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REVIEW

Targeting WEE1 Kinase in Gynecological Malignancies

Wenhao Zhang[1,2], Qingli Li[1,2,*], Rutie Yin[1,2,*]

[1]Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, People's Republic of China; [2]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Rutie Yin, Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, 610041, People's Republic of China, Email yrtt2013@163.com; Qingli Li, Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, People's Republic of China, Email liqingli73@163.com

Abstract: WEE1 kinase is involved in the G2/M cell cycle checkpoint control and DNA damage repair. A functional G2/M checkpoint is crucial for DNA repair in cancer cells with p53 mutations since they lack a functional G1/S checkpoint. Targeted inhibition of WEE1 kinase may cause tumor cell apoptosis, primarily, in the p53-deficient tumor, via bypassing the G2/M checkpoint without properly repairing DNA damage, resulting in genome instability and chromosomal deletion. This review aims to provide a comprehensive overview of the biological role of WEE1 kinase and the potential of WEE1 inhibitor (WEE1i) for treating gynecological malignancies. We conducted a thorough literature search from 2001 to September 2023 in prominent databases such as PubMed, Scopus, and Cochrane, utilizing appropriate keywords of WEE1i and gynecologic oncology. WEE1i has been shown to inhibit tumor activity and enhance the sensitivity of chemotherapy or radiotherapy in preclinical models, particularly in p53-mutated gynecologic cancer models, although not exclusively. Recently, WEE1i alone or combined with genotoxic agents has confirmed its efficacy and safety in Phase I/II gynecological malignancies clinical trials. Furthermore, it has become increasingly clear that other inhibitors of DNA damage pathways show synthetic lethality with WEE1i, and WEE1 modulates therapeutic immune responses, providing a rationale for the combination of WEE1i and immune checkpoint blockade. In this review, we summarize the biological function of WEE1 kinase, development of WEE1i, and outline the preclinical and clinical data available on the investigation of WEE1i for treating gynecologic malignancies.

Keywords: WEE1 inhibitor, cell cycle, gynecological malignancies, adavosertib, clinical trials

Introduction

Tyrosine kinase WEE1 is crucial for DNA damage repair (DDR) and cell cycle regulation. A family of 14 serine/threonine protein kinases known as cyclin-dependent kinases (CDKs), regulate cell entry into different cell cycle phases by binding to cyclin subunits and phosphorylation.[1] For example, CDK1 binds to cyclin B, regulates the G2/M checkpoint, and hinders DNA-damaged cells from going through mitosis. Through phosphorylation of CDK1 at tyrosine residue 15 (Y15), WEE1 keeps CDK1 in an inactive state before mitosis, which induces G2/M cell cycle arrest in response to DNA damage, and provides time for DDR.[2] Targeted inhibition of WEE1 results in elevated CDK1 activity, and cells pass the G2/M checkpoint without sufficient DDR, which eventually results in genomic instability, aberrant mitosis, and cellular death.[3] In addition, previous studies have revealed that WEE1 is involved in homologous recombination (HR) repair, replication fork stabilization, and cell size coordination.[4–6] This effect is more prominent in tumor cells, as they often have tumor suppressor p53 protein deletion, resulting in a deregulated G1 checkpoint and relying heavily on the G2/M checkpoint to avert excessive DNA damage, aberrant mitosis, and cell death. Interestingly, as the most lethal gynecological cancer, the majority of high-grade serous ovarian cancer (OC) and uterine serous carcinoma (USC) have TP53 mutations.[7,8] Moreover, human papillomavirus (HPV)-related cervical cancer (CC) exhibits high levels of replication stress due to the loss of p53

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control of the G1/S checkpoint caused by HPV E6 and E7 proteins.[9] The hallmark features of cervical, ovarian and uterine cancer make them vulnerable to therapeutic interventions on the G2/M checkpoint, making WEE1 a compelling new target for treating these tumors. The effects of WEE1 inhibition in gynecologic tumors have been shown in a number of preclinical investigations, and positive clinical trial data have also been released. In the current review, we enumerate the biological role of WEE1 kinase and the potential of WEE1 inhibitor (WEE1i) for treating gynecological malignancies and whether it could be translated into the clinic as one of the safe targeted drugs in the future.

Method

We searched literature with the keywords "WEE1 inhibitor" and "gynecologic oncology" in 3 journal sources: PubMed, Scopus, and Cochrane. This narrative review was prepared based on studies related to treating gynecologic cancers with WEE1i. The authors use all original research and clinical reports published from 2001 to 2023 regarding the use of WEE1i in gynecologic oncology. The authors exclude irrelevant articles, which are clinical trials designed for solid tumors without reporting the exact gynecologic cancer patients recruited, research articles that do not clearly state the interventions, and other sources such as book chapters. After discussing the results, the authors reached an agreement.

WEE1 Kinase in Cell Cycle Regulation and DNA Damage Repair

The process of the cell cycle is strictly controlled and regulated. When cells encounter endogenous or exogenous sources that induce DNA damage, checkpoints can be used to arrest the cell cycle and provide time for DDR. This complex and precise machinery of cell cycle checkpoint control and DDR system ensures the stability of the genome.[1] Depending on the type of genotoxic stress, the ataxia-telangiectasia-related (ATR) or ataxia-telangiectasia mutated (ATM) protein kinase pathway is preferentially activated when DNA is damaged. Multiple DNA damage events activate ATR. Checkpoint kinase 1 (CHK1) is activated and phosphorylated by ATR activation, which in turn phosphorylates WEE1 and cell division cycle factor 25 (CDC25), causing WEE1 activation and CDC25 inactivation. The WEE1 will phosphorylate the CDK1/Cyclin B complex at the Tyr15 site of CDK1, resulting in inactivation of the complex and G2 phase cell cycle arrest, thereby facilitating DDR.[10,11] The ATM kinase is activated by double-strand DNA breaks (DSBs), which phosphorylates and activates checkpoint kinase 2 (CHK2), and subsequently promotes the cytoplasmic sequestration and inactivation of CDC25, which reduces the CDK1 activity and prevents cells entry into mitosis (Figure 1).

One of the key features of malignant tumor cells is uncontrolled proliferation, which is closely related to cell cycle dysregulation and abnormal DDR. The p53 protein checks for DNA damage during the G1/S phase and monitors the stability of the genome. However, tumor cells often have p53 protein deletion, resulting in a deregulated G1 checkpoint, providing tumor cells with the potential to accumulate mutations and propagate genomic instability.[12,13] Therefore, tumor cells harboring TP53 gene mutations rely heavily on the G2/M checkpoint to avert overload DNA damage, aberrant mitosis, and cell death. This implies that disruption of the G2/M checkpoint will primarily impact tumor cells, while cells with normal G1 checkpoints will be less affected. Thus, WEE1 inhibition in the context of TP53 mutation may compromise G1/S and G2/M simultaneously, driving tumor cells into unplanned mitosis and ultimately leading to their death, which is consistent with synthetic lethality.

Preclinical Studies of WEE1i in Gynecologic Cancers

The function of WEE1 in cell cycle regulation and DDR has led to its investigation as a potential therapeutic target for solid cancers. To date, numerous pharmacological inhibitors have been developed and validated in various tumor models, including Adavosertib (also known as AZD-1775 or MK-1775),[14] PD0166285,[15] PD0407824,[16] and the recently developed ZN-c3,[17] Debio 0123[18] and IMP7068.[19] Due to its high specificity, Adavosertib has been extensively investigated and is the most promising compound for WEE1i undergoing Phase II clinical trials.[20–24] Current literature reports the antitumor effects of WEE1i in a variety of in vitro and in vivo tumor models, either alone or in combination with other DNA-damaging modalities.[14,18,19,25–34]

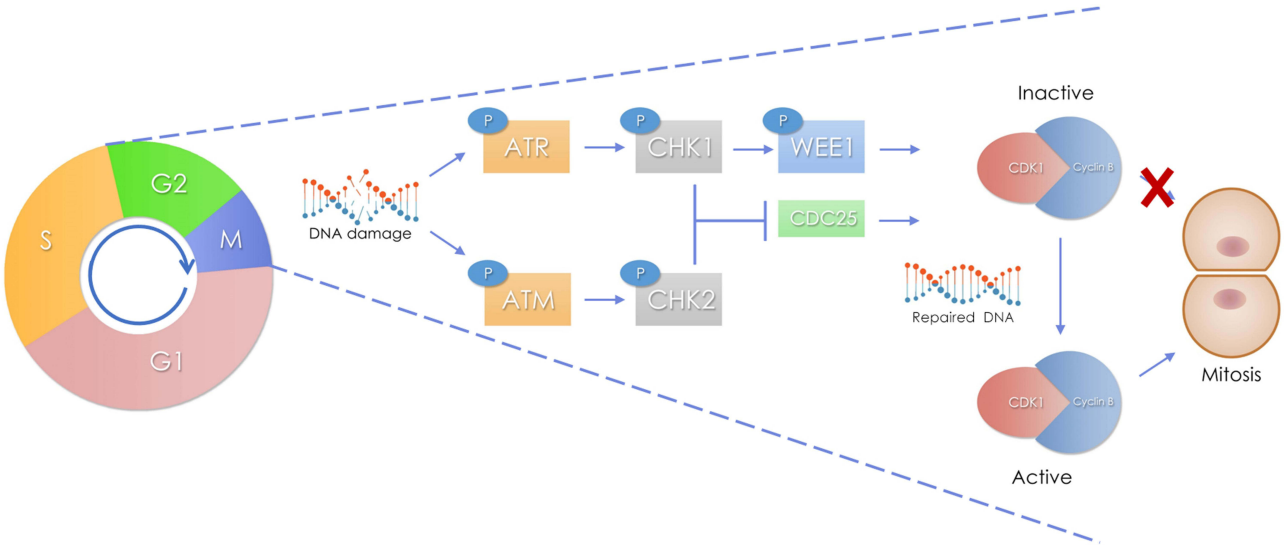

Figure 1 WEE1 kinase in cell cycle regulation and DNA damage repair. ATR or ATM are employed during the G2/M checkpoint to detect DNA damage, depending on the type of genotoxic stress. The phosphorylation of ATR leads to activation of CHK1, which subsequently activates WEE1 and inactivates CDC25. Active WEE1 phosphorylates the CDK1-CyclinB complex at tyrosine 15, keeping the complex inactive and preventing cells from entering mitosis. The activation of ATM phosphorylates and activates CHK2, and subsequently promotes the cytoplasmic sequestration and inactivation of CDC25, which reduces the CDK1 activity and prevents cells entry into mitosis. After DNA damage repair, WEE1 activity is attenuated, the inhibitory phosphorylation of CDK1 is prevented, and the inhibitory effect of CHK1 and CHK2 on CDC25 is abolished. CDC25 dephosphorylates CDK1-CylinB, activates the complex, and drives cells into mitosis.
Abbreviations: ATR, Ataxia-telangiectasia-related; ATM, Ataxia-telangiectasia mutated; CHK1, Checkpoint kinase 1; CHK2, Checkpoint kinase 2; CDC25, Cell division cycle factor 25/Cell division cyclin 25, CDK1, Cyclin-dependent kinase 1.

Monotherapy

WEE1 is frequently expressed in OC, and its expression is significantly higher following chemotherapy than in treatment-naive patients, which is also correlated with a worse overall survival (OS).[35] Besides OC, WEE1 is also highly expressed in CC,[36] and vulvar cancer (VC).[37] The proliferation of OC cells SKOV3 and OVCAR8 reduced when WEE1 was silenced by siRNA knockdown.[35] WEE1i reduced cell viability and induced apoptosis in WEE1-high expression CC cell lines.[36] In the models with p53 mutation, Adavosertib could significantly inhibit the growth of the endometrial cancer (EC) cells Hec50 and the OC cells OVCAR3.[25] Further in vivo studies demonstrated that Adavosertib exhibited antitumor activity in mouse OC xenograft models,[26] and its activity is associated with increased DNA damage. Recent research has revealed that the outer dense fiber of sperm tails 2–like (ODF2L) is a major contributor to OC cells' resistance to WEE1 inhibition.[38] ODF2L knockdown significantly increased sensitivity of OC cells to Adavosertib both in vitro and in vivo, indicating that low ODF2L levels may be a potential biomarker for WEE1i in OC.[38]

Combined with Chemotherapy

As a key kinase in DDR and cell cycle regulation, inhibiting WEE1 activity could theoretically enhance the antitumor effect of chemotherapy. To date, preclinical studies have revealed that WEE1i increases sensitivity to gemcitabine in gynecologic malignancies. Gemcitabine in combination with different dosages of Adavosertib showed significant cell death in OVCAR3 cells, EC cells Hec50, and KLE. WEE1 blockage markedly boosted the sensitivity of cells to low-dose gemcitabine, resulting in enhanced cell death in the M phase when the G2/M checkpoint was abrogated. This combination shows promise in the treatment of p53-mutant advanced and recurring gynecologic malignancies, and warrants future investigation in clinical trials.[25]

Combined with Radiotherapy

Preventing tumor cells from repairing ionizing radiation (IR)-induced DSBs results in cell death and increases radiosensitivity. Therefore, combining WEE1i with IR is reasonable to enhance the treatment effects of the tumor with dysregulated p53 signaling. Preclinical data suggest that WEE1i is a potential radiosensitizer, showing efficacy in OC and

CC cell lines when IR is combined with PD0166285. The G2/M checkpoint is abolished and correlated with the functional status of p53.[15,27,39] Furthermore, Adavosertib can radiosensitize CC both in vitro and in vivo, which was considered to have inactivated p53 functionality due to HPV infection.[28] However, another study showed that radiosensitization induced by WEE1i occurs in hepatocellular carcinoma cells regardless of their p53 mutational status.[29] Furthermore, few studies reported that WEE1 inhibition could induce radiosensitization in cancer stem cells, which correlates with the intrinsic radiosensitivity.[40,41] Given their findings, the exact cellular mechanisms underlying the radiosensitization by WEE1 inhibition remain unclear. The suppression of HR by WEE1i may be a plausible mechanism since HR plays a crucial role in radiation-induced DSBs repair.[6] Based on these data, clinical trials are designed to explore the radiosensitization effect of WEE1i in CC and VC.

Combined with PARP Inhibitor

Given the dependence on the WEE1-mediated G2/M checkpoint for poly (ADP-ribose) polymerase inhibitor (PARPi)-induced DSBs and the compromised HR triggered by WEE1i,[42] the combination of the two could theoretically provide clinical benefit for cancer patients. Regardless of the HR status, combinations of Adavosertib with Olaparib in OC cells demonstrated synergistic effects in both Olaparib-sensitive and -resistant sublines. This may suggest the addition of WEE1i may reverse PARPi resistance in OC.[30] In human EC and OC cells, Adavosertib significantly raised the sensitivity of Hec50 and OVCAR3 cells to Olaparib, with significantly enhanced apoptosis in mitosis, indicating that treated cells could not properly pass through the M phase.[25] Recently, Fang et al reported that synergy between PAPRi and WEE1i was most clearly manifest in KRAS or BRAF mutant OC cells that are resistant to PARPi.[31] The same study showed that using sequential rather than concurrent therapy for OC maintained the synergy of PARPi and WEE1i while reducing toxicity.[31] The above research results provide rationale and evidence for further clinical testing. This finding warrants further evaluation in clinical studies. The above research results provide rationale and evidence for further clinical testing. Currently, clinical trials designed to explore the combination of Adavosertib and Olaparib in the treatment of refractory solid tumors, including OC, are ongoing (Table 1).

Combined with Other Inhibitors

With the discovery of novel biological functions of WEE1, few preclinical studies have investigated the potential combination strategies for WEE1i in treating gynecologic cancers. In OC cells and PDX, the combination of Adavosertib and mTOR inhibitor AZD2014 synergistically inhibits tumor growth. Dual WEE1 and mTOR inhibition induced massive DNA replication stress, resulting in fork stalling and DNA damage that can explain the synergistic effect.[43] A study from the same group demonstrated that Adavosertib induces endoplasmic reticulum stress and activates the inositol-required enzyme 1α (IRE1α) branches of the unfolded protein response in TP53-mutant OC models. This finding leads to an encouraging synergistic antitumor effect of combining Adavosertib and an IRE1α inhibitor, MKC8866, in TP53-mutant OC cell lines and PDX.[44]

Given the crucial role of ATR as a DNA damage signal transduction kinase, cells with decreased ATR function will have impaired checkpoints and be more vulnerable to DNA damage and replication stress. Therefore, simultaneous inhibition of ATR and WEE1 might be more beneficial than single treatment. A recent study reported that WEE1i and ATR inhibitor (ATRi) combination is synergistic in OC and EC cells and PDX models by increasing replication stress, mitotic catastrophe, and cell death.[32] More importantly, the synergy was found to be in a CCNE1 copy number dependent manner, indicating that a high CCNE1 copy number is a potential genomic biomarker for response prediction. This discovery has important therapeutic significance since CCNE1 amplification is commonly seen in OC and EC and is associated with treatment resistance and a poor prognosis.[45,46] Further study confirmed the synergistic effect of Adavosertib and ATRi AZD6738 in various OC cell lines and the ID8 mouse OC model.[33] Additional mechanistic investigation found that WEE1i and ATRi combination can trigger immunogenic responses by upregulating the interferon responses, tumor-infiltrating lymphocytes and activating immune checkpoint programmed death-ligand 1 (PD-L1).[33] This finding suggested immune checkpoint blockade (ICB) in conjunction with dual inhibition of WEE1 and ATR may synergistically inhibit tumor growth to a greater extent. The following study further investigated the potential of WEE1i with ICB, demonstrating that WEE1i stimulates anti-tumor immunity and enhances sensitivity to ICB. In the ID8 OC

Table 1 WEE1 Inhibitor in Gynecologic Oncology Clinical Trials

Clinical Trial	Study Title	Arm	Patient Number	Efficacy	AEs	Country
NCT01164995 Phase II	Study with WEE1 Inhibitor MK-1775 and Carboplatin to Treat p53 Mutated Refractory and Resistant Ovarian Cancer	MK-1775 + Carboplatin	24 patients	Median PFS and OS were 5.3 and 12.6 months	Grade ≥3 thrombocytopenia (48%), neutropenia (37%)	Netherlands
NCT01357161 Phase II	A Study of MK-1775 in Combination with Paclitaxel and Carboplatin Versus Paclitaxel and Carboplatin Alone for Participants with Platinum-Sensitive Ovarian Tumors with P53 Mutation	A: MK-1775 + Paclitaxel + Carboplatin B: Placebo + Paclitaxel + Carboplatin	136 patients	Median PFS MK-1775 vs Control group 7.9 vs 7.3 months (P=0.080)	Grade ≥3 MK-1775 (78%) vs Control (41%) SAEs MK-1775(65%) and Control (20%)	Global Multicenter
NCT02151292 Phase II	Gemcitabine Hydrochloride with or without WEE1 Inhibitor MK-1775 in Treating Patients with Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	A: MK-1775 + Gemcitabine B: Placebo + Gemcitabine	99 patients	PFS Combination vs Gemcitabine alone 4.6 vs 3.0 months Median OS Combination vs Gemcitabine alone 11.4 vs 7.2 months	No significant difference between two groups	USA Canada
NCT01748825 Phase I	AZD-1775 for Advanced Solid Tumors	AZD-1775 dose escalation	42 patients	6 patients had PR (all gynecological cancer), recommended dose for phase II study: 300 mg qd	DLT were grade 4 hematologic toxicity and grade 3 fatigue	USA
NCT02272790 Phase II	Adavosertib Plus Chemotherapy in Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	A: Adavosertib + Gemcitabine B: Adavosertib + Paclitaxel C: Adavosertib + Carboplatin D: Adavosertib + PLD	94 patients	Carboplatin plus weekly Adavosertib has the highest response rate (66.7%), with 100% DCR, and median PFS 12.0 months	Grade ≥3 neutropenia (47.9%), anemia (33.0%), thrombocytopenia (31.9%), diarrhea and vomiting (10.6%)	USA Canada Netherlands
NCT03668340 Phase II	AZD-1775 in Women with Recurrent or Persistent Uterine Serous Carcinoma or Uterine Carcinosarcoma	AZD-1775	34 patients	1 CR, 9 PR, the 6-month PFS rate 47.1%	Diarrhea (76.5%), fatigue (64.7%), nausea (61.8%), and hematologic AEs	USA
NCT04590248 Phase II	A Study of Adavosertib as Treatment for Uterine Serous Carcinoma	Adavosertib	109 patients	Ongoing	NA	Global Multicenter

(*Continued*)

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Table 1 (Continued).

Clinical Trial	Study Title	Arm	Patient Number	Efficacy	AEs	Country
NCT03345784 Phase I	Testing AZD-1775 in Combination with Radiotherapy and Chemotherapy in Cervical, Upper Vaginal and Uterine Cancers	Radiation therapy + Adavosertib + Cisplatin	Estimated: 33 patients	Ongoing	NA	USA Canada
NCT03579316 Phase II	Adavosertib With or Without Olaparib in Treating Patients with Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Adavosertib Adavosertib + Olaparib, Ceralasertib + Olaparib	Estimated:104 participants	Ongoing	NA	USA
NCT02576444 Phase II	A Phase II Study of the Olaparib Alone and in Combination with AZD-1775, AZD5363, or AZD6738 in Advanced Solid Tumors OLAParib COmbinations (OLAPCO)	AZD-1775 + Olaparib	Estimated: 64 participants	Ongoing	NA	USA
NCT04158336 Phase I/II	A Study of ZN-c3 in Participants with Solid Tumors, including Epithelial Ovarian Cancer, Fallopian Tube Cancer, Peritoneal Cancer	ZN-c3 dose escalation and expansion	Estimated: 110 patients	Ongoing	NA	USA
NCT04516447 Phase Ib	A Study of ZN-c3 in Patients with Platinum-Resistant Ovarian Cancer	A:ZN-c3 + Carboplatin B:ZN-c3 + PLD C:ZN-c3 + Paclitaxel D:ZN-c3 + Gemcitabine	Estimated: 140 patients	Ongoing	NA	Global Multicenter
NCT04814108 Phase II	A Study of ZN-c3 in Women with Recurrent or Persistent Uterine Serous Carcinoma	ZN-c3 single	Estimated: 108 patients	Ongoing	NA	Global Multicenter
NCT05431582 Phase I	A Study of ZN-c3 and Bevacizumab ± Pembrolizumab in Metastatic CCNE1 Amplified and TP53 Mutant Solid Tumors	A:ZN-c3 + Bevacizumab B:ZN-c3 + Bevacizumab + Pembrolizumab	Estimated: 74 patients	Ongoing	NA	USA
NCT05109975 Phase I	A Study to Evaluate Safety and Preliminary Anti-tumor Activity of Debio 0123 as Monotherapy in Adult Participants with Advanced Solid Tumors	Debio 0123 dose escalation	Estimated: 130 participants	Ongoing	NA	USA Switzerland
NCT03968653 Phase I	Study of Oral Debio 0123 in Combination with Carboplatin in Participants with Advanced Solid Tumors	Debio 0123 + Carboplatin	Estimated: 130 participants	Ongoing	NA	Netherlands Spain
NCT04768868 Phase I	The Safety and Pharmacokinetics Preliminary Efficacy of IMP7068 in Patients with Advanced Solid Tumors	IMP7068 dose escalation	150 participants	Ongoing	NA	USA China

Abbreviations: AEs, adverse event; SAEs, serious adverse event; Qd, once a day; PFS, progression-free survival; OS, overall survival; DLT, dose limiting toxicities; CR, complete response; PR, partial response; DCR, disease control rate; NA, not applicable.

xenografts model, Adavosertib and anti-PD-L1 considerably slowed the growth of tumors and improved mouse survival without causing noticeable side effects.[47] These findings provide a rationale for the combination of WEE1i and ICB, though more evidence is needed to verify the feasibility of this strategy before its implementation in clinical settings.

Clinical Studies of WEE1i in Gynecologic Cancers

Ovarian Cancer

As the most lethal gynecological cancer, the majority of high-grade serous OC has TP53 mutation,[7] making WEE1 inhibition a rational and promising way to kill OC cells. In patients with TP53-mutant epithelial OC resistant to paclitaxel and carboplatin (TC) within three months, a phase II clinical trial (NCT01164995) conducted in the Netherlands confirmed the safety and effectiveness of Adavosertib and carboplatin. Patients received carboplatin and oral Adavosertib (225 mg twice a day for 5 times in a 21-day cycle) until disease progression. Of the 24 patients enrolled, 21 achieved evaluable efficacy endpoints. The remission rate was 43%, with one patient achieving long-term complete remission.[20] The median progression-free survival (PFS) and OS were 5.3 and 12.6 months, respectively. The most common grade ≥ 3 adverse events (AEs) were thrombocytopenia (48%) and neutropenia (37%). This is the first clinical study to demonstrate that Adavosertib can enhance the efficacy of carboplatin in TP53-mutant tumors.[20] A multicenter randomized phase II clinical study conducted by Oza et al (NCT01357161) evaluated the effect of Adavosertib combined with TC vs TC alone in platinum-sensitive TP53-mutant OC patients. A total of 136 subjects were recruited and randomly assigned to Adavosertib plus TC treatment or placebo plus TC treatment until disease progression or a total of six cycles. The findings demonstrated that PFS was significantly extended in the Adavosertib group as compared to the placebo group; nevertheless, anemia (Adavosertib 53%; placebo 32%), vomiting (63%; 27%), diarrhea (75%; 37%), and all grade ≥3 (78%; 65%) AEs increased.[21] Furthermore, the study identified possible biomarkers for the best response population. Patients with TP53 hotspot mutations or a missense mutation experienced the greatest treatment benefit, while patients with a truncation or splice-site mutation benefited the least from treatment. Besides TP53 mutation, patients with BRCA1/2 or CCNE1 mutations benefit more from Adavosertib; however, due to the limited patient numbers, conclusions remain elusive. Recently, The Lancet published the findings of a multicenter phase II clinical trial which recruited 99 patients with platinum-resistant and platinum-refractory high-grade serous OC (NCT02151292). The patients were divided into two groups: 65 patients in the experimental group received oral Adavosertib (175 mg, once a day, 1, 2, 8, 9, 15, 16 days, a cycle of 28 days) combined with gemcitabine; 34 cases in the control group received gemcitabine monotherapy until the disease progressed or the experiment was terminated due to intolerable AEs. The baseline of patients did not differ significantly between the two groups. The Adavosertib combination group outperformed the gemcitabine monotherapy group in terms of PFS (4.6 vs 3.0 months) and median OS (11.4 vs 7.2 months). Besides grade ≥3 hematologic AEs (neutropenia (combined 62% vs gemcitabine 30%) and thrombocytopenia (31% vs 6%)) there was no discernible difference in other AEs between the two groups. This is the first clinical trial demonstrating improved PFS and OS when OC patients treated with gemcitabine combined with Adavosertib.[22] In patients with primary platinum-resistant OC, a recent clinical study (NCT02272790) evaluated the pharmacokinetics, safety, and effectiveness of Adavosertib when combined with four chemotherapeutic agents: carboplatin, gemcitabine, paclitaxel, or pegylated liposomal doxorubicin. Among the 94 enrolled patients, three had confirmed a complete response (CR) and 27 had confirmed a partial response (PR). The response rate (66.7%) was highest with carboplatin plus weekly Adavosertib, with a 100% disease control rate and a median PFS of 12.0 months. The most common grade ≥3 AEs across all cohorts were neutropenia (47.9%), anemia (33.0%), thrombocytopenia (31.9%), diarrhea (10.6%) and vomiting (10.6%).[23] The results demonstrated that the combination of WEE1i and carboplatin was the most promising, however, further studies are needed to optimize the dose, schedule, for reducing toxicities. The recurrence of OC following surgery and first-line chemotherapy is one of the primary challenges in the management of OC. Especially after recurrence, when the cancer develops platinum resistance, the response rate to first-line or even second-line chemotherapy is low. In this scenario, it is possible that the OC inherent resistance may be due to reduced immunosurveillance and drug-resistant cells. Promisingly, the aforementioned clinical trials demonstrated the clinical benefit of WEE1i combined with traditional chemotherapy in platinum-resistant OC.

The effect of Adavosertib monotherapy in patients with solid tumors has been investigated recently (NCT01748825).[48] Adavosertib was administered once daily to study participants using a 3+3 escalation design (200 mg starting dose for 1–5 days and 8–12 days in 21-day cycles). Forty-two patients in all were included in the study, of whom six had a confirmed PR, all of them were gynecological cancer patients: four with OC and two with EC. The most common AEs attributed to Adavosertib were gastrointestinal and hematologic toxicities, however, ≤12% and ≤29% of these gastrointestinal and hematologic AEs were ≥ grade 3. This study recommends the recommended dose of 300 mg orally once daily for a phase II study and indicates a promising role of Adavosertib monotherapy in the management of gynecologic tumors.

The recently developed ZN-c3 demonstrated a significantly greater selectivity for WEE1 over other kinases when compared to Adavosertib, which is expected to have a superior safety profile and is particularly well suited for combination therapies.[17] ZN-c3 has quickly transited to phase I/II clinical testing either as a monotherapy or combined with other DNA-damaging therapies. The results from a Phase I dose-escalation clinical study demonstrated that ZN-c3 was efficient and tolerable in patients with advanced solid tumors.[49] Currently, three clinical trials are underway in OC with ZN-c3, including studies in patients with solid tumors (NCT04158336, NCT05431582), and in patients with platinum-resistant OC (NCT04516447). Table 1 summarizes clinical trials testing WEE1i in gynecologic oncology.

Endometrial Cancer

As the most common gynecological cancer, EC typically has a good prognosis. With the improved understanding of the cancer genome, the Cancer Genome Atlas Program (TCGA) carried out a genomic analysis of 373 EC, stratifying them into four distinct prognostic groups: POLE ultramutated, mismatch repair-deficient (MMRd), p53 mutant/abnormal (p53abn), and NSMP (non-specific molecular profile).[8] The new classification integrates molecular features with clinicopathological characteristics to define a more precise risk assessment.[8,50] For instance, regardless of the tumor's grade and histotype, POLE ultramutated tumors (4–12% of EC) have a favorable prognosis.[51] Compared to other molecular subtypes, p53-abnormal tumors (8–24% of EC) have an aggressive behavior; in fact, they are usually serous carcinomas, clear cell carcinomas, and other special pathological types.[51,52] As a distinct histologic subtype of EC, USC has limited effective therapies and it accounts for up to 40% of deaths of EC.[53] More than 90% of USC had TP53 mutations, which are associated with a high amount of oncogene-driven replication stress,[8,54] suggesting that WEE1i might represent a beneficial new targeted treatment for USC. A single-arm phase II clinical study reported good efficacy of Adavosertib in treating advanced refractory USC (NCT03668340).[55] The study included 34 patients who received oral Adavosertib (300 mg once daily) in a 21-day course. The results showed that one case achieved CR, nine cases achieved PR, the 6-month PFS rate was 47.1%, and the median duration of efficacy maintenance was nine months. Frequently observed grade ≥ 3 AEs include anemia (23.5%), thrombocytopenia (17.6%), and neutropenia (32.4%). Thirty-two tumor samples were available for molecular characterization, all tumors exhibited a TP53 mutation, and 31% had evidence of amplification or gain in CCNE1, which indicates that besides TP53 mutation, CCNE1 amplification may be associated with response. Based on the promising results from this proof-of-concept phase II trial, ADAGIO (NCT04590248): an international phase IIb study of Adavosertib in females who have persistent or recurrent USC,[24] and a Phase II study of ZN-c3 in recurrent USC (NCT04814108) were conducted.

Cervical Cancer

The development of CC corresponds to functional p53 inactivation by HPV infection.[56] Although most women could be affected by HPV, few of them will develop a persistent or progressive disease until invasive form. This is especially true for women infected with high-risk HPV that can integrate virus DNA with cervical epithelial cells chromosomal DNA.[57] Certain markers, like p16ink4a, p16, E-cadherin, Ki67, pRb, and p53, have been demonstrated to be able to identify intraepithelial lesions that have a higher likelihood of evolving into invasive forms. Other markers, like CEA, SCC-Ag, and CD44, have been developed to identify invasive forms.[58] The E6 proteins from HPV-16 and HPV-18 bind to p53, promoting the degradation of p53 via the ubiquitin pathway.[9] This suggests that the WEE1 is a potential treatment target for CC. Though preclinical studies demonstrated the antitumor activity of WEE1i in CC cell lines, no relevant clinical studies have been carried out to assess the monotherapy in CC.[36] A phase I trial has been initiated to explore the AEs and

optimal dose of Adavosertib combined with external beam irradiation (EBRT) and cisplatin for CC patients (NCT03345784). Patients received EBRT on days 1–5, oral Adavosertib on days 1, 3, 5, concurrently with intravenous cisplatin weekly. In the absence of intolerable AEs or disease progression, treatment is continued for up to five weeks. According to the preliminary results that were recently published[34], ten patients were enrolled (nine locally advanced CC and one EC), and the recommended phase II dose could not be determined due to clinical toxicity and early trial closure. The overall response rate at 4 months was 71.4%, including four complete responses. At 2 years follow-up, 86% of patients were alive and progression-free.[34] While overlap toxicity is a challenge, the preliminary efficacy of Adavosertib in conjunction with chemoradiation is encouraging.

Other Gynecological Cancers

WEE1i was not assessed in any of the studies for vaginal, vulvar, or other specific gynecological malignancies, and there was no reporting of individual patient data for vaginal and vulvar cancers in the solid tumor trials.

Discussion and Conclusions

As the gatekeeper of the G2/M checkpoint, WEE1 kinase presents a highly promising therapeutic strategy in the fight against gynecologic malignancies. A number of phase I and II clinical studies have confirmed the efficacy and safety of Adavosertib alone or in combination with other DNA damaging treatments in gynecological tumors. The concept is primarily investigated in OC and EC, whether it applies to vaginal, vulvar, or other specific gynecological malignancies is currently unknown. TP53 hotspot and missense mutation, BRCA1/2 mutation, and high CCNE1 copy number may be possible biomarkers for the response. It is expected that relevant Phase III clinical trials will be carried out in the near future and Adavosertib has the potential to be the first WEE1i for treating gynecological malignancies. Meanwhile, we are also looking forward to the clinical trial results of other WEE1i that are currently in pipeline testing. Numerous preclinical studies showed the encouraging outcomes of the innovative combination of immunotherapy, radiotherapy and targeted medicines like PARPi and ATRi with Adavosertib, however, overlapping toxicity is challenging. Our findings are consistent with a recently published systematic review.[59] Strengths of their work include a systematic search approach, the inclusion of all clinical trials, and structured reporting of the results. But our work is not without merit. In addition to summarizing the clinical data from WEE1i in treating gynecologic oncology, we have also provided a thorough analysis of preclinical data (cells and animal studies) and the rationale for clinical testing. We did not include some ongoing solid tumor clinical trials as they did in the systematic review since the exact number of gynecologic cancer patients recruited in these trials is still unknown, which may generate confusion.

Future efforts should be made to determine the off-target effect of the WEE1i to improve the therapeutic index and cytotoxicity profile, to investigate the adequate dose and schedule in WEE1i treatment strategy, to search for biomarkers for patient selection, and to understand resistance mechanisms.

Abbreviations

DDR, DNA damage repair; CDKs, Cyclin-dependent kinases; HR, Homologous recombination; WEE1i, WEE1 inhibitor; ATR, Ataxia-telangiectasia-related; ATM, Ataxia-telangiectasia mutated; CHK1, Checkpoint kinase 1; CHK2, Checkpoint kinase 2; CDC25, Cell division cycle factor 25/Cell division cyclin 25; DSBs, Double-strand DNA breaks; OS, Overall survival; PFS, Progression-free survival; AEs, Adverse events; OC, Ovarian cancer; EC, Endometrial cancer; CC, Cervical cancer; VC, Vulvar cancer; HPV, Human papillomavirus; CR, Complete response; PR, Partial response; PDXs, Patient-derived xenografts; PD-L1, Programmed death-ligand 1; ICB, Immune checkpoint blockade; TC, Paclitaxel and carboplatin; USC, Uterine serous carcinoma; EBRT, External beam irradiation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

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Disclosure

The authors declare that there are no conflicts of interest.

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