International Journal of Medical Sciences And Clinical Research (ISSN – 2771-2265)
VOLUME 02 ISSUE 10 PAGES: 21-30
SJIF IMPACT FACTOR (2021: 5. 694) (2022: 5. 893)
OCLC – 1121105677 METADATA IF – 5.654
Publisher: Oscar Publishing Services

Journal Website: https://theusajournals.com/index.php/ijmscr

Research Article

ASCYTE IN OVARIAN CANCER: NEW OPPORTUNITIES FOR RESEARCH

Submission Date: October 01, 2022, Accepted Date: October 07, 2022,
Published Date: October 21, 2022
Crossref doi: https://doi.org/10.37547/ijmscr/Volume02Issue10-05

Rakhimov Nodir Makhammatkulovich
Samarkand State Medical University, Uzbekistan

Shakhanova Shakhnoza Shavkatovna
Samarkand State Medical University, Uzbekistan

Abdurakhmonov Zhurabek Amrilloevich
Samarkand State Medical University, Uzbekistan

ABSTRACT

Malignant ascites is frequently found in OC, with about 10% of patients suffering from recurrent OC. More than a third of ovarian cancer patients have ascites at diagnosis, and nearly all have ascites at recurrence. The presence of ascites correlates with peritoneal spread of ovarian cancer and is associated with a poor prognosis of the disease. Malignant ascites acts as a reservoir of a complex mixture of soluble factors and cellular components that provide a tumor-stimulating microenvironment for tumor cells. Ascites -derived malignant cells represent a major source of morbidity and mortality in ovarian cancer patients. Subpopulations of these tumor cells have increased resistance to therapy and the ability to distal metastasis and recurrence. The anti-angiogenic targeted agents bevacizumab and pazopanib also showed good effects in the symptomatic treatment of malignant ascites OC, significantly prolonging the time to the next paracentesis. Thus, we conclude that further large-scale studies are needed to find out whether the reduction in ascites with these targeted drugs leads to an increase in the duration of tumor-related survival or not.

KEYWORDS

Ovarian cancer, ascites, targeted therapy, bevizumab, pazopanib.

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INTRODUCTION

Inclusive literature search was carried out by cross - referencing by keywords and then using literature references classified in preliminary sequence in the second stage to reduce the search volume. After documenting this core compendium of studies, the inclusion and exclusion criteria were formulated. The study included literature on targeted therapy in the treatment of ovarian cancer ascites ; the relevance of targeted therapy for the treatment of the disease; specifics of targeted therapy in the treatment of ovarian cancer; assessment of response after treatment; ongoing surveillance and recurrence of ovarian cancer. Evaluation terms included : ovarian cancer ascites, targeted therapy in the evaluation of ovarian cancer, recent innovations in targeted therapy for the treatment of ovarian cancer.

Epithelial ovarian cancer (OC) is the eighth most lethal gynecological malignancy in the world and the leading cause of gynecological cancer death in industrialized countries [21]. It is characterized by the spread of the tumor into the peritoneum and the development of malignant ascites, as well as the absence of specific symptoms in the early stages of the disease [35]. More than 200,000 cases of ovarian cancer are diagnosed each year , but 120,000 deaths are due to late detection [3]. Almost 70% of all patients have stage III and IV disease, although late detection of OC is not associated with the absence of symptoms, but the symptoms are rather nonspecific. Most patients suffer from pain in the abdomen, gastrointestinal tract, urination or pelvis, which rarely attracts the attention of the attending physician. This is the reason for the late detection of OC [36].

Currently, aggressive cytoreductive surgery followed by carboplatin and paclitaxel based on adjuvant chemotherapy is the “gold standard” [28]. However, the majority of patients will have disease progression with the development of resistance to chemotherapy in the future, which prompted us to explore new therapeutic methods, since the overall survival for patients who undergo surgery with adjuvant chemotherapy is only approximately 30% [13]

According to Simpson-Abelson MR et all. h anniy metatase in OC occurs through the direct spread of the tumor to areas adjacent to the primary tumor [38].

The epithelial-mesenchymal transition is involved in the formation of metastases, which leads to the migration of tumor cells to distant sites, after which the mesenchymal-epithelial transition occurs to accumulate in the tissue where the metastasis is located [1].

To date, there has not yet been a single consensus and opinion regarding the specific treatment of malignant ascites in patients with OC [12].

According to the National Cancer Institute, malignant ascites is defined by the accumulation of fluid containing cancer cells in the abdominal cavity [28].

Malignant ascites also typically has high levels of lactate dehydrogenase compared to non-malignant peritoneal effusions, indicating a high rate of tumor cell proliferation and rapid disease progression [5]. Malignant ascites is more common in OC than in any other tumor type; OC is known to cause intraperitoneal metastases [33].

There are several traditional treatment options for ascites, including salt restriction, diuretics, radioactive isotopes, paracentesis, and shunt placement. However, these methods have only a limited

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therapeutic effect and can cause significant toxic and side effects [12].

When the ovarian tumor capsule breaks down and the malignant cells disperse into the abdominal cavity, the cells survive as single cells or as free-floating multicellular inclusions in ascites called spheroids [2]. These spheroids adhere to the mesothelial extracellular matrix, which allows them to be fixed as secondary lesions of the pelvic organs [37]. Tumor cells in OC-associated malignant ascites trigger the recurrence of the disease. Mortality of patients is mainly associated with widespread metastasis of serous surfaces and concomitant peritoneal or pleural effusion [6]. The effusion accumulates as a result of lymphatic obstruction, activation of native mesothelial cells by a metastatic process, and increased vascular permeability indirectly triggered by vascular endothelial growth factor (VEGF) and interleukins of the 6th and 8th orders [14]. In addition, tumor cells themselves accumulate on the surface of the peritoneum, causing mechanical obstruction and preventing the absorption of intraperitoneal fluid. In malignant ascites, peritoneal fluid secretion is enhanced by VEGF stimulation [8].

A study by Schön-Günter and Mannel to evaluate the incidence of malignant ascites in ovarian malignancies found that although malignant ascites is rare in FIGO stage I OC (17%), it is found in the vast majority of patients with stage II/III tumor in 89% [35]. However, this study did not distinguish between epithelial and non-epithelial neoplasms. Commonly reported symptoms of malignant ascites include anorexia, bloating, dyspnea and respiratory distress, fatigue, insomnia, and abdominal pain [11].

Normal treatment of malignant ascites is generally unsatisfactory. Repeated paracentesis of intraperitoneal fluid provides only temporary relief and is not satisfactory due to the lack of causal therapy, which requires repeated drainage, depending on the severity of ascites. Protein loss and hypovolemia also increase the incidence of circulatory disorders. Finally, the risk of bowel perforation during paracentesis is certainly higher if performed more frequently [43]. Thus, advances in understanding the mechanisms that trigger malignant OC-associated effusion and the development of new therapies are imperative to improve the outcome of patients with malignant ascites.

Targeted therapy has recently been developed as a promising alternative treatment option for malignant ascites. Since angiogenesis is known to be a significant contributor to the formation of ascites, anti-angiogenic agents have been tested for this purpose. Bevacizumab and the novel VEGF agent pazopanib have been investigated and clinical efficacy has been proven in cohorts of patients with heavy pretreatment [10]

Pathophysiological aspects of malignant ascites .

Under normal physiological conditions, the capillary membranes of the abdominal cavity continuously release free fluid to maintain lubrication of the serous surfaces of the peritoneal membrane, so that a solution easily passes between the peritoneum and adjacent organs. Two-thirds of this peritoneal fluid is reabsorbed into the lymphatic channels of the diaphragm and pushed into the right subclavian vein by negative intrathoracic pressure [15]. In cases of disseminated intra -abdominal cancer, tumors cause a further increase in peritoneal fluid production due to increased tumor microvasculature leakage and lymphatic obstruction [4]. As a result, the accumulation of fluid in the abdominal cavity exceeds the reabsorption of fluid, which leads to the accumulation of ascites. It is assumed that the

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circulation of ascitic streams in the abdominal cavity dictates the ways in which ovarian cancer spreads [42]. The physiological factors that govern this process are gravity, diaphragmatic pressure, organ mobility, and depressions formed by key anatomical structures [34].

The three most common intra-abdominal sites of ovarian cancer metastasis are the greater omentum, right subdiaphragmatic region, and pouch of Douglas, areas that have easy access to ascites. Detached ovarian tumor cells, either singly or in the form of multicellular spheroids, are largely colonized in these distant sites by the flow of ascites; however, little is known about the effect of ascites flow on the heterogeneity of metastatic ovarian tumors that colonize at distant sites [34].

In a study by Latifi et al . It has been demonstrated that both adherent and non-adherent tumor cells are present in malignant ascites. The aim of their study was to separate these two types in culture. Interestingly, adherent tumor cells in ascitic fluid expressed rather mesenchymal features, while non-adherent cells had an epithelial phenotype, as they expressed epithelial cell adhesion molecule (EpCAM) and cytokeratin-7 (Latifi A et all conducted an experiment with mice injected intraperitoneally with either adherent or non-adherent cells.Mice injected with non-adherent cells developed tumors and malignant ascites within 12-14 weeks.In contrast, mice injected with adherent cells remained tumor-free for 20 weeks [26].

In a study by Simpson-Abelson MR et all. ovarian tumor-associated ascitic fluid has been shown to inhibit T-cell-induced nuclear factor-kappa-B (NF-κB) receptor and activated T-cell signaling nuclear factor (NFAT) in T-cell-associated tumors. In fact, the T cells present in ovarian tumor ascites do not respond properly to stimulation through the T cell receptor. Thus, NF-κB and NFAT activation is reduced, as is the proliferation of these immunosuppressed T cells. Interestingly, T cell anergy in ascites is due to fluid soluble factors. Since these T cells are analyzed in the absence of ascites, they acquire their normal function, and this effect is quickly restored when ascitic fluid is added to the T cells. This may explain why human tumors grow despite the presence of T cells and other immune response cells. The immunosuppressive effect of cellular or soluble biological factors on T cells and the accumulation of these immunosuppressed cells in tumors has already been proven by Simpson - Abelson MR et all . also demonstrated that the delay in NF-κB and NFAT signaling is located upstream of phospholipase C, as the signaling phosphorylation pattern of normal T cell receptors was compared to that of T cells in ascites. In addition, T cells derived from normal donated peripheral blood were incubated with (cirrhotic) ascitic fluid and showed the same T cell receptor signaling. Thus, it is assumed that ascitic fluid has an immunosuppressive effect on T cells, causing them to become anergic to various stimuli. Targeting soluble factors that induce T cell immunosuppression will undoubtedly be a future therapeutic option for the treatment of OC . [38].

Davidson and colleagues investigated active biochemical events in malignant ascites and pleural effusion. Patients with malignant effusion due to OC were included in this study . Expression and activation of selected signaling proteins in effusion samples were studied using protein microarrays using antibodies [9]. Malignant effusions (>80% malignant cells) were differentiated from benign effusions . Malignant effusion samples were characterized by higher expression of protein kinase B, activated extracellular signal kinase, cyclic adenosine monophosphate-responsive element binding protein, and N- terminal kinase c-JUN. Interestingly, there were no differences in signal profiles between pleural effusion and ascites.

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In group 1 patients, high p38 expression and a high ratio of phosphorylated to non-phosphorylated epidermal growth factor receptor (EGFR) were associated with poor survival, while the amount of N-terminal phospho-c-JUN kinase was associated with poor outcome in group 2. This The study shows that there is a clear dysregulation in proliferation, survival, and apoptotic signaling in OC effusion samples , and that some of the signaling proteins may influence patient outcome. With this knowledge, the authors wanted to accelerate the invention of new targeted therapeutic agents against ascites associated with OC [9].

In patients with chemoresistant disease included in this study, epithelial, mesenchymal and cancer stem cell selective markers were examined and compared between adherent and non-adherent tumor cells. Non-adherent cells showed increased mRNA expression of E-cadherin, epithelial cell adhesion molecule, transcription signal transducer and activator 3, and octamer-binding transcription factor 4, while adherent cells showed increased mRNA expression of differentiation cluster 44, template metallopeptidase 9, and octamer-binding transcription factor 4. transcription factor 4. Patients with chemoresistant tumors had more oncogenic epithelium [26]. It was also evident that non-adherent epithelial cells had increased mRNA expression of genes associated with cancer stem cells. Since cancer cells in OS-associated ascites are associated with disease recurrence, the information presented in this study may contribute to a better understanding of the cellular biology of tumor cells within ascites.

Angiogenesis of ascites

Antiangiogenic agents for malignant ascites. In healthy individuals, there is a balance of pro-angiogenic and anti-angiogenic signals (excluding wound healing and embryonic development), providing a calm vascular environment [12]. In the tumor microenvironment, the pro-angiogenic signaling cascade dominates the anti-angiogenic pathway, leading to the formation of new blood vessels [7]. When the tumor diameter exceeds 1–2 mm, angiogenesis becomes necessary for tumor growth [31].

Angiogenesis is mainly regulated by members of the VEGF family of growth factors and receptors, and ascites formation is also dependent on VEGF. Tumor vessels are rather disorganized, twisted and tend to leak [16]. Since VEGF-dependent signaling is blocked, the formation of malignant ascites is also reduced [12]. VEGF expression has been detected in OC in various assays, and in addition, the degree of VEGF expression has been shown to be associated with poor prognosis [27].

As cancer cells proliferate, secretion of VEGF occurs, which stimulates neovascularization, delivering nutrients to the tumor, promoting metastasis. It has been shown that during disseminated intra-abdominal metastasis, cancer cells produce an increased load on the abdominal fluid and microvascular permeability increases [39]. This results in significant ascites. According to Zebrowski and colleagues, VEGF proteins are increased in malignant peritoneal effusion compared to non-malignant cirrhotic ascites [44].

It has already been shown in mouse models that inhibition of VEGF signaling is associated with a distinct reduction in ascites formation and a reduction in tumor burden [41]. It has also been evident in animal models that VEGF production of cancer cells is directly correlated with tumor cell-induced ascitic fluid production). Based on these findings, the use of bevacizumab and pazopanib for the treatment of malignant ascites was investigated in subjects

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receiving heavy prior therapy and suffering from OC [23].

Vascular endothelial growth factor is found in high abundance in the ascites of ovarian cancer patients and plays a central role in modulating the oncogenic characteristics of ovarian cancer cells. VEGF is overexpressed in ovarian tumor cells and is associated with poor prognosis [24]. It has been reported that high VEGF production from primary tumors correlates with increased metastasis and worse prognosis compared to tumors with low VEGF secretion [40]. Retroviral forced expression of VEGF in ovarian cancer cells has been shown to drastically shorten the onset of ascites [8]. One of the mechanisms by which VEGF modulates peritoneal membrane permeability is through downregulation of the tight junction protein claudin 5 in peritoneal endothelial cells. In addition, it has been shown that VEGF induces tyrosine phosphorylation in the cadherin-catenin complex, which leads to a decrease in the strength of the endothelial junction and an increase in permeability [19]. Several factors have been shown to influence the production of VEGF by ovarian cancer cells. These include hypoxia, LPA, tumor necrosis factor, matrix metalloproteinases, insulin-like growth factor, epidermal growth factor, platelet-derived growth factor, and transforming growth factor beta [29]

Consistent with these studies, systemic administration of VEGF-Trap has been shown to prevent ascites accumulation and inhibit the growth of disseminated cancer in a mouse model, suggesting that VEGF expression is critical for ascites accumulation and progression of ovarian cancer. Several VEGF-targeting drugs have been evaluated in phase II trials in women with recurrent ovarian cancer. Bevacizumab, a humanized anti-VEGF monoclonal antibody, is currently in several Phase III trials with encouraging results [43].

Bevacizumab . In a study by Numnum et al. four patients with recurrent OC and ascites were treated with the anti-VEGF monoclonal antibody, bevacizumab. All four patients responded to this therapy, experiencing symptomatic relief of ascites. After initiation of bevacizumab therapy, therapeutic paracentesis was not required, according to a duration of up to six months [30].

Moreover, Hamilton and colleagues reported a case in which a patient with progressive, recurrent OC and severe symptomatic ascites was treated with intraperitoneal bevacizumab. After administration of two doses of bevacizumab, the patient experienced symptomatic relief and improved quality of life [20].

Two other reports of cases of non-targeted use of bevacizumab in 10 patients suffering from therapy-resistant ascites. Symptomatic improvement was observed in all patients and lasted approximately 2-6 months [23].

El Shami and colleagues conducted a study in which the safety and tolerability of intraperitoneal bevacizumab was tested in nine patients with refractory ascites due to rectal, breast, uterine, and ovarian cancer. Surprisingly, the malignant effusion was eliminated in all patients after only one dose, with no recurrence during a follow-up period of more than two months [13].

Pazopanib is an oral multitarget tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3, platelet growth factor receptor (PDGFR) -α and -β. An open-label Phase II study evaluated oral monotherapy with pazopanib in patients with low volume recurrent ovarian cancer

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with a complete CA-125 response to initial platinum-based chemotherapy and a subsequent increase in CA-125. Patients were treated with pazopanib (800 mg once daily) until progressive disease or unacceptable toxicity. The ORR was 18% in patients with measurable disease at baseline [17]. The international Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom 16 (AGOOVAR 16) was a phase III randomized control trial evaluating the role of pazopanib in the maintenance treatment of FIGO stage II-IV ovarian cancer without progression after primary therapy consisting of surgery and at least five cycles platinum/taxane chemotherapy; patients were randomized 1:1 to receive pazopanib (800 mg once daily) or placebo for up to 24 months. Maintenance pazopanib prolonged PFS compared with placebo (17.9 vs. 12.3 months, respectively). Pazopanib maintenance therapy provided a median PFS improvement of 5.6 months in patients with advanced ovarian cancer who did not progress after first-line chemotherapy. Data RAs do not provide any benefits. Grade 3 or 4 side effects hypertension (30.8%), neutropenia (9.9%), liver-related toxicity (9.4%), diarrhea (8.2%), fatigue (2.7%), thrombocytopenia (2.5%) and palmoplantar erythrodysesthesia (1.9%) were significantly higher in the pazopanib group. Treatment discontinuation associated with adverse events was higher among patients treated with pazopanib (33.3%) compared with placebo (5.6%) [25]

CONCLUSION

In summary, the new therapeutic approaches for OC - associated malignant ascites that we discussed in this review: for the use of targeted therapy in malignant ascites, it is necessary to carefully select patients and determine their risk factors in order to minimize the number of side effects. Further comparative analyzes and assessment of patient quality of life are the next steps to be taken before these new drugsYou will be included in daily clinical practice. In addition, clinical trials need to be conducted in larger patient series to see if bevacizumab and pazopanib are useful not only in relieving symptoms, but also in prolonging tumor-related overall survival.

REFERENCES

1. Ahmed N, Thompson EW, Quinn MA Epithelial-mesenchymal interconversions in normal ovarian surface epithelium and ovarian carcinomas: an exception to the norm. J Cell Physiol 213(3): 581-588, 2017.
2. Ahmed N, Stenvers KL : Getting to Know Ovarian Cancer Ascites: Opportunities for Targeted Therapy-Based Translational Research. Front Oncol 25;3: 256, 2013
3. Arni S, Cabiddu M, Ghilardi Muersperg N, Wong AS, Choi KC, Kang SK, Leung PC Ovarian surface epithelium: biology, endocrinology, and pathology. Endocr Rev 22(2): 255-288, 2011)
4. Adam RA, Adam YG. Malignant ascites: past, present, and future. J Am Coll Surg (2014) 198(6):999–101110.1016/j.jamcollsurg.2014.01.03517).
5. Bansal S, Kaur K, Bansal AK: Diagnosing ascitic etiology on a biochemical basis. Hepatogastroenterology 45(23): 1673-1677, 2008
6. Bonnefoi H, A'Hern RP, Fisher C, Macfarlane V, Natural history of stage IV epithelial ovarian cancer. J Clin Oncol 17(3): 767-775, 2009
7. Burger RA Overview of anti-angiogenic agents in development for ovarian cancer. Gynecol Oncol 121(1): 230-238, 2011
8. Byrne AT, Ross L, Holash J, Nakanishi M, Hu L, Hofmann JI, et al. Vascular endothelial growth factor-trap decreases tumor burden, inhibits

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OCLC – 1121105677 METADATA IF – 5.654
Publisher: Oscar Publishing Services

ascites, and causes dramatic vascular remodeling in an ovarian cancer model. Clin Cancer Res (2013) 9(15):5721–8).

9. Davidson B, Espina V, Steinberg SM, Florenes VA, Proteomic analysis of malignant ovarian cancer effusions as a tool for biologic and prognostic profiling. Clin Cancer Res 12(3 Pt 1): 791-799, 2016).
10. Eskander RN, Tewari KS Emerging treatment options for management of malignant ascites in patients with ovarian cancer. Int J Womens Health 4: 395-404, 2012
11. Easson AM, Bezjak A, Ross S, The ability of existing questionnaires to measure symptom change after paracentesis for symptomatic ascites. Ann Surg Oncol 14(8): 2348-2357, 2017.
12. Eskander RN, Randall LM Bevacizumab in the treatment of ovarian cancer. Biologics 5: 1-5, 2011
13. El-Shami K, El-Kerm Y Open-label safety and efficacy pilot trial of intraperitoneal bevacizumab as palliative treatment in refractory malignant ascites. J Clin Oncol 25(No. 18S(20 Suppl)): 9043, 2017).
14. Fang X, Yu S, Bast RC, Aggarwal BB, Lu Y, Mechanisms for lysophosphatidic acid-induced cytokine production in ovarian cancer cells. J Biol Chem 279(10): 9653-9661, 2014).
15. Feldman GB, Knapp RC. Lymphatic drainage of the peritoneal cavity and its significance in ovarian cancer. Am J Obstet Gynecol (1974) 119(7):991–4
16. Ferrara N VEGF as a therapeutic target in cancer. Oncology 69(Suppl 3): 11-16, 2005
17. Friedlander M, Hancock KC, Rischin D, et al. A phase II, open-label study evaluating pazopanib in patients with recurrent ovarian cancer. Gynecol Oncol. 2010;119:32–37du Bois A, Floquet A,
18. Gynecol Oncol (2012) 127(1):210–610.1016/j.ygyno.2012.05.002
19. Herr D, Sallmann A, Bekes I, Konrad R, Holzheu I, Kreienberg R, et al. VEGF induces ascites in ovarian cancer patients via increasing peritoneal permeability by downregulation of Claudin
20. Hamilton CA, Maxwell GL, Chernofsky MR, Bernstein SA, Intraperitoneal bevacizumab for the palliation of malignant ascites in refractory ovarian cancer. Gynecol Oncol 111(3): 530-532, 2008 .
21. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ: Cancer statistics, CA Cancer J. Clin 55(1): 10-30, 2015).
22. Jemal A, Siegel R, Ward E, Hao Y, : Cancer statistics 2009. CA Cancer J Clin 59(4): 225-249, 2009
23. Kobold S, Hegewisch-Becker S, Oechsle K, Jordan K, Intraperitoneal VEGF inhibition using bevacizumab: a potential approach for the symptomatic treatment of malignant ascites? Oncologist 14(12): 1242-1251, 2017 .
24. Kassim SK, El-Salahy EM, Fayed ST, Helal SA, Helal T, Azzam Eel D, et al. Vascular endothelial growth factor and interleukin-8 are associated with poor prognosis in epithelial ovarian cancer patients. Clin Biochem (2004) 37(5):363–910.1016/j.clinbiochem.2004.01.014 .
25. Kim JW, et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. J Clin Oncol. 2014;32:3374–3382].
26. Latifi A, Luwor RB, Bilandzic M, Nazaretian S, Isolation and characterization of tumor cells from the ascites of ovarian cancer patients: molecular phenotype of chemoresistant ovarian tumors. PLoS One 7(10): e46858, 2012 .
27. Monk BJ, Han E, Josephs-Cowan CA, Pugmire G, Burger RA Salvage bevacizumab (rhuMAB

International Journal of Medical Sciences And Clinical Research (ISSN – 2771-2265)
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OCLC – 1121105677 METADATA IF – 5.654
Publisher: Oscar Publishing Services

VEGF)-based therapy after multiple prior cytotoxic regimens in advanced refractory epithelial ovarian cancer. Gynecol Oncol 102(2): 140-144, 2006 .

28. National Comprehensive Cancer Network NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Ovarian cancer: including fallopian tube cancer and primary peritoneal cancer 2013;. Accessed 10/25, 2013).

29. Nuzhat Ahmed, Kaye L. Stenvers Getting to Know Ovarian Cancer Ascites: Opportunities for Targeted Therapy-Based Translational Research Front Oncol. 2013; 3: 256. Published online 2013 Sep doi: 10.3389/fonc.2013.00256

30. Numnum TM, Rocconi RP, Whitworth J, Barnes MN : The use of bevacizumab to palliate symptomatic ascites in patients with refractory ovarian carcinoma. Gynecol Oncol 102(3): 425-428, 2016

31. Ozols RF, Bundy BN, Greer BE, Fowler JM, Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 21(17): 3194-200, 2003

32. Petrelli F A novel perspective for an orphan problem: old and new drugs for the medical management of malignant ascites. Crit Rev Oncol Hematol 79(2): 144-153, 2011

33. Perez RP, Godwin AK, Hamilton TC, Ozols RF Ovarian cancer biology. Semin Oncol 18(3): 186-204, 2011

34. Rizvi I, Gurkan UA, Tasoglu S, Alagic N, Celli JP, Mensah LB, et al. Flow induces epithelial-mesenchymal transition, cellular heterogeneity and biomarker modulation in 3D ovarian cancer nodules. Proc Natl Acad Sci U S A (2013) 110(22):E1974–8310.1073/pnas.1216989110

35. Shen-Gunther J, Mannel RS Ascites as a predictor of ovarian malignancy. Gynecol Oncol 87(1): 77-83, 2002

36. Stirling D, Evans DG, Pichert G, Shenton A, Kirk EN, Rimmer S, Steel CM, Lawson S, Screening for familial ovarian cancer: failure of current protocols to detect ovarian cancer at an early stage according to the international Federation of gynecology and obstetrics system. J Clin Oncol 23(24): 5588-5596, 2005).

37. Shield K, Ackland ML, Ahmed N, Rice GE Multicellular spheroids in ovarian cancer metastases: Biology and pathology. Gynecol Oncol 113(1): 143-148, 2009

38. Simpson-Abelson MR, Loyall JL, Lehman HK, Human ovarian tumor ascites fluids rapidly and reversibly inhibit T cell receptor-induced NF-kappaB and NFAT signaling in tumor-associated T cells. Cancer Immun 13: 14, 2013

39. Solle E,Ttaucher V Malignant Ascites in Ovarian Cancer and the Role of Targeted Therapeutics Anticancer Research April 2014 vol. 34 no. 4 1553-1561

40. Shaxanova Sh Sh, Raximov N.M. Improving the combined treatment tactics of many osteogen metastases of malignant tumors of the urinary-body system. Web of Scientist: International Scientific Research Journal 2022/4/30, P 1145-1149.

41. Santin AD, Hermonat PL, Ravaggi A, Cannon MJ, Pecorelli S, Parham GP. Secretion of vascular endothelial growth factor in ovarian cancer. Eur J Gynaecol Oncol (2009) 20(3):177–8153.

42. Stoelcker B, Echtenacher B, Weich HA, Sztajer H, VEGF/Flk-1 interaction, a requirement for malignant ascites recurrence. J Interferon Cytokine Res 20(5): 511-517, 2015).

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Publisher: Oscar Publishing Services

43. Tan DS, Agarwal R, Kaye SB. Mechanisms of transcoelomic metastasis in ovarian cancer. Lancet Oncol (2006) 7(11):925–3410.1016/S1470-2045(06)70939-1
44. Urges A, Wimberger P, Kumper C, Gorbounova V, Effective relief of malignant ascites in patients with advanced ovarian cancer by a trifunctional anti-EpCAM x anti-CD3 antibody: a phase I/II study. Clin Cancer Res 13(13): 3899-3905, 2016
45. Zebrowski BK, Liu W, Ramirez K, Markedly elevated levels of vascular endothelial growth factor in malignant ascites. Ann Surg Oncol 6(4): 373-378,2016