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THE IMPACT OF BODY MASS INDEX ON THE RISK OF DEVELOPING SERIOUS ADVERSE EVENTS IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER

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One of the essential drugs used to treat patients with metastatic non-small cell lung cancer (mNSCLC) is bevacizumab. Bevacizumab is associated with a significant number of severe adverse events. The relationship between body composition and the risk of hemorrhagic, thromboembolic events, and hypertension remains unclear. Therefore, our study aimed to establish a correlation between survival, these adverse events, and body mass index (BMI).

Materials and methods. Eighty-seven patients with mNSCLC treated in the Sumy Regional Clinical Oncology Center were involved in the retrospective study. Data on sex, age, weight, height of patients, results of coagulogram, and blood count tests were collected from the primary medical documentation no more than one week before the start of bevacizumab therapy. BMI was calculated based on data on the weight and height of patients according to the formula: weight/height^2 (kilograms/per square meter). Patients with BMI <25 kg/m^2 were included in the underweight and normal weight groups. Those whose BMI was ≥25 kg/m^2 were included in the overweight and obese group. Adverse event severity was determined using the Common Terminology Criteria for Adverse Events (CTCAE, version 5). Chi2 test for categorical variables, Fisher's exact test, multivariate Cox regression analysis and Kaplan-Meier method were used for statistical analysis.

Results. According to the results of univariate analysis, it was established that each clinicopathological characteristic does not have a statistically significant correlation with BMI. However, multivariate analysis showed that patient sex (P=0.011) and blood platelet level (P=0.045) correlated with OS. The median overall survival (OS) in women was 16.0 months versus 9.1 months in men. Median OS in patients with platelets less than 280 g/L was 13.5 months versus 7.4 months in those with 280 g/L or higher.

Conclusions. BMI does not impact on OS and risk of thromboembolism, bleeding, and hypertension in patients with mNSCLC receiving bevacizumab therapy. Women and those whose baseline platelet count is less than 280 g/L have better survival.

Keywords: bevacizumab, lung cancer, adverse events, sex, survival.

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ВПЛИВ ІНДЕКСУ МАСИ ТІЛА НА РИЗИК РОЗВИТКУ ТЯЖКИХ НЕБАЖАНИХ ЯВИЩ У ПАЦІЄНТІВ З МЕТАСТАТИЧНИМ НЕДРІБНОКЛІТИННИМ РАКОМ ЛЕГЕНЬ

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Бевацизумаб – таргетний препарат для лікування метастатичного недрібноклітинного раку легень (мНДКРЛ). Мета дослідження – встановити наявність кореляції між виживаністю, небажаними явищами та індексом маси тіла (ІМТ). У дослідженні взяли участь 87 пацієнтів з мНДКРЛ. Пацієнти з ІМТ < 25 кг/м^2 були включені до групи з недостатньою/нормальною вагою, ≥25 кг/м^2 – надлишковою вагою/ожирінням. Встановлено, що на загальну виживаність (ЗВ) впливають стать пацієнта (P=0,011) та рівень тромбоцитів (P=0,045). Медіана ЗВ у жінок становила 16,0 місяця проти 9,1 місяця у чоловіків. Медіана ЗВ у пацієнтів з рівнем тромбоцитів менше 280 г/л становила 13,5 місяця проти 7,4 місяця у тих, чий рівень тромбоцитів був 280 г/л або вище.

Висновки. ІМТ не впливає на виживаність та ризик розвитку тромбоемболій, кровотеч та артеріальної гіпертензії. Кращу ЗВ мають жінки та ті пацієнти, чий базовий рівень тромбоцитів менше 280 г/л.

Ключові слова: бевацизумаб, рак легень, небажані події, стать, виживаність.

Introduction. In Ukraine, 21% of cancer deaths are related to lung cancer. Lung cancer is an important social problem, and effective treatment of patients is the primary task of oncology [1]. Patients with metastatic tumors require special attention because, despite contemporary therapeutic approaches, they have low survival.

One of the essential drugs used to treat patients with metastatic non-small cell lung cancer (mNSCLC) is bevacizumab. Bevacizumab is an anti-vascular endothelial growth factor-A (VEGF-A) monoclonal antibody approved by the Food and Drug Administration for the first-line treatment of recurrent, locally advanced, or mNSCLC. Bevacizumab is recommended for use in combination with platinum-based chemotherapy in patients with non-squamous NSCLC [2].

In the last decade, clinical oncology has increasingly paid attention to the role of body mass index (BMI) in the

effectiveness of therapy and survival of patients with various malignant neoplasms. According to scientific literature, the impact of BMI is ambiguous. It may depend on the cancer type [3], the stage of the disease [4], the age of the patient [5], and the applied therapeutic regimens [6].

Bevacizumab is associated with a significant number of severe adverse events. The most common among them are thromboembolism, arterial hypertension, and bleeding. The therapeutic dose of bevacizumab is calculated based on the patient's current weight, so overweight and obese patients receive higher therapeutic doses compared to those whose weight is normal or underweight. The half-life of bevacizumab does not depend on the kidneys and liver function. However, weight, serum albumin, and gender significantly affect pharmacokinetic parameters [7].

In lung cancer patients, thromboembolism occurs 20 times more often than in the population of healthy people. Cancer cells can interact with vascular endothelial cells, increase platelet aggregation, and stimulate the synthesis of procoagulants. The combined effect of the listed factors leads to hypercoagulation [8]. Bevacizumab, blocking VEGF, can potentiate this process. On the other hand, a high level of interferon regulatory factor 7 (IRF7) and a low level of interferon-induced protein with tetratricopeptide repeats 2 (IFIT2) indicate a significant density of micro vessels in adenocarcinomas, which is a risk factor for bleeding [9]. Overweight and obese patients receiving higher therapeutic doses of bevacizumab may have a higher risk of complications. However, the relationship between body composition and the risk of hemorrhagic, thromboembolic events, and hypertension remains unclear.

The aim of our study was to establish a correlation between survival, BMI and hemorrhagic, thromboembolic events, and hypertension.

Materials and methods. ***Research design.*** Eighty-seven patients with mNSCLC treated in the Sumy Regional Clinical Oncology Center were involved in the retrospective study. To be included in the study, patients had to meet the following criteria: histologically confirmed mNSCLC, history of bevacizumab therapy (minimum two cycles), IV stage of the disease, available results of blood count tests and coagulogram no more than seven days before the start of bevacizumab therapy. Patients with other malignant tumors and without the complete results of laboratory tests were not included in the study. The study was approved by the Local Ethics Committee of the Sumy Regional Clinical Oncology Center (protocol 3/3 dated January 15, 2024). It was conducted following the ethical principles of the Declaration of Helsinki.

Patient treatment, data collection, and analysis. Patients received bevacizumab in combination with chemotherapy as first-line therapy. The drug was administered intravenously every three weeks at a dose of 15 mg/kg. Doses of chemotherapy were calculated according to the instructions for drugs to treat NSCLC. After completing 4–6 courses of this treatment regimen, patients without disease progression continued to receive bevacizumab monotherapy at the same dose and frequency until disease progression or completion of 24 months of treatment, whichever occurred first. Data on sex, age, weight, height of patients, results of coagulogram, and blood count tests were collected from the primary medical documentation no more than one week before the start of bevacizumab therapy. Activated partial thromboplastin time (APTT) and international normalized ratio (INR) were considered key parameters of the coagulogram. The average values for each parameter were the cut-off point for APTT, INR, and blood platelets.

BMI was calculated based on data on the weight and height of patients according to the appropriate formula: weight/height^2 (kilograms/per square meter). According to the World Health Organization classification, patients with BMI <25 kg/m^2 were included in the underweight and normal weight groups. Those whose BMI was ≥25 kg/m^2 were included in the overweight and obese group. The occurrence of an adverse event was considered the presence of corresponding data in the medical documentation. Adverse event severity was determined using the Common Terminology Criteria for Adverse Events (CTCAE, version 5). Overall survival (OS) was calculated as the difference between the date of registration of an adverse event and the date of initiation of bevacizumab therapy.

Statistical analysis. Univariate analysis of the relationship between BMI and clinicopathological characteristics of patients was performed using the Chi^2 test for categorical variables and Fisher's exact test. Pearson's test was used to compare indicators between patients with underweight/normal weight and overweight/obese. Multivariate Cox regression analysis was used to assess the risk of death from mNSCLC. The difference in patients' survival depending on the identified independent predictors of death was graphically demonstrated using Kaplan-Meier curves. The results were considered statistically significant at P≤0.05. The Stata V.18.0 software environment (StataCorp, Texas, USA; https://www.stata.com; 2024) was used for statistical analysis.

The results. The study involved 87 patients with mNSCLC, among whom 55 had side effects of more than 2 degrees of severity associated with bevacizumab therapy. In the group of patients with insufficient and normal weight, 24 cases of thromboembolism, bleeding, or arterial hypertension were registered. In the overweight and obese group, the frequency was slightly higher – 31 cases. Two cases of thromboembolism and 1 case of pulmonary bleeding resulted in the death of the patients. All of them were registered in the overweight and obese group (Table 1).

Table 1

Frequency of thromboembolism, bleeding, and arterial hypertension depending on BMI

Adverse events of bevacizumab	Underweight and normal weight, n=24	Overweight and obesity, n=31
Arterial embolism (ischemic stroke)	1	1 (1)
Venous thromboembolism (pulmonary embolism, thrombophlebitis)	3	2 (1)
Pulmonary bleeding/ hemoptysis	3	2 (1)
Gastrointestinal bleeding	2	0
Nasal bleeding	1	1
Arterial hypertension	10	18
Thrombocytopenia	4	7

** The number of fatal events is indicated in parentheses.*

Table 2

Baseline clinicopathological characteristics of patients according to BMI

Clinicopathological characteristics	Total number of patients (%) n=87	Underweight and normal weight (%) n=42	Overweight and obesity (%) n=45	P value
Age (years), n (%) Medium Range <65 ≥65	 60 33–82 58 (66.6) 29 (33.3)	 60 33–77 19 (45.2) 23 (54.8)	 59 38–82 23 (51.1) 22 (48.9)	0.649
Sex, n (%) Women Men	 25 (28.7) 62 (71.3)	 9 (21.4) 33 (78.6)	 16 (35.6) 29 (64.4)	0.146
Metastasis in the liver Present Absent	 23 (26.4) 64 (73.6)	 11 (26.2) 31 (73.8)	 12 (26.7) 33 (73.3)	0.960
APTT. seconds <34.9 ≥34.9	 45 (51.7) 42 (48.3)	 22 (52.4) 20 (47.6)	 23 (51.1) 22 (48.9)	0.383
INR <1.2 ≥1.2	 42 (48.3) 45 (51.7)	 20 (47.6) 22 (52.4)	 22 (48.9) 23 (51.1)	0.507
Platelets. g/L <280 ≥280	 54 (62.1) 33 (37.9)	 23 (54.8) 19 (45.2)	 31 (68.9) 14 (31.1)	0.352

The time of onset of thrombotic, hemorrhagic events, and arterial hypertension differed significantly. Thus, an average of 72 days (interval 34–110) passed from the start of bevacizumab therapy before the onset of thromboembolism. Bleeding was observed on average after 219 days (interval 35–408), arterial hypertension – after 91 days (interval 30–126), and thrombocytopenia – after 116 days (interval 7–322). The data are not statistically reliable due to the insufficient number of cases. However, they demonstrate a tendency for the studied adverse events to occur.

Univariate analysis was used to determine the correlation between BMI and the risk of thromboembolism, bleeding, and hypertension. Table 2 presents the patients' baseline clinicopathological characteristics, coagulogram parameters, and blood count tests, which reflect the blood coagulation function before the start of treatment.

In general, 42 (48.3%) patients were underweight and normal, 45 (51.7%) were overweight and obese. The research group included 25 (28.7%) women and 62 (71.3%) men. The average age of the patients was 60 years (range 33 to 82). Most were younger than 65 years old – 58 (66.6%), without liver metastases – 64 (73.6%), and with a baseline level of platelets less than 280 g/L.

According to the results of univariate analysis, it was established that each clinicopathological characteristic does not have a statistically significant relationship with BMI. However, multivariate analysis showed that patient sex (P=0.011) and blood platelet level (P=0.045) correlated with OS. Women and patients with a platelet level of less than 280 g/l had better OS. Accordingly, the risk of severe adverse events is much lower in this category of patients. At the same time, no relationship was found between BMI and OS in patients with mNSCLC treated with bevacizumab (Table 3).

The median OS in women was 16.0 months versus 9.1 months in men. Median OS in patients with platelets less than 280 g/L was 13.5 months versus 7.4 months in those with 280 g/L or higher (Fig. 1).

Table 3

Multivariate analysis of the risk of death in patients with mNSCLC treated with bevacizumab

Clinicopathological characteristics	Hazard Ratio	95% CI	P value
Age (<65 versus ≥65)	1.01	0.61–1.66	0.975
Sex (women versus men)	2.01	1.17–3.46	0.011
BMI (<25 versus ≥25)	0.88	0.56–1.37	0.576
Metastasis in the liver (absent versus present)	0.88	0.53–1.46	0.632
APTT (<34.9 versus ≥34.9)	0.82	0.47–1.43	0.491
INR (<1.2 versus ≥1.2)	1.22	0.71–2.08	0.473
Platelets (<280 versus ≥280)	1.69	1.01–2.83	0.045

Discussion. This study showed that BMI does not impact the risk of thromboembolism, bleeding, and hypertension. In addition, BMI was not associated with worsening or improvement of OS in mNSCLC patients treated with bevacizumab. Interestingly, sex and the baseline level of blood platelets were the independent predictors of OS. Women and those whose baseline platelet count was less than 280 g/L had better survival.

The obtained results can be considered promising, as they are an additional cause for discussion about changing the dosing strategy of bevacizumab. The current dose calculation method is based on the patient's weight, while fixed doses can have the same effectiveness. The pharmacokinetics of monoclonal antibodies, including bevacizumab, is complex and depends on many factors. The distribution of monoclonal antibodies is limited by blood plasma and extracellular fluid; that is, the volume of distribution is limited [10]. The basis of monoclonal antibodies is immunoglobulin G (IgG), which has polar properties and a small volume of distribution. These molecules accumulate mainly in blood plasma without spreading to adipose tissue [11]. During the therapy of cancers, patients with a

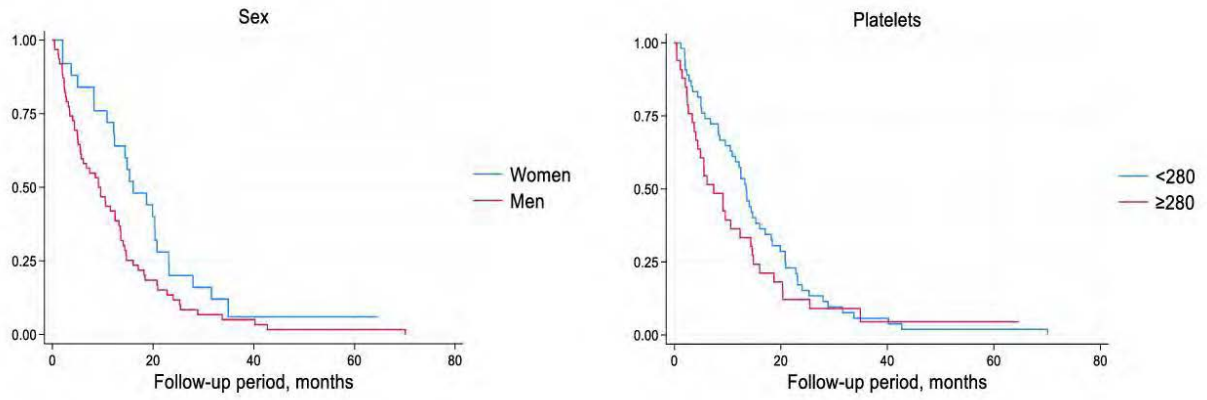

Fig. 1. Kaplan–Meier curves showing patients' OS by sex and platelet count

higher BMI receive higher doses of monoclonal antibodies. However, the paradox is that with an increase in the amount of adipose tissue, the blood volume remains close to the patient's ideal weight or even reduced; that is, a directly proportional dependence is not observed. This tendency is typical for patients of both sexes [12]. Accordingly, weight-dependent dosing of monoclonal antibodies results in higher concentrations of the drug in the blood of obese patients, which may lead to more severe side effects.

Our study did not find a relationship between the frequency of thromboembolism, bleeding, hypertension, and BMI. Protection against overdose and adverse events is likely provided by the major histocompatibility complex-related class I receptor (FcRn). Its role is to regulate serum IgG levels by protecting against lysosomal degradation. FcRn is most actively expressed in endothelial cells and ensures the recirculation of IgG between the intracellular protein reservoir and blood circulation. In this way, IgG homeostasis is maintained. Since adipose tissue has a low level of FcRn expression, this leads to faster elimination of monoclonal antibodies in overweight and obese individuals [13]. The mechanisms described above explain the lack of influence of BMI on the frequency of thromboembolism, bleeding, and arterial hypertension.

In the scientific literature, the dosage of monoclonal antibodies remains debated. In particular, Heinhuis et al. [14] and Hendrikx et al. [15] are inclined to the opinion of the expediency of fixed doses. We cannot draw similar conclusions based on the data obtained in our study. Since the safety profile and OS were not correlated with BMI, it can be assumed that weight-based dosing does not increase the risk of severe adverse events and does not influence treatment efficacy.

According to our study's results, independent predictors of OS in patients with mNSCLC treated with bevacizumab were sex and blood platelet level. Multivariate analysis demonstrated that women had better survival. Interestingly, according to data from the Phase I clinical trial of MYL-1402O, the clearance of bevacizumab is 26% higher in men than in women [16]. The half-life of this targeted drug is 20 days. For the treatment of mNSCLC, it is administered intravenously once every 21 days. The higher clearance in men may lead to a premature decrease in the concentration of bevacizumab in the bloodstream, resulting in worse treatment outcomes. In addition, according to the results of our study, overweight and obesity are more common in women. As discussed above, this causes them to receive a higher dose of bevacizumab without a direct relationship between weight and circulating blood volume. In turn, this leads to a higher drug concentration in the blood.

The role of platelets in the progression of malignant neoplasms is well-covered in scientific sources [17; 18]. The basis of the development of thromboembolism is the hyperactivation of platelets. Dudiki et al. [19] explained the interaction between platelets and cancers. They demonstrated that platelets very efficiently and rapidly engulf small extracellular vesicles (sEVs) from cancer cells. This is due to the high expression of the sEV-CD63 protein. The absorption of sEVs is accompanied by the accumulation of RNA specific for cancer cells, the activation of platelets, and their prothrombotic effect. The authors highlighted the prognostic and diagnostic value of platelet-associated cancer markers.

Larsen et al. [20] investigated the risk of bleeding depending on the level of platelets in patients with hematological malignancies and solid tumors. The authors concluded that a decrease in the level of platelets below 100 g/L is associated with a high risk of bleeding. In this case, patients with hematological neoplasms require mandatory prophylactic transfusion of platelets, while patients with solid tumors require a more individualized approach, depending on the clinical picture. Generally, a lower platelet count is associated with a lower risk of disease progression and a lower incidence of thromboembolic events.

Conclusions. BMI does not impact the risk of thromboembolism, bleeding, and hypertension in patients with mNSCLC receiving bevacizumab therapy. OS of this category of patients does not depend on the body's consumption. Sex and level of blood platelets are independent predictors of OS. Women and those with a baseline platelet count of less than 280 g/L have better survival.

Conflicts of interest. The authors declare no conflict of interest.

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