2

Chemoresistance in Ovarian Cancer: The Role of Malignant Ascites

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Abstract: Ascites is an inflammatory process that induces the abnormal accumulation of a large amount of fluid into the peritoneal cavity. This pathological condition is observed in many neoplasms harboring peritoneal dissemination, a common feature in advanced ovarian cancer. In almost all patients, recurrent disease is accompanied by the accumulation of malignant ascites and is associated with chemoresistance and poor prognosis. The malignant ascites comprises a reservoir of a complex mixture of cellular components and soluble factors which provides a pro-inflammatory and tumor-promoting microenvironment for cancer cells. Moreover, tumor cells exhibit cancer stem-like phenotypes, acquire enhanced resistance to therapies, and higher capacity for metastatic spread and recurrent disease. The accessibility to malignant ascites and its cellular components makes it a unique source to track tumor progression and a key element to overcome chemoresistance.

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INTRODUCTION

Ascites can occur in different diseases, including cirrhosis, pancreatitis, nephritis, heart failure, and cancer (1, 2). Malignant ascites (MA) refers to a pathological accumulation of fluid into the peritoneal cavity, being present in several neoplasms e.g., ovarian, endometrial, pancreatic, gastric, colorectal, liver, and peritoneal malignancies (1, 3–5). Also, ascites can occur at a lower frequency in extra-abdominal tumors, e.g., lung and breast cancers (3, 4). This inflammatory condition occurs as a disruption in the balance of fluid production and reabsorption (4, 6) by different pathophysiologic mechanisms including increased vascular permeability—largely driven by upregulation of vascular endothelial growth factor (VEGF)—peritoneal lymphatic obstruction, and high levels of fluid production (3, 4, 7, 8). The presence of MA is often indicative of tumor cells in peritoneal cavity or peritoneal carcinomatosis (7) and can cause several comorbidities e.g., dyspnea, abdominal tenderness and painfulness, nausea, anorexia, fatigue, early satiety, weight change, and compromised movements (3, 9).

MA is considered a hallmark in advanced ovarian cancer as more than one-third of the patients develop this condition (6, 9, 10) and occurs in all epithelial ovarian cancer subtypes, including serous [i.e., low-grade and high-grade serous carcinomas (HGSC)], clear cell, mucinous, and endometrioid carcinomas (10, 11). MA accumulation is significantly higher in HGSC, the most aggressive subtype (10, 12).

MA containing a variety of cellular and acellular components associated with poor prognosis, provides a nurturing environment for cancer progression, metastasis, chemoresistance, and recurrence (Figure 1A) (3–6, 13). Also, the immunological constituents of MA enhance an inflammatory environment through the secretion of pro-inflammatory cytokines and chemokines accelerating disease progression (6, 13). Chemotherapeutic agents can prevent MA accumulation, however, chemoresistant or recurrent disease commonly develop intractable ascites that lead to a worse prognosis (4, 6). A persistent accumulation implies a repeated paracentesis for palliation, however, this temporary solution to relieve symptoms may lead to clinical complications, such as catheter-associated infections (3, 6, 13). Nevertheless, this regularity allows sampling cellular and acellular components from MA during tumoral progression, providing a unique opportunity for translational research (5, 14).

TRANSCOELOMIC DISSEMINATION

The most common route of dissemination in ovarian cancer is the transcoelomic spreading across the peritoneal cavity (15, 16), but, less commonly, can also occur by lymphatic and hematogenous spreading (6, 15). Transcoelomic dissemination leads to peritoneal carcinomatosis, a more diffuse and widespread metastatic form that have a high negative impact in surgical resectability (17). This metastatic route is a more efficient process for cancer spread since tumor cells follow the

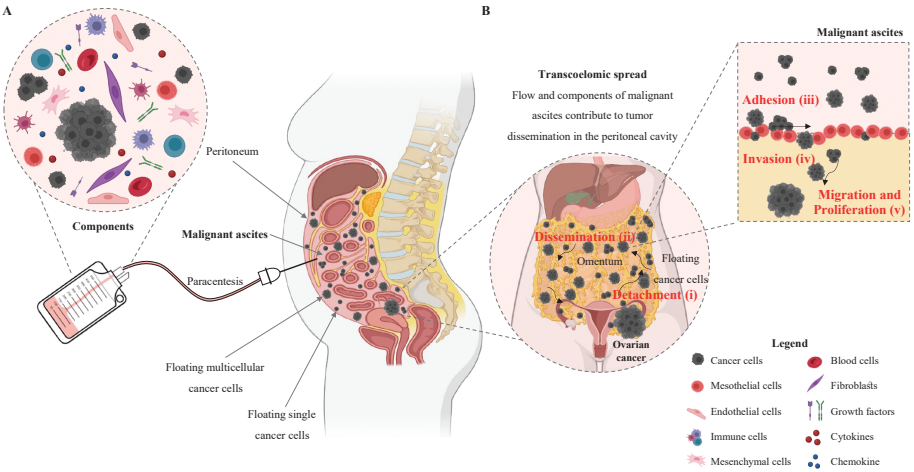

Figure 1 The accumulation of malignant ascites in ovarian cancer. A, Malignant ascites comprising cancer and non-cancer cells (e.g., fibroblasts, mesothelial, endothelial, immune, mesenchymal and blood cells) and acellular components (e.g., growth factors, cytokines, and chemokines). **B,** Malignant ascites contributes to transcoelomic dissemination, i.e., ovarian cancer cells detach from primary tumor in single or multicellular spheroids (i) and travel to other peritoneal sites (ii). Ovarian cancer cells adhere and implant on the peritoneum and peritoneal organs surface (e.g., omentum), where they clear the mesothelial lining (iii), invade the submesothelial extracellular matrix (iv), migrate, and proliferate creating secondary lesions (v). MA, malignant ascites; OC, ovarian cancer.

dynamics of peritoneal fluid until they meet the mesothelial lining, where they implant and aggregate (8). Metastatic implants are dispersed in areas with constant and extensive contact to peritoneal fluid, especially the omentum, Pouch of Douglas and right subphrenic region (18, 19). In ovarian cancer, peritoneal metastasis involves shedding of cells from primary tumor, dissemination in the abdominal cavity, attachment and invasion of the mesothelial lining, and colonization of intra-peritoneal organs (Figure 1B) (16, 20). Indeed, MA is described as a requirement for transcoelomic metastasis facilitating the dissemination of tumor cells and acting as a growth-promoting environment (20, 21) and is also reported as a promotor of lymphatic and hematogenous dissemination (22).

THE MICROENVIRONMENT OF MALIGNANT ASCITES

MA is composed of tumor and non-tumor cells (e.g., fibroblasts, adipocytes, mesothelial, endothelial, and inflammatory cells) (6, 23) and a liquid acellular fraction, all contributing to tumor progression, metastasis, and chemoresistance (7, 24). Frequently, MA contain cell aggregates (both cancer and non-cancer cells) forming spheroids that have a higher metastatic potential (25, 26). Several *in vitro* multicellular spheroids systems present anoikis resistance (27), restricted access and limited efficacy of cytotoxic drugs (25, 28) and slowly cycling and quiescent states becoming more chemoresistant (29, 30). Lafiti *et al.* showed that 95% of chemoresistant patients had an increased proportion of spheroids in its MA when

compared to chemo-naïve (25%) (26). Moreover, MA liquid fraction contain tumor-derived circulating free DNA (cfDNA) that presents an opening for tracking changes in the mutational profiles that cause chemoresistance and relapse (5).

The acellular components of MA involve a dynamic reservoir of pro- and anti-tumorigenic factors, comprising cytokines (31-35), chemokines, growth factors (36), integrins (37, 38) and metabolites contributing to metastasis and chemoresistance (5, 23, 28). In ovarian cancer, the cytokine profiles of MA demonstrated high levels of pro-tumorigenic (e.g., interleukin (IL)-6, IL-8, IL-10 and IL-15) and reduced levels of anti-tumorigenic (e.g., IL-2, IL-5, IL-7 and IL-17) factors contributing to a pro-inflammatory and immunosuppressive tumor microenvironment (4, 23, 34, 39). IL-6 and IL-10 are both correlated with poor prognosis and reduced therapy response (32, 40). High levels of IL-6 promotes MA accumulation, and ovarian cancer progression (40) and dissemination (41, 42). It is also associated with shorter progression free survival (PFS) (40, 43), poor overall survival (OS), reduced initial therapy response, and development of chemoresistance (35).

In ovarian cancer, high levels of VEGF are correlated with MA accumulation (36, 44) and poor prognosis (45). Zhan *et al.* showed that MA has high levels of VEGF compared to benign ascites and is associated with poor survival rates (36). Also, VEGF is commonly related with advanced-stage disease, high tumor grade, and increased metastatic potential (7). In ovarian cancer tissues, high epidermal growth factor receptor (EGFR) expression is often associated with aggressive, invasive, and metastatic disease (46, 47) and decreased OS and disease-free survival (48). Extracellular vesicles comprise another class of factors abundantly expressed in MA being important mediators of crosstalk between cancer cells and their microenvironment (49, 50). A recent study demonstrated that extracellular vesicles containing glycolytic pathway-related proteins can transmit chemoresistance to other tumor cells, facilitating disease progression (51). The proteomic profiling of MA enables the identification of possible therapeutic options to overcome ovarian cancer chemoresistance (52-55). Based on high-resolution mass spectrometry analysis, Ahmed *et al.* identified differential expression of 178 diminished, and 175 enriched proteins in MA of chemoresistant ovarian cancer patients compared to MA of chemonaïve patients (52).

Both cellular and acellular components display crucial roles in regulating proliferation, metastasis, and chemoresistance. Hence, exploring MA cell populations and signaling molecules during disease progression, and specially over the course of therapy (e.g., comparing patients in remission versus relapse), will be crucial to improve patient outcomes (5).

THE MANAGEMENT OF MALIGNANT ASCITES AND CHEMORESISTANCE

Over the last decades, the standard care for advanced ovarian cancer patients is based on platinum (e.g., Carboplatin) and taxane-based (e.g., Paclitaxel) chemotherapy following cytoreductive surgery (56, 57). In some cases, neoadjuvant chemotherapy is performed as alternative to standard treatment procedures (58, 59). The management of MA can be performed by aspiration during debulking surgery, chemotherapeutic schemes, or a paracentesis procedure (i.e., removing MA

inserting a wide-bore needle percutaneously through abdominal wall) (5, 7). Paracentesis is the most frequent procedure providing immediate relief symptoms, however, requires repeated drawings and can cause serious comorbidities and complications, such as draining site continuous leakage or bowel perforation (4, 60, 61). Most of the chemoresistant patients present intractable MA being submitted to repeated paracentesis during its' clinical course (4, 7).

Drainage catheter is placed percutaneously in the peritoneal cavity is an alternative intervention for MA management, being easy to self-drain, increasing patient independence, and diminishing the necessity for constant paracentesis at the hospital (62). It has been shown that intraperitoneal (IP) catheters drainage is a successful procedure and have a low complication rates supporting their use as first-line approach in refractory MA (63). Recently, Fotopoulou *et al.* demonstrated that in patients with hepatic and ovarian malignancies, subcutaneously implanted Sequana Medical Alfapump System, which continuously drains MA via urinary bladder, reduced the number of paracenteses from 4 to 1 (64, 65). However, more studies are essential to include catheter drainage as a routine procedure in oncological practices.

IP chemotherapy, i.e., the administration of high chemotherapy concentrations in the peritoneal cavity, directly exposes of peritoneal organs surfaces to chemotherapy agents compared to intravenous management and minimizes the toxicity of systemic chemotherapy (3, 4). A study performed in ovarian cancer patients at stage III with optimally debulked showed that IP administration as first-line treatment had a 16-month survival benefit (66). However, less than half of women completed all chemotherapy cycles, and it was shown a higher complication and toxicity rates in these patients (66). Early phase trials studying chemotherapy to control MA indicate that IP is the most effective method to deliver chemotherapy (4). Hyperthermic intraperitoneal chemotherapy (HIPEC), a combination of cytoreductive surgery and high concentration of heated chemotherapeutic agents, can reduce MA (67), since cytoreductive surgery removes macroscopic tumor implants, and IP act directly in the peritoneal cavity improving drug absorption and efficacy, targeting the remaining microscopic tumoral implants (68, 69). In advanced ovarian cancer with extensive peritoneal metastasis, HIPEC can be effective in improving patient survival (70, 71). Van Driel *et al.* showed in stage III ovarian cancer patients that combining cytoreductive surgery with HIPEC resulted in longer OS and PFS compared to surgery alone (72). Nevertheless, it is difficult to include HIPEC as a standard treatment as several studies demonstrate significant variation in patient outcome, as they use different chemotherapeutic drugs, concentrations, temperatures, and procedures duration leading to heterogenous and incomparable studies (70, 73). Thus, we need more well-designed trials to reach a more specific conclusion regarding the use of IP and HIPEC as a crucial armamentarium for ovarian cancer.

Studies focused on pharmacological therapy to MA management are limited and include antiangiogenic and metalloproteinase (MMP) inhibitors, and immunological modulators (4, 74–77). Bevacizumab is an anti-angiogenic targeting VEGF that delays the recurrent disease and palliate symptoms associated with MA accumulation (4, 78, 79). Numnum *et al.* reported that Bevacizumab treatment reduced the levels of MA allowing the discontinuation of repeated paracentesis (78). Several phase III trials in ovarian cancer, e.g., GOG18 (NCT00262847) and ICON7 (NCT00483782) added Bevacizumab to standard treatments and reported improved PFS and OS in patients with advanced stage disease (80, 81). Also, the randomized clinical trials OCEANS (NCT00434642)

and AURELIA (NCT00976911) indicate that Bevacizumab can provide benefits, delaying the recurrences in platinum-sensitive and platinum-resistant ovarian cancer (82, 83). In previously mentioned trials, Bevacizumab was not introduced with primary intention of affecting MA but revealed very effective in the reduction of its' formation (84, 85). Recently, a study demonstrated that IP administration of Bevacizumab present an acceptable safety profile and reduces the formation or delay MA accumulation in chemoresistant patients (86). A pilot study using Aflibercept (VEGF inhibitor) showed that this drug increased the time between paracentesis (87). Moreover, preclinical models demonstrated that Aflibercept prevent MA accumulation and inhibits tumor proliferation through VEGF blockade, however, it was observed an increased risk of morbidity associated with bowel perforation (75, 85). Batimastat (MMP inhibitor) has been used in animal models studies and demonstrated to decrease tumor growth, metastasis, and MA volume (88, 89). However, a Phase I study that administered Batimastat intraperitoneally in ovarian cancer patients found that the decreased MA volume was limited to a small number of patients (90, 91). Using an ovarian cancer mouse model, Zhao *et al.* demonstrated that Losartan (antihypertensive therapy targeting renin-angiotensin system) as a matrix-depleting strategy enhances the efficacy of Paclitaxel and reduces MA (92). Octreotide (Somatostatin analogue) is particularly useful for chylous ascites (a rare form containing large amounts of triglycerides), reducing splanchnic blood flow, contributing to a decreased lymph flow and bowel obstructive symptoms (7). Jatoi *et al.* revealed that a monthly intramuscular injections of long-acting Octreotide delayed the need for paracentesis from 14 to 28 days (93). The efficacy of Batimastat, Losartan and Octreotide is still under scrutiny and more studies are needed to clarify is role in MA management.

Several studies suggest improvements in the management of MA using immunological approaches including IP triamcinolone (76), IP interferon α and β (94), tumor necrosis factor (95) and even non-pathogenic infectious agents (96, 97). Recently, a prospective randomized phase II/III trials were conducted in ovarian cancer patients with MA using Catumaxomab, a trifunctional IgG2 antibody (anti-CD3, anti-EpCAM and anti-Fc receptors) that generates a strong immune reaction response against tumor cells (4, 61, 77). Heiss *et al.* demonstrated that IP administration of Catumaxomab leads to longer paracentesis-free survival, fewer ascites-related symptoms, and improved palliation (77). In 2009, Catumaxomab became the first therapeutic agent approved for MA management in Europe (4, 77).

Summing up, the previously described treatment options revealed a limited success in the management of MA in ovarian cancer patients. It is crucial to test more effective drugs and to develop improved methods for drug delivery to prevent MA accumulation during the ovarian cancer patient's clinical course.

MALIGNANT ASCITES AS AN OPPORTUNITY FOR TRANSLATION RESEARCH

MA is an exceptionally good source for research due to easy accessibility, repeated collection, capacity for reflecting primary tumor, metastatic implants, and tumor microenvironments. MA enables successive sampling of the milieu and therefore,

an ideal resource for translational studies including prediction of drug response and monitoring drug efficacy (4, 5, 98). MA accumulation is more frequently observed in recurrent cases and is absent in cases where patients respond to therapy (5). The understanding of the mechanisms involved in accumulation of MA and metastatic spread of ovarian cancer will allow the identification of potential drug targets that could be used to overcome chemoresistance. The pathways responsible for driving EMT phenotypic changes are responsible for spheroids tumorigenicity and can be potential targets (5, 99). Saine *et al.* reported that high expression levels of signal transducer and activator of transcription 3 (STAT3) in MA-derived ovarian cancer cells promote invasion and metastasis (100). In mouse models, it was shown that STAT3 inhibitors reduced chemoresistance and spheroid tumorigenicity (100, 101). Other studies showed that transforming growth factor (TGF)-β present in MA cells is a major driver in metastatic spread (99, 102). Acellular components provide a microenvironment that sustain cancer cells survival and potentiate the discovery of new treatment strategies based on disrupting this tumoral environment (103). By analyzing malignant effusions from ovarian cancer patients, Davidson *et al.* demonstrated high expression levels of AKT, cAMP-responsive element binding protein (CREB) and JUN N-terminal kinase (JNK) compared to benign effusions (104). Also, high levels of p8, and an increased ratio of phosphorylated EGFR and phosphorylated JNK were associated with worse outcome (104). Thus, all mentioned proteins and respective pathways are potential therapeutic targets for overcoming chemoresistance and the abrogation of peritoneal metastization of ovarian cancer.

A PERSONALIZED MEDICINE APPROACH FOR OVARIAN CANCER USING MALIGNANT ASCITES

The frequency of MA occurrence at first presentation, and subsequent relapse in ovarian cancer, provides a highly accessible pool of biologic material to track the sensitivity or resistance of tumor cells, as it captures several populations that compose the tumor microenvironment (4, 5). Serial samples, e.g., pre- and post-chemotherapy could be compared to assess molecular changes that may be predictive of therapeutic responses (103-105).

Conventional treatment strategies just allow a “one-size-fits-all” treatment based on a limited panel of drugs excluding alternative opportunities (106). The use of patient-derived tumor cells allows the association of specific tumor characteristics with a personalized treatment (106). Recently, patient-derived organoids (PDOs) emerged as a powerful modeling approach in cancer research (107-110) as many studies, in different cancer models, established PDOs that recapitulate the features from original derived lesions (111-116). Recently, Velletri *et al.* used ovarian cancer clinical samples across primary tumours and metastatic sites and demonstrated that MA-derived organoids retain key subpopulations and recapitulate features of the original samples acting as ‘patient-matched avatars’ that can be used in a precision oncology platform (117, 118). Moreover, other groups have demonstrated the capacity for growing tumor cells from MA *in vitro* for drug sensitivity testing (106, 119) and predicting clinical responses to therapy through assessment of biomarkers present in MA tumor cells (32, 120, 121). A study by Bi *et al.* demonstrated that

PDOs can be established in a high percentage of cases to perform drug tests in a timely manner and that PDOs have the potential to identify more efficient regiments (106). In addition, they demonstrated a specific case in which the PDO revealed patients resistance to standard therapy (106). Another study showed that the exposure of MA-derived spheroids to a panel of drugs can reflect the patients' therapy responses and identify the best viable candidates (122).

Many co-clinical trials (i.e., preclinical studies and clinical trials are conducted in parallel) are currently underway in different tumoral contexts, including ovarian cancer, comparing therapy responses in PDOs to corresponding patient outcomes, e.g., NCT04555473 and NCT05175326. This new strategy enables real time data integration to accurately stratify and customize treatment of patients (123). Additional clinical trials propose to evaluate therapeutical responses in PDOs to predict the clinical drug efficacy and choose the best regimen for each patient to guide clinical decisions, e.g., NCT04279509 and NCT04768270.

The establishment of PDOs from MA offers a valuable preclinical platform since they can be obtained with high efficiency in a short-period time, since MA contain cellular aggregates that are "natural" PDOs floating in the ascitic fluid (124). These systems can be used in drug efficacy tests using a range of approved and novel compounds (single or combined regiment) in a case-specific and in an acceptable time frame to predict therapy responses and guiding clinical decisions (Figure 2) (106, 125-128).

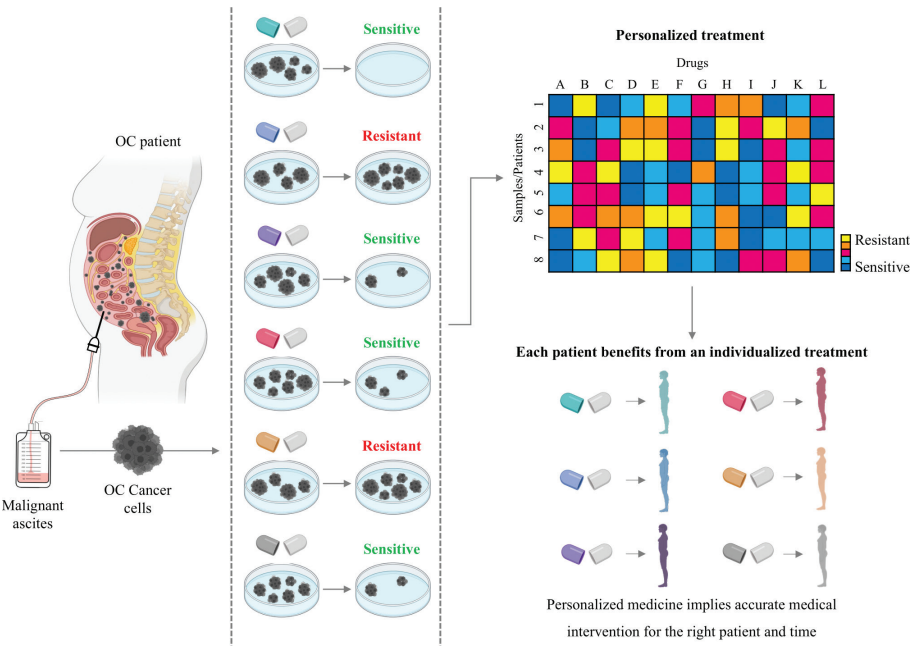

Figure 2 A personalized medicine approach in ovarian cancer using malignant ascites. Malignant ascites obtained from ovarian cancer patients by paracentesis will be used to make PDOs models and exposed to a panel of drugs to predict patients' responses. The most promising drugs will be selected to be administrated in the corresponding patient. MA, malignant ascites; OC, ovarian cancer; PDOs, patient-derived organoids.

CONCLUSION

Currently, therapeutic options for MA management generate initial acceptable responses but the efficacy in very low in the long-term. The accumulation of MA embodies the poorest outcomes representing a significant clinical challenge for ovarian cancer management. However, MA constitutes a unique opportunity for translational research. Large volumes of MA can be removed from patients, often repeatedly, representing a successive sampling of the tumor milieu in which ovarian cancer spreads making this an ideal source of biologic material to monitor chemoresistance and test several therapeutical options ex-vivo.

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