Perspective

Colorectal cancer treatment: is Bevacizumab the best option?

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Submitted May 25, 2012. Accepted for publication Jun 18, 2012.
DOI: 10.3978/j.issn.2224-4778.2012.06.03
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Colorectal cancer (CRC) is the third most common neoplastic disease worldwide and the second leading cause of cancer death in the western world (1).

Angiogenesis has been identified as an important process for the progression of solid tumors, because new blood vessel formation provides a route for their growth and for the spreading of malignant cells from the primary neoplastic lesion to distant organs (2).

Vascular endothelial growth factor (VEGF) is overexpressed in about 60% of human cancers (3) and is involved in the angiogenetic process and in cancer progression because it stimulates the growth of new blood vessels. Anti-VEGF drugs like bevacizumab (Avastin®) can be administered alone or added to conventional regimens reducing tumor and metastatic growth, normalizing vascular permeability, improving drug delivery to the tumor (4) and inducing tumoral dormancy through regression of the vascularization itself.

Starting from 2004 the introduction of molecular target therapies in CRC led to the development new combinations of treatments with monoclonal antibodies and chemical inhibitors directed to EGFR (Epidermal Growth Factor Receptor) and VEGF.

In a recent paper published on JCO on January 2012, Meyerhardt J.A. and coll. examined the Surveillance, Epidemiology, and End Results (SEER) - Medicare linked database, identifying 2,526 patients with stage IV colorectal cancer diagnosed between 2002 and 2007 (5).

This study aims to consider a large number of stage IV CRC patients in order to evaluate real-world outcomes of available medications and to give clinicians a complete scenario for treatment decisions.

The authors examined two cohorts: The first one including patients diagnosed between 2002 and 2007 with stage IV colon or rectal cancer and treated with a fluoropyrimidine (either FU or capecitabine) and either oxaliplatin or irinotecan within 6 months of diagnosis, while in the second cohort they restricted the analysis to patients diagnosed between 2004 and 2007, when bevacizumab and other later-line therapy (like anti-EGFR drugs) were commercially available.

The primary end point considered was overall survival, defined as the time intervening between the beginning of chemotherapy and the death of patient: authors observed a statistically significant improvement in overall survival associated to the addition of bevacizumab to fluoropyrimidine and either oxaliplatin or irinotecan (median overall survival 19.0 months with bevacizumab *vs*. 15.9 months without bevacizumab) although the adjusted Hazard Ratio was 0.93 when the subset of patients diagnosed between 2004 and 2007 was considered.

Also cardiac toxicity, stroke, venous thrombosis, and Gastrointestinal (GI) perforation events were examined as a secondary endpoint, since the major adverse effects were well available. Within the first 6 months of therapy bevacizumab has been related with a more elevated stroke frequency (4.9% *vs*. 2.5% without bevacizumab), whereas a lower rate of cardiac events was recorded in patients treated with bevacizumab compared with those treated without bevacizumab (11.5% and 14.5%, respectively).

Several phase III studies analyzed the effectiveness of different combinations of chemotherapy, and one these initial studies evaluated the effect of the association of bevacizumab with IFL (Irinotecan + Fluorouracil + Leucovorin), indicating a significant improvement in median Overall Survival (OS) in patients receiving bevacizumab plus IFL (15.6 to 20.3 months for IFL *vs*. IFL + bevacizumab).

Subsequently oxaliplatin was introduced and approved

for its usage in association with all types of intravenous chemotherapy, and the combination of FOLFOX (Folinic acid + Fluorouracil + Oxaliplatin) plus bevacizumab became the standard regimen for CRC treatment in US.

A variety of phase III studies explored then the effectiveness of bevacizumab in these different combinations without comparing the effectiveness of the same chemotherapy in the absence of bevacizumab. Only a phase III study examined oxaliplatin-based chemotherapy and shown that the association of bevacizumab to oxaliplatin resulted slightly favorable compared to the advantage observed for IFL based regimens.

In conclusion Meyerhardt J.A. and coll. study shed a light in the evaluation of the effectiveness of bevacizumab in a large cohort extracted from the SEER-Medicare linked database, which represents the vast majority of US CRC patients. This work allows to analyze a variety of chemotherapy regimens without the stringent treatment options of a particular clinical trial. These results suggest that the benefit associated with bevacizumab treatment seems to be limited to irinotecan based regimens, compared with oxaliplatin-based chemotherapy, and that the major side effects are augmented risks of stroke and GI perforation, without involving myocardial infarction.

Cite this article as: Bagnasco L, Piras D. Colorectal cancer treatment: is Bevacizumab the best option? Transl Gastrointest Cancer 2012;1(3):250-251. DOI: 10.3978/j.issn.2224-4778.2012.06.03

However, although these results could not be generalized for the entire population, they represent an interesting and innovative approach to evaluate CRC treatment options from a wider and more critical point of view.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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