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BEVACIZUMAB WITH CHEMOTHERAPY IN ADVANCED SMALL BOWEL ADENOCARCINOMA

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ABSTRACT

Small bowel adenocarcinoma (SBA) is a rare disease; it represent less than 1% of gastrointestinal cancers. In metastatic setting, the standard treatment is chemotherapy using fluoropyramidine and platinum agents or irinotecan. Bevacizumab is a recombinant humanized monoclonal antibody that blocks vascular endothelial growth factor. It has proven survival benefits in multiple cancers. However, only a very few data are available about the efficacy of bevacizumab in SBA. We evaluate in this literature review its efficacy and its toxicity in SBA.

Small bowel adenocarcinoma (SBA) is a rare disease; it represent less than 1% of gastrointestinal cancers. In patients with metastatic disease, the prognostic is rather poor and the median overall survival (OS) of patients undergoing chemotherapy is approximately 14 months. SBA is not very sensitive to chemotherapy. Various anticancer drugs have been tested (Adriamycine, Mytomycin C, Fluorouracile, Cisplatin, Oxaliplatin, Carboplatin and Irinotecan) with low response rate and reduced survival. The most used regimens are an association between fluoropyrimidine and platinum agents or irinotecan (1).

Angiogenesis is the process by which new blood vessels are created from pre-existing vessels. It is essential for the growth and development of normal cells and tissues during embryonic and neonatal development and of tumor cells. Solid tumors rely on having an extensive network of blood vessels for growth and survival. The key mediator of angiogenesis, vascular endothelial growth factor-A (VEGF-A), is critical for the growth of tumors and their subsequent metastasis and is known to initiate angiogenesis. Bevacizumab is a recombinant humanized monoclonal antibody that blocks VEGF. It prevents the activation of VEGF receptor and the signaling cascade, thereby inhibiting tumor growth, autocrine/paracrine growth factor release and metastasis. Bevacizumab has proven survival benefits in multiple cancers and it is approved by the Food and Drug Administration for treatment of metastatic colorectal cancer, non-squamous cell lung cancer, glioblastoma, metastatic renal cell carcinoma and metastatic carcinoma of the cervix but not for SBA. All malignant epithelial cells types of the gastrointestinal tract including small bowel adenocarcinoma express VEGF strongly, in contrast to adenoma, hyperplasic polyps and normal epithelium (2). Recently, a study of 54 patients with SBA confirmed these data; 91% of these patients' tissue showed expression of VEGF-A with high levels expression in 44% of patients (3). These findings suggest that bevacizumab may be effective in SBA.

Only a very few data are available in the literature about the efficacy of bevacizumab in SBA. The first case report was reported by Tsang et al. in 2008. The patient was 68-year-old woman with advanced jejunal adenocarcinoma. She received 8 cycles of gemcitabine, oxaliplatin and bevacizumab with a partial response and a 12-month progression free survival (PFS) (4). One year later, Stec et al. reported another case of a 45-year-old woman with metastatic jejunal adenocarcinoma treated by FOLFIRI (Fluorouracile, Leucovorin and Irinotecan) plus bevacizumab. After 13 cycles of treatment, the patient presented complete response and she was alive without disease progression 28 months after her first presentation (5). Recently, another case was reported by Nagarai et al. The patient was a 45-year-old man presented with recurrent duodenal adenocarcinoma. He was treated by FOLFOX (Fluorouracile, Leucovorin and Oxaliplatin) plus bevacizumab for 12 doses followed by capecitabine/ bevacizumab for 2 years. The patient presented complete response and he continues to be disease-free 8 years after (6).

A retrospective study has evaluated the results of treatment with chemotherapy with or without bevacizumab in 28 patients with metastatic SBA. The addition of bevacizumab was associated with an increase of objective response rate (58.3% versus 43.7%), progression free survival (9.6 versus 7.7 months) and overall survival (18.5 versus 14.8 months) but it was not statistically significant. Otherwise, it does not cause an excess of significant toxicity (7).

Recently, two others retrospective studies have shown a possible benefit of bevacizumab-containing chemotherapy in patients with advanced SBA (8-9).

In the first study, 33 patients with advanced SBA from 6 hospitals in Japan, who received chemotherapy from 2008 to 2016, were retrospectively examined for background, clinical course and outcome. Median overall survival (OS) was 13 months. Nine of the 33 patients received bevacizumab and median OS for this group was 21.9 months. No unexpected serious adverse events were observed (8).

The second study included 27 patients with SBA from ten hospitals participating in the Osaka Gut Forum between April 2006 and March 2014. All of them received chemotherapy. The median OS was 14.8 months. Bevacizumab was administered to 8 patients plus chemotherapy in first or second-line treatment. Multivariate analysis revealed that a platinum-based regimen was a significant positive prognostic factor (p=0.0373) with bevacizumab (p=0.0121). Toxicities higher

than grade 3 occurred in 8/27 patients. However, serious side effects due to bevacizumab were not experienced (9). The results of the present study indicate that chemotherapy containing molecular targeted agents is a well-tolerated and effective treatment option for SBA.

The most important study available to date is a phase 2, single-arm, single-center, open-label study evaluating XELOX (capecitabine and oxalopltin) plus bevacizumab in patients with untreated, advanced SBA or ampullary adenocarcinoma. Thirty patients were enrolled (23 had SBA). The treatment was generally well supported. The response rate was 48.3%, the PFS and the OS were 8.7 and 12.9 months respectively (10).

In conclusion, literature data state that there is a possible benefit of bevacizumab in the treatment of SBA without major added toxicity. However, randomized prospective trials are needed to evaluate this association.

Conflicts of interest:
The authors have no conflicts of interest to declare.

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