Clinical and Cost Effectiveness of Bevacizumab + FOLFIRI Combination Versus FOLFIRI Alone as First-Line Treatment of Metastatic Colorectal Cancer in South Korea

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ABSTRACT

Background: Bevacizumab has been extensively investigated in combination with various standard chemotherapies in the treatment of metastatic colorectal cancer (mCRC). However, a comparison to irinotecan + infusional 5-fluorouracil/leucovorin (FOLFIRI) is lacking.

Objective: To explore clinical effectiveness and cost-effectiveness of adding bevacizumab to a regimen of FOLFIRI for the first-line treatment of mCRC in the Republic of Korea by conducting an indirect treatment comparison.

Methods: A health-economic model was developed to investigate the possible health outcomes (life-years gained [LYG]), direct costs, and incremental cost-effectiveness ratio (ICER) of adding bevacizumab to a FOLFIRI regimen. Data on progression-free and overall survival were derived from randomized clinical trials and were used in the indirect treatment comparison. The annual discount rate for costs and outcomes was 5%. A lifetime horizon of 8 years was used. Sensitivity analyses were carried out on all pivotal model assumptions.

Results: Incremental mean overall survival among patients treated with bevacizumab + FOLFIRI varied between 8.6 and 15.7 months compared with patients treated with FOLFIRI alone. The deterministic base-case result was 1.177 LYG. The discounted ICERs ranged from μ31.8 to μ39.5 million/LYG, with the base-case result being μ34.5 million/LYG. Treatment effect had the most impact on the outcomes in this model.

Conclusions: Although there is no formal threshold for ICER per LYG in Korea, funding may be considered for bevacizumab + FOLFIRI, particularly if the severity and end-of-life nature of mCRC is taken into account. (*Clin Ther*. 2012;34:1408–1419)

Key words: antineoplastic combined chemotherapy protocol, bevacizumab, colorectal neoplasms, cost-effectiveness, indirect comparison, Republic of Korea.

INTRODUCTION

Approximately 1 million new cases of colorectal cancer (CRC) are diagnosed each year.[1] In South Korea, CRC is now the second most frequent cancer in men, with 13,670 new cases per year (46.9 per 100,000 men) and is the third most frequent cancer in women, with 9405 new cases per year (25.6 per 100,000

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women).[2,3] The treatment of metastatic CRC (mCRC) has been associated with a significant burden to health care systems. The total direct economic burden of CRC comprises costs of screening, surveillance, diagnosis, hospitalization, surgery, radiotherapy, anticancer agents, supportive care, physician charges, clinic visits, laboratory fees, and medications. As the incidence of mCRC increases with age, the economic burden can be expected to rise steadily as populations age.[4,5] Patients diagnosed with advanced, metastatic disease have a very poor prognosis, with a 5-year survival rate of just 0% to 5%.[6]

Significant developments in the treatment of mCRC have occurred in recent years.[7,8] With developments in systematic chemotherapy, progression-free survival (PFS) and overall survival (OS) times have increased in mCRC.[8] The addition of irinotecan to bolus 5-fluorouracil (FU)/leucovorin (LV) (IFL) was associated with increased PFS and OS in patients with mCRC.[9] Survival was further increased with the combination of irinotecan or oxaliplatin with infusion-based 5-FU or doublet chemotherapy such as infusional 5-FU/LV + irinotecan (FOLFIRI) or infusional 5-FU/LV + oxaliplatin (FOLFOX).[10–13]

Novel targeted therapies have also contributed to the recent progress in the treatment of mCRC. Bevacizumab, a humanized monoclonal antibody, inhibits vascular endothelial growth factor, a key mediator in angiogenesis,[14–16] and has been associated with improved response rates, OS, and PFS in patients with mCRC when combined with a broad range of background chemotherapies.[17–23]

Bevacizumab in combination with various chemotherapies, including IFL[20] but not FOLFIRI (in which 5-FU/LV is administered by continuous infusion), has been extensively investigated in large-scale, randomized clinical trials. The administration of 5-FU/LV by continuous infusion has been associated with less toxicity and slightly better efficacy compared with bolus administration.[7] For this reason, infusional regimens have become more widely used, with IFL being replaced with FOLFIRI in many countries, including the United States. However, no head-to-head, large-scale, randomized, controlled comparisons of FOLFIRI with and without bevacizumab have been published.

To estimate the relative clinical and cost-effectiveness of adding bevacizumab to a regimen of FOLFIRI as first-line treatment of mCRC in Korea, a cost-effectiveness model was developed. Due to the lack of a direct comparison, a double indirect treatment comparison (ITC) was performed to assess the incremental efficacy of adding bevacizumab to a regimen of FOLFIRI.

METHODS

Clinical Studies and Indirect Comparisons

A double ITC analysis was used for comparing the clinical outcomes of 2 treatments, bevacizumab + FOLFIRI and FOLFIRI alone. The efficacy data were derived from 2 Phase III randomized clinical studies that recruited patients with previously untreated mCRC, the ARTIST (Avastin and iRinotecon in firsT lIne metaStatic colorecTal cancer)[19] and BICC-C (Bolus, Infusional, or Capecitabine with Camptosar-Celecoxib)[17] studies.

The ARTIST study enrolled 214 patients at 12 centers in China. Patients were randomly assigned to receive bevacizumab + modified IFL (mIFL) (n = 142) or placebo + mIFL (n = 72). The full analysis set comprised a total of 203 patients (139 and 64 patients in the bevacizumab + mIFL and mIFL arms, respectively).[19]

The BICC-C study was initially designed for comparing FOLFIRI, mIFL, and oral capecitabine + irinotecan (CapeIRI). After the approval of bevacizumab by the US Food and Drug Administration, the BICC-C study was subsequently amended to compare bevacizumab + FOLRIFI to bevacizumab + mIFL, while CapeIRI was discontinued due to toxicity concerns.[17] Hence, in the BICC-C study, patients received either mIFL, FOLFIRI, or CapeIRI in period 1, and bevacizumab + FOLFIRI or bevacizumab + mIFL in period 2. The treatment cycles are described in detail in Table I.[19]

The only available Phase III randomized studies that have investigated the efficacy of bevacizumab + FOLFIRI were the BICC-C study[17] and a more recent study conducted in Greece.[24] The latter study was evaluated but not considered for inclusion in the present analysis due to the limitations and shortcomings related to the design.[25] The comparator arm in the BICC-C study was bevacizumab + IFL, hence the need for an indirect comparison to allow a comparison of bevacizumab + FOLFIRI to FOLFIRI alone. In a targeted literature search to identify studies that have investigated the efficacy of the appropriate irinotecan-based chemotherapy regimens and the addition of bevacizumab to