Original Article

Clinical Response and the Safety of Bevacizumab-awwb Treatment in Patients with Metastatic Colorectal Cancer: A Case Series and Review of the Literature

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Key Words
Biosimilar;
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Background. Bevacizumab-awwb (MVASI®) is the first and only bevacizumab biosimilar to be made available in Taiwan. However, its extrapolation of indication and the lack of available real-world clinical data have raised some concern. This article is aimed at presenting our real-world experience in the use of MVASI for treating patients with metastatic colorectal cancer (mCRC) for purposes of evaluating tumor response and safety.

Materials and Methods. Adult patients from a single institution initiating either MVASI or Avastin use following a mCRC diagnosis during the period of May 2020 to August 2021 were included in the study. Each patient's demographics and tumor characteristics were collated retrospectively. We have described treatment patterns and evaluated treatment efficacy stratified by initiating either or MVASI or Avastin in first line therapy and had at least six months of follow-up period.

Results. In MVASI group, a total of 16 patients were identified, with 2 being excluded due to incomplete therapy and lost follow-up. The mean age of the subjects was 58.8 years. Most patients had a left-sided colorectal tumor (85.7%) and subsequently underwent a primary tumor resection (85.7%) prior to systemic antineoplastic therapy. The disease-control rate (DCR) was 85.7%. Only two patients (14.3%) encountered adverse events during therapy. In Avastin group, a total of 20 patients were identified with one being excluded due to lost follow-up. The mean age was 67.4 years. Thirteen patients had a left-sided colorectal tumor (68.4%) and seventeen patients (89.5%) underwent primary tumor resection before systemic therapy. The disease-control rate (DCR) was 73.7%.

Conclusion. Our early experiences suggest the clinical adoption of bevacizumab-awwb (MVASI) has potential to serve as an alternative Avastin in treating mCRC patients. The strategy of switching between the biosimilar and reference product is currently controversial, and therefore further studies are still required.

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Colorectal cancer (CRC) is the third most common type of cancer globally, and the fourth leading cause of cancer deaths, accounting for 8.6% of all tumor-related mortality,[1] ranking it in the top three of incidence rates for adult cancer patients in Taiwan.[2] If diagnosed at an early stage, colorectal cancer is generally associated with a good prognosis. However, nearly 25% of patients are presented with an initial diagnosis of stage IV, with approximately half of CRC patients eventually developing metastatic disease. The 5-year survival rate for non-metastatic colorectal cancer is 90.6%, while for distant metastasis it is 14.7%.[3] Consequently, a more advanced stage of colorectal cancer is associated with a higher mortality rate. Fortunately, treatment for metastatic colorectal cancer (mCRC) has evolved significantly, making for great progress in survival rates over the past 20 years. In the era when fluorouracil (FU) was being used as the sole active agent, the median overall survival (OS) of patients with mCRC participating in clinical trials was approximately 11 to 12 months. Several factors have since contributed to improvements in clinical outcomes, with one crucial factor being the development of novel biologic therapies targeting either epidermal growth factor signaling or angiogenesis. The median OS of patients with mCRC in the modern era has risen to approximately 30 months since either Anti-epithelial Growth Factor Receptor (Anti-EGFR) or Anti-vascular Endothelial Growth Factor (Anti-VEGF) was approved by the FDA.[4]

Bevacizumab, a monoclonal antibody directly binding to Vascular Endothelial Growth Factor (VEGF) and preventing it from interacting with VEGFR-1 and VEGFR-2 on endothelial cells contributes to the regression of existing tumor vasculature and blockage of new vessel growth, thereby inhibiting tumor growth.[5] The efficacy and safety of bevacizumab has been validated in numerous randomized trials which have been conducted since 2004.[6] FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin and irinotecan) plus bevacizumab resulted in a median overall survival rate of 29.8 months and a median progression-free survival rate of 12.3 months in a Triplet plus Bevacizumab (TRIBE) trial.[7] Bevacizumab is currently part of standard first-line treatment for mCRC and used in combination with various chemotherapy backbones according to NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer, Version 2.2021.[8]

Although targeted antineoplastic biologic therapies such as bevacizumab are associated with significant clinical benefits, certain barriers to these treatments exist under different circumstances, for example, the relatively high expense for patients who can't afford the treatment.[9] Biosimilar is a term used to identify a biological product that is highly similar in high-order structure and functional activity to an original product, without any clinically meaningful deference being seen from the existing biologics. Biosimilars thereby provide an alternatively cost-effective therapy for health care systems, while also increasing patient access to these agents.

Bevacizumab-awwb (MVASI) is the first antineoplastic biosimilar, as well as the first bevacizumab biosimilar to be approved by the U.S. FDA. Its approval in September 2017 was based on a totality of evidence, including results from a comparative clinical trial which demonstrated there was no clinical difference in safety or efficacy with bevacizumab (Avastin®) in a non-small cell lung cancer (NSCLC) setting. MVASI conducts an extrapolation indication for mCRC patients based on the scientific justification regarding knowledge of the mechanism of action, pharmacokinetics, efficacy, safety and immunogenicity of the reference product (RP).[10-12] However, the inadequate real-world experience surrounding MVASI still raises some concerns regarding oncological efficacy, adverse effects, and clinical outcome of interchangeability and post-approval surveillance.[13] Therefore, we would like to present our clinical experience surrounding the use of MVASI in evaluating both its safety and efficacy for mCRC patients.

Materials and Methods

We conducted this retrospective review on the use of MVASI (MVASI™, Amgen Inc.) in order to evaluate patient response and its safety as seen in a single-institution series during the period from May 2020 to August 2021. We identified patients diagnosed with

metastatic colorectal cancer, aged ≥ 18 years, who had initiated MVASI or had switched from reference bevacizumab in first line therapy and had at least six months of follow-up period. We also retrospectively reviewed the use of reference bevacizumab (Avastin) under the same conditions to serve as a comparison group. Initial work-up included general history and a physical examination, as well as common hematology, biochemistry and serum biomarkers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA-199) tests. For further imaging study, chest X-rays, abdominal sonographies and computed tomographies (CTs) or magnetic resonance imaging (MRI) were performed. Bone scans or positron emission tomography (PET) were performed selectively if specific sites showing metastases were suspected. Patient demographics, as well as tumor characteristics including age, gender, Eastern Cooperative Oncology Group (ECOG) performance, medical costs from either self-paid expenses or National Health Insurance (NHI) coverage, primary tumor location, genomics of K-ras status, and any metastatic organs were all collated prior to therapy. We outlined the treatment pattern, which included chemotherapy backbone, lines of systemic therapy, and duration of treatment. Patients with prior Avastin® utilization were those who had previously received Avastin® following a mCRC diagnosis, and who later switched to MVASI, regardless of disease progression. The period for the first response assessment with CT or another imaging study was typically 3 months after initial work-up had been performed. Treatment responses were classified according to the response evaluation criteria in solid tumors (RECIST).[14] This study was a descriptive analysis, with no formal hypotheses being tested. All enrolled patients received a comprehensive assessment and an informed consent regarding the potential pros and cons associated with the differences between the bevacizumab biosimilar and the reference product (Avastin®).

Results

Patient demographics & tumor characteristics

We identified a total of 16 patients who were ever receiving MVASI and 20 patients who were receiving Avastinas the first line systemic therapy for mCRC during the period of May 2020 to August 2021 (Table 1). In MVASI group, two patients who refused to complete chemotherapy due to personal reasons and were lost during follow-up were excluded. Mean age of the patients was 58.8 years and all had an ECOG performance status grade of either 0 or 1 at MVASI initiation. Eight male patients were identified. While eleven patients were covered by the National Health Insurance plan, the remaining paid their medical costs out-of-pocket. Whether these self-paid expenses were covered by commercial insurance policies was not investigated. Twelve patients had a primary left-sided colorectal tumor (85.7%) and two patients had a right-

Table 1. Patient demographics & tumor characteristics

	MVASI group (n = 14)	Avastin group (n = 19)
Age – years, mean (range)	58.8 (40-75)	67.4 (43-85)
Gender – no. (%)	Male: 8 (50%)	Male: 8 (42.1%)
ECOG ≤ 1	14 (100%)	19 (100%)
Medical cost – no. (%)	Self-paid: 3 (21.4%), NHI coverage: 11 (78.6%)	-
Primary tumor location – no. (%)	Left side: 12 (85.7%), Right side: 2 (14.3%)	Left side: 13 (68.4%), Right side: 6 (31.6%)
Primary tumor resection – no. (%)	12 (85.7%)	17 (89.5%)
Metastatic site – no. (%)	One site: 8 (57.1%) – liver: 5, bone: 2, ovary: 1	One site: 12 (63.2%) – liver: 7, lung: 5
	Two sites – liver & lung: 1 (7.1%)	Two sites: 2 (10.5%) – liver & lung: 2
	Peritoneal seeding: 5 (33.3%)	Peritoneal seeding: 5 (26.3%)
Metastatic resection – no. (%)	4 (28.6%)	2 (10.5%)
K-ras mutation positive – no. (%)	13 (92.9%)	16 (84.2%)

ECOG, Eastern Cooperative Oncology Group; NHI, National Health Insurance.

sided colon tumor (14.3%). Most patients (85.7%) had previously undergone primary tumor resection prior to systemic antineoplastic therapy. Eight patients had only one metastatic site or organ, one had both liver and lung metastasis simultaneously, and five had peritoneal seeding with or without other distant metastasis. Only four patients eventually underwent surgery for metastatic resection. All patients underwent an All-RAS gene mutation test prior to systemic antineoplastic therapy, of which thirteen (92.9%) presented a positive K-ras mutation. In Avastin group, one patient lost follow-up was excluded. Mean age of the patient was 67.4 years and eight male patients were idenfitied. Thirteen patients had a left-sided colorectal tumor (68.4%) and six patients had a right-sided colon tumor (31.6%). Seventeen patients (89.7%) had primary tumor resection before systemic therapy. Twelve patients had only one metastatic site or organ, two had both liver and lung metastasis simultaneously, and five had peritoneal seeding with or without other distant metastasis. Only two patients underwent surgery for metastatic resection. Sixteen patients (84.2%) had positive K-ras mutation.

Treatment patterns & clinical outcomes

As shown in Fig. 1, at MVASI initiation (an intravenous dose of 5 mg/kg), a total of eleven patients received chemotherapy backbone as FOLFIRI. Their treatment consisted of a 180 mg/m^2 intravenous infusion of irinotecan for 120 minutes followed by a 400 mg/m^2 intravenous infusion of leucovorin for 120 minutes, a 400 mg/m^2 intravenous bolus of fluorouracil, and a 2400 mg/m^2 continuous infusion of fluorouracil for 48 hours. Additionally, two patients received FOLFOX, consisting of a 85 mg/m^2 intravenous infusion of oxaliplatin concurrent with a 400 mg/m^2 intravenous infusion of leucovorin for 120 minutes, followed by a 400 mg/m^2 intravenous bolus of fluorouracil, and total 2400 mg/m^2 continuous infusion of fluorouracil for 48 hours, while the remaining patients received oral chemotherapy drugs, including tegafur-uracil or capecitabine. At least 8 treatment cycles were repeated every 14 days. Three patients had experienced prior Avastin utilization and later switched to MVASI due to economic reasons. Only two patients ever experienced adverse events, leukopenia and shortness of breath, and both had their symptoms relieved quickly after receiving supportive treatment, with the two of them continuing their subsequent cycles of MVASI without another adverse event occurring. Overall, the disease control rate (DCR) was 85.7%, with one patient showing complete response, seven partial response, and four stable disease. Amongst patients switching from Avastin to MVASI, one of the three showed disease progression, while none experi-

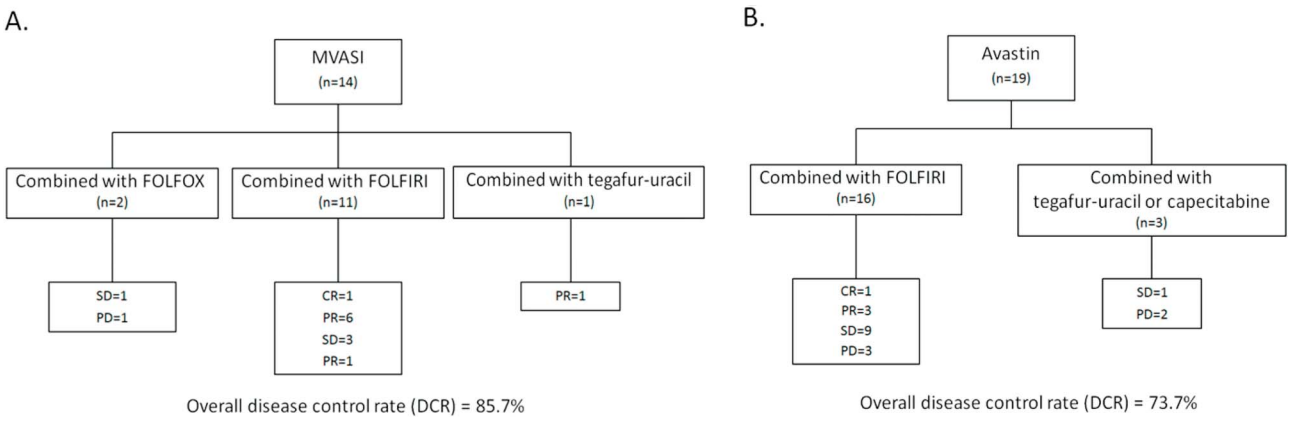

Fig. 1. Treatment flow chart related to outcomes. (A) In MVASI group, a total of 1 patient with complete response (CR), 7 patients with partial response (PR), 4 patients with stable disease (SD) and 2 patients with progressed disease (PD). The disease control rate was 85.7%. (B) In Avastin group, a total of 1 patient with complete response, 3 patients with partial response, 10 patients with stable disease and 5 patients with progressed disease. The disease control rate was 73.7%.

enced any adverse effects. On the other hand, the dose regimen of Avastin and chemotherapy backbone was identical to that of Mvasi's group. A total of sixteen patients received chemotherapy backbone as FOLFIRI and the remaining patients received oral chemotherapy drugs. The disease control rate was 73.7%, with one patient with complete response, three partial response, ten stable disease and five progressed disease.

Discussion

According to the rapid development seen in screening methods and the profound experience of novel antineoplastic therapies, survival outcomes in patients with colorectal cancer have been greatly improving.[15] In general, treatment of colorectal cancer is based on the patient's disease stage, pathological features, microsatellite instability status, genomics, possible adverse effects from treatment, age, performance status and patient preference. The mainstay of systemic treatment is oxaliplatin- and irinotecan-based regimens (including FOLFOX, CAPEOX and FOLFIRI), with or without biologic therapies, including anti-angiogenic or anti-epithelial growth factor monoclonal antibodies.[8] Pivotal trials based on anti-angiogenic therapy for CRC were initiated in 2004, and comprised the phase II and phase III AVF2107 trials.[6] Hurwitz et al. confirmed their superiority, where a median PFS of 10.6 months for chemotherapy combined with bevacizumab was better than that of 6.2 months for only chemotherapy with a placebo. Benefits in median overall survival duration (OS: 20.3 vs. 15.6 months) were also noted [6] Several trials, as well as analyses investigating the effectiveness and safety of bevacizumab monotherapy or bevacizumab-containing chemotherapy, have recently been held which indicate that the use of bevacizumab as a part of first-line treatment for mCRC was associated with an improvement in either OS or PFS.[16,17] Hurwitz et al., in 2009 indicated that both patients experiencing K-ras mutation and wild genotype may benefit from bevacizumab,[16] while Hegewisch et al., in 2018 indicated that both left- and right-sided colon tumor patients reported a favorable response to bevacizumab.[17] Herbert et al. indicated that higher incidence rates (78.1%) of grade ≥ 3 adverse events such as hypertension (7.7%), proteinuria (1.7%), bleeding (4.0%), wound healing complications (0.9%), gastrointestinal perforations (2.2%), and venous thromboembolic events (8.2%) occurred with bevacizumab treatment,[20] while it still remained relatively safe and effective in elderly patients with mCRC concomitant as most adverse events were deemed clinically manageable.[21]

Despite the advantages of bevacizumab, certain factors have limited access to this optimal treatment for some mCRC patients. For example, a cross-sectional questionnaire survey in 2007 involving Canadian medical oncologists treating mCRC patients found that although all respondents considered bevacizumab as a component of the ideal first-line regimen, only 18% could use bevacizumab routinely.[22] Access-related issues as a barrier to prescribing bevacizumab were also frequently cited by physicians of emerging markets. Lack of reimbursement, as well as high out-of-pocket costs, were also cited as predominant concerns, with nearly half of physicians prescribing a bevacizumab biosimilar, if one was available on the premise of it having non-inferior outcomes and a lower cost.[23]

The current NHI reimbursement policy for CRC treatment in Taiwan generally adheres to the NCCN guidelines. The NHI has approved a 36-week bevacizumab regimen in combination with FOLFIRI, FOLFOX or fluorouracil-based chemotherapy as first-line treatments for mCRC. Currently, single-agent fluoropyrimidine is the preferred option for maintenance therapy in Taiwan. Amongst all antineoplastic agents, the number of prescriptions as well as the expense of monoclonal antibodies including bevacizumab and cetuximab (anti-EGFR), have steadily increased in Taiwan, reaching 2.1-fold (2.75% to 5.79%) and 1.6-fold (14.63% to 23.84%) respectively, between 2009 and 2012.[24] Thus, the cost of the targeted therapy and NHI's reimbursement guidelines are likely to influence the treatment choice for many patients, while also significantly impacting the overall budget and disbursement policy of the NHI.[25]

In recent years, the expiration of pharmaceutical

patents has offered an opportunity to develop biosimilar products for current therapies. According to the U.S. FDA's definition, a biosimilar product is highly similar to the reference product, not withstanding minor differences in their clinically inactive components, while also possessing no clinically meaningful differences to the reference product in terms of their safety, purity and potency.[26] The causal savings in development costs for a biosimilar product and its impact on pricing due to commercial competition would provide the potential to both widely increase patient access and lower the healthcare budget.[27] ABP-215 (US: MVASI™ [MVASI] approved in September 2017; EU: MVASI™ [bevacizumab] approved in January 2018; Amgen Inc.) is the first approved biosimilar for bevacizumab (Avastin®) and was launched in a real-world setting in July 2019. A comprehensive stepwise assessment for the totality of evidence was comprised of analytical characteristics for structural and functional similarity, a pharmacokinetic study conducted in healthy adult men (n = 202), as well as a comparative clinical trial evaluating its efficacy and safety in patients with stage IV or recurrent squamous non-small cell lung cancer (n = 642).[28-30] The validated totality of evidence supported the approval of ABP-215, as well as scientific justification for its extrapolation to all approved treatments where bevacizumab could be used as a reference product in metastatic colorectal cancer and other cancers, with an exception for regulatory exclusivities.[11,32] The interchangeability between biosimilars and reference products remains controversial. The U.S. FDA acknowledges that approval of a biosimilar does not automatically imply interchangeability, and therefore additional designated switching studies are still required in order to demonstrate the interchangeability of biosimilars. However, the European Medicines Agency does not offer any recommendations on whether a biosimilar product is interchangeable with its reference product.[33] In Taiwan, a switching policy has not yet been fully established, however a physician could still prescribe a biosimilar product for an eligible patient who had received prior reference product treatment, provided that a comprehensive clinical evaluation and the process of informed consent was ensured. Jin R, et al. conducted the first study describing the real-world utilization of MVASI from the first 12 months following market entry across all approved tumor types in both RP-naïve patients and patients who were previously treated with RP, with no distinctive differences in patient characteristics between the two groups.[34]

A retrospective, real-world study which had enrolled a total of 304 patients diagnosed with mCRC who initiated MVASI as either first- or later-line treatment, demonstrated that most patients (83%) experienced no disease progression between their last treatment with the reference product and the starting of treatment with a bevacizumab biosimilar.[35] The characteristics of the patient population included in our study are generally consistent with those of the Chinese mCRC population. Wang F et al. (2021) conducted an efficacy analysis of bevacizumab (Avastin®) combined with chemotherapy in a total of 611 Chinese mCRC patients, where the disease control rate was 89.40% and any adverse events associated with bevacizumab was found to be 46.98%.[36] Our findings suggest that the efficacy of bevacizumab-awwb (MVASI®) was comparable with previous studies regarding a bevacizumab reference product, when used exclusively as first-line therapy. However, due to the limitation about the lack of subclassification of patients naïve to Avastin and switchers in MVASI group, as well as the immortal time before switching to MVASI may have biased the efficacy and safety analysis in switchers. It is our belief that any policy of switching between MVASI and the reference product should be taken cautiously.

Conclusions

This study is aimed at presenting our initial experience in the real-world use of bevacizumab-awwb (MVASI®), the first and only bevacizumab biosimilar available to date in Taiwan. Our early experiences suggest the clinical adoption of bevacizumab-awwb (MVASI) has potential to serve as an alternative Avastin in treating mCRC patients, while the switching strategy is lacking experience, further studies are still required.

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Author Contributions

Dr. Chun-Yen Hung analyzed the clinical data and wrote the original manuscript.

Dr. Chou-Pin Chen and Dr. Chou-Chen Chen were both involved in patient enrollment and administration of antineoplastic therapy.

All authors contributed to editing the manuscript and approved the final version.

Availability of Data and Materials

All data generated and analyzed during this study are included in this published article.

Declarations

This study was approved by the Institutional Review Board of Taichung Veterans General Hospital (No:CE21171A) and written informed consent was obtained from each patient. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for Publication

Not applicable.

Competing Interests

The authors declare they have no competing interests in this work.

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原　著

轉移性大腸癌患者接受 Bevacizumab-awwb 治療的臨床反應與安全性：個案系列及文獻回顧

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目的　Bevacizumab-awwb (MVASI®) 是第一個且目前唯一在台灣上市的 bevacizumab 生物相似藥。然而，其適應症的外推和缺乏現實世界的臨床數據引起了一些關注。本文旨在介紹我們使用 MVASI 治療轉移性結直腸癌 (mCRC) 患者方面的真實世界經驗，並以評估腫瘤反應和安全性。

材料與方法　我們收錄 2020 年 5 月至 2021 年 8 月期間在單一機構診斷為 mCRC 後開始使用 MVASI 或 Avastin 的成年患者。回顧性收集每位患者的人口統計學和腫瘤特徵數據。我們描述了治療模式並根據首線治療中的 MVASI 或 Avastin 開始進行評估，並具有至少六個月的隨訪期。

結果　在 MVASI 組中，共確定了 16 名患者，由於療程不完整和失去追蹤而排除了 2 名患者。被納入患者的平均年齡為 58.8 歲。大多數患者有左側結直腸腫瘤 (85.7%)，在全身抗腫瘤治療之前進行原發腫瘤切除手術 (85.7%)。疾病控制率 (DCR) 為 85.7%。在治療期間，只有兩名患者 (14.3%) 出現了不良事件。在 Avastin 組中，共確定了 20 名患者，其中一名因失去追蹤而被排除。平均年齡為 67.4 歲。十三名患者患有左側結直腸腫瘤 (68.4%)，十七名患者 (89.5%) 在全身治療之前接受了原發腫瘤切除手術。疾病控制率 (DCR) 為 73.7%。

結論　我們的早期經驗表明，Bevacizumab-awwb (MVASI) 在治療 mCRC 患者中具有作為 Avastin 替代品的潛力。目前，生物相似藥和參考製劑之間切換的策略仍存在爭議，因此仍需要進一步研究。

關鍵詞　生物相似藥、艾法施 (MVASI®)、轉移性大腸直腸癌。