thrombocytopenia, than were seen with oral UFT. Incidence rates
for adverse events were derived from clinical trial data for each agent.[9-19] The study also used the two unpublished clinical trials as source material.[10,11] An incidence rate for each adverse event was estimated by determining the number of patients experiencing a specific adverse event in each study. The data were summed across all studies and an average incidence rate was obtained. The physician panel identified treatment practices to be assigned to each grade-specific adverse event. It should be noted that some degree of variability in treatment preference existed among physicians, with some physicians advocating more aggressive treatment than others. In cases where variability in preference was seen, a consensus of opinions was developed and used for the purposes of this study. This consensus, however, may not represent actual treatment in all cases. As such, it may be a potential limitation to the study, addressed by the sensitivity analysis described later in this article.

Once the treatment algorithms were established, a cost dictionary was developed to assign a specific cost to each health-care resource identified. The cost dictionary for Brazil was based on information from surveys completed by the local health-care institutions in São Paulo, Brazil. Appropriate economic modifications were applied to the Brazilian data to derive a cost dictionary for Argentina that accurately reflected its economic environment. Treatment pathways and cost dictionaries provide the basic building blocks for total-cost-of-treatment models and comparative economic analyses. The cost of each health-care resource used in the treatment algorithms was obtained from the cost dictionaries and applied to the treatment algorithms for each country. These costs were aggregated across the total duration of therapy to obtain an average total cost of treatment for both adjuvant and metastatic colorectal cancer.

A cost-minimization analysis was performed, comparing a UFT-based combination regimen to a 5-FU-based regimen, in both countries and in both clinical settings (ie, adjuvant and metastatic). A cost-minimization analysis assumes equivalent efficacy for both treatment alternatives and focuses on the total cost of treatment as the only comparative parameter across the two treatment alternatives. Cost-minimization was the analytic technique of choice, as the two alternative treatments have similar efficacy profiles.

**Sensitivity Analysis: Rationale**

The frequent use of secondary data, combined with the need to make assumptions regarding one or more variables, can introduce uncertainty into the study results. Changes in one or more of these assumptions could significantly affect the end results of the study. Sensitivity analysis determines whether the conclusions reached in a study are sensitive to the values of various parameters in the study. This technique tests the robustness of the results and assists in validating the assumptions made throughout the study. Therefore, the results obtained from the cost-minimization analysis were subjected to a multivariate sensitivity analysis, whereby each relevant variable was varied within a 20% range, using the Monte Carlo simulation technique. This simulation technique involves varying multiple input variables simultaneously and examining the effects on the results. This analysis is performed using computer-aided simulations and provides a relative measure of the robustness of the final results.

**Results**

**Brazil: Adjuvant Chemotherapy**

In adjuvant chemotherapy for colorectal cancer, the total average cost per patient of an oral UFT/leucovorin regimen was $9,624 (R10,307 Brazilian reals), only marginally ($30)(R32) less expensive than the present standard of 5-FU/leucovorin or 5-FU/levamisole, costing $9,654(R10,340) (exchange rate: $1.00 US equals approximately 1.071 Brazilian reals). Table 1 illustrates the costs for each treatment component for these two treatments, and the difference in average costs between the two treatments. The cost minimization analysis shows that the higher cost of UFT chemotherapy is adjusted by the lower cost of managing the adverse events associated with UFT.

**Brazil: Chemotherapy for Metastatic Disease**

A cost comparison conducted for patients with metastatic disease yielded a cost differential of $312 (R335) between the two treatment regimens. The total average cost per patient receiving UFT was $10,179 (R10,901), as compared to $10,491 (R11,236) with a 5-FU-based regimen. Table 2 illustrates the costs for each treatment component and the difference in average costs between the two treatments.

**Argentina: Adjuvant Chemotherapy**

When UFT and 5-FU-based chemotherapy for adjuvant therapy of colorectal cancer were compared in Argentina, UFT emerged as a cost-efficient alternative to a 5-FU-based regimen. With a total cost
of $12,295 (P12,292 Argentine pesos) for the UFT regimen (exchange rate: $1.00 US equals approximately 0.9998 Argentine pesos), $782 (P782) of savings are generated relative to the $13,077 (P13,074) cost of the 5-FU-based regimen.

Table 3 illustrates the costs for each treatment component and the difference in average costs between the two treatments. The analysis showed that the cost of chemotherapy was almost identical across both treatment regimens. However, due to the superior adverse-event profile of oral UFT, the UFT regimen resulted in a lower cost of adverse-event management than the 5-FU regimen. As a result, the total cost of treatment with a UFT-based regimen was substantially lower than the cost of a 5-FU-based treatment regimen.

**Argentina: Chemotherapy for Metastatic Disease**

In Argentina, the difference in total cost between UFT and 5-FU-based chemotherapy for metastatic colorectal cancer was the greater, with UFT showing a substantial cost advantage over 5-FU. The total cost of the UFT regimen, $12,369 (P12,367), was substantially lower than $13,557 (P13,555), the cost of a 5-FU-based regimen [a difference of $1,188 (P1,188)]. Table 4 illustrates the costs for each treatment component for these two treatments, and the difference in average costs between the two treatments.

**Sensitivity Analysis**

A multivariate Monte Carlo analysis was performed on the estimated average costs for adjuvant and metastatic chemotherapy in both countries. All study variables were varied simultaneously to test the robustness of the analysis. Even when the costs are varied within a 20% range, the results show that, except in the case of adjuvant chemotherapy in Brazil, the UFT/leucovorin regimen has a cost advantage over the 5-FU-based combination chemotherapy. Figure 1, Figure 2, Figure 3, and Figure 4 illustrate the results of the sensitivity analysis in detail.

**Conclusions**

Increasingly, studies of health economics are being used for the unbiased evaluation of chemotherapeutic treatment decisions. In this study, quantifying treatment cost results indicated an economic advantage for oral UFT over a 5-FU-based regimen in the treatment of colorectal cancer in Brazil and Argentina.

Though some variation in costs is due to physician treatment preferences (ie, timing of lab procedures and diagnostics), the predominant cost drivers for UFT and 5-FU-based regimens are drug acquisition costs and adverse-event management costs, respectively. In addition to the cost of the modulator, leucovorin has a major impact on the final result, specifically in the UFT regimen. The fact that the physician panel generally selected levamisole as an immunomodulator with 5-FU in the adjuvant setting also negatively affects the cost advantage that the UFT regimen has over 5-FU-based therapy.

In Argentina, the economic differentials are similarly driven by drug costs for UFT and adverse-event management costs for 5-FU. The surveyed physicians use leucovorin with 5-FU in the adjuvant setting, unlike the Brazilian physicians, thereby providing a more balanced view when comparing therapies.

Oral UFT may have a positive quality-of-life impact for patients in addition to the estimated economic benefit. Further, the mild toxicity profile of UFT markedly reduces clinic visits and significantly reduces venipuncture procedures. A prospective study determining the impact on quality of life would fully account for the pharmacoeconomic benefit that UFT provides in the treatment of colorectal cancer in Brazil and Argentina.

This pharmacoeconomic model suggests that UFT in the treatment of colorectal cancer in Brazil and Argentina is both a useful and economical alternative to standard 5-FU-based chemotherapy. However, prospective economic research and quality-of-life evaluations are required to fully estimate the pharmacoeconomic impact of oral UFT.

**References:**


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