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Cost-Effectiveness Analysis of Systemic Therapies in Advanced Pancreatic Cancer in the Canadian Health Care System

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ABSTRACT

Objectives: To assess the cost-effectiveness of gemcitabine (G), G + 5-fluorouracil, G + capecitabine, G + cisplatin, G + oxaliplatin, G + erlotinib, G + nab-paclitaxel (GnP), and FOLFIRINOX in the treatment of advanced pancreatic cancer from a Canadian public health payer's perspective, using data from a recently published Bayesian network meta-analysis. **Methods:** Analysis was conducted through a three-state Markov model and used data on the progression of disease with treatment from the gemcitabine arms of randomized controlled trials combined with estimates from the network meta-analysis for the newer regimens. Estimates of health care costs were obtained from local providers, and utilities were derived from the literature. The model estimates the effect of treatment regimens on costs and quality-adjusted life-years (QALYs) discounted at 5% per annum. **Results:** At a willingness-to-pay (WTP) threshold of greater than $30,666 per QALY, FOLFIRINOX would be the most optimal regimen. For a WTP threshold of $50,000 per QALY, the probability that FOLFIRINOX would be optimal was 57.8%. There was no price reduction for nab-paclitaxel when GnP was optimal. **Conclusions:** From a Canadian public health payer's perspective at the present time and drug prices, FOLFIRINOX is the optimal regimen on the basis of the cost-effectiveness criterion. GnP is not cost-effective regardless of the WTP threshold.

Keywords: advanced pancreatic cancer, Bayesian network meta-analysis, chemotherapy, cost-effectiveness analysis, economic evaluation, gemcitabine.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in Canada, with a median overall survival (OS) of 3 to 5 months without treatment for those with metastatic disease [1]. With fewer than 5% of patients surviving 5 years, prognosis remains poor as mortality rates in pancreatic cancer closely reflect the incidence rates [2]. The availability of new drugs and combinations, however, has significantly improved the outcome of patients with metastatic pancreatic cancer (MPC), increasing the median OS to 8 to 12 months.

For over a decade, gemcitabine (G) alone has been considered the standard of care for the treatment of MPC because of the promising results of a landmark phase III randomized controlled trial (RCT) that compared G with 5-fluorouracil [3]. Since the publication of this study, many cytotoxic and targeted agents have been tried in combination with G [4–9]. Among these trials, only three have shown statistically significant improvements in median OS and survival rates compared with G monotherapy [3,4,10]. Consequently, G + erlotinib (GE), FOLFIRINOX, and G + nab-paclitaxel (GnP) have emerged as alternatives to G monotherapy for the treatment of chemotherapy-naive patients with MPC.

Despite the success of these treatments in improving the life expectancy of patients with MPC, they are also associated with greater side effects and higher costs than G monotherapy. Furthermore, at present there is a lack of direct pairwise comparisons between these combination therapies. Thus, in a previous study we performed a Bayesian network meta-analysis (NMA) to determine the most effective treatment for advanced pancreatic cancer, taking into account the efficacy and safety profiles of each regimen [11]. A Bayesian NMA, an extension of the traditional pairwise meta-analysis, is used to simultaneously compare multiple interventions even in the absence of direct evidence (i.e., RCTs). In our previous study, we found that FOLFIRINOX had the highest probability of being the best regimen (83%), followed by GnP (11%), on the basis of OS data [11]. In addition, both these regimens had no significant differences in toxicities and the OS

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hazard ratio for FOLFIRINOX versus GnP was 0.79 (range 0.50–1.24) [11].

For optimal resource allocation, decision makers require both efficacy and relative cost data to evaluate trade-offs when choosing between multiple interventions. Because many of the therapies included in this analysis have not been directly compared in head-to-head RCTs, our previously conducted NMA synthesized effectiveness evidence from all sources (direct and indirect) for use in this cost-effectiveness model. The objective of this study was to assess the incremental cost-effectiveness of the alternative treatment options for advanced pancreatic cancer. This was achieved through the development of a decision analytic model populated with data from our previously conducted Bayesian NMA.

Methods

Analytical Framework

We used decision analytic modeling to simulate the lifetime outcomes with different chemotherapeutic regimens in the treatment of advanced pancreatic cancer. A time horizon of 10 years, which effectively equates to a lifetime horizon given the extremely poor prognosis of patients with advanced pancreatic cancer, was adopted for this analysis [2]. Outcomes were assessed in terms of cost and quality-adjusted life-years (QALYs), with cost-effectiveness assessed through estimation of incremental cost-effectiveness ratios (ICERs). Optimal treatment options can be inferred through the conduct of a sequential cost-effectiveness analysis. For this study, the Canadian public health payer's perspective was adopted [12].

Patient Population

Analysis was conducted for a patient cohort representing patients receiving first-line treatment for advanced pancreatic cancer or adenocarcinoma. In the base-case analysis, the mean age of the cohort was 63 years, with 60% of the cohort being male.

Comparators

The predefined basis of this economic evaluation was to conduct a cost-effectiveness analysis on the basis of the regimens included in our recently published NMA [11]. Therefore, the comparators included were G alone (the previous standard of care), G + 5-fluorouracil (GF), G + capecitabine (GCap), G + cisplatin (GCis), G + oxaliplatin (GOx), G + erlotinib (GE), G + nab-paclitaxel (GnP), and FOLFIRINOX. G + tegafur/gimeracil/oteracil (S-1) was excluded in this economic evaluation because S-1 is not approved and marketed in Canada.

Model

We developed a Markov model to estimate the costs and QALYs associated with therapies for advanced pancreatic cancer. The model consisted of three states relating to disease progression: preprogression, postprogression, and death (Fig. 1). During the preprogression state, however, patients can experience side effects from therapy. This can be characterized as having multiple preprogression states (substates)—one relating to the absence of side effects and others relating to the presence of neuropathy, fatigue, diarrhea, febrile neutropenia, and/or rash.

The cycle length was assumed to be 4 weeks. Side effects were assumed to commence at the onset of treatment—within the first cycle—with patients remaining in the relevant health state for a period of time on the basis of the duration of the side effect.

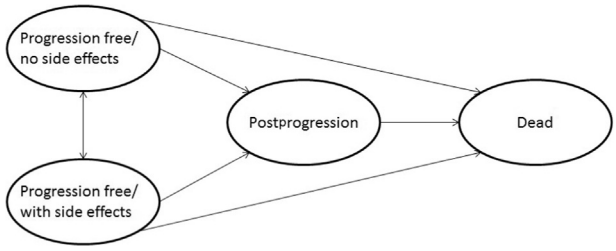

Fig. 1 – Markov model. The model is used to estimate the costs and QALYs associated with therapies for advanced pancreatic cancer. The model consists of three primary states: preprogression, postprogression, and death. Within the preprogression state patients can have either an absence or a presence of side effects. Patients in the preprogression state can transition either to the postprogression state or death or remain in the preprogression state (transition between progression-free survival/with side effects and progression-free survival/with no side effects). Patients in the postprogression state can transition to death or remain in the postprogression state—patients cannot return to the preprogression state. Death is an absorbing state. QALYs, quality-adjusted life-years.

Transition Probabilities

On the basis of the Markov model, patients in the preprogression state can either transition to the postprogression state or death or remain in the preprogression state. Patients in the postprogression state can transition to death or remain in the postprogression state—patients cannot return to the preprogression state. The detailed methods for determining all transition probabilities are provided in Appendix A in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.11.002.

Briefly, for estimation of the transition from preprogression to postprogression or death, we derived data from a published clinical trial based on the methods of Guyot et al. [13] and Van Hoff et al. [14]. The trial was chosen on the basis of there being sufficient data to derive individual patient data as well as its clinical relevance to the Canadian population. The time-dependent probability of transition from the preprogression state was derived through appropriate parametric survival analysis [15]. The chosen model, a Weibull distribution, was judged adequate in that it had both the best fit and a strong clinical face validity. We then applied data from the NMA to estimate transitions for all therapies. To incorporate the impact of side effects into this analysis, pooled estimates of the incidence of each side effect were derived from available trials of G and then odds ratios were applied from the NMA to estimate incidence for other therapies. For sensitivity analysis, this approach was repeated using data from five alternative clinical trials [10,15–18].

Costs

Costs for individual therapies were derived from present funding arrangements under the New Drug Funding Program of the Ontario Public Drug Plan, which covers hospital-administered drugs. For drugs not covered under this program, present costs from the Princess Margaret Hospital in Toronto were applied. Costs were based on target dosage of the drug therapies (mg/m^2/cycle), dose intensity in clinical practice, wastage, administration costs, medical management costs, pharmacy costs, and concomitant medications. The starting dose of the regimens used in this analysis are specified in Appendix B. Analysis assumed an average body surface area of 1.8 m^2. Although drug acquisition costs were considered fixed, both body surface area and dose intensity were considered uncertain. To model a reasonable