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Review Article

Paclitaxel targets VEGF-mediated angiogenesis in ovarian cancer treatment

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Abstract: Ovarian cancer is one of the gynecologic cancers with the highest mortality, wherein vascular endothelial growth factor (VEGF) is involved in regulating tumor vascularization, growth, migration, and invasion. VEGF-mediated angiogenesis in tumors has been targeted in various cancer treatments, and anti-VEGF therapy has been used clinically for treatment of several types of cancer. Paclitaxel is a natural antitumor agent in the standard front-line treatment that has significant efficiency to treat advanced cancers, including ovarian cancer. Although platinum/paclitaxel-based chemotherapy has good response rates, most patients eventually relapse because the disease develops drug resistance. We aim to review the recent advances in paclitaxel treatment of ovarian cancer via anti-angiogenesis. Single-agent therapy may be used in selected cases of ovarian cancer. However, to prevent drug resistance, drug combinations should be identified for optimal effectiveness and existing therapies should be improved.

Keywords: Paclitaxel, ovarian cancer, vascular endothelial growth factor (VEGF), angiogenesis

Introduction

Ovarian cancer is one of the most common and lethal cancers in women. It is a significant public health burden all over the world. In the UK, 7,116 women were diagnosed with ovarian cancer in 2011, and 4,271 deaths from ovarian cancer occurred in 2012 (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/incidence/). An estimated 21,290 new cases and 14,180 deaths attributed to ovarian cancer will be occurred in 2015 in the US (http://seer.cancer.gov/statfacts/html/ovary.html) [1]. Due to lack of a specific prodromal symptomatology and effective screening strategies, ovarian cancer is difficult to identify, so patients are already at the advanced stage of the disease upon diagnosis. The strongest known risk factors are old age and presence of certain gene mutations [2]. Moreover, age, performance status, tumor histology, optimal cytoreduction, and chemotherapy (e.g., platinum-based regimens) are key prognostic factors. In spite of numerous efforts in improving disease management and technology advances [3], the prognosis for patients with high-grade ovarian cancer has barely changed over the last 30 years, leaving a five-year survival rate of only 30% [4].

Conventional treatment strategy for ovarian cancer relies on surgical cytoreduction, followed by adjuvant chemotherapy [5-7]. A combination of maximal surgical debulking and platinum-based chemotherapy has been the standard treatment methods for advanced ovarian cancer since the mid-1990s [8, 9]. This chemotherapy is widely accessible for patients with ovarian cancer, and approximately 70% to 80% of patients respond well to this regimen [10]. However, the remaining patients usually develop resistance to chemotherapy or ultimately suffer incurable recurrence; the average five-year survival rate of these patients is lower than 50% [4, 11]. Given the limitations of a number of treatment options, identifying new effective drugs and establishing better treatment strategies are urgently needed. In the past decade, tremendous progress has been made on the discovery and development of novel therapeutic strategies parallel to our better understanding of the disease etiology [12, 13]. Many molecule-targeted therapies are being passionately investigated for ovarian cancer treatment [13].

Many active cytotoxic drugs and an increasing number of biological agents are becoming available. For example, antiangiogenic agents (such as bevacizumab, cediranib, and pazopanib [14]) and PARP inhibitor olaparib have been demonstrated to effectively treat ovarian cancer [15, 16]. The Bcl-2 family of apoptosis regulators, autotaxin, and mevalonate pathway have also been reported as therapeutic targets [1, 13]. Novel therapies have provided new insights to target-based therapies. In this article, we aim to review the current advances of treatment on ovarian cancer via antiangiogenesis, focusing on paclitaxel.

VEGF-mediated angiogenesis in cancer treatment

Angiogenesis is a process that is critical for supplying oxygen and nutrients through the formation of new blood vessels, and thus, has an implication in cancer growth [17]. Vascular endothelial growth factor (VEGF) is the most notable pro-angiogenic factor in the microenvironment, which plays key roles in physiological angiogenesis during embryogenesis, skeletal growth, and reproductive function [18, 19]. VEGF is overexpressed in the majority of solid tumors promoting tumor neovasculature [18]. It is also associated with tumor progression and poor prognosis for different cancers [20], including lung [21], colorectal [22], stomach [23], pancreatic [24], prostate [25], breast [26], and ovarian cancers [27, 28]. For example, high expression level of VEGF-A is reportedly associated with poor survival in ovarian cancer patients [29], and VEGF-D participates in the process of lymphatic metastasis of epithelial ovarian cancer [30]. VEGF receptor (VEGFR) is aberrantly activated in subsets of ovarian tumors [31, 32].

Recent studies have provided insights into the mechanism of VEGF in influencing tumor progression, such as targeting immune cells that are present in the tumor microenvironment [33], consequently affecting the host's response to tumors [33]. In addition, VEGF receptors might regulate the function of fibroblasts in the tumor stroma [28]. VEGF secreted by tumor cells functions in an autocrine manner dominantly via VEGF receptor tyrosine kinases (RTKs) and neuropilin-mediated signaling pathways [34-36]. It can facilitate the function of cancer stem cells and promote dedifferentiation, which enhances growth, survival, migration, and invasion of cancer cells, as well as epithelial mesenchymal transition [35-37]. Furthermore, the phosphatidylinositol 3-kinase (PI3K)/AKT and MAPK pathways have been identified as the dominant signaling pathways involved in the mechanism through which VEGF exerts its influence [13, 36].

Angiogenesis is a hallmark of cancer [34] in regulating tumor growth and lethality [38, 39], it is targeted by various cancer therapies that focus on drugs that inhibit VEGF [40]. Angiogenesis via multiple RTK-related pathways promotes ovarian cancer growth and dissemination, which are rate-limiting steps in tumorigenesis and malignant progression [41]. Antiangiogenic agents could potentially be effective therapies in improving outcomes of the disease; bevacizumab, a monoclonal antibody, sequesters VEGF [42], whereas vinblastine, paclitaxel, and docetaxel are microtubule-interfering agents [43]. Inhibitors of VEGF receptor tyrosine kinase, such as pazopanib, cediranib, sorafenib, nintedanib, and anti-integrin antibody, which inhibit both angiogenesis and metastasis, are being intensely investigated [1, 44, 45].

Paclitaxel, its mechanisms, and drug-resistance

Paclitaxel (or taxol), a natural product extracted from the bark of the Pacific yew tree *Taxus brevifolia*, is a widely used agent for treatment of a variety of tumors, including lung, breast, head, and neck cancers, Kaposi's sarcoma, and ovarian cancer [43, 46-49]. Paclitaxel is a diterpene alkaloid drug that possesses a variety of pharmacological properties, such as destabilization of microtubules by disassembly and blockage of cell cycle, causing cell death and inducing apoptosis, autophagy, and antiangiogenesis [50].

Paclitaxel functions as a radiosensitizer targeting tubulin; it is also a cytoskeletal drug [51, 52]. Paclitaxel treatment against KB cells might down-regulate the expression of polycomb repressive complex 1 and cyclin B2, resulting in microtubule polymer stabilization, and thus, preventing it from disassembly. It could further interfere with mitotic spindle formation, chromosome segregation, and cell division [50]. A

mitotic arrest [53] characterized by blocking the G2/M phase of the cell cycle and modulating the radioresponsiveness of tumor cells, could be induced [46].

Paclitaxel acts against diseases through triggering various cancer cell deaths via apoptosis through several pathways, including activation of the death receptor pathway, mitochondrial pathway, and cysteine aspartic-specific protease (caspase) cascades [46]. Paclitaxel also induces upregulation of the proapoptotic proteins Bax [54] and Bak [48, 55], as well as downregulation and inactivation of the antiapoptotic protein, Bcl-2 [56, 57].

Paclitaxel induces autophagy to inhibit tumorigenesis by raising the expression levels of autophagy protein 5 and Beclin-1, which are required for autophagosome formation. It can enhance the expression of p53 and LC3B (an ingredient of the autophagosome), thus regulating initiation of autophagy [58]. Paclitaxel-induced autophagy is critical in modulating caspase-independent cancer cell death. In addition, paclitaxel has been reported to significantly diminish microvessel density and decrease VEGF synthesis in vivo. Moreover, antiangiogenic effects of paclitaxel might be due to its preferential accumulation in endothelial cells [59].

Interestingly, paclitaxel activates cell survival pathways, such as the Raf/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase pathway and PI3K/AKT signaling pathway to antiapoptosis [60]. Furthermore, paclitaxel increases the expression of survival factors, such as apoptosis inhibitor survivin [61] and the cyclin-dependent kinase inhibitor protein, p21/WAF1/Cip1 [62, 63], by inducing persistent activation of cyclin B-cdk1, which leads to the phosphorylation and stabilization of surviving proteins [64]. Thus, the combined use of paclitaxel with MEK inhibitors or paclitaxel with PI3K inhibitors might be promising strategies for chemotherapy.

Although paclitaxel presents significant anticancer effects, cytotoxic efficacy on normal cells and drug resistance exist. One of the major dose-limiting side effects of paclitaxel is distal axonal polyneuropathy (mainly sensory polyneuropathy) [65-67]. At present, the mechanism of paclitaxel resistance is not fully understood because of the complexity of tumor drug resistance, which is implicated in multiple genes and processes. However, according to recent studies, changes of the A-tubulin gene and its associated protein might lead to paclitaxel resistance in ovarian cancer patients [68]. Multidrug resistance 1 might also contribute to paclitaxel resistance [50, 69, 70]. Paclitaxel resistance has also been suggested to be involved with alterations in cell death response, deletion of multiple apoptotic factors by the upregulation of the autophagic pathway, and collateral sensitivity to platinum [71]. In addition, human melanoma A375 cells produce resistance to paclitaxel (0.001 μmol/L to 0.1 μmol/L) by activating the MAPK and PI3K/AKT signaling pathways [71].

Clinical evidence of paclitaxel and bevacizumab in treating ovarian cancer

In ovarian cancer, chemotherapy is needed in Stage I Grade 3 lesion or Stage II disease. A randomized trial concluded that three cycles of paclitaxel at 175 mg/m^2 for 3 h plus carboplatin AUC of 7.5 is recommended [72].

In advanced ovarian cancer, after several trials, the patient showed excellent response rate to paclitaxel [73]. Platinum-paclitaxel doublets were tested in two trials [73, 74], and established a front-line therapy in ovarian cancer. Although two subsequent trials have raised questions in the respect of benefit from paclitaxel [75, 76], acknowledgement of the limitations of these trials [75, 77] has led to the acceptance of this front-line therapy practice, which remains unchanged. Further trials [78-80] aim to decrease the side effects of cisplatin-supported carboplatin by combining cisplatin with paclitaxel, which is commonly used in current clinical practice. Recently publicized trials demonstrated that dose-dense treatment offered better survival or less toxicity than conventional treatment [81, 82]. After its safety was confirmed, bevacizumab has been witnessed in several large clinical trials to bring significant progression-free survival and improvement after incorporating it into the paclitaxel-carboplatin doublet [83-87]. Another trial demonstrated a significant decrement of quality-of-life due to this drug [88], but another study showed that this decrement did not persist [89].

In recurrent ovarian cancer, paclitaxel demonstrates benefits in both platinum-sensitive and platinum-resistant patients. Regarding to platinum-sensitive recurrence, several studies do not support single-agent paclitaxel as an option [90, 91] but prefer platinum-paclitaxel doublet because its advantages were justified in another set of trials [92-94]. In platinum-resistant recurrence, a response rate of about 20% is observed with single-agent paclitaxel [95]. Many trials have been conducted positively to determine which schedule and dose of paclitaxel could bring optimal benefit and least side effects [96]. In actuality, arguments never cease, weekly doses of paclitaxel proved to possess the same efficacy but attenuated toxicity [97-103], considered to be an optimal schedule. Although single-agent bevacizumab demonstrated an inspiring response rate of about 15%-20% in two trials [104, 105], relative side effects paralleled. Bevacizumab has also been evaluated in combination with several other chemotherapy agents, including paclitaxel [106]; it turned out anti-tumor activity and manageable toxicity in recurrent ovarian cancer [107-119].

Paclitaxel and bevacizumab in treating other cancers

Paclitaxel has been used in treating several cancers, including breast cancer, lung cancer, head and neck cancer, and advanced stage of Kaposi's sarcoma. In metastatic breast cancer, paclitaxel intervenes in both doxorubicin-naive and doxorubicin-refractory diseases, resulting in a response rate of 35%-55% and above 20%, respectively [120, 121]. In platinum-resistant ovarian cancer recurrence, weekly regimen was superior to thrice-a-week schedule [122]. Paclitaxel also showed increasing rate of disease-free survival and overall survival in early breast cancer according to a meta-analysis [123]. Paclitaxel exhibited evident benefits in non-small cell lung cancer patients consulting a systematic review [124]. Interestingly, in advanced cases of ovarian cancer, bevacizumab exhibited apparent curative benefits when incorporated into a paclitaxel-carboplatin regimen in a large randomized trial and subsequent meta-analysis [125, 126]. In recurrent or metastatic head and neck cancers (R/M HNSCC), paclitaxel showed 40% response rate and an overall nine-month survival in several phase II trials [127]. Nowadays, the combination of paclitaxel-cetuximab in treating patients with platinum-resistant R/M HNSCC is proposed, as supported by a recent study [128]. Moreover, Paclitaxel has also been effective in treating Kaposi's sarcoma in several studies [129, 130].

So far as to Bevacizumab, which is used in breast, lung, colorectal, glioblastoma, and renal cancer standard therapies, in breast cancer, the bevacizumab-paclitaxel combination was approved as a first-line treatment of HER-2-negative meditative breast cancer in 2008 by the US Food and Drug Administration after the significant progression-free survival confirmed in several studies [131]. However, in 2010, this approval was reversed because of side effects of using this drug [132]. Use of bevacizumab remains controversial in the treatment of breast cancer [133]. In lung cancer, bevacizumab is associated with improved survival benefits [134-136]. In colorectal cancer, bevacizumab is beneficial for progression-free survival or time-disease progression when integrated into fluoropyrimidine-based chemotherapy [137]. A meta-analysis also concluded that adding bevacizumab to first-line chemotherapy in advanced colorectal cancer proved magnifying efficacy [138]. As to recurrent glioblastoma, single-agent bevacizumab improved response and progression-free survival in several studies [139-142]. When combined with other chemotherapy drugs, bevacizumab amplified efficacy [143-146]. For renal cell carcinoma (RCC), bevacizumab combined with interferon-α is the first-line treatment for metastatic RCC in Europe and US, after showing significant clinical benefits [147].

Conclusion

Although molecule-targeted anticancer treatments for ovarian cancer are currently available, challenges still abound in the chemotherapy approaches, which combines either single-based or combination drugs with other diverse biological treatments, optimal timing, and treatment sequencing. Due to its notable effects, antiangiogenic therapies and paclitaxel-based combination therapies have presented an amplified synergy effect when used in targeting ovarian cancer. Furthermore, treatment based on radiation and accompanied by paclitaxel, which proved to be effective in inhib-

iting NSCLC tumor growth [48], is considered to be a treatment foundation against ovarian cancer. Paclitaxel combined with either MEK inhibitors or PI3K inhibitors might also enhance curative rate but might induce unacceptable levels of toxicity to normal cells in clinical settings. Thus, more investigations are left to be conducted to enhance effectiveness and reduce toxicity. From where we stand now, new drugs with acceptable non-cumulative toxicity, reduced risk of recurrence after positive clinical response, and improved survival constitution, will push great advances in curing ovarian cancer patients, especially those who developed drug resistance to normal chemotherapies.

Disclosure of conflict of interest

None.

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