Capecitabine or infusional 5-fluorouracil for gastroesophageal cancer: a cost–consequence analysis

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ABSTRACT

Background

In patients with advanced gastroesophageal cancer, the phase III Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) trial demonstrated equivalent clinical efficacy when capecitabine (X) was substituted for 5-fluorouracil (5FU) in the epirubicin–cisplatin–5FU (ECF) regimen. The present analysis compares the direct medical costs associated with both regimens.

Methods

This cost–consequence analysis of direct medical costs took resource utilization data from the REAL-2 trial where available. Direct medical costs were derived from the perspective of the Canadian public health care system in 2008 Canadian dollars. Mean cost per patient on each treatment arm was calculated.

Results

Drug costs from start of treatment until first progression, including pre- and post-chemotherapy medications and administration costs, totalled $5,344 for ECF as compared with $3,187 for ECF. Costs for treatment of adverse events were estimated at $2,621 for ECF as compared with $3,397 for ECF. An additional cost of $873 was associated with insertion of an implanted venous access. Total incremental cost of ECF over ECF was $508.

Conclusions

In advanced gastroesophageal cancer, capecitabine is an attractive alternative to 5FU. Although the drug cost per se is greater, use of capecitabine is associated with decreased consumption of hospital resources. Not only does capecitabine fit with patient preference for oral therapy, it also avoids the inconvenience and complications of central venous access.

KEY WORDS

Capecitabine, cost–consequence analysis, gastroesophageal cancer, infusional 5FU

1. INTRODUCTION

Globally, gastric and esophageal cancers are, respectively, the 2nd and 6th most common causes of cancer-related deaths; they are also an important cause of cancer-related morbidity. Surgical resection remains the definitive curative treatment for early-stage disease; however, most patients present with inoperable or metastatic disease. Consequently, overall 5-year survival rates are in the range 15%–25%².

In advanced disease, palliative chemotherapy holds proven benefit in both survival and quality of life (QoL) outcomes when compared with best supportive care alone³⁻⁵, with the 3-drug regimen ECF [epirubicin 50 mg/m² and cisplatin 60 mg/m² every 3 weeks, plus infusional 5-fluorouracil (5FU) 200 mg/m² daily] being a treatment standard⁶⁻⁷.

Challenges in the successful delivery of the ECF regimen include the need for a central venous access and an ambulatory infusion pump for administration of the 5FU, and the potential complications that the access and pump present. Capecitabine (Xeloda: Hoffmann–La Roche, Basel, Switzerland) is an orally administered prodrug of fluorouracil that generates 5FU predominantly within tumour cells by thymidine phosphorylase.⁸ Substitution of capecitabine for infusional 5FU avoids the inconvenience of central venous access and the need for an infusion pump. In addition, in the setting of similar efficacy, most patients prefer oral to intravenous cytotoxic therapy regimens⁹. Substitution of oral for infusional therapy can reduce the time and travel burden for patients and can ease the burden on limited hospital resources. The phase III Randomized ECF for Advanced and...
Locally Advanced Esophagogastric Cancer 2 (REAL-2) trial suggests that in the ECF regimen, capecitabine can be substituted for infusional 5FU without compromising efficacy 10.

Using a 2×2 factorial design, the REAL-2 trial assigned 1002 patients with advanced esophagogastric cancer to 3 weeks of epirubicin and cisplatin with either capecitabine (ECX) or infusional 5FU (ECF), or to epirubicin and oxaliplatin with either capecitabine (ECX) or infusional 5FU (ECF). The study was significantly powered to demonstrate non-inferiority in overall survival for the triplet therapies containing capecitabine compared with 5FU and for the therapies containing oxaliplatin compared with cisplatin. The groups showed no significant difference in terms of objective response rate (40.7%, 46.4%, 42.4%, and 47.9% with ECF, ECX, ECF, and ECX respectively) or progression-free survival (PFS: 6.2 months, 6.7 months, 6.5 months, and 7.0 months respectively). For the capcitabine–5FU comparison, the hazard ratio (HR) for death in the capcitabine group was 0.86 [95% confidence interval (CI): 0.80 to 0.99] with the upper limit of the confidence interval excluding the predefined non-inferiority margin of 1.23. The 1-year survival rate in the ECF group was 37.7% (compared with 40.8% in the ECX group), and median survival was 9.9 months in both groups. Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, version 3. Mean scores on the Global Health Status subscale of that instrument showed no significant differences between the ECF group and the other treatment groups at baseline and at 12 weeks.

Non-inferiority of capcitabine compared with 5FU was further confirmed in a phase III trial from Asia 11. The ML17032 trial randomized 316 patients with previously untreated gastric cancer to receive intravenous cisplatin 80 mg/m² on day 1, with either capcitabine (CX) 1000 mg/m² twice daily, days 1–14, or 5FU (CF) 800 mg/m² daily by continuous infusion, days 1–5. The primary endpoint was non-inferiority for PFS. In the CX arm, PFS was 5.6 months, and in the CF arm, it was 5 months (HR: 0.81; 95% CI: 0.63 to 1.04), which was below the predefined margin of 1.25 for non-inferiority. The median overall survival with CX and CF was similar (10.5 months vs. 9.3 months, \( p = 0.27 \)).

A meta-analysis of the REAL-2 and ML17032 trials confirmed that, in patients treated with capcitabine combinations, overall survival was superior (HR: 0.87; 95% CI: 0.77 to 0.98) to that in patients treated with 5FU combinations 12.

With ECF and ECX having equivalent clinical efficacy and QOL scores, other factors take on greater importance in a decision about whether to adopt this therapeutic strategy. In recent years, the increase in the numbers and costs of treatments available to cancer patients has resulted in increased scrutiny of the impact of newer therapies on health care budgets. Although the decision to adopt a new treatment should not be based primarily on economic factors, cost of care is an important consideration in most health care systems. In addition to clinical benefit, drug cost, and QOL, a treatment’s safety profile, its convenience for patients, and its hospital resource utilization can all affect the overall cost of therapy. In view of increasing constraints on health care expenditures, the economic implications of treatment with capcitabine as an alternative to 5FU should be considered.

2. METHODS

Our cost–consequence analysis of ECF compared with ECX uses the published REAL-2 trial data and is based on the equivalent efficacy between treatment arms reported in that randomized phase III trial. Resources and costs were determined from start of treatment until first progression. The analysis was done from the perspective of the Canadian public health care system, and only direct medical resource utilization and costs were considered. Where available, clinical data were extracted from the REAL-2 trial (chemotherapy doses, including actual dose administered; duration of treatment; and antiemetic therapy). In addition, available data on incidence and severity of toxicities were used.

Costs were determined at Princess Margaret Hospital (PMH) and are presented in 2008 Canadian dollars. Only grade 3 and 4 toxicities based on the U.S. National Cancer Institute’s Common Toxicity Criteria, version 2.0, were considered. Resource utilization for management of toxicities was determined using published practice guidelines, standard Canadian oncology practice, and expert opinion where appropriate.

2.1 Determination of Cost

2.1.1 Cost of Chemotherapy
Chemotherapy cost included drug acquisition, preparation, and administration. Chemotherapy unit administration costs were derived from an earlier analysis and include attributable hotel costs (facilities cost, overhead, medical and surgical supplies) 13. Pharmacist and pharmacy technician salaries and direct nursing care were based on a time-and-motion study at PMH 13. Physician fees were obtained from the 2008 Ontario Health Insurance Plan (OHIP) fee schedule 14.

2.1.2 Cost of Emergency Room Visits and Acute Care Hospitalization
Costs of emergency room (ER) visits, including management, operational, and nursing fees; drug costs; medical, surgical, and miscellaneous supplies (including office supplies, therapeutic and diagnostic supplies); sundry costs; equipment and overhead costs (administration, facilities, housekeeping,
utilities) were updated from an earlier analysis, using the Canadian consumer price index (CPI) 13.

Acute hospitalization costs were derived from the Ontario Case Costing Acute Inpatient Database 2003/2004 and adjusted to 2008 costs using the Canadian CPI. The Ontario Case Costing Acute Inpatient Database provides information on the cost of an International Classification of Disease 10 coded admission 13, with breakdown into direct and indirect costs. Physician fees, modelled on Canadian oncology practice, were added based on the 2008 OHIP fee schedule.

2.1.3 Cost of Outpatient Visits
The cost of outpatient visits was updated (Canadian CPI) from an earlier analysis 13. The hotel approximation method was used, and it included institutional costs that could be attributed to the gastrointestinal cancer clinic at PMH, averaged over the number of visits. The average cost of nursing and supportive care staff, including benefits, educational leave, and hours attributed to the gastrointestinal cancer clinic and workload, were determined. Physician fees were based on the 2008 OHIP fee schedule.

2.1.4 Costs for an Implanted Venous Access
Insertion costs for an implanted venous access were based on actual practice at the University Health Network, plus physician fees (2008 OHIP fee schedule). Total cost included direct patient care (nursing, device, and supply costs) and interventional radiology overhead costs (management and operational support, equipment, and allocated department sundry costs) (Marincic T, University Health Network accounting, April 2008, personal communication).

2.1.5 Other Costs
Cost per unit for red blood cells was provided by the Canadian Blood Services from a high-level costing study (Hannach B, April 2008, personal communication). All transfusions were assumed to be administered in the outpatient setting; additional hotel costs were therefore included. The cost of visiting the outpatient transfusion unit was derived from staff salaries; attributable hotel costs, including facility cost; and medical and surgical supply.

Oral medication cost (including capecitabine) was based on PMH acquisition cost without adjustment for dispensing or mark-up.

Investigation costs were determined from the OHIP 2008 fee schedule, including professional and technical components.

2.2 Determination of Resource Utilization

2.2.1 Cytotoxic Agents
Median dose and duration of treatment was obtained from the REAL-2 trial. Median actual dose administered, which accounted for dose reductions, was provided.

2.2.2 Adverse Events
Grade 3 and 4 adverse event data were obtained from the REAL-2 trial and used to estimate the resources utilized in the treatment of adverse events. Only adverse events with a 2% or greater difference in incidence between the two treatment arms were included. Given the low incidence of grade 4 events with capecitabine and 5FU in analyses 16, grade 3 and 4 nausea and vomiting and diarrhea were costed as grade 3 toxicities. All thromboembolic events were assumed to be deep vein thromboses. All grade 3 and 4 adverse events were assumed to occur only once per treatment course, on the assumption that physicians would modify treatment to minimize further toxicity.

Table I summarizes the adverse events that occurred with a difference in incidence of 2% or more between the treatment arms in the REAL-2 trial, together with the proposed resources utilized for their management 17–19.

3. RESULTS

Table II gives the demographic profile of the patients enrolled in the REAL-2 trial, with characteristics well balanced between the two groups.The predominance of adenocarcinoma reflects its rising incidence in the gastric cardia and gastroesophageal junction 20. Tables III and IV summarize unit costs and estimated resource utilization. Table V shows the total costs for both treatment arms.

The mean cost of chemotherapy drugs per patient is higher in the ECX group and represents the highest contributor to total cost in both arms. Considering chemotherapy drugs alone, the incremental cost of ECX over ECF is $441 per cycle. When considering costs over the entire treatment course, the incremental cost for drug alone (includes antiemetics) increases significantly, to $2741.87, reflecting the longer duration of treatment with ECX (121 weeks for ECX vs. 110 weeks for ECF). The mean number of treatment administration visits almost tripled in the ECF group (approximately 10 extra visits/5.24 cycles) which is reflected in the increased cost for ECF administration ($1145.83 vs. $560.97). Although the adverse event profile was similar between the treatment groups, minor differences in the incidence of serious events (such as febrile neutropenia and venous thrombosis) that heavily affect resource utilization and cost had significant effects on the overall cost difference, with an incremental cost of $776.54 for ECF over ECX for adverse event treatment.

3.1 Sensitivity Analysis

One-way sensitivity analysis demonstrated that the incremental cost of ECX over ECF was most sensitive to changes in capecitabine cost (Figure 1). A variation in the cost of capecitabine of ±20% changed the incremental cost of total treatment in a range from
A 20% increase in the cost of treating thromboembolic events, which may capture possible pulmonary embolic events, had little effect on overall cost difference.

4. DISCUSSION

Our study, conducted from the perspective of the Canadian health care system, identifies capecitabine as an affordable substitute for infusional 5FU in the ECF regimen for the treatment of advanced gastroesophageal cancer.

Drug cost is the major driver of expense in the ECX arm, with an incremental cost of $2,741.87 over ECF.
This incremental cost is partially offset by the greater cost of administration in the ECf treatment group ($1,145.83 for ECf vs. $560.97 for ECx), which reflects the reduction in scheduled visits for chemotherapy administration associated with ECx. The reduction in the number of patient visits not only represents an important economic advantage, but also has a practical effect in increasing patient convenience and facilitating greater patient throughput in treatment centres. Interestingly, as seen in the sensitivity analysis, a reduction of approximately 20% in the cost of capecitabine in this analysis leads to cost neutrality—that is, no difference in cost between ECx and ECf.

Costs for an implanted venous access are also underestimated in this analysis. In the absence of further data, we have considered insertion costs alone, which undervalues the global costs associated with central venous access devices. Of patients treated with 5FU in the REAL-2 trial, 10% required device removal secondary to line complications. Data regarding those complications are not provided, although it is likely that device-related thrombosis and infection are captured in the adverse event profile and are therefore accounted for in our analysis. Central line removal and complications may further narrow the cost difference between the two treatments; they are unquestionably a potential cause of significant morbidity in this population.

Availability of individual patient data would have strengthened this analysis. In the absence of individual toxicity management, assumptions were made regarding general toxicity management. However, any cost difference between the treatment groups is likely to be small. The assumptions made regarding toxicity management are based on standard international guidelines and peer-reviewed publications. Where multiple treatment options were possible, we used the option corresponding to standard clinical practice in a large oncology centre, confirmed using expert opinion.

No indirect costs are included in this analysis. The ECx regimen is associated with fewer scheduled hospital visits, an important consideration when access to treatment centres is difficult. In addition
to transportation costs, there are the indirect costs associated with work absence and loss of productivity for both the patient and relatives who accompany the patient for treatment. Not only do those factors affect cost, but they also potentially affect utility measures. The REAL-2 trial reported no differences in QOL scores between the treatment arms, but we have no direct measures of utility. It might be expected that patient convenience could potentially convert to greater utility in the ECF arm.

To date, few economic evaluations have been published comparing the substitution of capecitabine for 5FU in the treatment of gastroesophageal cancer. By comparison, capecitabine has been more extensively evaluated in colorectal cancer. Two large prospective pharmacoeconomic and cost analyses, and a retrospective claims database analysis, have confirmed that capecitabine-based therapy has a favourable cost profile when compared with infusional 5FU in patients with colorectal cancer. A recent systematic review also reports consistent evidence for the cost-effectiveness of capecitabine in the adjuvant or metastatic setting for colorectal cancer. It is acknowledged that not all patients with gastroesophageal cancer will be suitable for this regimen. Patient compliance and ability to swallow oral medication, which can be a problem in a disease in which dysphagia is often a feature, affect the decision to treat with ECF. However, in patients deemed suitable, our analysis confirms that ECF is a reasonable and affordable option when compared with ECF. Administrators of public or group practice plans should consider these data and support patient and specialist choice to substitute capecitabine for 5FU in the ECF regimen. The increase in cost is modest in an uncommon disease, with clear advantages in terms of convenience and a decrease in the use of hospital resources (that is, chemotherapy administration).

5. CONFLICT OF INTEREST DISCLOSURES

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6. REFERENCES


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