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The economic impact of cytoreductive surgery and tyrosine kinase inhibitor therapy in the treatment of advanced gastrointestinal stromal tumours: A Markov chain decision analysis ☆

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Abstract ***Purpose:*** The current first-line treatment for patients with recurrent or metastatic gastrointestinal stromal tumours (GIST) is management with tyrosine kinase inhibition (TKI). There is an undefined role for surgery in the management of these patients. This study uses a cost analysis to examine the economic impact of treating patients with TKI in combination with surgery at different time-points in their treatment trajectories.
Methods: A Markov chain decision analysis was modelled over a 2-year time horizon to determine costs associated with surgery in combination with imatinib mesylate (IM) or sunitinib malate (SU) in seven scenarios varied by TKI agent, dose and disease status (stable versus localised progressive disease). Rates of disease progression, surgical morbidity, mortality and adverse drug reactions were extracted from the existing literature. Deterministic sensitivity analyses were performed to examine changes in cost due to variations in key variables.
Results: The least-costly scenario was to perform no surgery. The most costly scenario was to perform surgery on patients with localised progressive disease on IM 800 mg. The overall range of costs clustered within approximately $47,000 (USD). Variations in surgical cost, surgical mortality and cost of IM demonstrated thresholds for changing the least-costly scenario within plausible tested ranges.
Conclusion: Costs of surgical intervention at different time-points within the treatment course of patients with advanced GIST fluctuate within a relatively narrow range, suggesting that

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costs arise primarily from the administration of TKI. The decision to pursue cytoreductive surgery should not be based on cost alone. Future studies should incorporate health-state utilities when available.

1. Introduction

Gastrointestinal stromal tumours (GIST) are the most common soft tissue mesenchymal tumours of the gastrointestinal system [1]. Histologically, they are usually characterised by the presence of a cell surface tyrosine kinase receptor (KIT), which is a molecular target for treatment [2,3].

The primary management of operable GIST involves complete surgical resection accompanied by tyrosine kinase inhibition (TKI) based on histologic criteria [1]. However, recurrence with localised or distant disease portends a 5-year survival as low as 54%. Furthermore, up to 50% of patients present with unresectable or metastatic disease [4]. Median survival for patients with advanced disease, prior to the advent of TKI, was 10–23 months [4,5], as response to conventional cytotoxic chemotherapy regimens was a dismal 5–10% [6,7].

In 2000, imatinib mesylate (IM, Gleevec, Novartis Pharmaceuticals, Basel, Switzerland), a tyrosine kinase inhibitor of KIT and platelet derived growth factor α, were applied to patients with locally advanced, recurrent and metastatic GIST [8]. IM achieved partial response or disease stability in up to 80% of patients, with an accompanying 2-year survival of 75–80% [8–10]. Although complete response radiographically is rare, durable response for a median of 18–24 months is reported [9–11].

Resistance to IM therapy is believed to arise from secondary KIT mutations. Sunitinib malate (SU, Sutent, Pfizer, New York), a multi-targeted inhibitor, was approved in 2006 for management of patients with IM intolerance or refractory/progressive GIST on IM. Median progression-free survival (PFS) on SU with IM-resistance is 24.6 weeks [12].

The development of molecular drug resistance in the natural history of GIST has prompted clinicians to integrate surgery into management of these patients. The goals of surgery are to remove or cytoreduce clones that are resistant to TKI, and to potentially prolong progression-free intervals and survival [13,29]. Several single-institution studies have reported the feasibility of these operations with 2-year PFS of 52–80% after complete resection for IM-responsive or stable disease [13–17,36]. However, patients in these studies are heterogenous with respect to the activity of their disease, the duration of TKI prior to resection, the extent of disease, the timing of surgery in relation to disease activity and the extent of resection. Furthermore, with only one of these studies offering prospective analysis [36], and none with prolonged follow-up, the ultimate effect of surgery on quality-of-life, PFS and overall survival (OS) is unknown.

Targeted molecular therapies can be costly for insurance payers and/or individuals, but have been shown in pharmacoeconomic studies to be cost-effective [18,19]. Surgical procedures increase overall management costs. However, if surgery can improve PFS, OS and/or quality-of-life, it is critical to optimise its integration with TKI. Further, with the increasing popularity and interest in the concept of oligometastases and their management, analyses addressing the impact of metastasectomy are needed. Since outcome data on these patients are immature, clinicians require present-day tools to inform decision-making in advanced GIST. This study aims to model costs associated with TKI with the inclusion of surgery at different time-points within the treatment trajectory of patients with advanced GIST in order to determine an economically optimal management strategy.

2. Methods

2.1. Model design

A Markov chain cohort simulation model was used in this cost analysis. Although the effect of surgery on quality-of-life is clearly recognised, a cost-utility analysis was not undertaken as there are no published reports of utilities for patients with metastatic and/or recurrent GIST. Although utilities for other metastatic gastrointestinal and soft tissue tumours exist [20–22], the pathobiology and natural history of GIST is markedly different from other tumours and therefore it is inaccurate to extrapolate these quality-of-life measures. Post-surgery utilities for metastatic/recurrent GIST are not included in any existing studies. Cost alone was therefore used as primary outcome in this model.

Markov modelling has two primary advantages over simple decision analysis for this clinical scenario. First, recurrent/ongoing risk (e.g. death, recurrence) is continually simulated over a defined time horizon. Second, sensitivity analyses are used to incorporate uncertainty into the model and ascertain the relative influence of variable factors both within and beyond expected ranges. Modelling provides an ideal approach to this clinical scenario as randomised clinical trial data are not available.

A *time horizon* of 2 years was chosen for this model as IM and SU have median progression-free survivals of 18 months and 24 weeks, respectively [9–12]. Surgery, as an additive treatment strategy, should be considered during this time period in order to evaluate its effect on responsive