Complications of palliative antiangiogenic therapy in patients with colorectal cancer

Małgorzata Domagała-Haduch[1], MD, Marek Jasiówka, MD, PhD[2], Łukasz Nowak, MD, PhD[3], Ida Cedrych, MD, PhD[1]

[1] Department of Systemic and Generalized Malignancies, Maria Sklodowska-Curie Memorial Institute of Oncology, Krakow Branch, Poland

[2] Department of Gynecologic Oncology, Center of Oncology, Maria Sklodowska-Curie Memorial Institute of Oncology, Krakow Branch, Poland

[3] Department of Anaesthesiology and Intensive Care, Maria Sklodowska-Curie Memorial Institute of Oncology, Krakow Branch, Poland

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ABSTRACT

Introduction: Bevacizumab is an antiangiogenic drug used in the therapy of numerous solid tumours including colorectal adenocarcinoma. The efficacy and safety of bevacizumab has been demonstrated in many multicenter clinical trials. The scope of this paper is to analyze the safety profile of bevacizumab in patients with stage IV colorectal cancer.

Aim of the study: Analysis of toxicity and safety of the treatment with bevacizumab patients with colorectal cancer in the metastatic stage.

Material and methods: Retrospective analysis of medical records of 42 patients with advanced colorectal cancer treated in the Department of Systemic and Generalized Malignancies, Maria Skłodowska-Curie Memorial Institute of Oncology, Kraków Branch, in the period 2007–2014.

Results: The median time of treatment with bevacizumab was 6 months. The median duration of progression-free survival (PFS) was 8.5 months. Toxicity of treatment with bevacizumab affected 43 percent of patients. The most common adverse events observed was hypertension and bleeding. In 6 patients (14.3%) the treatment with bevacizumab was interrupted due to adverse events (thromboembolic events, bleeding and gastrointestinal perforation).

Conclusions: Bevacizumab is a safe therapeutic option in patients with metastatic colorectal cancer, provided that patients are provided close oncological and general medical monitoring.

KEY WORDS: bevacizumab, colorectal cancer, adverse effects, treatment safety

Correspondence:
Małgorzata Domagała-Haduch, MD
Department of Systemic and Generalized Malignancies,
Maria Sklodowska-Curie Memorial Institute of Oncology, Krakow Branch
31-115 Kraków, ul. Garncarska 11
e-mail: malgorzatadom@interia.pl

INTRODUCTION

The generation of new blood vessels – the angiogenesis – is pivotal in the process of tumour growth. It has been known since the 1970s that without new vessels tumours are not capable of sustaining growth over the diameter of 2 centimetres [1]. The process of angiogenesis is induced by the vascular endothelial growth factor (VEGF). The VEGF is a family of signalling proteins possessing the activity of growth factors. They all act by binding to the specific tyrosine kinase receptors (VEGFR). The VEGF family is subdivided into subtypes (VEGF-A to VEGF-D, placental growth factor – PGF) [2, 3]. The most important subtype is the VEGF-A. To underline it's leading role in the process of angiogenesis it is sometimes referred to as "the VEGF". Among the receptor subtypes the most important is the VEGFR-2. The VEGFR-1 subtype functions as a modulator of the VEGFR-2 activity, and VEGFR-3 is involved in lymphatic angiogenesis [4]. Overexpression of VEGFR has been described in many different tumours, among them colorectal cancer [5]. There is a plethora of evidence supporting the association between the density of tumour vasculature and the rate of growth and propensity towards forming metastases [6].

The above presented data had served as a basis for the development of drugs inhibiting the angiogenesis [7]. One of the first and most extensively studied drugs in this class is bevacizumab. Bevacizumab is a humanized monoclonal antibody disrupting the function of the VEGFR and thus inhibiting tumour growth and limiting the capability to form metastases [8]. In patients with disseminated colorectal cancer, treatment with bevacizumab combined with first and second line chemotherapy has been demonstrated to be effective. The benefits comprise increased response rate (RR), prolonged progression free survival (PFS) and overall survival (OS) [9–11].

Bevacizumab has a distinct toxicity profile. The most common adverse effects include:

- hypertension
- proteinuria
- neutropenia.

Serious, but very rare, adverse events include [12]:

- bowel perforation
- thromboembolic complications
- haemorrhages
- infections.

Ranpura et al. in their metaanalysis conclude that treatment with bevacizumab combined with chemotherapy therapy is associated with increased treatment related mortality, with following adverse events related to mortality: haemorrhage, neutropenia and gastrointestinal perforation [13]. It should be noted however, that while bevacizumab treatment increases the odds of many adverse events it reduces the incidence of anemia and fatigue during chemotherapy [14].

AIM OF THE STUDY

In this paper we present data from our institution concerning toxicity of combined bevacizumab and chemotherapy treatment in stage IV colorectal cancer.

MATERIAL AND METHODS

Medical records of 42 patients with metastatic colorectal cancer treated with bevacizumab in combination with chemotherapy were retrospectively analyzed. All the patients were treated in the Department of Systemic and Generalized Malignancies of the Maria Skłodowska-Curie Memorial Institute of Oncology during the period 2007–2014.

Bevacizumab treatment was conducted concurrently with first or second line chemotherapy. Data regarding treatment toxicity were based on the results of anamneses, physical examination, as well as laboratory and imaging studies.

All the patients treated with the angiogenesis inhibitor had distant metastases. The study population comprised 28 (66.7%) males and 14 (33.3%) females. The median age at the diagnosis was 56 years (range 27–68). Additional co-moribidities were present in 22 (52.4%) patients, and are presented in the table 1.

TABLE 1.
General co-morbidities in the study population

Disease	Number of patients (%)
arterial hypertension	8 (43%)
type 2 diabetes mellitus	3 (7.1%)
ischemic heart disesase	2 (4.8%)
hyperthyroidism	1 (2.4%)
nephrolithiasis	1 (2.4%)

All the patients with co-morbidities were adequately treated by appropriate specialists, and possible contraindications to bevacizumab were excluded before starting the treatment.

The initial tumour staging according to WHO was as follows:

- II stage: 5 patients (12%)
- III stage: 11 patients (26.2%)
- IV stage: 26 patients (61.8%).

The primary tumour had been resected in 40 patients (95%). Adjuvant treatment, such as pre- or postoperative radiotherapy, chemotherapy, or radiochemotherapy had been employed in 16 patients (38%).

At the moment of initiation of bevacizumab therapy, all the patients had distant metastases.

Table 2 presents the localization of the first diagnosed distant metastasis. In 13 (31.7%) patients distant metastases to more than one organ were detected. The median time from the initial diagnosis to the discovery of distant metastases was 11 months (0.5–29 months).

TABLE 2.
Localization of first diagnosed distant metastasis.

Site	Number of patients (%)
liver	32 (76.2%)
lung	3 (7.1%)
retreperitoneal lymph nodes	2 (4.8%)
peritoneum	1 (2.4%)
ovarium	1 (2.4%)
mesentery	1 (2.4%)
other (adipose tissue, cervical lymphatic nodes)	2 (4.8%)

The median haemoglobin concentration at the discovery of distant metastases was 13.6 g/dl (9–16.3 g/dl), and the median CEA concentration 12 ng/ml (0.5–2500 ng/ml). All the patients were in good physical condition at the commencement of the treatement – performance status (PS) 0–1.

Bevacizumab with chemotheraphy was used in the first line treatment in 11 (26.2%) and in the second line treatment in 28 (66.7%). In 3 (7.1%) patients bevacizumab was employed during the subsequent treatments. The first evaluation of the response to treatment was planned after 12 weeks after the beginning of treatment, regardless of the end of the treatment with bevacizumab.

The median time of bevacizumab treatment was 6 months (0.5–23 months). In 18 (42.9%) patients the treatment was interrupted because of tumour progression. In 6 (14.3%) patients the interruption was due to adverse effects of bevacizumab therapy. In 3 (7.1%) additional patients the treatment was interrupted due to the severe toxicity of concomitant chemotherapy. In 2 (4.8%) patients the treatment was interrupted on patients request – due to fatigue caused by the systemic therapy.

At the time of analysis, 13 patients were still receiving the treatment.

RESULTS

The response to treatment after 12 weeks of bevacizumab was:

- complete remission: 4 patients (9.5%)
- partial remission: 10 patients (24%)
- stable disease: 23 patients (54.5%)
- disease progression: 5 patients (12%).

The median PFS was 8.5 months. In the subgroup analysis in patients treated with bevacizumab concurrently with the first line chemotherapy the median PFS was 9 months, while in patients treated with bevacizumab as the second line treatment the median PFS was 8 months.

In the table 3 we present the adverse events categorized according to the Common Terminology Criteria for Adverse Events ver. 4.0 (CTCAE).

TABLE 3.
Adverse events during bevacizumab therapy according to CTCAE 4.0 .

Adverse event	Number of patients (%)
hypertension	6 (14.3%)
bleeding	4 (9.5%)
pulmonary artery embolism	2 (4.8%)
proteinuria	2 (4.8%)
gastrointestinal perforation	2 (4.8%)
inferior vena cava thrombosis	1 (2.4%)
mesenteric embolism	1 (2.4%)

TABLE 4.
Serious (G3-G4 according to CTCAE 4.0) adverse events

Adverse events	Number of patients (%)
bleeding	2 (4.8%)
gastrointestinal perforation	2 (4.8%)
pulmonary embolism	2 (4.8%)
inferior vena cava embolism	1 (2.4%)
mesenteric embolism	1 (2.4%)

In 3 patients there were two adverse events. There were no deaths related to adverse events in the study population.
The following adverse events were the cause of bevacizumab treatment termination:

- pulmonary artery embolism (1 patient)
- mesenteric embolism with gastrointestinal perforation (1 patient)
- gastrointestinal perforation with bleeding (1 patient)
- pulmonary embolism with massive epistaxis (1 patient)
- gastrointestinal bleeding (1 patient)
- vena cava inferior thrombosis (1 patient).

DISCUSSION

The role of bevacizumab in the treatment of advanced colorectal cancer, ovarian cancer, renal cancer and various other tumours is well established [15, 16]. Toxicity is one of the major factor limiting its therapeutic potential (as in the case of most anticancer therapies).

In the studied population, we observed a treatment interruption rate due to adverse effects of 14.3%. In the study conducted by Hurwitz et al. the treatment was interrupted because of toxicity in 8.4% patients [17]. The relatively high treatment interruption rate may have been caused by a lack of expertise in the adverse events management during the first years after the introduction of bevacizumab. This may have caused an increased tendency to discontinuation of the treatment instead of attempting to continue it and manage the symptoms.

Thromboembolic events occurred in 4 patients (9.6%). In published studies the rate of thromboembolic events varied between 8% and 19% [9, 18, 19]. Of the thromboembolic events observed in the study population only one was arterial, the rest being venous. All the patients with thromboembolic complications were receiving low molecular weight heparins as a prophylaxis at the moment of the event. It should be also noted, that all those patients had undergone primary tumour resection at least 6 months before the initiation of the antiangiogenic treatment. The relatively high occurrence of venous thrombosis in comparison to arterial thromboembolic events is in accordance with results of other studies – for example in the metanalysis of Nalluri et al. venous thromboembolism occurred in 11.4% of patients [19], while the incidence of arterial thromboembolism is much lower – in the metaanalyses of Scappaticci et al. and Schutz et al. was respectively 3.8% and 2.6% [20, 21].

Bleeding was observed in 9.6% patients. Serious bleedings occurred in 4.8% (in both cases serious gastrointestinal bleeding). The literature data suggest a slightly lower (2–3%) incidence of serious bleeding during bevacizumab therapy [18, 22, 23].

Gastrointestinal perforation was observed in 4.8% patients. In published studies the incidence of this complication did not exceed 2% [9, 18, 23]. In both cases the patients had cardiovascular comorbidities – hypertension, and one of the patients also coronary artery disease. Potential correlation between cardiovascular comorbidities and gastrointestinal perforation could be suggested only after analysis of much larger quantity of patients.

One patient (2.4%) developed atrial fibrillation with fast ventricular rate during the treatment with bevacizumab. The patient needed hospitalization and the treatment was stopped. Some authors suggested a link between bevacizumab treatment and atrial fibrillation, but the data are scarce [24]. However, given the relatively high incidence of atrial fibrillation among older patients, it would not be substantiated to infer a causal relationship in this case.

Arterial hypertension is a hallmark complication of bevacizumab treatment. The pathomechanism of this complication is not fully understood, but two effects are suggested. First it has been shown that bevacizumab inhibits nitrous oxide synthesis, and second it has been suggested, that bevacizumab may cause cholesterol embolisation syndrome [25]. Of note is the relation between hypertension and treatment efficacy – therapy with bevacizumab is more effective in patients who develop hypertension [26, 27]. The hypertension usually responds well to treatment, and only in sporadic cases mandates bevacizumab therapy termination [28]. In the study population the incidence of hypertension was 14.3%. This value does not differ from the results obtained by other authors (4–35%) [9, 22, 25]. In no cases the hypertension was the cause of treatment interruption –

all the patients could be successfully managed with additional antihypertensives.

Another complication typical for the VEGF inhibitors is the proteinuria. In the study population the incidence of proteinuria was 4.8% and the severity of proteinuria was G1 according to the CTCAE 4.0 in all the cases. In the study by Lafayette et al. the incidence of proteinuria in the bevacizumab group was 8.4% [29]. Also the occurrence of proteinuria has been linked to the effectiveness of bevacizumab therapy [27].

SUMMARY

Bevacizumab is a valuable and safe therapeutic option for carefully selected patients with disseminated colorectal cancer. However while the life threatening complications are rare, it is mandatory to maintain strict oncological monitoring and to promptly employ causative/symptomatic treatment when appropriate.

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Authors' contributions:
Małgorzata Domagała-Haduch: data collecting and analysis, editing of the article
Marek Jasiówka: data analysis, editing of the article
Łukasz Nowak: data analysis, co-editing of the article
Ida Cedrych: co-editing of the article.