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ORIGINAL

CLINICAL EFFICACY AND SAFETY OF BEVACIZUMAB COMBINED WITH LOBAPLATIN PERFUSION IN TREATING MALIGNANT PLEURAL-PERITONEAL EFFUSIONS IN ATHLETIC PATIENTS

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ABSTRACT

Objective: This study aims to assess the clinical efficacy and safety of bevacizumab combined with lobaplatin perfusion in treating malignant pleural-peritoneal effusions, particularly in athletic patients who may have specific physiological considerations due to their high physical activity levels. **Methods:** A total of 84 athletic patients with malignancies accompanied by malignant pleural-peritoneal effusions were selected at our hospital from May 2020 to May 2022. They were randomized into two groups: the combination group received bevacizumab with lobaplatin perfusion, while the single drug group received only lobaplatin perfusion. We compared clinical outcomes, levels of vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1α (HIF-1α), and carcinoembryonic antigen (CEA) in the effusions. Additionally, the self-rating depression scale (SDS), self-rating anxiety scale (SAS), and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) were utilized to assess patients' psychological well-being and quality of life. Adverse effects were also recorded. **Results:** The combination group showed a higher total effective rate of treatment compared to the single drug group ($P<0.05$). Post-treatment, there was a significant reduction in the levels of VEGF, CEA, and HIF-1α in the

combination group (P<0.05). Improvements in QLQ-C30 scores were observed in both groups, with higher scores in the combination group. Additionally, decreases in SAS and SDS scores were more pronounced in the combination group (P<0.05). The overall incidence of adverse reactions did not differ significantly between the groups (P>0.05). **Conclusion:** For athletic patients with malignant pleural-peritoneal effusions, the combination of bevacizumab and lobaplatin perfusion demonstrates greater efficacy and comparable safety to lobaplatin alone. This treatment approach offers potential advantages for athletic patients, considering their unique physiological and psychological needs.

KEYWORDS: bevacizumab, lobaplatin, malignant pleural-peritoneal effusion, malignancy, safety

1. INTRODUCTION

Malignant pleural-peritoneal effusion refers to the fluid in the thoracoabdominal cavity caused by malignancies originating from the pleuroperitoneal membrane or malignancies metastasizing to the pleuroperitoneal membrane from other sites, which is one of the main concomitant symptoms of advanced malignancies. Once malignant pleural-peritoneal effusion is formed, it indicates that the primary tumor has focal or adjacent important organ metastasis, losing the opportunity for surgical radical treatment, seriously affecting athletic patients' survival quality and shortening their survival period (Kamal, 2019; Rashid-Farokhi & Afshar, 2017). Pleural-peritoneal effusion is difficult to treat and prone to recurrence, making it a more difficult clinical problem. Therefore, how to effectively remove pleural-peritoneal, relieve symptoms and prevent recurrence of pleural-peritoneal is one of the keys to improve the quality and prolong the survival time of athletic patients (Prasad, Khandelwal, Kumar, Chaturvedi, & Kumar, 2021; Robeva & Murrugarra, 2016; Zhang et al., 2021). Clinically, athletic patients with malignant pleural-peritoneal effusions are mostly in the malignant stage, with poor nutritional status and difficulty in tolerating systemic chemotherapy, so intrathoracic perfusion therapy has become an indispensable and important tool in clinical treatment because of the small adverse effects and more accurate efficacy of intracavitary local drug administration. The efficacy of intracavitary perfusion with chemotherapeutic agents such as cisplatin and lobaplatin has been confirmed in a large number of clinical practices, but thoracoabdominal chemotherapy can only penetrate a few millimeters into the tumor, and the effect is still not yet ideal (Akıncıoğlu, Akıncıoğlu, Öktem, & Uygur, 2021; Mizutani et al., 2020; Zhou, Li, Hu, & Xie, 2021). Recently, vascular endothelial growth factor (VEGF) has been found to be highly expressed in pleural-peritoneal effusions and to play an important role in the formation and development of hydrothorax and ascites (Jiang et al., 2016). Bevacizumab, a monoclonal antibody that inhibits VEGF, is gradually being

used in the clinical treatment of malignant thoracic and abdominal effusions, with high efficiency either by intravenous injection or pleural-peritoneal perfusion (Xing et al., 2018; Yajima et al., 2019). However, there are no clear answers to the questions of how conventional chemotherapeutic agents for pleural-peritoneal effusions should be used in conjunction with new anti-vascular targeted agents and how to select agents for pleural-peritoneal effusions for athletic patients with different strength scores. Therefore, the clinical efficacy and safety of bevacizumab combined with lobaplatin perfusion in the treatment of malignant pleural-peritoneal effusions were analyzed to provide new options and ideas for future clinical treatment.

2. Materials and methods

Eighty-four athletic patients with advanced tumors confirmed by cytopathology or imaging of hydrothorax and ascites combined with malignant pleural-peritoneal effusions admitted to our hospital from May 2020 to December 2021 were included in this study. The group was divided into bevacizumab combined with lobaplatin (combination group) and lobaplatin monotherapy group (monotherapy group) according to the random number table method, with 42 cases in each group. The clinical baseline data of the two groups is shown in Table 1, and the differences between both groups were not statistically remarkable (P>0.05). The experiment was approved by the ethics committee of our hospital and all study subjects signed the informed consent form.

Table 1: Clinical baseline data of both groups

	COMBINATION (N=42)	SINGLE DRUG (N=42)	χ^2 OR T	P
AGE	62.2±5.4	61.5±6.3	0.547	0.586
BMI（KG/M²）	26.5±1.2	26.6±1.1	0.398	0.692
LOCATION OF FLUID ACCUMULATION			0.198	0.657
PLEURAL EFFUSION	16（38.10）	18（42.86）		
ABDOMINAL FLUID	26（61.90）	24（57.14）		
SEX			0.194	0.659
MALE	25（59.52）	23（54.76）		
FEMALE	17（40.48）	19（45.24）		
TYPE OF TUMOR			1.338	0.931
LUNG CANCER	9（21.43）	10（23.81）		
STOMACH CANCER	8（19.05）	6（14.29）		
COLORECTAL CANCER	7（16.67）	5（11.90）		
PANCREATIC CANCER	5（11.90）	7（16.67）		
OVARIAN CANCER	5（11.90）	4（9.52）		
BREAST CANCER	8（19.05）	10（23.81）		

2.1 Inclusion and exclusion criteria

Inclusion criteria: athletic patients were clearly diagnosed with malignant pleural-peritoneal effusions by imaging, pathological histology or cytology; there were no obvious abnormalities in liver and kidney function, blood routine, pulmonary function and electrocardiogram; no other chemotherapy was administered within the last month and no relevant drugs were injected into the thoracoabdominal cavity; expected survival was greater than 3 months. Exclusion criteria: end-stage athletic patients; athletic patients undergoing concurrent other related treatments; athletic patients with non-cancerous pleural-peritoneal effusion; athletic patients with communication disorders and psychiatric abnormalities.

2.2 Methods

Firstly, after ultrasound localization, a thoracoabdominal catheter was routinely left in place to adequately drain the fluid and perform abdominal perfusion. Athletic Patients in both groups were treated with dexamethasone 5 mg by intraperitoneal instillation before drug injection, and the single drug group was treated with lobaplatin injection (30 mg/m^2 in 50 mL saline) by instillation once/week. In the combination group, bevacizumab injection was added to the single drug group for intravitreal administration again (200 mg dissolved in 100 mL saline) once/week. Athletic Patients were noted to change the position once in 15 min after drug injection in the order of affected side - contralateral side - supine - prone - upright position to make full contact between the drug and the abdominal cavity, and the vital signs of athletic patients were closely observed. Athletic Patients in both groups were treated continuously for 3 weeks.

2.3 Outcome measures

(1) After treatment, the efficacy of treatment was evaluated according to the criteria for evaluating the efficacy of malignant pleural-peritoneal effusions developed by the World Health Organization (WHO): complete remission (CR): the effusion disappeared completely and lasted for at least 4 weeks; partial remission (PR): fluid accumulation decreased significantly (> 50%) and maintained for more than 4 weeks; no response (NS): the accumulation of fluid continued or occurred rapidly, or the amount of fluid was reduced by less than 50%. Total effective rate = (CR + PR)/total × 100%.

(2) Before and after treatment, 5 mL of pleural-peritoneal effusion was extracted from both groups, and the levels of VEGF, hypoxia-inducible factor-1α (HIF-1α) and carcinoembryonic antigen (CEA) were measured by automatic enzyme-linked immunoassay analyzer.

(3) The self-rating anxiety scale (SAS), self-rating depression scale (SDS) (Ramsaran, Seeram, Cury, & Shujaat, 2015) and the European

Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Hao, Huang, & Xu, 2021) were used to evaluate athletic patients' psychology and quality of life before and after treatment. Higher SAS and SDS scores indicate more severe negative psychological emotions. The QLQ-C30 includes five dimensions: somatic functioning, cognitive functioning, role functioning, social functioning and emotional functioning, with higher scores indicating better quality of life.

(4) Athletic Patients' adverse reactions during treatment, such as fever, granulocytopenia, nausea and vomiting, were counted, and the incidence of adverse reactions was calculated (when multiple adverse reactions were present in the same athletic patient, each adverse reaction was counted independently).

2.4 Statistical methods

SPSS 23.0 software was used for statistical analysis, and the counting data were expressed as (%) and compared using the chi-square test. The measurement data are expressed as ($\bar{\chi}$±s) and compared using independent samples t-test with paired t-test. A difference of statistical significance was indicated at P<0.05.

3. Results

3.1 Comparison of treatment outcomes

Altogether 21.43% (9 cases) of athletic patients in the combination group had a treatment outcome of NS, with an overall treatment efficiency of 78.57%. While 42.86% (18 cases) of the single drug group were NS, with an overall effective rate of 57.14%. The total effective rate of treatment was higher in the combination group than in the single drug group (P<0.05) (Table 2).

Table 2: Results of both treatment groups

GROUPS	N	CR	PR	NS	TOTAL EFFECTIVE RATE
COMBINATION	42	15（35.71）	18（42.86）	9（21.43）	78.57%
SINGLE DRUG	42	9（21.43）	16（38.10）	18（42.86）	57.14%
X^2					4.421
P					0.036

3.2 Comparison of VEGF, CEA and HIF-1α levels

Before treatment, the differences in VEGF, CEA, and HIF-1α were not statistically marked in both groups (P>0.05), and were reduced after treatment, with the reduction of VEGF, CEA, and HIF-1α in the combination group being

more significant than that in the single drug group (P<0.05) (Fig 1).

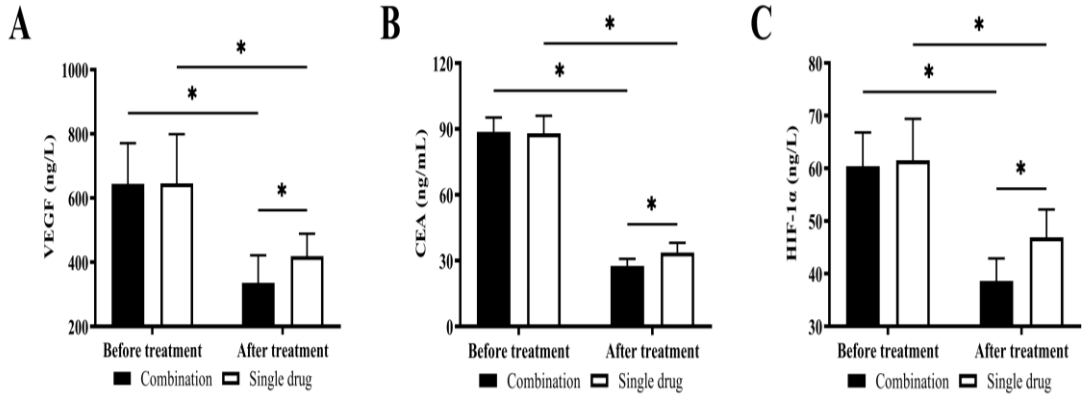

Figure 1: Comparison of VEGF, CEA, and HIF-1α between both groups before and after treatment. A) Comparison of VEGF. B) Comparison of CEA. C) Comparison of HIF-1α. *P<0.05.

3.3 Comparison of quality of life

No difference was seen in the comparison of QLQ-C30 scores for each dimension between the two groups before treatment (P>0.05), and the scores increased after treatment. The scores of somatic, cognitive, role, social and emotional functions were higher in the combination group than in the single drug group (P<0.05) (Fig 2).

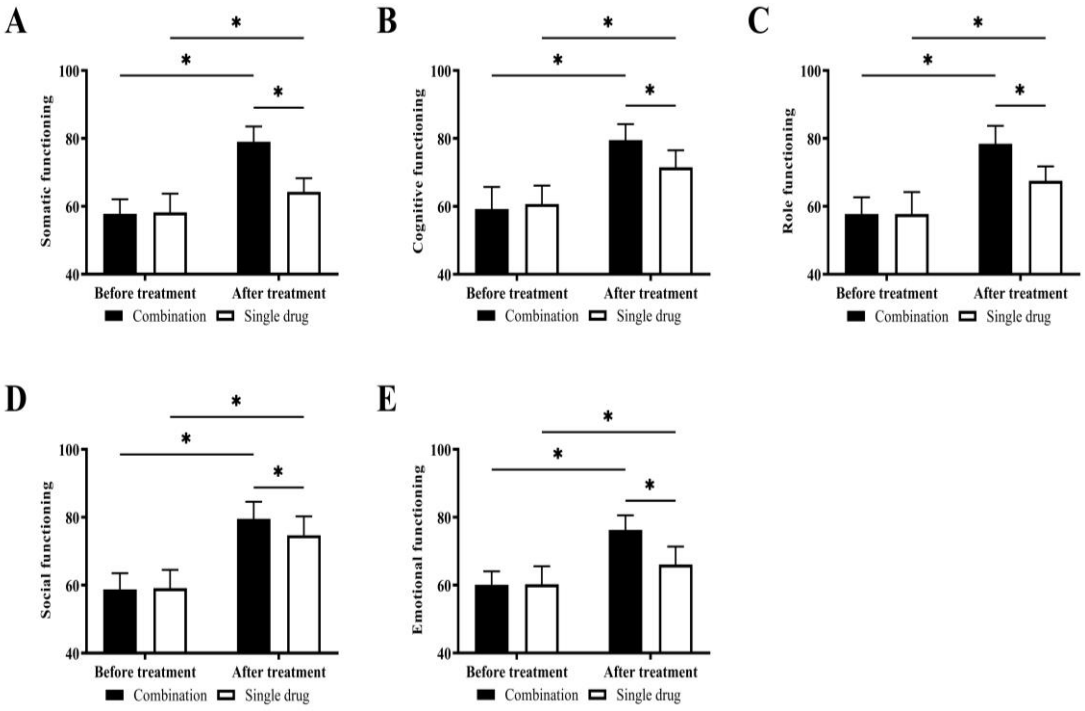

Figure 2: Comparison of QLQ-C30 scores between the two groups before and after treatment. A) Somatic function scores. B) Cognitive function scores. C) Role function scores. D) Social function scores. E) Emotional function scores. *P<0.05.

3.4 Comparison of psychology

Similarly, no difference was seen in the SAS and SDS scores between the two groups before treatment (P>0.05), and the scores were even lower in the combination group than in the single drug group after treatment (P<0.05). The SAS and SDS scores were lower in both groups after treatment than before treatment (P<0.05) (Fig 3).

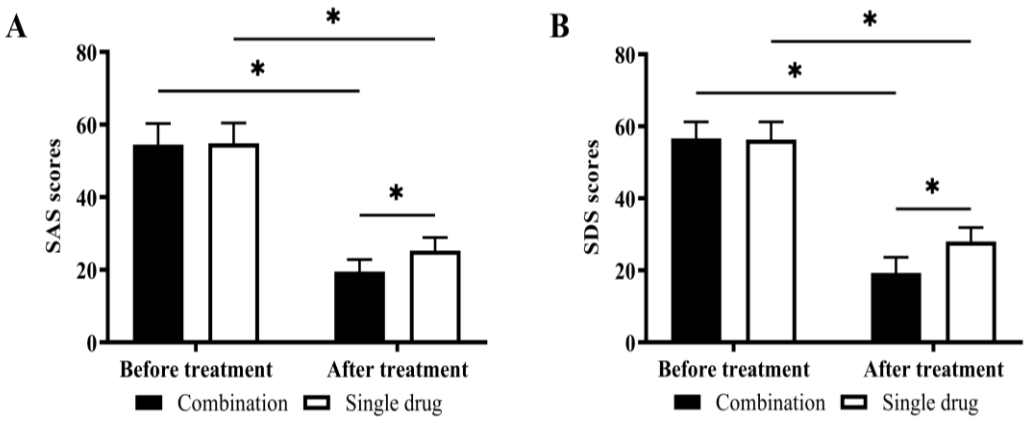

Figure 3: Comparison of SAS and SDS scores between both groups before and after treatment. A) SAS scores. B) SDS scores. *P<0.05.

3.5 Incidence of adverse reactions in both groups

During the treatment, adverse reactions such as fever, granulocytopenia, nausea and vomiting occurred in both groups, and both occurred by liver function impairment and bone marrow suppression, with the total incidence of adverse reactions in the combination group being 40.48% and in the single drug group being 35.71%. The difference in the total incidence of adverse reactions between the two groups was not statistically remarkable (P>0.05) (Table 3).

Table 3: Adverse effects during treatment

GROUPS	N	FEVER	GRANULOCYTOPENIA	NAUSEA AND VOMITING	FATIGUE	WEIGHT LOSS	LIVER FUNCTION IMPAIRMENT	BONE MARROW SUPPRESSION	TOTAL INCIDENCE OF ADVERSE REACTIONS
Combination	42	2(4.76)	4(9.52)	2(4.76)	3(7.14)	1(2.38)	1（2.38）	4(9.52)	40.48%
Single drug	42	1(2.38)	3（7.14）	2(4.76)	3(7.14)	2(4.76)	1（2.38）	3(7.14)	35.71%
χ^2									0.202
P									0.653

4. Discussion

Malignant pleural-peritoneal effusion is a common complication of advanced malignancy, and the median survival of such athletic patients is only 3-12 months (Husson et al., 2020). The clinical treatment of athletic patients with advanced malignancies combined with malignant pleural-peritoneal effusions aims to control local symptoms, and intracavitary perfusion is the most common means (Uhlenbruch, Keymel, & Krüger, 2020).

Recently, as the relationship between VEGF and malignant plural cavity effusion formation and prognosis has been continuously confirmed, it is believed that targeting VEGF intervention therapy may be a therapeutic breakthrough for malignant thoracic and abdominal effusions (Assoun, Brosseau, Steinmetz, Gounant, & Zalcman, 2017). Bevacizumab, the first anti-VEGF drug approved by the US Food and Drug Administration (FDA), has now been shown to be effective in improving the control of pleural effusions (Rosen, Jacobs, & Burkes, 2017). Thus, this study has an important clinical reference value by analyzing the effect of bevacizumab combined with lobaplatin infusion in the treatment of pleural-peritoneal effusions.

In the current study, we found that the clinical efficacy of athletic patients in the combination group was higher than that of the single drug group, and the levels of VEGF, CEA, and HIF-1α decreased more significantly after treatment, indicating that bevacizumab combined with lobaplatin perfusion therapy can further deplete VEGF levels in athletic patients with malignant pleural-peritoneal effusions, inhibit tumor angiogenesis, and improve the therapeutic effect. This is also consistent with the results of previous studies (Cohen, Gootenberg, Keegan, & Pazdur, 2007). It is well known that bevacizumab specifically blocks the binding of VEGF to its receptor, promoting tumor vascular degeneration and ensuring the normalization of the remaining vessels (Yanagihara et al., 2014).

Also, bevacizumab has been shown to block tumor cell growth, proliferation, and metastasis (Lee, 2022) and is therefore extremely common in clinical antitumor therapy. Lobaplatin, as the most commonly used chemotherapeutic drug for pleural effusion, has a significant inhibitory effect on the formation of pleural effusion and clear cytotoxic effects on a variety of animal and human tumor cell lines, and is a 3rd generation platinum-based anticancer drug with the advantages of high stability, broad anticancer spectrum, and strong antitumor activity (Albakri, Ahmad, & Mohamed, 2021).

We hypothesize that the combination of bevacizumab and lobaplatin can play a synergistic role, in which bevacizumab improves vascular permeability and thus relieves the osmotic pressure between tumor tissues, allowing lobaplatin to act directly on tumor lesions, enhancing local drug levels and

improving treatment quality. Besides, we also found no significant difference in adverse effects in the combination group compared to the single drug group as well, which once again illustrates the clinical applicability of bevacizumab and lobaplatin. Meanwhile, a lower complication rate in athletic patients treated with bevacizumab versus lobaplatin was seen in the study of (Lee, 2022), which could corroborate the results of our experiment.

On the other hand, we also found that the QLQ-C30 score results were all higher in the combination group after treatment compared with the single drug group, indicating that bevacizumab combined with intracavitary infusion of lobaplatin could improve athletic patients' symptoms of dyspnea, sleep disturbance, and pain caused by malignant pleural-peritoneal effusions, thus improving their quality of life.

The reduction of SAS and SDS scores in the combination group indicated that bevacizumab combined with intravitreal infusion of lobaplatin could also more effectively relieve athletic patients' psychological stress and enhance their confidence in overcoming the disease(Diaz et al., 2017). This is also due to the superior therapeutic effect of bevacizumab in combination with lobaplatin and its high safety profile. The above experimental results also fully confirm the future value and applicability of bevacizumab combined with lobaplatin intracavitary perfusion in clinical practice, which can provide more reliable prognosis for patients with malignant pleural-peritoneal effusions(Okuchi et al., 2010).

Since there are no uniform clinical guidelines for the treatment of malignant pleural-peritoneal effusions with bevacizumab combined with intracavitary perfusion of lobaplatin, there may be room for optimization and improvement in the selection of drug dose and timing. Also, the number of cases included in this study was small and there may be a chance of statistical calculation. In addition, we need to extend the follow-up period of athletic patients so as to assess the long-term prognostic impact of bevacizumab combined with lobaplatin intravitreal infusion therapy.

5. Conclusion

The findings from this study provide significant insights into the treatment of malignant pleural-peritoneal effusions, especially in the context of athletic patients. The combination of bevacizumab and lobaplatin perfusion has demonstrated greater efficacy compared to lobaplatin perfusion alone. Notably, the total effective rate of treatment was higher in the combination group, and the levels of key biomarkers like VEGF, CEA, and HIF-1α were significantly reduced post-treatment. These results are particularly encouraging given the specific physiological demands and recovery expectations of athletic patients.

Moreover, the study observed improvements in quality of life, as

measured by the EORTC QLQ-C30, along with reductions in anxiety and depression scores, indicating not only a physical but also a psychological benefit from the combination treatment. This aspect is crucial for athletic patients, whose mental well-being is deeply intertwined with their physical health, especially when facing serious health challenges like malignant effusions.

Importantly, the overall incidence of adverse reactions was comparable between the two groups, suggesting that the addition of bevacizumab to lobaplatin does not increase the risk of negative side effects. This safety profile is critical in ensuring that the treatment regimen does not impede the athletic patient's overall health and ability to return to their physical activities.

In conclusion, the combination of bevacizumab and lobaplatin perfusion emerges as a superior treatment option for malignant pleural-peritoneal effusions in athletic patients. It offers enhanced efficacy without compromising safety, addressing both the physiological and psychological aspects of patient care. These findings underscore the potential of tailored treatment strategies that consider the unique needs of specific patient groups, such as athletes, in managing complex medical conditions.

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