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REVIEW

New Agents and Radiotherapy in Gynecological Cancers

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SUMMARY

Approximately 50% of cancer patients require radiotherapy (RT) during their treatment. In addition to concurrent systemic therapies for curative or adjuvant purposes, metastatic disease will require conventional fractionation or stereotactic body RT/radiosurgery (SBRT/SRS). Recently, the number of systemic treatment options has increased significantly with the introduction of immune checkpoint inhibitors (ICIs) and a wide variety of targeted agents. It is important for the radiation oncologist to be knowledgeable about targeted therapy and immunotherapy agents used in gynecologic malignancies, their side effects, and their management. Unexpected serious toxicities, such as hypertension, bleeding, thromboembolism, and a 1-2% risk of gastrointestinal perforation, can occur with bevacizumab. Therefore, concomitant administration of bevacizumab and RT is currently not recommended outside of clinical trials. An increased risk of side effects has been reported when the interval between bevacizumab and RT is <10 months. Several studies showed the association and low toxicity profile of SBRT and poly ADP-ribose polymerase inhibitors (PARPis) in patients with oligometastatic ovarian cancer. Although the concurrent use of programmed cell death protein 1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors and RT seems appropriate in the treatment of gynecological malignancies, more data are needed regarding their use with other agents.

Keywords: Adverse effects; endometrial neoplasms; immunotherapy; ovarian neoplasms; radiotherapy; targeted molecular therapy; uterine cervical neoplasms.

INTRODUCTION

Approximately 50% of cancer patients will receive radiotherapy (RT) at some point during their treatment.[1,2] In addition to concurrent systemic therapies for curative or adjuvant purposes, metastatic disease will require conventional fractionation or stereotactic body radiotherapy/radiosurgery (SBRT/SRS). Consequently, patients currently receiving targeted agents or immune check point inhibitors (ICIs) are often referred for RT.[3,4] While combining these agents concurrently with RT can improve tumor control, increased toxicity is a potential threat.[5] Therefore, the side effects of the agents used and their effects on RT should be well understood. This article examines the considerations that should be taken into account when treating patients with gynecologic cancer who will undergo RT.

TARGETED AGENTS AND IMMUNOTHERAPY AGENTS USED IN GYNECOLOGICAL CANCERS

Cervical Cancer

Targeted/immunotherapy agents used in the treatment of cervical cancer with a histopathological diagnosis of squamous cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma: Pembrolizumab is recommended for concurrent chemoradiotherapy (CRT). For recurrent or metastatic disease, pembrolizumab, bevacizumab, or atezolizumab are recommended in

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Table 1 Targeted agents used in cervical cancer, endometrial cancer, and potential targeted therapies in ovarian cancer

Cervical cancer		
Squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma		
Chemoradiation	Recurrent or metastatic disease	
	First-line therapy	Second-line or Subsequent therapy
Pembrolizumab	Pembrolizumab	Pembrolizumab
	Bevacizumab	Tisotumab vedotin
	Atezolizumab	Cemipilimab
		Nivolumab
		Trastuzumab deruxtecan
		Neratinib
		Selpercatinib
		Larotrectinib
		Entrectinib
		Reprotrectinib
Small cell neuroendocrine cervical cancer		
	Recurrent or metastatic disease	
	First-line therapy	Second-line or subsequent therapy
	Atezolizumab	Bevacizumab
	Durvalumab	
	Bevacizumab	
Endometrial carcinoma		
Primary or Adjuvant Therapy (Stage I-IV)		
	Pembrolizumab	
	Dostarlimab	
	Durvalumab	
	Trastuzumab	
	Bevacizumab	
Recurrent disease		
First-line Therapy	Second-line or subsequent therapy	
Pembrolizumab	Bevacizumab	Nivolumab
Dostarlimab	Temsirolimus	Trastuzumab deruxtecan
Durvalumab	Cabozantinib	Larotrectinib
Trastuzumab	Lenvantinib	Entrectinib
Bevacizumab	Pembrolizumab	Repotrectinib
	Dostarlimab	
	Avelumab	
Ovarian Cancer – potantial targated therapies		
Epithelial		Non-epithelial
PARP inhibition	ATP pathway inhibition	FOXL2 inhibition
FRalfa inhibition	PI3K/AKT inhibition	DICER-1 inhibition
VEGF inhibition	Immunotherapy	
DDR pathway inhibition	HER2- targeted therapy	
MAPK pathway inhibition	ATR pathway inhibition	
Hormonal therapy		

PARP: Poly ADP-ribose polymerase; FRα: Folate receptor alpha; VEGF: Vascular endothelial growth factor; DRR: DNA damage response; MAPK: Mitogen-activated protein kinase; ATP: Aadenosine triphosphate; PI3K/AKT: Phosphoinositide-3 kinase/ Protein kinase B, also known as AKT; HER2: Human epidermal growth factor receptor 2; ATR: Ataxia telangiectasia and Rad3-related kinase; FOXL2: Forkhead box protein L2

combination with first-line chemotherapy (CT). For recurrent or metastatic disease, pembrolizumab, tisotumab vedotin, cemiplimab, nivolumab, neratinib, selpercatinib, laroterctinib, enterctinib, and reportrectinib are recommended as second-line therapy. For small cell neuroendocrine cervical cancer, atezolizumab, durvalumab, and bevacizumab can be used in combination with first-line CT[6] (Table 1).

Endometrial Cancer

For the primary or adjuvant treatment of endometrial carcinoma (stages I-IV), new systemic therapy can be used in combination with CT, such as pembrolizumab, dostarlimab, durvalumab, trastuzumab, or bevacizumab. For recurrent disease, pembrolizumab, dostarlimab, trastuzumab, or bevacizumab can be used in combination with CT agents as first-line therapy. Second-line therapy includes pembrolizumab, lenvatinib, dostarlimab, avelumab, nivolumab, trastuzumab, deruxtecan, larotrectinib, entrectinib, and repotrectinib[7] (Table 1).

Ovarian Cancer

Poly ADP-ribose polymerase inhibitors (PARPis), folate receptor alpha (FRα) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, DNA damage response (DDR) pathway inhibitors, mitogen-activated protein kinase (MAPK) pathway inhibitors, adenosine triphosphate (ATP) pathway inhibitors, phosphoinositide-3 kinase/ Protein kinase B, also known as AKT (PI3K/AKT) inhibitors, immunotherapy, human epidermal growth factor receptor 2 (HER2)-targeted therapies, ataxia telangiectasia and Rad3-related kinase (ATR) pathway inhibitors, and hormonal therapies can be used in epithelial ovarian cancers. Forkhead box protein L2 (FOXL2) inhibitors can be used in granulosa cell tumors and DICER-1 inhibitors can be used in Sertoli-Leydig cell tumors, which are non-epithelial ovarian tumors[8] (Table 1).

NEW DRUGS AND NEW TREATMENT STRATEGIES FOR GYNECOLOGICAL CANCERS

Antibody-drug Conjugates

Antibody-drug conjugates (ADCs) are agents that contain a monoclonal antibody conjugated to a CT agent via a linker. ADCs were developed to provide highly targeted delivery of cytotoxic agents to cancer cells and have limited off-target systemic effects. Folate receptor alpha is frequently overexpressed in ovarian cancer and limited expression in non-cancerous cells. Mirvetuximab soravtansine is an anti-FRα ADC that has been tested in the phase III MIRASOL trial in high-FRα platinum-resistant ovarian cancer and has demonstrated clear benefit[9] In cervical cancer, the anti-tissue factor ADC tisotumab vedotin has been shown to improve overall survival as a second-line monotherapy and has promising activity in combination.[10] Other targets of interest include sodium-dependent phosphate transporter 2b (NaPi2b), mesothelin, trophoblast cell surface antigen 2 (Trop-2), HER2, and cadherin 6 (CDH6). Human epidermal growth factor receptor-2 overexpression occurs in approximately 35% of endometrial cancers, and ADCs targeting HER2 may be a promising treatment option; studies are ongoing.[11]

Agents Targeting DNA Damage

The DNA damage response is a network of pathways activated in response to DNA damage; it represents the coordinated activity of DNA repair and cell cycle checkpoints. Defects in the DDR cause genome instability, leading to cancer initiation and progression, but it also represents a potential therapeutic target. In gynecological malignancies, cell cycle checkpoint inhibitors (ATM, ATR, WEE1, or checkpoint kinase 1 [CHK1]) have been investigated alone or in combination with CT or PARPis. The WEE1 inhibitor adavosertib is the most extensively studied, with promising results reported in patients with ovarian and endometrial cancer. Hematological toxicity, both when used alone and particularly in combination strategies, remains one of the major obstacles to the development of these agents.[11]

The PARP family consists of 17 PARP proteins with a conserved domain that catalyzes the transfer of ADP ribose to target proteins or nucleic acids. PARP1 and PARP2 are the best-characterized and targeted first-generation PARPs. There are differences between the agents in PARP capture, selectivity, and pharmacology. The next-generation, highly selective PARP1 inhibitor AZD5305 has demonstrated higher efficacy and better tolerability than first-generation PARPs, and early-phase studies are ongoing. Inhibiting DDR pathways stimulates antitumor immunity and provides the biological rationale for combining DDR inhibitors with ICIs.

Combinations of ICIs [programmed cell death protein 1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors or cytotoxic T lymphocyte antigen 4 (CTLA-4) inhibitors] and PARPis are being investigated in ovarian cancer, including in the first-line and relapsed settings. Phosphoinositide-3 kinase inhibitors reduce BRCA expression, resulting in a homologous recombination deficiency (HRD) phenotype; alpelisib has shown synergism with olaparib in preclinical models of ovarian cancer.[11]

New Immunotherapy Approaches

TIGIT (T-cell immunoreceptor with Ig [immunoglobulin] and ITIM [immunoreceptor tyrosine-based inhibitory motif] domains) is another immune checkpoint receptor emerging as a therapeutic target. TIGIT is present on most natural killer (NK) cells and other T cell subsets, including regulatory T cells (Tregs), memo-

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ry and activated T cells, and T helper cells. TIGIT binds to the poliovirus receptor (PVR), a key regulator of cell-mediated immunity, inhibiting the cytotoxic activity, degranulation, and cytokine secretion of NK cells.

In cervical cancer, HPV E6 and E7 oncoproteins can increase the expression of immunosuppressive cytokines, including TGFβ. TGFβ overexpression promotes tumorigenesis through epithelial-mesenchymal transition (EMT), fibroblast activation, angiogenesis, and immunosuppression. High TGFβ levels are associated with resistance to immunotherapy, and its inhibition has been shown to enhance the activity of anti-PD-1/PD-L1 agents.

Combinations of ICIs (anti-PD-1/PD-L1 + anti-CTLA-4 and bispecific antibodies) have shown promising results in gynecologic malignancies. Therapeutic DNA vaccines against HPV have shown evidence of efficacy, particularly when combined with anti-PD-1/PD-L1 agents in cervical cancer. Recently, combinations of immunotherapy agents with CT and antiangiogenic agents have been shown to improve outcomes in patients with cervical and endometrial cancer.[11]

PELVIC RT AND NEW AGENTS – AGENTS FREQUENTLY USED IN DAILY PRACTICE

The phase 3 ENGOT-cx11/GOG 3047/KEYNOTE-A18 study provided evidence for the concurrent use of ICI with RT. Eligible patients with newly diagnosed, high-risk (FIGO 2014 stage IB2 IIB with node-positive disease or stage III-IVA regardless of node status), locally advanced, histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous cervical cancer were randomized 1:1 to receive five cycles of pembrolizumab (200 mg) or placebo every 3 weeks, followed by 15 cycles of pembrolizumab (400 mg) or placebo every 6 weeks, in combination with concurrent CRT. Patients were stratified according to the type of external beam RT planned at randomization, cervical cancer stage at screening (FIGO 2014 stage IB2–IIB node-positive vs. III–IVA), and planned total RT dose (external beam RT plus brachytherapy) (<70 Gy vs. ≥70 Gy; 2 Gy equivalent dose).

Median overall survival was not reached in either group; overall survival at 36 months was 82.6% (95% CI 78.4–86.1) in the pembrolizumab-CRT group and 74.8% (70.1–78.8) in the placebo-CRT group. The hazard ratio for death was 0.67 (95% CI 0.50–0.90; p=0.0040), and the primary protocol-specified objective was met. Grade 3 or higher adverse event rates occurred in 413 of 528 patients (78%) in the pembrolizumab-CRT group and in 371 of 530 patients (70%) in the placebo-CRT group; the most common adverse events were anemia, decreased white blood cell count, and decreased neutrophil count. Potentially immune-mediated adverse events occurred in 206 of 528 patients (39%) in the pembrolizumab-CRT group and 90 of 530 patients (17%) in the placebo-CRT group. Pembrolizumab plus CRT significantly improved overall survival in patients with locally advanced cervical cancer.[12]

The investigators subsequently published patient-reported outcomes (PROs). Of the 1060 randomized participants, 1008 (95.1%) were included in the PRO full analysis set population. No significant differences were observed between groups on any of the prespecified PRO instruments. Pembrolizumab plus CCRT did not adversely affect participants' health-related quality of life.[13]

RT may be required before or after bevacizumab is used to treat recurrent or metastatic cervical cancer. Unexpected serious toxicities, such as hypertension, hemorrhage, thromboembolism, and a 1–2% risk of gastrointestinal perforation, may occur. Therefore, concomitant administration of bevacizumab and RT is currently not recommended outside of clinical trials. The use of bevacizumab before or after RT increases the risk of fistula formation in patients with cervical cancer. Shorter rectal intervals and higher RT doses have been associated with an increased risk of fistula formation. Close monitoring for fistula formation is necessary in patients who receive RT before or after bevacizumab. It has been reported that the risk of side effects increases when the interval between bevacizumab and RT is <10 months.[14–17]

Studies have been initiated in the RAINBO clinical research program to evaluate the molecular characteristics of adjuvant treatment for endometrial cancer. In the p53 abnormal stage IA-III patient group with myometrial invasion, concurrent CRT with cisplatin was administered in one arm, while CRT was added to the other arm. In the MMR-deficient stage II (with lymphovascular space invasion)/III patient group, RT was added in one arm, and durvalumab was added to RT in the other arm. Information on side effects obtained from these studies will be valuable.[18]

Gauduchon et al.[19] evaluated the survival benefit of continuing PARPi therapy in 74 patients with oligometastatic ovarian cancer treated with local therapy. These patients were progression-free or had not been referred for a new CT regimen for approximately 1 year. Eighty-nine percent (n=59/66) of patients reported no serious adverse events during local therapy. Serious ad-

verse events (one pneumothorax and one sepsis) were observed in 2/66 patients. Regarding PARPi therapy, dose reductions due to side effects were performed in 37/71 (52.1%) patients before local therapy. PARPi therapy was well tolerated after local therapy, with 12 patients (16.2%) experiencing a Grade 2 or higher adverse events. Only 6 patients (8.1%) discontinued PARPi due to toxicity [asthenia and anorexia (n=3), hematological toxicity (n=2), myelodysplastic syndrome (n=1)].

In their observational, retrospective, multicenter study (Epimetheo), Macchia and colleagues analyzed the efficacy and safety of SBRT during PARPi maintenance in patients with oligometastatic ovarian cancer. SBRT was used to treat 74 ovarian cancer patients with a total of 158 lesions (98 lymph node and 60 parenchymal lesions) who were under PARPi maintenance. Olaparib, niraparib, and rucaparib were administered to 41.9%, 48.6%, and 9.5% of patients, respectively. Complete response, partial response, stable disease, and progressive disease were observed in 115 (72.8%), 32 (20.3%), 9 (5.7%), and 2 lesions (1.3%), respectively. Serious toxicities were reported in less than 3% of patients. This study reports the association and low toxicity profile of SBRT with PARPi in patients with oligometastatic ovarian cancer.[20]

IMMUNOTHERAPY: SIDE EFFECTS

The median duration of GI toxicity with ICI is 6 weeks, with a wide range (1–108 weeks), but usually occurs 5–10 weeks after onset. It typically involves the descending colon and closely resembles inflammatory bowel disease. It is characterized by prominent mixed inflammatory cell infiltrates in the lamina propria and chronic inflammatory damage (crypt disintegration and Paneth cell metaplasia).

Management of ICI - Associated Colitis

For Grade 1 colitis (<4 stools per day increase from baseline), only supportive care is recommended. ICI therapy can be continued or stopped. Consider gastroenterology referral for persistent symptoms.

For Grade 2 colitis (4–6 stools per day increase from baseline), stop ICI and initiate supportive care. Refer to gastroenterology for endoscopic evaluation. Start prednisone or equivalent corticosteroids at 1 mg/kg daily until symptoms improve to Grade 1, then taper over 4–6 weeks. If the colitis is steroid-resistant and requires more potent agents such as anti-TNF (infliximab) or anti-integrin (vedolizumab), endoscopic evaluation and GI findings may be helpful. Endoscopic features can assist in this decision. If symptoms improve to Grade 1 or less and fecal calprotectin returns to normal, ICI can be restarted. However, colitis flare-ups can still occur.

For Grade 3 colitis (≥7 stools per day), discontinue ICI and initiate supportive therapy. Perform endoscopic evaluation. Initiate corticosteroids, 1–2 mg/kg/day prednisone or equivalent (consider IV methylprednisolone) daily until symptoms improve to Grade 1, then taper over 4–6 weeks. Consider early evaluation of more effective agents, such as anti-TNF (infliximab) or anti-integrin (vedolizumab), and hospitalization if dehydration or electrolyte imbalance occurs. If CTLA-4 agents are present, discontinue with caution and permanently discontinue.

For Grade 4 (life-threatening) colitis, hospitalize and permanently discontinue ICI. Follow guidelines for Grade 3. Other considerations for patients with refractory colitis are Fecal microbiota transplantation, JAK inhibitors (tofacitinib), IL-12 blocking antibodies (ustekinumab).

Hematologic Toxicity

Autoimmune hemolytic anemia and thrombocytopenia may occur with ICI therapy. Refer to a hematologist for bone marrow biopsy if necessary. Consider symptomatic treatment with transfusion and growth factors. Evaluation of steroids, second-line immunosuppressants such as IVIG, rituximab, etc., may be considered. ICI therapy should be discontinued while toxicity is managed. Continuing therapy requires a careful balancing of risks and benefits.

Endocrinopathies - Management

Endocrinopathies are quite common with ICI therapy, and TSH (thyroid-stimulating hormone) should be routinely monitored throughout therapy. Both hypothyroidism and hyperthyroidism are common. Endocrine referral (levothyroxine and hydrocortisone) is recommended to assist with replacement therapy. If symptoms are mild, ICI can be continued.[21,22]

CONSENSUS RECOMMENDATIONS ON THE SAFETY OF COMBINING RT OF THE ABDOMEN/PELVIS WITH ICIS, VEGF(R) INHIBITORS, OR MULTITARGETED TYROSINE KINASE INHIBITORS

Combining RT with targeted agents or immunotherapy may provide better outcomes but may also increase toxicity. Due to the lack of high-quality toxicity data and evidence-based data, the European Society for Medi-

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Table 2 Radiotherapy scenario examples

RT scenario	Example
Low-dose palliative RT	Examples: 1x8, 2x8, 5x4, 10x3 Gy. Often used in patients with metastases and for palliation of symptoms. It generally has a lower risk of RT-induced toxicity. However, low-dose whole-brain RT is relatively toxic compared with local high-dose stereotactic RT for brain.
High-dose conventionally fractionated RT	Examples: 33x2 Gy (5 times per week), 5x5 Gy (Daily) or similar. Often used in teratments with curative/radical or (neo) adjuvant intent.
High-dose stereotactic RT	Examples: ≥14 Gy in 1 fraction, 60 Gy in 5-8 fractions, or similar. Often used in treatments with curative/radical intent. Radical, high-dose stereotactic RT is also increasingly used in the oligometastatic or oligoprogressive setting or to treat brain metastases.

RT: Radiotherapy; Gy: Gray

Table 3 Consensus recommendations for the combination of radiotherapy with PD-(L)1 inhibitors, CTLA-4 inhibitors, VEGF(R) inhibitors, and TKIs in abdominal/pelvic irradiation

Agent combined with radiotherapy	Radiotherapy scenario	Recommendation
PD-(L)1 inhibitor	Low-dose palliative	Minor/no adaptation
	High-dose conventionally fractionated	Minor/no adaptation
	High-dose stereotactic	Minor/no adaptation
CTLA-4 inhibitor	Low-dose palliative	Minor/no adaptation
	High-dose conventionally fractionated	Major adaptation
	High-dose stereotactic	Major adaptation
VEGF(R) inhibitor	Low-dose palliative	Major adaptation
	High-dose conventionally fractionated	Major adaptation
	High-dose stereotactic	Major adaptation
TKI	Low-dose palliative	Major adaptation
	High-dose conventionally fractionated	Major adaptation
	High-dose stereotactic	Major adaptation

PD-1: programmed cell death protein 1; PD-L1: programmed cell death-ligand 1; CTLA-4: Cytotoxic T lymphocyte antigen 4; VEGF(R): Vascular endothelial growth factor (receptor); TKI: Tyrosine kinase inhibitor

cal Oncology (ESMO) and the European Society for Radiotherapy and Oncology (ESTRO) have developed multidisciplinary, evidence-based consensus statements on the safety of combining RT with such agents.

They established definitions for the expected risk of combined therapy and associated safety measures:

Not combining: Consider protracted drug interruption or no RT, to avoid a drug–RT interaction.

Major adaptation: Consider a clinically relevant drug interruption/dosage reduction or a major RT adaptation.

Minor/no adaptation: Consider a clinically insignificant drug interruption/dosage reduction, a minor RT adaptation, or no adaptations.

Additionally, RT scenario examples were created in three groups: Low-dose palliative RT, High-dose conventionally fractionated RT, and High-dose stereotactic RT (Table 2).

In the combination of PD-(L)1 inhibitors and abdomen/pelvic RT, minor/no adaptation is recommended in all three RT scenarios, while with the combination of CTLA-4 inhibitors and abdomen/pelvic RT, minor/no adaptation is recommended only in the low-dose palliative RT scenario. In other agent and RT scenarios, major adaptation is recommended. Consensus recommendations for the combination of RT with PD-(L)1 inhibitors, CTLA-4 inhibitors, VEGF(R) inhibitors, and TKIs in abdominal/pelvic irradiation are presented in Table 3.[23]

CONCLUSION

Recently, the number of systemic treatment options has increased significantly with the introduction of ICIs and a wide variety of targeted agents. This has

led to improved treatment outcomes in nearly all cancer types and a variety of disease states. It is important for the radiation oncologist to be familiar with targeted therapy and immunotherapy agents used in gynecologic malignancies, their side effects, and their management. The data of the use of curative, stereotactic ablative, or palliative RT while continuing systemic treatment with these agents is increasing. Currently, the concurrent use of PD-(L)1 inhibitors and RT in the treatment of gynecologic malignancies appears appropriate, but more data are needed regarding their use with other agents.

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