Treatment of cervical cancer: recent achievements and future development

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Abstract
Over the last two decades the widespread use of the screening tests, leading to early detection of pre-invasive lesions, has dramatically reduced morbidity and mortality related to cervical cancer (CC), nevertheless CC remains a major health problem, especially in developing countries, where most cases are still diagnosed at late stages. Optimizing treatment is subject of constant research but there are several unanswered questions, including whether radiotherapy is preferred over surgery and which patients should receive neoadjuvant and/or adjuvant chemotherapy. A center's experience and the accessibility of radiotherapy are often the main factors guiding clinicians' choices in the approach to locally-advanced disease, which can be treated with different modalities such as chemoradiation and surgery, with or without neoadjuvant and/or adjuvant chemotherapy. Several regimens have been evaluated in the metastatic and recurrent setting, although platinum-based doublets have remained the standard of care for years. Recently, the encouraging results achieved by inhibiting tumor angiogenesis led to the approval of bevacizumab as an addition to conventional chemotherapy. Immunotherapy is another approach that is rapidly gaining credibility in multiple malignancies and several novel agents are under development in the CC population. Although CC has historically been considered 'chemoresistant', a number of new approaches to therapy, including angiogenesis blockage and immunotherapy, provide hope for more effective treatment.

Key words: bevacizumab, cervical cancer, chemoradiation, immunotherapy

Introduction

Uterine cervical cancer (CC) is the second most common gynecological malignancy, and represents a major cause of morbidity and mortality in developing countries, where more than 70% of cases are diagnosed at advanced stages [1-5]. CC is also a major health issue in Europe, with 54,517 new cases and 24,874 deaths every year [1-5]. According to the International Federation of Gynecology and Obstetrics (FIGO), CC is staged into 'earliest stages' (IA1 to IIA1), which are usually treated with surgery [6, 7]; 'intermediate stages' (IB2 to IVA), which generally require chemoradiation; and 'advanced stages' for which palliative chemotherapy is the only option [8]. Management of the earliest stages of CC is not discussed in this paper. Despite the significant survival improvements achieved with the widespread utilization of CC screening tests, many women experience disease recurrence (recurrence rate 10-20% in IB-IIA and 50-70% in IIB-IVA) [8]. Therefore, significant research effort is going in to exploring new therapeutic strategies. This paper reviews the therapeutic options for CC at different disease stages.

Locally-advanced cervical cancer (LACC)

According to European and American CC treatment guidelines [4, 5], radiotherapy (RT) and/or chemotherapy (CT) in addition to, or as an alternative to, surgery should be considered for all stages from IB2 to IVA. Therefore, for the purposes of this review, the term 'locally advanced' refers to these disease stages, which account for almost 32% of all diagnoses with an overall 5-year survival rate of approximately 40-50% [9].

Chemoradiation

RT alone is not enough to control locally advanced disease; it is estimated that more than 35% of women with IB2-IVA CC have persistent disease after radiation, while the addition of CT improves survival by about 10% [10].

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Concurrent chemoradiation (CT-RT)

CT-RT became part of routine clinical following the publication, in 1999, of an alert of the National Cancer Institute [11] recommending that 'concomitant (cisplatin-based) CT-RT instead of radiotherapy alone should be adopted in women with cervical cancer'. This recommendation was based on the results of 5 randomized controlled trials [12-16].

Subsequently a meta-analysis including 15 CT-RT trials of 3452 patients with IB2-IV CC was performed [17]. CT-RT was mainly platinum-based (11 trials), external beam radiation was adopted in all the studies (total dose 40-61 Gy), and 14 trials also included brachytherapy; treatment duration ranged from 40 to 70 days. After a median follow-up of 5.2 years, CT-RT compared to RT was associated with a 5-year survival benefit of 6% (hazard ratio [HR] 0.81; p<0.001); this benefit was seen across all disease stages from IB2 to IVB with significant variations across the groups.

The treatment of women with stage IB bulky disease deserves particular attention in the light of the paper published by Keys et al. in 1999 [12] which focused on 374 patients with IB2 CC, excluding the high-risk category (evidence of nodes metastases on the imaging). The two arms of the trial consisted of CT-RT with weekly intravenous (IV) cisplatin 40 mg/m^2 *versus* RT alone. There was a statistically significant benefit for the CT-RT group both in progression-free survival (PFS) (p<0.001) and overall survival (OS) (p=0.008); 80% of patients did not experience disease recurrence and 85% were alive 4 years after starting treatment.

Based on available literature about radiation in a CT-RT regimen, the total dose on the tumor should be 80-90 Gy (brachytherapy included), the pelvic sidewall should receive 50-65 Gy, and the approximate treatment duration should not exceed 8 weeks [18]. With the recent advances in 3D image-based external beam treatment-planning, intensity-modulated radiotherapy (IMRT), volumetric modulated therapy (RapidArc®), and 3D image-guided brachytherapy, it is possible to achieve more homogeneous higher dosages to macroscopic disease, sparing normal tissue at the same time.

Sequential chemoradiation

Dividing treatment in two phases, one of CT and another of RT, has been reported by several authors. However, a large meta-analysis published in 1998 [19] concluded that such strategy was detrimental for survival and it was therefore abandoned worldwide in favor of concurrent CT-RT. The failure of sequential CT and RT may be due to a number of factors, both clinical (i.e. CT-related mortality and patients reluctance to have a long treatment course) and biological (e.g. the potential accelerated repopulation of resistant tumor clones – after effective CT, cancer shrinkage might be followed by faster tumor regrowth) [20, 21].

A Cochrane review about neoadjuvant CT (NACT) in CC was published in 2004 [22]. This included 23 trials in a total of 2946 women. The conclusion was that dose-dense CT (between-dose interval of ≤14 days or cisplatin dose intensity ≥25 mg/m^2/week) was associated with significant survival benefit compared to regimens with longer intervals between cycles or lower cisplatin dose intensities (risk of death decrease of 71% [p=0.046] and 9% [p=0.02], respectively).

These findings may partially explain the negative results of the previous meta-analysis. However, the lack of robust data about the equivalency or the superiority of the sequential CT-RT approach compared to the concurrent CT-RT does not allow recommendation of this strategy for use outside clinical trials. A randomized clinical trial is in progress to help answer this question (INTERLACE; NCT01566240).

Neoadjuvant chemotherapy (NACT) followed by surgery

NACT is more popular at centers where accessibility to RT is limited and the surgical approach is strongly entrenched.

Two randomized phase III trials comparing NACT followed by radical surgery (RS) with RT reported longer survival for the NACT/surgery group [23, 24]. A meta-analysis including 5 studies (n=872) [25] reported a 35% reduction in the relative risk of death in patients treated with NACT *versus* RT (HR 0.65; p<0.0004). However, the quality of RT in these trials has been severely criticized by several authors due to lower total dose as well as prolonged total treatment time. It is argued that 'bad' RT is being compensated for by NACT.

Which drug regimen should be adopted in the NACT setting is still debated: most trials have included combinations of cisplatin, taxanes, irinotecan, vinorelbine and gemcitabine, with reported response rates (RR) of 70-100% [26].

NACT followed by surgery can be considered an effective treatment modality in LACC, and is particularly feasible in countries where radiation equipment may be insufficient [1]. However, the possible limitation of this strategy relates to the cumulative toxicity of multimodal treatment where RS plus radical pelvic/abdominal RT is used for patients with pathologic risk factors [1]. The on-going EORTC trial (EORTC-55994, NCT00193739), comparing NACT plus RS with CT-RT, will hopefully clarify which is the best treatment modality.

CT-RT as neoadjuvant treatment before surgery is another potential strategy. Several authors support such approach on the basis of a reported survival benefit [26-30], especially in patients with bulky residual disease (≥2 cm) at completion of CT-RT [26]. The rationale is that in case of poor response to CT-RT, a survival advantage may be achieved by removing the CT-RT-resistant foci. However, the toxicity induced by a triple modality treatment strategy is an important concern, although two large studies have reported encouraging safety data [30, 31].

Adjuvant chemotherapy

CT should be considered after initial treatment in patients at higher risk of systemic relapse. In contrast with initial results that suggested a lack of survival improvement in IB-IIB CC [32, 33], Peters et al. showed that PFS and OS were significantly longer in patients with IA2-IIA disease treated with 3-weekly cisplatin-fluorouracil after surgery [7]. Subsequently, Monk et al. reported a survival benefit in women with CC and node metastases (two or more) treated with postoperative RT plus adjuvant CT rather than RT alone [34].

Adjuvant CT has also been proposed after NACT and RS. Sananes et al. evaluated the combination of cisplatin, methotrexate and cyclophosphamide, given 3-weekly, after NACT and RS (stage IB-IIIB) [35]. After a median follow-up of 75 months, OS was 88%, 78% and 50% for patients with stage IB, IIB and IIIB disease, respectively. Angioli et al. [36] assessed the cisplatin-paclitaxel doublet (CDDP-PTX) in 246 women with IB2-IIB disease who undergone NACT and RS; 4 cycles of postoperative CT were associated with a 5-year OS of 77% and 5-year disease-free survival (DFS) of 61%. Outside the clinical trial setting, adjuvant CT should be reserved for high-risk groups, such as those with tumors with node metastases and lymphovascular space involvement.

Several ongoing international clinical trials are evaluating the role of adjuvant CT as surgery followed by chemoradiation in an early stage high-risk population (RTOG 0724; NCT00980954), chemoradiation in locally advanced disease (OUTBACK; NCT01414608) or post chemoradiation with 3D image-guided brachytherapy in locally advanced disease (EMBRACE; NCT00920920).

Advanced and recurrent cervical cancer

Stage IVB/recurrent CC is generally non-curative and remains a major cause of cancer-related death. For patients with limited metastatic disease or central isolated pelvic recurrences, localized radiation or exenterative surgery may be appropriate. However, CT remains the only therapeutic option for patients with distant metastases or inoperable recurrences even though, compared with breast and ovarian cancer, CC is considered chemoresistant [8].

Single agent CT and combination therapy

Cisplatin is the most active single agent and the cisplatin-paclitaxel doublet has been the standard of care since other platinum combinations have not demonstrated superiority, although replacing paclitaxel with topotecan or gemcitabine might be reasonable for patients with residual neurotoxicity [37].

Following a Gynecologic Oncology Group (GOG) phase II trial testing first-line cisplatin in 25 patients [38], a phase III study (GOG 43) comparing different schedules of cisplatin (3-weekly 50 mg/m^2 *vs* 3-weekly 100 mg/m^2 *vs* 20 mg/m^2/day for 5 days) was conducted; RR was 20.7%, 31.4%, and 25.0% respectively, median PFS was 3.7, 4.6 and 3.9 months, respectively and there was no significant between-group difference in survival (Table 1) [39]. Other platinum analogues as well as non-platinum agents [40-44] demonstrate lower RR and PFS than cisplatin alone in non-randomized cohort studies [37].

With respect to CT combinations, a number of phase III trials have been performed, mainly from the GOG. The GOG 110 compared cisplatin + mitolactol with cisplatin + ifosfamide and cisplatin alone. Compared with cisplatin alone, cisplatin-ifosfamide recipients had a higher RR (31.1% *vs* 17.8%; p=0.004) and longer PFS (4.6 *vs* 3.2 months; p=0.003) but also had more toxicity (leucopenia, renal and CNS toxicity, peripheral neurotoxicity) and no OS benefit was noted [45]. The GOG 149 trial evaluated cisplatin-ifosfamide, with or without bleomycin, and did not report any advantage with respect to RR, PFS and OS [46]. The GOG 169 study compared cisplatin-paclitaxel with cisplatin alone in patients with stage IVB, recurrent or persistent CC [47]. The doublet was superior in terms of RR (36% *vs* 19%; p=0.002), progression-free interval (PFI; 4.8 *vs* 2.8 months; p<0.001) and quality of life, but OS was not statistically different between the groups (9.7 *vs* 8.8 months). GOG 179 had three treatment arms: cisplatin alone, cisplatin-topotecan, and cisplatin, methotrexate, vinblastine and doxorubicin (MVAC) [48]. The study was amended to a two-arm study after 4 deaths occurred in the MVAC group. The results showed that cisplatin-topotecan was associated with a statistically significant advantage both in OS (9.4 *vs* 6.5 months; p=0.017) and PFS (4.6 *vs* 2.9 months; p=0.014) compared with cisplatin alone (Table 1) [48]. This was the first time that a platinum-combination had shown survival benefit over cisplatin alone; although it was argued that most patients enrolled in the trial had already received cisplatin which might explain the poor outcome in the single-agent arm.

Table 1. Phase II/III clinical trials for advanced and recurrent cervical cancer

Trial	Reference	Drug/Regimen	Patients (N)	RR (%)	PFI (months)	OS
GOG 43	Bonomi et al. 1985 [39]	C (50 *vs* 100 *vs* 20 mg/m^2)	150 *vs* 166 *vs* 128	20.7 *vs* 31.4 *vs* 25.0	3.7 *vs* 4.6 *vs* 3.8 (p=0.015)	7.1 *vs* 7.0 *vs* 6.1
GOG 110	Omura et al. 1997 [45]	C *vs* C+IFO	140 *vs* 151	18 *vs* 31 (p=0.004)	3.2 *vs* 4.6 (p=0.003)	8.0 *vs* 8.3 (NS)
GOG 149	Bloss et al. 2002 [46]	C+IFO *vs* C+IFO+B	146 *vs* 141	32 *vs* 31 (NS)	4.6 *vs* 5.1 (NS)	8.5 *vs* 8.4 (NS)
GOG169	Moore et al. 2004 [47]	C *vs* C+P[a]	134 *vs* 130	19 *vs* 36 (p=0.002)	2.8 *vs* 4.8 (p<0.001)	8.8 *vs* 9.7 (NS)
GOG 179	Long et al. 2005 [48]	C *vs* C+Topo	146 *vs* 147	13 *vs* 27 (p=0.004)	2.9 *vs* 4.6 (p=0.014)	6.5 *vs* 9.4 (p=0.017)
GOG 204	Monk et al. 2009 [49]	C+P[a] *vs* C+V *vs* C+G *vs* C+Topo	103 *vs* 108 *vs* 112 *vs* 111	29 *vs* 26 *vs* 22 *vs* 23 (NS)	5.8 *vs* 4.0 *vs* 4.7 *vs* 4.6 (p=–0.06 *vs* 0.04 *vs* 0.19)	12.9 *vs* 10.0 *vs* 10.3 *vs* 10.3 (NS)
GOG 240	Tewari et al. 2014 [50]	Chemo[b] *vs* Chemo[b] +Bevacizumab 15 mg/kg	225 *vs* 227	36 *vs* 48 (p=0.008)	5.9 *vs* 8.2 (p=0.002)	13.3 *vs* 17 (p=0.004)
	Monk et al. 2009 [52]	CT[c]+Bevacizumab 15 mg/kg	46	11	3.4	7.3
	Monk et al. 2010 [53]; Monk and Pandite 2011 [54]	Pazopanib 800 mg *vs* Lapatinib 1,500 mg	74 *vs* 78	9 *vs* 5	4.5 *vs* 4.3 (p<0.013)	12.4 *vs* 11.0 (p=0.407)
	Symonds et al. 2014 [55]	CT[d]+Cediranib 20 mg *vs* CT[d]+placebo	34 *vs* 35	–	8.8 *vs* 7.5 (p=0.046)	–
	Basu et al. 2014 [56]	3 or 4 doses of ADXS11-001 (at 1×10^9 CFU)+CDDP	110	11	–	28% (18 months survival)

B: bleomycin 30 units; C: cisplatin 50 mg/m^2; CDDP: cisplatin; G: gemcitabine 1,000 mg/m^2 on days 1 and 8; IFO: ifosfamide 5 g/m^2; NS: not significant; OS: overall survival; PFI: progression free interval; RR: response rate; Topo: topotecan 0.75 mg/m^2 on days 1-3; V: vinorelbine 30 mg/m^2 on days 1 and 8.
a. Paclitaxel 135 mg/m^2; b. Cisplatin 50 mg/m^2 + paclitaxel 135-175 mg/m^2 or paclitaxel 175 mg/m^2 + topotecan 0.75 mg/m^2 on days 1-3; c. Cisplatin 50 mg/m^2 + paclitaxel 135-175 mg/m^2 or paclitaxel 175 mg/m^2 + topotecan 0.75 mg/m^2 on days 1-3; d. Carboplatin (AUC 5) and paclitaxel (175 mg/m^2).

Based on the above data, GOG 204 was designed to definitively establish the optimal cisplatin doublet [49]. Doublets with vinorelbine, gemcitabine or topotecan did not provide any RR, PFS or OS advantage compared with cisplatin-paclitaxel. Given that most patients are initially treated with concomitant cisplatin, the GOG 240 study was designed to compare cisplatin plus paclitaxel with or without bevacizumab *versus* non-platinum doublet chemotherapy of topotecan plus paclitaxel with or without bevacizumab. This study showed that non-platinum doublet (topotecan plus paclitaxel) chemotherapy was not superior to platinum doublet (cisplatin plus paclitaxel) chemotherapy with respect to RR and OS.

With the data for the two chemotherapy regimens combined, the addition of bevacizumab to chemotherapy was associated with increased OS (17.0 *vs* 13.3 months; HR for death 0.71; 98% confidence interval 0.54-0.95; p=0.004 in a one-sided test) and higher RR (48% *vs* 36%; p=0.008) (Table 1) [50]. Finally, a Japanese study, JCOG0505, has reported non-inferiority of carboplatin-paclitaxel *versus* cisplatin-paclitaxel (median OS 17.5 *vs* 18.3 months, respectively) [51]. However, for platinum-naïve patients, the cisplatin combination remains the agent of choice.

Future perspectives

Anti-angiogenesis agents and other biologics

Bevacizumab was the first new drug approved for the treatment of CC in more than 8 years. The GOG 227C study was a multicenter phase II trial investigating bevacizumab monotherapy in patients with recurrent CC; median PFS was 3.4 months and median OS was 7.3 months (Table 1) [52]. In GOG 240, bevacizumab (15 mg/kg) was administered 3-weekly in addition to CT and compared with CT alone. Compared with CT alone, the bevacizumab plus CT group showed a significantly higher RR (48% *vs* 36%; p=0.008) and PFS (8.2 *vs* 5.9 months, HR 0.67; p=0.002). Furthermore, the death rate was reduced (HR 0.71; p=0.004) and median OS was 17 months *versus* 13.3 months. Conversely, in the beva-

cizumab *versus* CT alone arm there was an increased incidence of hypertension (≥grade 2, 25% *vs* 2%), thromboembolic events (≥grade 3, 8% *vs* 1%) and gastrointestinal fistulas (≥grade 2, 33% *vs* 0%), although quality of life remained equivalent across the two patient groups [50]. An ongoing trial studying bevacizumab in association with CBDCA-PTX in this setting is particularly focused on safety and may potentially address the major toxicities issues (NCT02467907).

Other antiangiogenetic agents and tyrosine kinase inhibitors (TKIs) have been evaluated as possible therapeutic options for advanced CC. A phase II, 3-arm trial compared pazopanib, lapatinib and with pazopanib + lapatinib [53]. The combination prematurely discontinued for futility and excessive toxicity, but pazopanib monotherapy was associated with a higher PFS than lapatinib (4.5 *vs* 4.3 months; $p<0.013$), but no significant OS advantage was observed (12.4 *vs* 11.0 months; $p=0.407$) [54]. Cediranib was investigated in another phase II trial involving 80 patients that compared cediranib + CT with CT alone (Table 1) [55]. A significant improvement in median PFS was seen with cediranib compared with CT alone (35 *vs* 30 weeks; $p=0.046$), and the toxicity profile of the combination was favorable [55]. Unfortunately, many other biologic agents, such as cetuximab, erlotinib and sunitinib have failed to demonstrate a PFS and/or OS benefit in this setting. A trial of the TKI nintedanib in patients with advance or recurrent CC is currently underway (NCT02009579). This phase II study is evaluating the efficacy of nintedanib *versus* placebo in combination with 6 cycles of 3 weekly carboplatin/paclitaxel followed by nintedanib/placebo maintenance. The primary endpoint is PFS, and the estimated primary completion date is May 2017.

Immunotherapy

Immunotherapy represents a fascinating and promising strategy for treating CC and many other malignancies. Various therapeutic human papilloma virus (HPV) vaccines targeting HPV E6/E7 antigens have been investigated in advanced CC, of which ADXS11-011 is the best known. In a phase II study involving 110 patients, administration of 3 or 4 doses of ADXS11-011 together with cisplatin was associated with a RR of 11% and an 18-month survival rate of 28% [56].

Other interesting targets in terms of immunotherapy are the cytotoxic T-lymphocyte-associated molecule-4 (CTLA-4) and the programmed death receptor-1 (PD-1) [57]. The CTLA-4 receptor is expressed on T lymphocytes and acts to inhibit their activation; the monoclonal antibody ipilimumab inhibits CTLA-4, promoting an immune response against the tumor [58]. PD-1 is expressed by activated T-cells; when it binds to its ligand (PD-L1/B7-H1) T-cell function is downregulated and tumor cells are allowed to directly halt antitumor T-cell activity by a mechanism known as 'adaptive resistance'. Inhibition of PD-1 or PD-L1 using monoclonal antibodies, such as nivolumab, improves the T-cell response [59]. Nivolumab for advanced CC is currently being tested in a phase II trial and ipilimumab is being investigated in two different studies (NCT01693783 and NCT01711515 [GOG 9929]). It is too early to draw conclusions about immunotherapy in CC, but this strategy may well represent the most exciting field of antitumor research in the near future.

Conclusion

Much work is required to improve the survival and quality of life of women with CC. Although early diagnosis represents a goal which has been partially achieved in several regions, prevention needs to be heavily promoted in developing countries. Since chemoradiation remains the standard of care for locally-advanced disease, access to RT needs to be improved and acquisition of modern equipment encouraged. For patients with advanced stage CC, palliative systemic therapy is the only option and the outcome if often poor. Hopefully, the addition of anti-angiogenesis agents to conventional CT and novel immunotherapy agents may significantly contribute to improve response and survival rates.

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