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Original Research

Cost-effectiveness analysis of the use of comprehensive molecular profiling before initiating monoclonal antibody therapy against metastatic colorectal cancer in Japan

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ABSTRACT

Introduction: Comprehensive molecular profiling has become a pivotal component of precision medicine involving anti-epidermal growth factor receptor (EGFR) monoclonal antibody therapy for metastatic colorectal cancer. The objective of this study was to determine the cost-effectiveness of comprehensive molecular profiling before initiating anti-EGFR therapies for metastatic colorectal cancer.
Methods: A Markov model simulating the health outcomes and total costs was developed to estimate the life years and quality-adjusted life years (QALYs) gained by metastatic colorectal cancer patients treated with anti-EGFR drug. The cost-effectiveness of comprehensive screening versus *RAS* mutation screening was evaluated over a 5-year period using the incremental cost-effectiveness ratio (ICER). The ICER per additional QALY gained was calculated, and sensitivity analyses were performed to evaluate the robustness of the assumptions across a range of values. Analyses were made from the perspective of the Japanese healthcare payer.
Results: Comprehensive screening before monoclonal antibody therapy provided 0.063 additional QALYs (0.075 life years) at the cost of 268,274 Japanese Yen (JPY). The ICER was 4,260,187 JPY/QALY compared to *RAS* screening. The median progression-free survival obtained by sensitivity analyses for the subgroup not responding to anti-EGFR therapy showed that comprehensive screening and panitumumab prices had the strongest influence on cost-effectiveness.
Conclusion: The incremental cost per QALY gained indicated that comprehensive screening was more cost-effective compared to *RAS* screening. With a willingness-to-pay value of 6 million JPY/QALY, comprehensive screening can be considered for the genetic testing of patients before providing monoclonal antibody therapy.

1. Introduction

Colorectal cancer is one of the most prevalent cancers in Japan and the second-leading cause of cancer deaths [1]. In 2013, 557 billion Japanese Yen (JPY) were spent in Japan on the management of colorectal cancer [2].

Surgery is the treatment of choice for early-stage colorectal cancer, while most patients with advanced colorectal cancer who have lymph node metastasis receive chemotherapy. The purpose of using chemotherapy for unresectable metastatic colorectal cancer is to prolong survival, while maintaining quality of life. Incidentally, at the time of diagnosis, the disease is already at an advanced stage in 56% of patients [2].

Targeted therapies have recently been developed as alternative treatment options for metastatic colorectal cancer. According to the Japanese Society for Cancer of the Colon and Rectum Guidelines, the anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, panitumumab and cetuximab, and bevacizumab, which binds

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the vascular endothelial growth factor (VEGF), may be considered as first-line treatment options in combination with chemotherapy for selected patients with metastatic colorectal cancer [3].

Clinical trials have demonstrated that EGFR-targeted therapies are ineffective in patients with tumors harboring a mutation in the *RAS* oncogene [4,5]. Current Japanese guidelines recommend that all patients with metastatic colorectal cancer should undergo *RAS* testing before treatment with an anti-EGFR drug is considered, and that panitumumab and cetuximab should not be administered to patients with known *RAS* mutations [2,3,6]. In addition, recent studies have reported that *PI3KCA/PTEN* deregulation is also predictive of the poor activity of anti-EGFR monoclonal antibodies [7,8]. More recently, Kameyama et al. identified six gene clusters that commonly show resistance to EGFR-targeted therapies, on Japanese cluster analyses. They suggested that patients with wild-type genes in all these clusters benefited from anti-EGFR therapies [9].

Testing of various mutations is necessary in precision medicine. Comprehensive molecular profiling could be used to identify the candidates who are likely to respond well to EGFR-targeted therapy. This could aid oncologists in selecting the optimal EGFR-targeted therapies for individual patients, thus reducing the cost of treating metastatic colorectal cancer.

However, conducting comprehensive molecular profiling before the initiation of monoclonal antibody therapy is more expensive than conducting *RAS* mutation testing. The cost-effectiveness of comprehensive molecular profiling to predict response or resistance to anti-EGFR therapies is yet to be studied [10–12]. The aim of this study was to evaluate the cost-effectiveness of comprehensive molecular profiling before the administration of anti-EGFR therapies in metastatic colorectal cancer.

2. Methods

2.1. Target population and strategy for mutation screening

We compared the cost-effectiveness of three strategies: anti-EGFR therapy without screening (No testing); *RAS* mutation screening before anti-EGFR therapy (*RAS* screening); comprehensive molecular profiling before anti-EGFR therapy using CancerPlex to screen for mutations that predict a poor response (Comprehensive screening). CancerPlex (KEW Group Inc.) is a next generation DNA sequencing test for solid tumors that can comprehensively identify genetic mutations in more than 400 genes [13].

Based on the Japanese guidelines for treatment of colorectal cancer [3], the first-line of anti-EGFR therapy was mFOLFOX6 (leucovorin-fluorouracil-oxaliplatin) plus panitumumab, while the alternative therapy was mFOLFOX6 plus bevacizumab and the second-line therapy was FOLFIRI (leucovorin-fluorouracil-irinotecan) plus bevacizumab. We assumed that patients whose disease progressed to the terminal stage received the best supportive care as third-line therapy (Table 1).

On day 1 of each 14-day treatment cycle, patients received either bevacizumab (5 mg/kg) followed by mFOLFOX6 (85 mg/m^2 oxaliplatin, 200 mg/m^2 L-leucovorin, intravenous bolus of 400 mg/m^2 fluorouracil, continuous infusion of 2400 mg/m^2 fluorouracil) or panitumumab (6 mg/kg) followed by mFOLFOX6. Patients progressing from first-line chemotherapy also received bevacizumab followed by FOLFIRI (similar to mFOLFOX6 regimen, but with 150 mg/m^2 irinotecan instead of oxaliplatin).

For this analysis, the root of the decision tree consisted of a hypothetical cohort of men with metastatic colorectal cancer before chemotherapy was given as the first-line of treatment; they weighed 60 kg, were 60 years old, and had a body surface area of 1.66 m^2.

We defined three subgroups of genetic mutations: the *RAS ± PTEN* subgroup, the resistant subgroup that included *PTEN + ERBB2*, *PTEN + SRC*, and *BRAF + RNF43* mutations, and the wild-type subgroup. We analyzed the progression-free survival (PFS) with anti-EGFR therapy in these subgroups retrospectively [9].

2.2. Disease modeling

We constructed the Markov model using three health states: progression-free survival (PFS), progressive disease (PD), and death. We assumed that patients who achieved PFS underwent either *RAS* screening or comprehensive screening before receiving combined therapy as the first-line regimen until the progression of disease. A proportion of patients with PD received second-line therapy, and those at the terminal stage discontinued aggressive chemotherapy and received the best supportive care. Transition probabilities of the health state were estimated based on the following equation:

Monthly transition probability $(p) = [1 - 0.5^{(1/\text{mediantimetoevent})}]$ [10].

Disease states in some patients changed from one 4-week cycle to the next. In the end, the period of 5 years was chosen to reflect the limited life expectancy of the patients.

2.3. Model parameters

The clinical efficacy of the first-line combination therapy (mFOLFOX6 plus bevacizumab) for metastatic colorectal cancer, as indicated by the median overall survival (OS) and PFS, and the occurrence of adverse events were calculated according to a previous study [14].

The median PFS for first-line combination therapy (mFOLFOX6 plus panitumumab) for each of the molecular subgroups were estimated based on a previous study [9]. As decisions about continuing or discontinuing anti-EGFR therapy were made at 3 months in clinical practice, the median PFS for patients with *RAS* mutations was also assumed to be 3 months. However, OS in each of the subgroups was unclear from previous study [9]. Therefore, the median OS was estimated from the median PFS according to the regression model for meta-analysis of the association between PFS and OS as reported by Chirila et al. [15]. Adverse events related to panitumumab treatment were obtained from the Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy (PRIME) study [16] (Table 2).

Medical costs pertaining to biomarker testing, drugs, outpatient chemotherapy, diagnostic imaging, and blood tests were included in this model. Since costs were estimated from the health care payer's perspective, only direct medical costs were included. The productivity and mortality costs were not included in the model.

The costs of mFOLFOX6 plus panitumumab, mFOLFOX6 plus bevacizumab, and FOLFIRI plus bevacizumab were calculated according to the Japanese drug tariff from 2014 and fees for medical care [17,18]. The prices of 100 mg vials of panitumumab and bevacizumab were 77,726 Japanese Yen (JPY) and 41,738 JPY, respectively. The cost of best supportive care was set to 218,600 JPY per month. This parameter was subjected to sensitivity analysis.

The model projected that patients who experienced skin toxicity would be treated with minomycin, heparinoids, hydrocortisone acetate ointment, and topical steroids for 3 months. Hypertension was assumed to have been managed with amlodipine and olmesartan in the outpatient setting. All costs are expressed in JPY using 2014 exchange rates reported by the Organization for Economic Co-operation [19,20] (Table 3).

Quality-adjusted life years (QALYs) were used as the primary measure of effectiveness in the current analysis. The values rep-