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Biosimilar

Real-World Evidence for Comparative Outcomes between Innovator and Biosimilar Bevacizumab in Advanced Colorectal Cancers

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Abstract

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Purpose Generic versions of bevacizumab are commonly used in India in patients with advanced/metastatic colorectal cancers (mCRCs), but there is limited real-world evidence (RWE) about their efficacy in comparison to the innovator bevacizumab.

Methods Patients diagnosed with mCRC between January 2017 and January 2022 and receiving a combination of chemotherapy and bevacizumab were retrospectively analyzed for demographic variables and survivals. The primary endpoint of the study was the estimation and comparison of median progression-free survival (mPFS) between patients receiving innovator versus generic bevacizumab as first-line therapy (CT1) by the Kaplan–Meier method.

Results A total of 944 patients were included in the analysis, of whom 652 patients (69%) received bevacizumab as CT1, 449 patients (48%) during second-line chemotherapy (CT2), and 74 patients (8%) during third-line therapy (CT3). The innovator was administered to 132 patients (14%), while the remaining 812 patients (86%) received a generic molecule. With a median follow-up of 18 months, there was no difference in mPFS between patients receiving the innovator or biosimilar (10 vs. 9.3 months, $p = 0.62$). Similarly, there was no difference in median overall survival (mOS) between patients receiving the innovator or biosimilar during CT1 (17.8 vs. 18 months, $p = 0.85$). Among the patients who received bevacizumab during CT2, there was no statistically significant difference in mPFS between the innovator and the biosimilar (5.5 vs. 5.8 months, $p = 0.97$), nor was there a difference in mOS between patients receiving the innovator or biosimilar during CT2 (8.15 vs. 8.58 months, $p = 0.16$).

Conclusion The current study offers RWE to suggest similar outcomes with innovator and generic bevacizumab when combined with chemotherapy in mCRCs. This has significant implications in India and other low- and middle-income countries besides providing oncologists with greater confidence to use these molecules in their clinical practice.

Keywords

- colorectal cancer
- bevacizumab
- biosimilar
- LMICS
- Real-world evidence

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Introduction

Bevacizumab is a humanized monoclonal antibody that binds to all circulating and soluble vascular endothelial growth factor-A (VEGF-A) isoforms. By binding to VEGF-A, bevacizumab prevents the interaction of VEGF-A with VEGF receptors, thereby inhibiting the activation of VEGF signaling pathways that promote neovascularization and carcinogenesis.[1]

Bevacizumab is one of the mainstays in managing advanced/metastatic colorectal cancers (mCRCs). It is used across scenarios in combination with chemotherapeutic agents and rarely alone as maintenance.[2–5] While bevacizumab was developed by Roche (Avastin, Roche), it went off patent in 2016, after which multiple biosimilars became available for Indian patients being treated with bevacizumab. These biosimilars were cheaper than the innovator molecule (Avastin, Roche). Although these biosimilars went through the due regulatory process before being available in the Indian market, there is limited real-world evidence (RWE) to suggest equivalence or similar outcomes with the use of these molecules. With this background, the investigators conducted a retrospective audit to compare the survival outcomes between patients with mCRC receiving the innovator and biosimilar molecules.

Materials and Methods

Patient Selection

The current retrospective study aimed to evaluate the survival of patients with mCRC receiving a combination of chemotherapy with bevacizumab, whether innovator or biosimilar. The innovator bevacizumab refers to Avastin (Roche), while the biosimilars used were Bevacirel (manufactured by Reliance Life Sciences), Bryxta (manufactured by Zydus Cadila), and Versavo (Dr. Reddy's Laboratories).[6–8] The investigators evaluated data from a prospectively maintained CRC database at Tata Memorial Hospital (TMH) and included patients who had been treated between January 2017 and January 2022. Patients included in the study satisfied the following criteria: histologically confirmed adenocarcinoma, radiologically confirmed unresectable or metastatic cancer, started on chemotherapy plus bevacizumab and had at least one follow-up visit documenting response postadministration, and had documented dates of starting and cessation of chemotherapy plus bevacizumab.

Clinical Data Collection and Endpoints

Data collected were demographic and clinical variables, details of chemotherapy plus bevacizumab administration in terms of first line, second line, or during later lines of therapy, adverse events, and oncologic outcomes. The primary endpoint of the study was a comparison of median progression-free survival (mPFS) between patients receiving innovator bevacizumab and generic bevacizumab as first-line therapy (CT1). Secondary endpoints included comparison of mPFS between patients receiving innovator bevacizumab and generic bevacizumab as second-line therapy (CT2), comparison of mPFS between patients receiving innovator bevacizumab and generic bevacizumab beyond second-line therapy (CT3), and comparison of median overall survival (mOS) between patients receiving innovator bevacizumab and generic bevacizumab as CT1.

Ethical Approval and Consent

The approval for the study was obtained from the Institutional Ethics Committee at TMH (IEC418). The approval included the requirement of a short telephonic consent for patient data accrued in TMH as part of ethics committee requirements. Data collection and handling were conducted as per the ethical guidelines of the Declaration of Helsinki.

Statistics

Data were analyzed using IBM SPSS version 20 (Armonk, NY, United States). Descriptive statistics such as median, frequency, and percentage were used to summarize the categorical variables. The primary endpoint of the study was the mPFS of patients receiving chemotherapy plus bevacizumab as CT1 and this was calculated from the date of diagnosis of starting CT1 to the date of progression, loss to follow-up, or death, whichever was earlier. mPFS during CT2 was similarly calculated. mOS during CT1 was calculated from the date of starting CT1 to the date of death or loss to follow-up, whichever was earlier. mOS during CT2 was similarly calculated. Survival analysis was performed using Kaplan–Meier estimates, and the log-rank test was used for bivariate comparisons.

Results

Baseline Characteristics

A total of 944 patients received bevacizumab during the study period. This included 652 patients (69%) who received bevacizumab during CT1, 449 patients (48%) during CT2, and 74 patients (8%) during CT3. A detailed report of the clinical characteristics of patients in the study is presented in ►Table 1, while the characteristics of systemic therapy received are presented in ►Table 2. Overall, 132 patients (14%) received the innovator, while 810 patients (86%) received a biosimilar molecule.

Survival Endpoints

With a median follow-up of 18 months, among the 652 patients who received bevacizumab during CT1, 83 patients (13%) received the innovator bevacizumab, while 569 patients (87%) received a biosimilar bevacizumab. There was no difference in mPFS between patients receiving the innovator or biosimilar (10 vs. 9.3 months, $p = 0.62$; ►Fig. 1). Similarly, there was no difference in mOS between patients receiving the innovator or biosimilar during CT1 (17.8 vs. 18 months, $p = 0.85$).

Among the 449 patients who received bevacizumab during CT2, 63 patients (14%) received the innovator bevacizumab, while 386 patients (86%) received a biosimilar bevacizumab. There was no statistically significant difference in mPFS between patients receiving the innovator and biosimilar (5.5 vs. 5.8 months, $p = 0.97$), and there was no difference in mOS between patients receiving the innovator or biosimilar during CT2 (8.15 vs. 8.58 months, $p = 0.16$).

Table 1 Baseline demographic and clinical characteristics ($n = 944$)

Characteristic	No. (percentage where applicable)
Median age (y)	
• Age <60	666 (70)
• Age ≥60	278 (30)
Gender	
• Female	305 (32)
• Male	639 (68)
Nature of metastatic CRC	
• De novo metastatic	627 (66)
• Recurrent metastatic	317 (34)
Location of primary tumor	
• Right sided	308 (33)
• Left sided	546 (58)
• Transverse	69 (7)
• Epicenter not identified	21 (2)
Prior local therapy	
• Resection of primary	317 (34)
• Radiotherapy to primary	96 (10)
Signet ring histology	
• Yes	72 (8)
• No	872 (92)
Mucinous histology	
• Yes	30 (3)
• No	914 (97)
Sites of metastases	
• Hepatic	486 (52)
• Peritoneal/omental	426 (45)
• Pulmonary	223 (24)
• Osseus	60 (6)
• Brain	8 (1)
• Leptomeningeal disease	0
• Others	NA
ECOG PS	
• 0	72 (8)
• 1	627 (66)
• 2	218 (23)
• >2	27 (3)

Abbreviations: CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

The complications related to bevacizumab were similar in both the groups and are described in ►**Supplementary Table S1** (available in the online version only). Even though perforations were numerically more in biosimilars, tumor perforations were also included in this, and separate data are not available. The data on the bleeding complications cannot be captured separately as tumoral bleeds are very common especially in the left-sided tumors.

Table 2 Details of bevacizumab administration (n = 944)

Characteristic	No. (percentage where applicable)
Receipt of bevacizumab (overall) • First line • Second line • Third line • Beyond third line	944 (100) 652 (69) 449 (48) 74 (8) 7 (<1)
Receipt of innovator bevacizumab • First line • Second line • Third line • Beyond third line	132 (14) 83 (9) 63 (7) 10 (1) 4 (<1)
Receipt of generic bevacizumab • First line • Second line • Third line • Beyond third line	812 (86) 569 (60) 386 (41) 64 (7) 3 (<1)

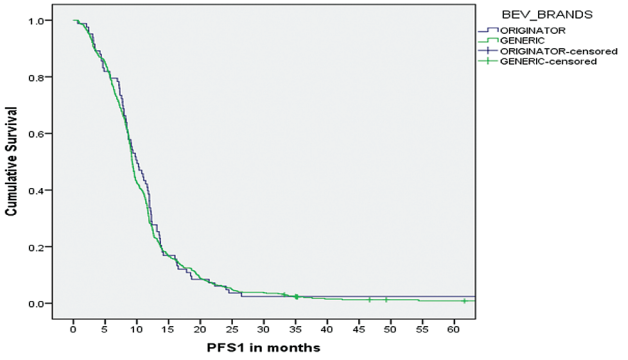

Fig. 1 Progression-free survival (PFS; first line) with the originator versus generic.

Discussion

The current study of more than 900 patients with mCRC provides RWE to suggest that there is similar efficacy between innovator and biosimilar bevacizumab across treatment lines. The results provide greater confidence to clinicians in using these biosimilars in patients in whom use of the innovator is not feasible.

The management of patients with cancers in India has its challenges and mCRC is no exception. Some of the major challenges include logistic and financial constraints. While the number of successful therapeutic options in mCRC has increased over the last two decades, access to these newer medications is limited in India, primarily due to cost constraints. This has been shown in studies from governmental tertiary cancer centers in India wherein the use of targeted therapy as part of first-line therapy has been only around 15%.[9,10] In such a scenario, the availability of efficacious and cost-effective biosimilars is of major benefit to patients

in their treatment journey. The biosimilars used in our institute are available at approximately 8 to 12% of the cost of the innovator bevacizumab.

However, it is important to ensure that logistics and cost alone are not determinants of the kind of therapy available to patients who can afford relatively little.[11] The overriding aim would be to provide appropriate and efficacious treatment options, and the current study throws light on the same in the space of mCRC. Hard endpoints such as PFS and OS have been examined in the current analysis and suggest similar outcomes among patients using the innovator and generic versions of bevacizumab. The above results, along with a smaller study previously published by our institute, suggest that the use of generic bevacizumab should be strongly considered given their efficacy as well as the financial advantages they offer.[12]

The current study, while offering RWE, has several caveats to be considered. Several factors such as chemotherapy backbone, biomarker status, patient performance status, and ability to receive multiple lines of therapy, besides the use of targeted therapy, affect outcomes in the management of mCRCs in the current era. These are variables that may have played a role in the current study in determining survival outcomes. We have not differentiated between the various generic molecules and outcomes associated with them as this was not part of the study plan. We have provided limited data on bevacizumab-related class side effects, which have an important bearing on the use of these molecules in clinical practice. The OS seen in the study would appear lesser than those published from current studies but are similar to previously published Indian data. There are multiple reasons for these decreased survivals, which are beyond the scope of the current analysis.

In conclusion, the current study offers RWE to suggest similar outcomes with innovator and generic bevacizumab when combined with chemotherapy in advanced colorectal cancers. This provides strong clinical evidence to back published pharmacokinetic and pharmacodynamic studies to suggest the efficacy of commonly used bevacizumab generics in Indian scenarios and provides oncologists with greater confidence to use these molecules in their clinical practice.

Funding
None.

Conflict of Interest
None declared.

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