Review Article

Systemic therapy for cervical carcinoma – current status

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Abstract

Two major treatment modalities in cervical cancer are radiation therapy (RT) and surgery. Chemotherapy continues to be the main form of systemic therapy adjunctive to definitive local therapies, and is used for palliation. Platinum-based regimens, administered concurrently with both definitive and postoperative RT, were demonstrated to provide significant survival benefits, whereas the beneficial effect of concurrent chemoradiotherapy in later-stage disease was smaller. The role of chemotherapy in addition to RT in IB1/IIA1 cervical cancer patients not undergoing surgery remains undefined. Likewise, the role of chemotherapy in combination with postoperative RT for patients with intermediate-risk factors for recurrence has not yet been verified. The recent standard for chemoradiotherapy is cisplatin alone administered weekly. Other cisplatin-based or non-cisplatin-based regimens have not been subjected to large clinical studies. The benefits of consolidation chemotherapy after chemoradiation for locally advanced cervical cancer are still undetermined. Neoadjuvant cisplatin-based chemotherapy followed by surgery has shown survival benefits, however its role in the era of chemoradiotherapy remains unclear. The combination of cisplatin and paclitaxel is considered a standard regimen in the palliative setting. There is no standard of care for second-line systemic therapy in advanced cervical cancer. Bevacizumab combined with palliative chemotherapy (cisplatin/paclitaxel or topotecan/paclitaxel) in the first-line treatment for recurrent/metastatic cervical cancer significantly improves overall survival when compared to chemotherapy alone. The role of immunotherapy in cervical cancer remains to be established. The optimal combined modality treatment including systemic therapy for cervical tumors of non-squamous histology remains a matter of debate. Ongoing accumulation of data on genomic and proteomic characteristics provides insight into the molecular heterogeneity of cervical cancer and paves the way for developing molecularly targeted therapies.

Keywords: Cervical cancer; chemotherapy; targeted therapy; immunotherapy

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Introduction

Cervical cancer (CC) is the fourth most common cancer in women, amounting to 528,000 new cases and 266,000 deaths annually worldwide (1). Despite advances in screening and treatment strategies, a significant number of CC patients, especially in less-developed countries, still present with advanced disease; and many others will develop failure after curative primary therapy. For most of these patients, palliative treatments remain the standard of care.

Radiation therapy (RT) along with radical surgery (RS) is the mainstay of CC treatment. The efficacy of both methods is similar in early disease [(International Federation of Gynecology and Obstetrics (FIGO) stages I, IIA)] (2), whereas RT is the treatment of choice in locally advanced CC (LACC; stages IB2, IIB to IVA). The efficacy of RT decreases with the tumor size. In consequence, 30%–70% of patients with LACC will experience loco-regional failure, with or without accompanying distant recurrence. In patients managed with RS, adverse pathological features include the involvement of lymph

nodes and parametrium, positive surgical margins, lymph-vascular space invasion (LVSI) or large and deep tumor invasion. Depending on various prognostic factors, reported pelvic recurrence rates after RS vary from 7% to 58%, with distant metastasis rates up to 41%. Nearly half of the patients with loco-regional failure will develop extrapelvic recurrence. Various efforts, including incorporation of systemic therapies, have been made to increase the efficacy of curative local therapies for LACC and high-risk early-stage patients. In advanced or recurrent patients who are not amenable to curative treatments, especially surgery (3), systemic therapy plays a major palliative role. Chemotherapy continues to be the established form of systemic therapy for CC. This article reviews the role of systemic therapy including chemotherapy, targeted therapy and immunotherapy for CC patients.

Chemotherapy combined with definitive local therapies

Concomitant chemotherapy and definitive RT

Selected randomized controlled trials (RCTs) addressing the role of chemotherapy combined with definitive RT are presented in *Table 1* (4-14).

Improved treatment outcomes with concomitant chemoradiotherapy (CCRT) may be due to increased killing of tumor cells, inhibiting repair of cell radiation damage, synchronization of tumor cells, recruiting non-proliferating tumor cells into the cell cycle, and sensitization of hypoxic tumor cells. However, these benefits are achieved at the expense of enhanced toxic effects.

Table 1 Selected phase III trials addressing the role of chemotherapy concomitant and adjunctive to RT

Author (ref.)	No. of eligible patients	FIGO stage	Histology	Study arms	Chemotherapy regimen	Survival
Keys *et al.* (1999) (4)	369	IB2	SCC, ADC, ADS	RT CCRT (both arms followed by S)	CDDP	4-year OS 74% *vs.* 83% (P=0.008)
Morris *et al.* (1999) (5,6)	403	IB2–IVA	SCC, ADC, ADS	RT CCRT	CDDP+5-FU	8-year OS 41% *vs.* 67% (P<0.0001)
Rose *et al.* (1999) (7,8)	526	IIB–IVA	SCC, ADC, ADS	CCRT CCRT CCRT	HU CDDP CDDP+5-FU+HU	2-year OS 50% *vs.* 66% *vs.* 67% (P=0.002) (10-year OS 34% *vs.* 53% *vs.* 53%)
Whitney *et al.* (1999) (9)	368	IIB-IVA	SCC, ADC, ADS	CCRT CCRT	HU CDDP+5-FU	5-year OS 43% *vs.* 55% (P=0.018)
Wong *et al.* (1999) (10)	220	I, II, III "bulky"	SCC	CCRT CCRT+ACT	EPI during RT and as ACT	5-year OS 68% *vs.* 79% (P=0.04)*
Pearsey *et al.* (2002) (11)	253	IB–IVA[1]	SCC	RT CCRT	CDDP	5-year OS 62% *vs.* 58% (NS)
Lorvidhaya *et al.* (2003) (12)	926	IIB–IVA	SCC, ADC, ADS	RT RT+ACT CCRT CCRT+ACT	MMC+oral 5-FU during RT ACT: oral 5-FU	5-year DFS 48.2% *vs.* 54.1% *vs.* 64.5% *vs.* 59.7%
Duenas-Gonzalez *et al.* (2011) (13)	515	IIB–IVA	SCC, ADC, ADS, poorly differentiated carcinoma	CCRT CCRT as above + ACT	CDDP+GEM during RT ACT: CDDP+GEM	3-year PFS 65% *vs.* 74% (P=0.029)
Wang *et al.* (2015) (14)	74	I, II[2], III, IVA	SCC	CCRT CCRT	CDDP CDDP+GEM	3-year OS 74.1% *vs.* 85.9% (NS)

FIGO, International Federation of Gynecology and Obstetrics; [1], IB2 and IIA (≥5 cm), IIB–IVA or histologically confirmed pelvic lymph node involvement; [2], I, II with histologically confirmed pelvic/paraaortic lymph node involvement; SCC, squamous cell carcinoma; ADC, adenocarcinoma; ADS, adenosquamous carcinoma; RT, radiation therapy; CCRT, concomitant chemoradiotherapy; S, surgery; ACT, adjuvant chemotherapy; CDDP, cisplatin; 5-FU, 5-fluorouracil; HU, hydroxyurea; EPI, epirubicin; *, calculated from survival curves; MMC, mitomycin C; GEM, gemcitabine; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; NS, not significant.

A series of RCTs were performed in the 1990s, comparing cisplatin-based CCRT with RT alone or RT combined with hydroxyurea in various stages of CC managed with definitive or preoperative irradiation (4,5,7,9). These trials, involved women with all stages of CC, and used different inclusion criteria, staging methods to rule out para-aortic node involvement (lymphangiography, computed tomography or surgical exploration), chemotherapy and RT schedules. The absolute survival benefits with the addition of cisplatin-based chemotherapy to RT ranged from 9% to 18%, with a significant reduction in the relative risk of recurrence and death (a mean of 50% and 30%, respectively). In consequence, in 1999 the US National Cancer Institute recommended the addition of cisplatin-based chemotherapy concomitantly with RT in all patients irradiated for CC (15).

The beneficial effect of chemotherapy added to RT in CC was demonstrated in meta-analysis of RCTs carried out between 1981 and 2000 (16). There was an apparent inconsistency among the control group setting of each study though. The overall hazard ratio (HR) of death was 0.71 (P<0.0001) in favor of chemotherapy; 0.70 (P<0.0001) and 0.81 (P=0.20), respectively for trials that did, and did not, use cisplatin. A greater beneficial effect was observed in trials including a high proportion of stage I and II patients. The highly significant reduction in the risk of both local recurrence and distant metastases suggests a systemic cytotoxic effect of chemotherapy.

The superiority of platinum-based [overall survival (OS): HR=0.83, P=0.017] and non-platinum-based CCRT (OS: HR=0.77, P=0.009) over RT alone was supported by meta-analysis conducted in 2010, which included individual patient data (IPD) from 13 trials published before 2005 (17). Significantly improved OS and progression-free survival (PFS) in the cisplatin-RT-treated subgroup of high-risk (LACC or bulky tumor) patients was demonstrated in 2016 meta-analysis, including recent data from 8 RCTs and 3 cohort studies (18). The pooled HR for OS and PFS were 0.68 and 0.63, respectively. The benefit of CCRT compared to RT alone seems to diminish in later-stage disease (16,19,20). Estimated absolute 5-year survival benefits are 10% at stages IA–IIA, 7% at stage IIB, and 3% at stages III–IVA (19). The lack of significant benefits of CCRT including cisplatin-based chemotherapy in some trials may be attributed to several factors, such as different study designs, patient characteristics, control settings, regimens used, RT duration, and duration of follow-up (6,11,20). As negative results of CCRT were noted in cohort studies in Asian women, a potential racial difference for different CCRT regimens was also suggested (18).

Increased peak concentration of cisplatin, surgery following CCRT, consolidation chemotherapy following CCRT, and neoadjuvant chemotherapy (NACT) before CCRT, were strategies expected to enhance the therapeutic efficacy of CCRT in CC patients with large tumors and radiologically enlarged lymph nodes (high-risk group) (21).

There is currently no published randomized data comparing definitive CCRT and RT alone in patients with stage IB1/IIA1 CC. More recent large retrospective analysis of stage IB1/IIA1 patients managed without surgery demonstrated an OS improvement with the addition of chemotherapy to RT (22).

Chemotherapy in postoperative setting for early-stage CC

The RCTs addressing the role of chemotherapy in the postoperative adjuvant therapy are presented in *Table 2* (23-27).

Postoperative platinum-based CCRT or RT alone decreases the risk of loco-regional recurrence and is recommended as the standard management in early-stage CC patients with high- or intermediate-risk factors for recurrence (15,25,28,29). However, a secondary retrospective analysis of the Gynecologic Oncology Group (GOG) trial demonstrated that the addition of postoperative chemotherapy to RT may be relatively less beneficial in patients with small (<2 cm) tumors (26). In patients with intermediate-risk factors the benefit of adjuvant CCRT over adjuvant RT alone remains unclear (30). Moreover, survival improvement with the addition of platinum-based chemotherapy to adjuvant RT in early stage CC (IA2–IIA), was at the expense of an increased risk of severe toxicity (31).

To reduce extrapelvic recurrence, postoperative chemotherapy alone using paclitaxel/cisplatin regimen was suggested as an alternative strategy (32). In a large subgroup of patients with pelvic and/or para-aortic metastasis, postoperative chemotherapy alone as compared to CCRT was associated with a higher local recurrence rate (23% *vs*. 14%, P=0.001), lower distant recurrence rate (19% *vs*. 24%, P<0.001) and similar specific CC mortality (33). Similar outcome with better toxicity profile of adjuvant chemotherapy (ACT) compared with CCRT for high-risk CC patients was demonstrated in another retrospective study (34).

Postoperative sequential chemotherapy including

Table 2 Phase III trials addressing the role of chemotherapy in the postoperative adjuvant therapy for early-stage CC with pathological risk factors

Author (ref.)	No. of eligible patients	FIGO stage	Histology	Study arms	Chemotherapy regimen	Survival
Curtin *et al*. (1996) (23)	89	IB–IIA[1]	SCC, ADC, Non-SCC	CT CT followed by RT and CT	BLE+CDDP	3-year OS 70% *vs*. 75% (NS)
Lahousen *et al*. (1999) (24)	76	IB–IIB[2]	SCC	CT RT NFT	BLE+CBDCA	5-year OS 86% *vs*. 80% *vs*. 81% (NS)
Peters *et al*. (2000) (25,26)	243	IA2–IIA[3]	SCC, ADC, ADS	RT CCRT+ACT	CDDP+5-FU (during RT and as ACT)	4-year OS 71% *vs*. 81% (P=0.007)
Sehouli *et al*. (2012) (27)	263	IB–IIB[4]	SCC, ADC, ADS	CCRT CT followed by RT	PTX+CBDCA	5-year OS 78.9% *vs*. 85.8% (P=0.25)

CC, cervival cancer; FIGO, International Federation of Gynecology and Obstetrics; [1], risk factors include pelvic lymph node metastasis and/or deep cervical invasion and/or tumor ≥4 cm and/or parametrial involvement and/or nonsquamous histology and/or positive surgical margins; [2], risk factors include pelvic lymph node metastases or parametrial involvement and/or vascular invasion; [3], risk factors include pelvic lymph node metastases and/or positive margins and/or parametrial involvement; [4], risk factors include vascular invasion and/or pelvic lymph node metastases and/or positive margins; SCC, squamous cell carcinoma; ADC, adenocarcinoma; non-SCC, non-squamous cell carcinoma; ADS, adenosquamous carcinoma; CT, chemotherapy; RT, radiation therapy; NFT, no further therapy; CCRT, concomitant chemoradiotherapy; ACT, adjuvant chemotherapy; BLE, bleomycin; CDDP, cisplatin; CBDCA, carboplatin; PTX, paclitaxel; OS, overall survival; NS, not significant.

paclitaxel/carboplatin preceding RT was not superior to standard CCRT with weekly cisplatin in high-risk CC (27).

Further improvement in adjuvant therapy should emerge from an improved definition of prognostic risk factors, better patient selection, and refinements in both local and systemic therapies (29).

Consolidation chemotherapy after concurrent chemoradiation

ACT following CCRT is expected to be the most beneficial for LACC. ACT in combination with CCRT was used in a few RCTs (10,12,25). The efficacy of ACT consisting of mitomycin C and oral 5-fluorouracil was directly addressed in the large study that compared RT alone with RT combined with concomitant, adjuvant or concomitant and ACT (12). Despite better loco-regional control in both CCRT arms, the metastatic rates were not significantly different through all four arms. In the Southwest Oncology Group (SWOG) trial, which showed a superiority of combined modality approach over postoperative RT alone, patients in the CCRT arm were additionally administered two cycles of consolidation cisplatin/5-fluorouracil chemotherapy (25). In a single institution study, the addition of epirubicin, administered during and after standard pelvic RT, significantly decreased the incidence of distant failure compared to the same RT, but there was no impact on the incidence of local recurrences (10).

A significant survival benefit for patients who underwent CCRT with weekly cisplatin and gemcitabine followed by 2 cycles of ACT including cisplatin/gemcitabine regimen at higher doses compared to the same CCRT alone was demonstrated (13). However, recent systematic review showed insufficient evidence supporting the use of ACT following CCRT (35).

Cytotoxic agents used in combination with RT

Owing to its convenience, favorable toxicity and relative effectiveness, cisplatin 40 mg/m^2 weekly for 6 weeks concurrent with radiation is widely accepted as the standard regimen of CCRT. Indeed, among the two approaches: weekly cisplatin or cisplatin plus 5-fluorouracil every 3 weeks, the former seems to be less toxic and more feasible. A variety of cisplatin regimens and doses have been combined with RT, however no larger trial addressed the optimal cisplatin scheduling. The substitution of cisplatin by carboplatin, a less nephrotoxic platinum analogue seems appealing and feasible (36), yet its beneficial effect remains to be established. In one study including IIB–IVA CC, tri-weekly cisplatin (75 mg/m^2 in 3 cycles) concurrent with RT was found more effective than the conventional weekly dose of 40 mg/m^2 in 6 cycles (5-year OS: 89% *vs*. 67%; HR=0.375), with similar compliance (37). Higher peak concentration of cisplatin reduced the percentage of distal failure (17% *vs*. 26%). However, the most recent meta-

analysis that included 5 RCTs demonstrated a similar therapeutic effect of weekly compared to tri-weekly regimen, and lower hematologic toxicity (38).

Since gemcitabine is a potent radiosensitizer, two RCTs have been undertaken to clarify the use of cisplatin and gemcitabine in combination with RT for CC patients (13,14). Duenas-Gonzalez *et al*. showed improved survival for the treatment of stage IIB–IVA CC by the addition of weekly concurrent gemcitabine and 2 cycles of adjuvant cisplatin/gemcitabine compared to standard single-agent cisplatin (HR=0.68, P=0.0224) (13). Combination chemotherapy showed a statistically significant advantage in distant failure rate (8.1% *vs*. 16.4%, P=0.005), whereas the difference in local failure rate was not significant (11.2% *vs*. 16.4%, P=0.097). No improvement from the addition of gemcitabine to weekly cisplatin in stage III, IVA CC was demonstrated in another small trial (14).

Several other agents and drug combinations, including the taxanes, have been investigated as radiation sensitisers in CC. The most recent review of 13 different chemotherapy regimens concomitant to RT in the treatment of LACC indicated that CCRT with cisplatin/docetaxel might be the most effective (39). However, weekly cisplatin remains the least toxic among all chemotherapy regimens in combination with RT.

NACT

The aim of chemotherapy preceding local modalities is to reduce the volume of disease, making the subsequent irradiation or surgery more effective, while controlling micrometastatic disease. The disadvantages of this strategy include the delay in the onset of local treatment, the possibility of accelerated repopulation of tumor cells, and the risk of developing radio-resistant cell clones. Therefore, it is important to select patients who will most likely benefit from NACT (40).

Several studies indicated beneficial effects of chemotherapy preceding RT or surgery (40,41). Surgical series including patients with FIGO stage I–IVA showed an operability rate of 48% to 100% following primary chemotherapy, with no increased surgery-related morbidity. Pathologically confirmed complete responses were achieved in 9%–27% of cases, and the incidence of lymph node metastases seemed to be markedly low, reducing the number of high-risk patients requiring postoperative RT. A survival benefit associated with NACT followed by surgery (NCS) compared to conventional RT was demonstrated in three RCTs (42-44). NACT in two studies consisted of vincristine/bleomycin/cisplatin regimen (42,43). The Italian study compared cisplatin-based NACT in LACC patients (44). Most importantly, in view of the recent CCRT studies, exclusive RT in the control arm in these studies may be viewed as suboptimal management.

Significantly better local control, PFS and OS, beside a significant decrease in adverse pathological findings in the NCS group compared to the surgery group was shown in the Cochrane review conducted in 2012 (45). Another review, however, has not shown an advantage for this approach in stage IB1–IIA CC (46). The benefit of NACT followed by surgery (±RT) versus definitive RT in LACC was demonstrated in systematic review and meta-analysis of IPD from 21 RCTs (47). No increased OS, despite a significant reduction in tumor volume by primary chemotherapy, was demonstrated in meta-analysis of RCTs comparing RT alone with RT preceded by chemotherapy (48). Apart from the limitations of meta-analysis, the results of these analyses should be interpreted in view of the current replacement of RT by CCRT as the standard management.

The efficacy of NACT followed by surgery versus cisplatin-based CCRT is addressed in the ongoing large RCT conducted by the European Organization for Research and Treatment of Cancer (EORTC) in patients with FIGO stage I–IIB CC.

Current studies investigate NACT with modern chemotherapy regimens, including irinotecan/nedaplatin followed by RS (49).

NACT with paclitaxel/carboplatin or cisplatin/gemcitabine before CCRT is another postulated strategy for potentially systemic LACC (21). Two cycles of cisplatin combined with gemcitabine as an upfront treatment for LACC patients managed with cisplatin-based CCRT did not show a meaningful improvement in small series (50).

ACT (but also adjuvant RT), as compared to no further treatment, does not seem to improve the clinical outcomes of patients with extra-cervical residual disease after platinum-based NACT followed by RS (51).

Palliative chemotherapy

Since current palliative systemic therapy offers only the modest gains in OS, it should consider not only the survival benefit, but also minimal treatment toxicity and positive impact on quality of life (QOL). For advanced, persistent or recurrent CC, cisplatin-based chemotherapy remains standard treatment, although its effect is of short duration

(52). Currently, recommended regimen is a combination of cisplatin/paclitaxel. Selected RCTs addressing the role of palliative chemotherapy are presented in *Table 3* (53-58). Significant increase in response rate (RR) (36% *vs*. 19%) and median PFS but not OS (9.7 and 8.8 months), with sustained QOL for this doublet compared to cisplatin alone was demonstrated in GOG RCT (53). Response was more frequent in patients with disease in non-irradiated sites (79% *vs*. 23%). Performance status 1 or 2, pelvic recurrence, prior radio-sensitizing chemotherapy, African American race, and first recurrence within 1 year of diagnosis were poor prognostic factors significantly and independently associated with reduced OS (59). The superiority of the doublet with cisplatin plus topotecan in terms of RR (27% *vs*. 13%), median PFS, but also median OS (9.4 *vs*. 6.5 months) was demonstrated in another GOG trial (54). A subsequent GOG trial compared four cisplatin doublets: cisplatin/paclitaxel (reference arm) against cisplatin/vinorelbine, cisplatin/gemcitabine, and cisplatin/topotecan (55). There were no significant differences in regard to RR, which were 29.5%, 25.9%, 22.3%, and 23.4% for cisplatin combinations with paclitaxel, vinorelbine, gemcitabine, and topotecan, respectively. Noninferiority of the carboplatin/paclitaxel doublet, compared to cisplatin/paclitaxel, was shown in the Japanese study (58). In a subset analysis of patients who had not received prior platinum, the cisplatin/paclitaxel doublet showed superior OS (median of 23.2 months *vs*. 13.0 months, respectively) and was less toxic.

There is currently no consensus on the standard care for second-line systemic treatment of recurrent/metastatic CC (60). There is also no evidence that treatment in the second-line setting improves OS compared to the best supportive care. Available single agents beyond first-line platinum-based therapy, including topoisomerase inhibitors, taxanes, alkylating agents and antimetabolites have limited efficacy in this setting (60,61).

Targeted therapy

Bevacizumab, a humanized monoclonal antibody targeting

Table 3 Selected phase III trials addressing the role of chemotherapy in stage IVB, recurrent or persistent CC

Author (ref.)	No. of patients	Histology	Reference regimen	Regimen investigated	Survival (months)
Moore *et al*. (2004) (53)	169	SCC	CDDP 50 mg/m^2 q 21 d	CDDP 50 mg/m^2 + PTX 135 mg/m^2/24 h q 21 d	PFS 2.8 *vs*. 4.8 (P<0.01)
Long *et al*. (2005) (54)	179	SCC, ADC, ADS	CDDP 50 mg/m^2 q 21 d	CDDP 50 mg/m^2 + TOP 0.75 mg/m^2 d 1–3, q 21 d MVAC[1]	PFS 2.9 *vs*. 4.6 (P<0.01)
Monk *et al*. (2009) (55)	204	SCC, ADC, ADS	CDDP 50 mg/m^2 + PTX 135 mg/m^2/24 h q 21 d	CDDP 50 mg/m^2 + TOP 0.75 mg/m^2 d 1–3, q 21 d CDDP 50 mg/m^2 + GEM 1,000 mg/m^2 d 1, 8 CDDP 50 mg/m^2 + VNR 30 mg/m^2	PFS 5.8 *vs*. 4.6 *vs*. 4.7 *vs*. 4.0 (NS)
Tewari *et al*. (2014) (56,57)	452	SCC, ADC, ADS	CDDP 50 mg/m^2 + PTX 135 mg/m^2/24 h or 175 mg/^{2} 3 h, q 3 w, or TOP 0.75 mg/m^2 d 1–3 + PTX 175 mg/m^2/3 h, d 1 q 3 w	CDDP 50 mg/m^2 + PTX 135 or 175 mg/m^2 + Bev 15 mg/kg q 3 w, or TOP 0.75 mg/m^2 d 1–3 + PTX 175 mg/m^2, d 1 + Bev 15 mg/kg q 3 w	OS 16.8 Bev + *vs*. 13.3 Bev– (P=0.007)
Kitagawa *et al*. (2015) (58)	244	SCC, ADC, ADS	CDDP 50 mg/m^2 + PTX 135 mg/m^2/24 h, q 3 w	CBDCA (AUC 5) + PTX 175 mg/m^2/3 h q 3 w	PFS 18.3 *vs*. 17.5 (NS)

CC, cervical cancer; SCC, squamous cell carcinoma; ADC, adenocarcinoma; ADS, adenosquamous carcinoma; CDDP, cisplatin; PTX, paclitaxel; TOP, topotecan; [1], MVAC arm (Methotrexate 30 mg/m^2 d 1, 15, 22 + vinblastine 3 mg/m^2 d 2, 15, 22 + doxorubicin 30 mg/m^2 d 2 + cisplatin 70 mg/m^2 d 2, q 21 d) closed prematurely due to severe adverse effect; GEM, gemcitabine; VNR, vinorelbine; Bev, bevacizumab; CBDCA, carboplatin; PFS, progression-free survival; OS, overall survival; NS, not significant.

vascular endothelial growth factor receptor (VEGFR) in combination with chemotherapy was approved as first-line therapy for advanced CC, with a significant OS improvement of 3.5 months (HR=0.77, P=0.007) as compared with chemotherapy alone (56,57). Chemotherapy in this pivotal RCT consisted of cisplatin/paclitaxel or topotecan/paclitaxel, continued until disease progression. Despite the higher rate of severe adverse events including genitourinary fistulas, thromboembolic events and hypertension, the addition of bevacizumab to chemotherapy did not adversely affect health-related QOL. More than 70% of patients in each group had previously received platinum-based CCRT. The role of bevacizumab in the first-line therapy of advanced and recurrent CC remains to be elucidated.

Cediranib and pazopanib are other anti-angiogenic agents that have shown promising efficacy in advanced CC. The addition of cediranib, a potent tyrosine kinase inhibitor of VEGFR1-3 and stem cell factor receptor (c-KIT), to chemotherapy in patients with metastatic or recurrent CC in the first-line setting was investigated in a randomized, placebo-controlled phase II trial (62). Six cycles of carboplatin/paclitaxel plus daily cediranib, continued until progression resulted in a significant improvement of PFS (8.1 *vs*. 6.7 months; HR=0.58; P=0.032) but not of OS. The RR of 64% in the cediranib group was the highest reported in this setting. Cediranib did not increase the rate of fistulae. In another study using pazopanib, a multi-targeted tyrosine kinase inhibitor (TKI) with activity against the VEGFR1-3, platelet-derived growth factor receptor (PDGFR) α and β and c-KIT, the median PFS was 12.4 months (63,64).

Other fundamental anti-angiogenic (sunitinib, sorafenib, nintedanib) and molecularly targeted agents (cetuximab, erlotinib, sunitinib, gefitinib or imatinib) have failed to show significant benefits in advanced CC (52).

Several targeted therapies, with or without chemotherapy, including non-VEGF-dependent angiogenesis inhibitors (eg. the angiopoietin axis inhibitor trebananib) and vascular-disrupting agents that target existing tumor vasculature are being investigated in CC patients (52,60,65,66). Signal transduction pathways relevant to cervical carcinogenesis that can be targeted include the phosphoinositide 3 kinase B-mammalian target of rapamycin pathway, homologous recombination deficiency pathways that can exploit synthetic lethality, and the Notch binary cell fate decision pathway, which might also represent viable therapeutic options in the future.

Immunotherapy

Immunotherapy with immune-checkpoint inhibitors has recently shown spectacular antitumor efficacy with durable responses in a variety of tumors (melanoma, renal and lung carcinomas). Given the presence of a virus in CC oncogenesis leading to antigen production, there is a strong rationale supporting the development of immunotherapy in this tumor. Significant programmed-cell-death protein 1 ligand (PD-L1) expression, a putative predictive marker for PD-1/PD-L1 inhibitors, was demonstrated in 38%–54%, 12%–29% and 14% of primary tumor samples of squamous cell carcinoma (SCC), adenosquamous carcinoma (ADS) and adenocarcinoma (ADC), respectively (67,68). Other studies showed PD-L1 expression of various degrees in all LACC and recurrent tumors, with no apparent difference between SCC and ADC (69,70). One study reported a positive correlation between HPV16E7 and PD-L1 expression (71).

There are multiple ongoing studies to evaluate the role of immune checkpoint inhibitors including pembrolizumab, durvalumab, tremelimumab, atezolizumab, nivolumab and ipilimumab in the upfront treatment, in combination with RT, after CCRT, as neoadjuvant therapy, and in recurrent setting (66,72). There are currently only four case reports on the use of pembrolizumab and nivolumab in the metastatic setting, including chemo-refractory and PD-L1-negative tumors (73-75). A rapid response or response following transit increase of lesions was reported. Of those, there was a case of neuroendocrine cervical carcinoma with near-complete systemic resolution of disease, ongoing at 10+ months after nivolumab, sandostatin and stereotactic body radiation therapy (SBRT; 20 Gy/4 fractions) including abdominal mass (76). The response seen outside the field of radiation, termed the “abscopal” effect, was probably mediated by radiation-induced cross presentation of tumor antigens resulting in immune activation. Tissue rebiopsy and comprehensive genomic profiling confirmed a high tumor mutational burden: 53 mutations per megabase with >19 considered high, multiple other alterations including a mismatch repair gene (*MSH2* gene) defect, and high microsatellite instability status.

Beside checkpoint inhibitors, therapeutic vaccines have been intensively studied in CC (65).

Role of systemic therapy in non-squamous histologies

Numerous studies have shown different outcomes

following primary RT or RS in particular histotypes of cervical tumors: but no RCT assessed the treatment efficacy in relation to CC cell types. Moreover, in some studies evaluating the combination of chemotherapy and local modalities, the accrual was restricted to SCC. The incidence of invasive ADC and its variants has increased over last decades; this type now amounts to about 20%–25% of all invasive CCs. Several retrospective studies and large national databases demonstrated poorer OS for ADC compared to similarly staged SCC (77). This was due to more aggressive behaviour of this type – frequent lymph node involvement, distant organ metastasis, or the relative radio- and chemoresistance of ADC (78). No survival improvement in non-SCC IIB, or more advanced CC was achieved with NACT (79). Similar outcomes of LACC with ADC or ADS histology compared to SCC were reported by others (80).

Significant differences in molecular and immunological profiles, between the two most common CC histotypes were recently shown (67,81). Notably, HER2 overexpression found in a half of ADC/ADS constituted an independent prognostic marker (82).

Only a few studies have reported separate outcomes for ADC. The role of tumor histology was evaluated in SWOG RCT of postoperative adjuvant CCRT for women with positive nodes, parametria or margins (25). This study demonstrated an apparently poorer 5-year PFS (40% *vs*. 65%) with RT alone, but similar outcomes with CCRT (80% *vs*. 77%), compared to ACT. Similar results were demonstrated in the large retrospective analysis of prospectively collected data on CCRT from the GOG trials that enrolled 1,671 patients (83). This analysis demonstrated that both main histotypes respond well to CCRT. Poorer outcome for advanced ADC/ADS as compared to SCC was noted for RT alone, and the use of cisplatin-based CCRT nullified this difference.

A recent study showed the therapeutic effect of both neoadjuvant and consolidation chemotherapy with CCRT in advanced ADC/ADS (84). In this study, 880 Chinese patients were randomly assigned to CCRT or CCRT preceded by one cycle of NACT and supplemented by two tri-weekly cycles of ACT with paclitaxel/cisplatin (135 mg/m^2 and 75 mg/m^2). Patients treated with NACT/ACT regimen showed a significantly longer DFS and OS. They had also decreased rates of both long-term local control and distant failure (P<0.05).

Small cell neuroendocrine carcinoma of the cervix, a rare histologic entity, is considered to confer a poor prognosis because of its early metastatic potential to both regional lymph nodes and distant sites. Due to the aggressive behaviour of this tumor, multimodality treatment including chemotherapy is advocated even in early-stage disease (85-87). The use of ACT alone or combined with RT was independent factors for improved survival in the largest series of small cell CC patients (85). The worse outcome with NACT was revealed. Cisplatin combined with etoposide appears to be the most commonly used regimen. Postoperative CCRT did not improve survival compared with ACT alone in another relatively large retrospective series (86).

Conclusions

Definitive CCRT is considered the standard treatment for stage IB2–IVA CC. The role of chemotherapy in addition to definitive RT for stage IB1/IIA1 CC patients remains undefined. The addition of cisplatin-based chemotherapy to postoperative RT significantly improves the outcome of patients with a high-risk for recurrence. The superiority of CCRT over RT alone in patients with intermediate-risk remains unknown. The most common chemotherapy schedule for a concomitant approach includes single-agent cisplatin administered at a weekly dose of 40 mg/m^2. Even though there is no convicting data on its superiority to other regimens, cisplatin alone is considered standard therapy due to its proven efficacy, ease of administration, and relatively low toxicity. In contrast to the concomitant approach, chemotherapy preceding RT does not seem to improve the outcome. A series of RCTs including stage IB to IIB patients, demonstrated the superiority of preoperative chemotherapy over RS or definitive irradiation alone. Currently, CCRT and chemotherapy followed by radical surgery are being compared in a large RCT performed by the EORTC. The combination of cisplatin and paclitaxel is considered a standard palliative regimen. Other cisplatin doublets were not superior to cisplatin/paclitaxel, whereas substituting carboplatin for cisplatin and topotecan, or gemcitabine for paclitaxel might be helpful for some patients, considering different toxicity profiles. Bevacizumab combined with chemotherapy was shown to significantly improve the outcome in advanced disease setting. Available data with immune checkpoint inhibitors in CC are scarce, but owing to the causative role of HPV, this tumor deserves further study. The optimal management including systemic therapy for non-squamous cervical tumors has not been determined. Ongoing

accumulation of data on genomic and proteomic characteristics provide insight into the molecular heterogeneity of CC, and may pave the way for developing distinct molecularly targeted therapies (88).

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Footnote

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