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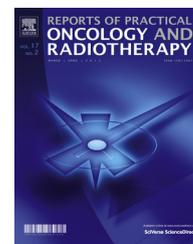
Review

Chemotherapy and molecular therapy in cervical cancer

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ABSTRACT

In recent years, the treatment of locally-advanced and metastatic cervical cancer has improved greatly due to the introduction of targeted therapies, new chemotherapy combinations, and emerging treatments. Candidates for potentially curative treatment are those patients with good functional status without associated comorbidities. Numerous trials have demonstrated that chemotherapy prolongs survival versus supportive care alone. In addition, polychemotherapy schemes are superior to single agent regimens. Targeted molecular agents have proven beneficial in the treatment of cervical cancer. Second-line treatment should be considered standard practice in patients with good functional status. Finally, given the poor survival outcomes in patients with metastatic disease, participation in clinical studies should always be considered the best option.

1. Background

Cervical cancer is one of the leading causes of morbidity and mortality worldwide, despite efforts to improve treatment outcomes. It is the fourth most common cancer, with a mean incidence rate of 9.0 cases per 100,000 persons in developed countries and 17.8 cases/100,000 in developing countries. Cervical cancer is closely associated with human papilloma virus (HPV) infection. Nearly 80% of cervical cancer-related deaths occur in low income countries with inadequate screening measures.[1,2] The treatment of early stage disease includes surgery and radiotherapy. The standard of care for locally advanced disease is radiotherapy in combination with cisplatin-based chemotherapy and this treatment may be curative in patients with limited metastatic involvement.

Prior to taking any therapeutic decisions, patient's clinical stage must first be determined according to the classification systems proposed by the International Federation of Gynecology and Obstetrics and the AJCC (American Joint Committee on Cancer). It is essential to determine whether the disease is curable or not as this will have an impact on the treatment decision. Patients with incurable disease may be candidates for palliative care. At diagnosis, most patients (60–85%) have

advanced disease (clinical stage III or IV), including distant metastatic disease located primarily in the supra- and infra-diaphragmatic nodes and/or to the bones, lungs, or liver. The development of targeted therapies in recent years has increased the limited treatment options for this aggressive disease.[3]

2. General aspects

The standard of care in most cervical cancers involves systemic platinum-based chemotherapy with concomitant radiotherapy. This combined modality has proven superior to radiotherapy alone for local and metastatic control, with better outcomes in terms of disease-free survival (DFS) and overall survival (OS). However, the use of concomitant chemoradiotherapy implies increased toxicity (both gastrointestinal and hematological), although this is considered manageable.

In early stage cervical cancer (i.e., clinical stage IA tumors with <6% chance of presenting pelvic or para-aortic nodal involvement), the treatment of choice is surgery. The selection of adjuvant therapy will depend on the risk of relapse: patients with a high risk of relapse – defined as presenting one or more of the following factors: positive pelvic nodes, parametrial invasion, positive surgical margins (parametrial/vaginal), and a probability of recurrence of 50–60% – require concomitant chemoradiotherapy.[4]

Patients with locally advanced disease (clinical stages IB2 to IVA) benefit from concomitant chemoradiotherapy. The benefits of concomitant therapy have been proven in five phase III studies, for more than a decade.

The first study is GOG 085 trial, Whitney et al. (randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB–IVA carcinoma of the cervix with negative para-aortic lymph nodes)[5]; 76 (43%) of 177 patients in the cisplatin/FU group had disease progression, whereas 101 (53%) of 191 in the HU group had disease progression. The progression free survival (PFS) was statistically significant favoring the CF regimen ($p = .033$).

The RTOG 90-01 trial, Morris et al. (pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer),[6] the five-year survival rates were 73% and 58% in the combined therapy and the radiotherapy (RT) alone arms, respectively ($p = .004$). Five-year cumulative disease-free survival rates were 67% and 40% in the combined therapy and RT groups, respectively ($p < 001$). The degree of adverse events was comparable for both treatment groups and, although the rates of hematologic effects were higher in the combined therapy group, these toxicities were reversible.

In the SWOG 8797 trial (GOG 109),[7] Peters et al., the PFS and OS are significantly improved in the patients receiving chemotherapy (CT). The PFS at 4 years is 63% with RT and 80% with RT-CT. The OS rate at 4 years is 71% with RT and 81% with RT-CT. Grades 3 and 4 hematologic and gastrointestinal toxicity were more frequent in the RT-CT group, but reversible.

In the four trial, GOG 120, for Rose PG (concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer),[8,9] both groups that received cisplatin had

longer PFS than the group that received hydroxyurea alone and the OS rate was higher in these groups as well (relative risks of death: 0.61 and 0.58, respectively).

In the fifth trial, the GOG 123 trial by Keys, (cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma),[10] the rates of PFS and OS were significantly higher in the combined therapy group at 4 years. The combined group had higher frequencies of transient grade 3 and 4 adverse hematologic effects (21% vs. 2% in RT group) and adverse gastrointestinal effects (14% vs. 5%, respectively).

All five of these studies have shown an improved OS and PFS if platinum was used with concomitant chemoradiotherapy with an absolute benefit of approximately 10–13% (Table 1). Therefore, concomitant CT and RT should be considered for all patients with cervical cancer. In Green et al. metaanalyses[11] included 4580 randomized patients, with 2865–3611 patients available for analysis (61–75%). Cisplatin was the most frequent chemotherapeutic agent and the benefit in PFS and OS was 16% and 12%, respectively, in this metaanalysis.

In a study conducted by Dueñas-González et al.,[12] gemcitabine was administered concomitantly with radiotherapy followed by weekly adjuvant gemcitabine and cisplatin, resulting in a 9% improvement in OS at 3-years versus standard care (concurrent cisplatin and radiation), with increased but still manageable hematological toxicity.

3. Adjuvant treatment in advanced disease

The OUTBACK randomized phase III trial, active, not recruiting, will evaluate adjuvant CT with paclitaxel and carboplatin after CT-RT with cisplatin as primary treatment compared with chemoradiation alone, on stage IB1 and positive nodes and IB2, II, IIIV or IVA. In this trial, the purpose of using poly-chemotherapy is to work in different ways to stop the growth and division of tumor cells through different mechanisms.[13]

The spatial cooperation is effective in cervical carcinoma. The interaction between RT and CT is used to improve loco-regional control of the disease. There have been described several mechanisms of interaction among those maneuvers. It has been demonstrated to cause the inhibition of DNA repair, but other effects such as cell/cycle synchronization, increased apoptosis, and inhibition of tumor cell proliferation are not clearly proven.[14,15]

Different data suggests, however, that the combined use of cisplatin and radiation therapy results in a higher level of tumoral cells killed by independent ways, additive toxicities and not precisely because of radiosensitization.[16]

3.1. Complications of treatment

Commonly acute effects of pelvic RT include diarrea and bladder irritation that usually are self-limited and the late effects included: recto-sigmoid complications, small intestine complications, genitourinary and vaginal complications in a 10% rate of major sequelae. The gastrointestinal tract is the most frequent late complication of RT alone.[17]

Concurrent treatment with CT-RT results in gastrointestinal and hematologic toxicity, principally. In Green

Table 1

Trial	N	Elegibility	Treatment	Radiation details	PFS	OS	Local failure	Distant failure	PCR
Keys, GOG 123	374	IB BULKY	Radiation alone + Hysterectomy	EBRT 45 Gy/1.8 Gy/day BT LDR 75 Gy Point A	67%	74%			
			CDDP 40 mg/m^2 weekly for 6 doses + RT + Hysterectomy		79%	83%			
Rose, GOG 120	526	IIB–IVA	CDDP 40 mg/m^2 at weeks 1–6 + RT	EBRT stage IIB: 40.8/1.7 Gy/day stage II–IVA: 51 Gy/1.7 Gy/day	67%				
			CDDP 50 mg/m^2 on days 1 and 29 + 5FU 4 g/m^2 as 96-h infusion, on days 1 and 29 + Hydroxyurea 2 g/m^2 orally twice weekly at weeks 1–6 + RT	BT 40 Gy (Point A) LDR total Point A: 80–81 Gy paramietrial boost to 55–60 Gy	64%				
			Hydroxyurea 3 g/m^2 orally twice weekly at weeks 1–6 + RT		47%				
Morris RTOG 90-01	403	IIB–IVA or IB–IIA >5 cm	CDDP 75 mg/m^2 4 h infusion + 5FU 4 g/m^2 96 h infusion days 1–5 for 3 cycles every 21 days + RT pelvis RT pelvic and paraaortic	EBRT 45 Gy/1.8 Gy/day, BT ≥40 Gy LDR total Point A: ≥85 Gy; parametrial boost to 55–60 Gy	61%	67%	85%	20%	
					46%	41%	35%	35%	
Whitney et al., GOG 085	385	11B–III	Hydroxyurea 80 mg/kg orally twice weekly at weeks 1–6 + RT	EBRT: stage IIB: 40.8/1.7 Gy/day; stage II–IVA: 51 Gy/1.7 Gy/day BT: 40 Gy (Point A) LDR,	57%				
			5-FU 1000 mg/m^2/day on 2, 3, 4, 5, 30, 31, 32 and 33 + CDDP 50 mg/m^2 day 1 and 29 + RT	total Point A: 80–81 Gy; parametrial boost to 55–60 Gy	67%				
Pearcey NCI/Canada	259	IB-IVA	CDDP 40 mg/m^2 weekly at 6 doses + RT	EBRT: 45 Gy/1.8 Gy/day, BT Point A dose of 35 Gy, total Point A: 80 Gy; RT within 7 weeks		62%			
			Radiation alone			58%			
Peters, GOG 109	268	IA2, IB, IIA Post-OP	CDDP 70 mg/m^2 + 5FU 96 h 1000 mg/m^2 for 4 cycles + RT	EBRT 49.3 Gy/1.7 Gy/day +/− para aortic irradiation	80%		81%		
			Radiation alone		63%		71%		
Dueñas-González	83	IB2, IIA, IIB	Cisplatin at 40 mg/m^2 every week × 6 + RT + hysterectomy	EBRT 50 Gy/2 Gy/day BT after hysterectomy in selected cases					55%
			Gemcitabine at 125 mg/m^2 plus cisplatin at 40 mg/m^2 every week × 6 + RT + hysterectomy						77%

EBRT, external beam radiation therapy; BT, brachytherapy; PFS, progression free survival; OS, over all survival; PCR, pathologic complete response.

metaanalysis,[11] the combined modality results in acute toxicity hematological and was severe or life-threatening in more patients in the CT-RT group than in the control group (neutropenia, 16% vs. 8%; platelets, 1.5% vs. 0.2%). Grade 3 or 4 gastrointestinal toxicity was also greater in the CT-RT group than in the control group (9% vs. 4%). The late toxicity was defined as toxicity beginning 42–90 days after completion of radiation. The main tissues affected by late toxicity were the bladder and gastrointestinal tract, with no evidence of differences between the treatment groups. A thromboembolic complications were noted in 16.7% of 48 patients who received chemoradiation, the routine use of erythropoietin increased incidence of thromboembolic complications.[18]

Actually, the use of intensity modulated radiation therapy (IMRT) could be to limit hematologic toxicity, and the use of coloning-stimulating factors.[19,20]

4. Systemic treatment in patients with distant metastasis or recurrent/persistent disease

At diagnosis, most patients with cervical cancer present with locally advanced or metastatic disease, which explains why mortality rates (16% at 5 years in patients with metastatic disease) are so high in this patient population.[21] These suboptimal outcomes have led to a search for new strategies, including modified CT schemes, targeted therapy, and immunotherapy.

The objectives of treatment are to control or delay the onset of symptoms, improve or maintain quality of life, and to prolong survival. In clinical trials, mean survival ranges from 9 to 13 months. However, outcomes have improved in recent years due to the growing use of targeted therapy.

Indications for systemic treatment include: clinical stage IVB and recurrent or persistent disease. Treatment options are currently based on the functional status of patients, with a range of possible CT regimens, including single-agent schemes, doublets, or even triplets.

Many chemotherapeutic agents are active in cervical cancer, including platinum-based agents (cisplatin, carboplatin), taxanes (paclitaxel), topotecan, vinorelbine, gemcitabine, ifosfamide, as well as other agents, including the targeted therapy bevacizumab.[22] Although all these medications are effective in palliating symptoms, the duration of response is usually less than 4 months. Objective response rates are better in non-irradiated areas and in chemotherapy-naive patients.

4.1. Single-agent chemotherapy

Cisplatin administered at a dose of 50 mg/m^2 every three weeks achieves response rates ranging from 20% to 38%, with a mean survival of 6–7 months.[23] Other compounds such as carboplatin, paclitaxel, ifosfamide, and topotecan offer similar results. The impact of palliative CT on survival has been demonstrated in several randomized trials of CT versus palliative care. Agents such as mitomycin C, irinotecan, gemcitabine, and vinorelbine present response rates ranging from 8% to 17%; in non-epidermoid histologies, response rates are 4.5% for gemcitabine, 31% for paclitaxel, and 7.1% for vinorelbine. The median response to paclitaxel is 4.8 months.[23]

4.2. Doublet or triplet chemotherapy

Compared to cisplatin monotherapy, the addition of paclitaxel and/or topotecan yields better treatment response rates and OS.

The phase III GOG 169 trial[24] compared cisplatin with or without paclitaxel in patients with stage IVB recurrent or persistent cervical cancer. Despite prior treatment with concomitant CT-RT, the patients in the trial were stage IVB. Patients received cisplatin at a dose of 50 mg/m^2 with or without paclitaxel (135 mg/m^2) every 3 weeks for six cycles. The response rate in the single-agent group was 19% versus 36% in the combined group ($p = 0.002$), with a median PFS of 2.8 versus 4.8 months ($p < 0.001$), respectively. The authors concluded that the combination of cisplatin plus paclitaxel was superior to cisplatin alone in terms of response rates and PFS.[24]

The GOG 179 trial[25] randomized patients to cisplatin with or without topotecan. Cisplatin administered at doses of 50 mg/m^2 every 3 weeks was compared to cisplatin 50 mg/m^2 on day 1 and topotecan 0.75 mg/m^2 on days 1–3 every 3 weeks; a third arm received methotrexate, vinblastine, doxorubicin, and cisplatin (this third arm was closed early due to treatment-related deaths). Patients in the doublet arm presented significantly better outcomes than those who received cisplatin alone, with a median OS of 9.4 versus 6.5 months ($p = 0.017$), median PFS of 4.6 versus 2.9 months ($p = 0.014$), and response rates of 27% versus 13%.[25]

Given these results, a subsequent study was conducted to determine the best cisplatin doublet. A total of 513 patients were randomized to four different treatment groups: (1) paclitaxel 135 mg/m^2 24 h infusion with cisplatin 50 mg/m^2 on day

2 every 3 weeks (reference arm); (2) vinorelbine 30 mg/m^2 on days 1 and 8 plus cisplatin 50 mg/m^2 on day 1 every 3 weeks; (3) gemcitabine 1000 mg/m^2 on days 1 and 8 plus cisplatin 50 mg/m^2 on day 1 every 3 weeks; or topotecan 0.75 mg/m^2 on days 1–3 and cisplatin 50 mg/m^2 on day 1 every 3 weeks. The paclitaxel/cisplatin regimen showed a better overall median survival than the other regimens.[26] Other studies have also shown a treatment response, even without combining platinum-based chemotherapy. A phase II trial that included paclitaxel at a dose of 175 mg/m^2 on day 1 combined with topotecan 1 mg/m^2 on days 1–5 of a 21-day cycle showed a 54% response rate, with PFS and OS of 3.7 and 8.6 months, respectively.[27]

Based on the data described above, the combination of cisplatin and paclitaxel is considered the first-line treatment of choice. Other options include cisplatin combined with topotecan or gemcitabine, or the combination of paclitaxel and topotecan.

4.3. Second line systemic treatment

Second-line therapies in cervical cancer show response rates ranging from 0% to 14%, with a median progression of 2–4 months.[23] Given these poor results, the emergence of new molecular therapies represent a promising new approach in the search for new opportunities for targeted treatment.

4.4. Targeted therapy

Targeted therapies have also been investigated in the treatment of advanced, persistent or recurrent disease. The GOG 227C trial[28] evaluated bevacizumab, a monoclonal antibody directed against the vascular endothelial growth receptor A (VEGF-A). This phase II study evaluated patients who had previously received 1–2 lines of systemic CT. The median duration of the response was 6.2 months, with PFS and OS, respectively, of 3.4 and 7.2 months.[28]

A subsequent phase III trial (GOG 0240)[29] evaluated four arms: cisplatin and paclitaxel with or without bevacizumab and topotecan and paclitaxel with or without bevacizumab. The combination of topotecan and paclitaxel was not superior to cisplatin and paclitaxel. Importantly, the addition of bevacizumab improved mean PFS by >2 months (8.2 versus 5.9 months) and mean OS by nearly 4 months compared to CT alone (17.0 vs. 13.3 months). Bevacizumab was associated with an increased incidence of grade 2 (G2) or higher hypertension, G3 or higher thromboembolic events, and G3 or higher gastrointestinal fistulas. Health-related quality of life was not significantly worse compared to CT alone. The combination of cisplatin, paclitaxel and bevacizumab is the new standard of care in the treatment of advanced and recurrent cervical cancer.[29]

4.5. Immunotherapy

The causal relationship between HPV infection and cervical cancer is well established, and HPV infection is involved in 80–90% of all cervical cancers.[30,31] HPV evades the immune system through increased PD-L1 (programmed death ligand 1) expression, thus allowing the virus to remain in the body

and to potentially develop a tumor. Nivolumab, an anti-PD-1 monoclonal antibody, has shown antitumor activity in several cancer types and could also be active against gynecological tumors associated with viral infections.[32]

The CheckMate 358 trial is an ongoing phase I/II trial of nivolumab in patients with virus-associated tumors to determine the efficacy and safety of this drug in recurrent or metastatic cervical, vaginal, and vulvar cancers.[33] Patients in that study receive a dose of 240 mg of nivolumab monotherapy every two weeks until disease progression or unacceptable toxicity. Interim findings indicate a 20.8% response in patients with PD-L1 expression and a stable disease in 70% of patients; median OS rates have not yet been determined.

4.6. *Human papilloma virus*

Another approach to the treatment of HPV-related cancers is vaccination. The innate immune response is responsible for limiting the viral load and plays an important role in eliminating HPV. However, in some cases, the host's immune response is unable to control the infection. In such cases, vaccination can induce a notable and sustained immune response, as evidenced by a rapid rise in antibodies. High serum levels correspond to high levels of antibodies in the cervix. Persistent HPV infection due to an inadequate or non-existent immune response can lead to cancer.[34,35]

The ADXS11-011 immunotherapy vaccine (Advaxis) is based on live attenuated *Listeria monocytogenes* bioengineered to secrete HPV-16-E7 (a fusion protein). Phase II studies show that Advaxis administered alone or with cisplatin demonstrate anti-tumor activity in recurrent or persistent cervical cancer, with good tolerance.[36] The phase III ADXS11-011 trial involving patients with locally-advanced, high-risk cancer treated with adjuvant Advaxis after chemo-radiotherapy (at weeks 3, 6 and 9 post CT-RT and then every 8 weeks for 1 year) versus placebo is currently ongoing.[37]

Other therapeutic platforms include local immunomodulators, recombinant vectors (vaccinia virus or *L. monocytogenes*), adaptive immunotherapy, and gene transfer. GN-00101 is a therapeutic vaccine consisting of a fusion protein containing an *Mycobacterium bovis* BCG heat shock protein (Hsp65) covalently linked to the entire sequence of HPV16-E7. This vaccine has shown an effective induction of tumor regression and has been associated with activity against anal and cervical intraepithelial neoplasia, genital warts, and recurrent papillomatosis. Maldonado et al. found a marked post-vaccination increase in CD8+ T cells infiltrating the tumor; this approach may achieve a better immune response through anti-PD1 antibodies.[38]

5. Other agents

5.1. *Conjugated monoclonal antibodies*

Tisotumab vedotin is a conjugated monoclonal antibody composed of a human tissue factor (TF) and an antimicrotubule agent. This antibody targets the TF, a transmembrane protein involved in angiogenesis and cell survival, which may be abnormally expressed in several different solid tumors,

including cervical cancer. With respect to the mechanism of action, the tumor cell binds to the monoclonal antibody through the TF, internalizing the antibody intracellularly, thus leading to enzymatic degradation and intracellular release of the antimicrotubule agent, which induces cell death by altering the microtubule and by release into the microenvironment.

A phase IIA 9310 trial (NCT02552121) evaluated tisotumab vedotin in patients with recurrent or persistent metastatic cervical cancer after first line systemic therapy. A 30-patient cohort received a dose of 2 mg/kg of weight every 3 weeks until progression and/or unacceptable toxicity. The response rate was 32%, with a median survival of 8.3 months and an acceptable toxicity profile. The most common adverse event was conjunctivitis, but this was controlled through a mitigation plan.[39]

5.2. *Ribonucleotide reductase (RNR) inhibitors*

The HPV oncoproteins, E6 and E7, activate RNR, which is necessary for the synthesis of deoxyribonucleotide acids. High levels of RNR are associated with a worse response to concomitant CT-RT in patients with cervical cancer. For this reason, RNR inhibitors, such as hydroxyurea, have been used to improve response to concomitant CT-RT in locally advanced cancer. The combination of Triapine (an RNR inhibitor) + concomitant CT-RT based on platinum is currently being under investigation. A phase I study found that the combination was well-tolerated. A phase II trial conducted by Kunos et al. evaluated Triapine + weekly cisplatin + RT in 24 treatment-naive patients (stages IB2–IIIB). The 3-year DFS in that trial was 80%.[40]

5.3. *PARP inhibitors*

PARP is activated in response to DNA damage. Blocking this enzyme prevents repair of single-strand breaks, thus leading to a build-up of these breaks. The inhibitors can trap the PARP1 and PARP2 enzymes at the site of DNA damage, thereby blocking DNA replication and causing cell death. Several studies have shown that PARP inhibitors act synergistically with RT to increase radiosensitivity. A phase I trial evaluated olaparib + carboplatin. An ongoing phase I/II trial is evaluating the combination of veliparib + carboplatin + paclitaxel, with results still pending.[23]

6. Conclusions

In recent years, the treatment of locally-advanced and metastatic cervical cancer has improved greatly due to the introduction of targeted therapies, new CT combinations, and emerging treatments. Systemic treatment with CT prolongs the survival of treated patients versus those who receive only supportive care.

In addition, polychemotherapy schemes are superior to single agent regimens. Targeted molecular agents in combination with RT have proven beneficial in the treatment of cervical cancer. Second-line treatment should be considered a standard practice in patients with a good functional status.

Paliation symptoms, oligo-metastatic disease control, minimum cost of toxicity are an acceptable and desirable goal in these patients. Finally, given the poor survival outcomes in patients with metastatic disease, participation in clinical studies should always be considered the best option.

Conflict of interest

None declared.

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