

Review

Pharmacological Treatment of Patients with Metastatic, Recurrent or Persistent Cervical Cancer Not Amenable by Surgery or Radiotherapy: State of Art and Perspectives of Clinical Research

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Received: 24 July 2020; Accepted: 16 September 2020; Published: 19 September 2020



Simple Summary: The aim of this review is to assess the available literature of the pharmacological treatment of patients with metastatic, recurrent or persistent cervical cancer not amenable by surgery or radiotherapy. The results and toxicities of cisplatin-based doublets are exhaustively described. The combinations of cisplatin plus paclitaxel with or without bevacizumab is the most active regimen in these clinical setting. Immune-check-point inhibitors and molecularly-targeted agents are promising fields of research.

Abstract: Cervical cancer patients with distant or loco-regional recurrences not amenable by surgery or radiotherapy have limited treatment options, and their 5-year overall survival (OS) rates range from 5% to 16%. The purpose of this paper is to assess the results obtained with chemotherapy and biological agents in this clinical setting. Several phase II trials of different cisplatin (CDDP)-based doublets and a phase III randomized trial showing a trend in response rate, progression-free survival, and OS in favor of CDDP + paclitaxel (PTX) compared with other CDDP-based doublets have been reviewed. The factors predictive of response to chemotherapy as well as the benefits and risks of the addition of bevacizumab to CDDP + PTX have been analyzed. The FDA has recently approved pembrolizumab for patients with recurrent or metastatic cervical cancer in progression on or after chemotherapy whose tumors were PD-L1 positive. Interesting perspectives of clinical research are represented by the use of immune checkpoint inhibitors alone or in addition to chemotherapy, whereas PARP inhibitors and PI3K inhibitors are still at the basic research phase, but promising.

Keywords: cervical cancer; chemotherapy; cisplatin; paclitaxel; bevacizumab; immune checkpoint inhibitors; phosphatidylinositol 3-kinase (PI3K) inhibitors; PARP inhibitors

1. Introduction

GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries have detected 569,874 new cases of cervical cancer and 311,365 deaths due to this tumor in 2018 [1]. The primary treatment of early stage disease is either surgery or definitive radiotherapy consisting of pelvic external beam radiotherapy plus brachytherapy [2–4]. According to the new 2018 FIGO staging system, tailored abdominal radical hysterectomy with bilateral pelvic lymphadenectomy is the preferred treatment for stage IA1 disease with lymph vascular space involvement (LVSI) and for stage IA2, IB1, IB2 and IIA1 disease, and definitive radiotherapy is an alternative option for patients not fit for surgery or who refuse surgery [2–6]. Concurrent cisplatin (CDDP)-based chemotherapy and radiotherapy (CCRT) plus brachytherapy is the standard of care for patients with locally advanced disease, i.e.,

in stage IB3-IIA2-IIB-III-IVA [2–6]. Platinum-based neo-adjuvant chemotherapy (NACT) followed by radical hysterectomy has been proposed as an alternative approach [7–12]. The achievement of an optimal pathological response is an independent prognostic factor for both disease-free survival (DFS) and overall survival (OS) [9,13]. The combination of paclitaxel (PTX) (175 mg/m² d1) + ifosfamide (IFO) (5 g/m² 24 hour-infusion d1) + CDDP (75 mg/m² d2) (TIP regimen) every 21 days (q21) has obtained the highest optimal pathological response rates, ranging from 43% to 48%, in the neoadjuvant setting [9,11]. Two recent randomized trials showed that CCRT achieves a better DFS and a similar OS compared to NACT followed by radical surgery in patients with 1994 FIGO stage IB2-II cervical cancer [14,15].

Cervical cancer relapses after primary treatment in approximately 10–20% of patients with early stage disease and no evidence of nodal metastases, and up to 64–70% of those with nodal metastases and/or locally advanced disease, and limited treatment options are available for these patients [16–18].

Radiotherapy or CCRT is the standard treatment for central or lateral pelvic recurrence in patients primarily treated with radical hysterectomy without adjuvant radiotherapy [16–20]. Radical hysterectomy has been seldom used in patients with small (<2 cm) persistent tumor or centrally located recurrence in the cervix or vaginal fornices after definitive radiotherapy [16,21–24]. This surgical approach obtained 5-year survival rates ranging from 49% to 84%, with a high rate of severe postoperative complications and especially of fistulas.

Pelvic exenteration with reconstructive procedures usually represents the only therapeutic option with curative intent in accurately selected women with central pelvic recurrence after radiotherapy, with perioperative mortality rates ranging from 1% to 10% and with 5-year survival rates ranging from 21% to 73% [18,25–31]. Complications have been reported in 49–57% of patients, most commonly fistulas, ureteral strictures, pyelonephritis, wound complications, or bowel obstructions. Some authors have suggested the use of NACT before pelvic exenteration [30].

Lateral pelvic recurrence in patients with prior radiotherapy is usually treated with chemotherapy with palliative intent [18], although Hockel [32] has proposed the use of laterally extended endopelvic resection in highly selected cases.

Radiotherapy or CCRT is recommended in patients with isolated para-aortic recurrence, who can however experience an unfavorable outcome because of systemic spread of disease [33–36]. Stereotactic body radiation therapy (SBRT), which delivers a much higher radiation dose to the tumor with a steep dose gradient outside the targets, is an interesting therapeutic tool for selected patients with oligometastatic disease, involving not only nodes, but also other sites such as lung, liver, and soft tissues [37–41]. Resection of isolated metastases can be sometimes proposed in selected patients, especially in those with solitary inguinal or lung metastases [42,43].

Pharmacological options for patients with distant or loco-regional recurrences not amenable by surgery or radiotherapy are limited [44–47]. Five-year OS rates range from 5% to 16% and fewer than 20% of patients survive one year.

The purpose of this paper is to assess the results obtained with chemotherapy and biological drugs in this clinical setting and to show the promising perspectives given by novel agents which are still at the basic research phase.

2. Single-Agent Chemotherapy

CDDP is the most active agent in this clinical setting, with response rates of 17–38% [5–11]. Most responses are partial and short-lived, with a median progression free survival (PFS) of approximately 3 months and median OS of 6.5–9 months [48–54]. Complete responses are predominantly seen in patients with extra-pelvic metastases rather than in those with pelvic failure.

A Gynecologic Oncology Group (GOG) trial randomly allocated 497 patients to receive either CDDP 50 mg/m² q21 or CDDP 100 mg/m² q21 or CDDP 20 mg/m² d1–5 q21 [49]. The response rates were 21%, 31%, and 25% respectively, median PFS ranged from 3.7 to 4.6 months, and median OS ranged from 6.1 to 7.1 months. CDDP 100 mg/m² achieved a significantly better response rate than

CDDP 50 mg/m², with higher bone marrow and renal toxicity and without any benefit in terms of PFS and OS.

In the experience of Lele and Piver [51], single-agent CDDP obtained an objective response in 4% of central relapses, 33% of liver metastases, 40% of supraclavicular nodal recurrences, and 48% of lung failures.

Several phase II studies have been conducted to identify other active drugs in this clinical setting [55–79] (Table 1). Higher response rates were obtained for lesions in previously non irradiated areas compared with those in irradiated fields. Median duration of response ranged from 2.5 to 6.5 months, and median OS ranged from 4.2 to 15.2 months. Nab-paclitaxel is a nanoparticle formulation of albumin-bound PTX, which can be delivered without premedication since the risk of hypersensitivity is very low [80]. It is noteworthy that the 29% response rate is the highest ever recorded in the GOG for a single-agent against platinum resistant disease [79]. This drug was equally active in patients who had primarily lymph node metastases or visceral metastases.

Table 1. Single agent activity in metastatic, persistent, or recurrent carcinoma of the uterine cervix.

Agent	Author	Dose	Histology	Patients	Response Rate
CBDCA	Areseneau [55] **	340–400 mg/m ² q28	S	39	28%
	McGuire [56] **	340–400 mg/m ² q28	S	175	15%
	Weiss [57] **	400 mg/m ² q28	S	41	15%
IFO	Meanwell [58]	5 g/m ² q21	S	30	33%
	Sutton [59] *	1.2 g/m ² d1–5 q28	S	30	11%
	Sutton [60] *	1.2–1.5 g/m ² d1–5 q28	NS	40	15%
VNR	Morris [61] **	30 mg/m ² q7	S	33	18%
	Lhommè [62] **	30 mg/m ² q7	S, NS	41	17%
	Muggia [63] *	30 mg/m ² d1, 8 q21	NS	28	7%
GEM	Schilder [64] *	800 mg/m ² d1, 8, 15 q28	S	27	8%
	Schilder [65] *	800 mg/m ² d1, 8, 15 q28	NS	19	4.5%
PTX	McGuire [66] **	135–170 mg/m ² q21	S	52	17%
	Kudelka [67] **	250 mg/m ² q21 (+GCSF)	S	32	25%
	Curtin [68] *	135–170 mg/m ² q21	NS	42	31%
DCX	Garcia [69] *	100 mg/m ² q21	S	23	9%
	Pearl [70] *	35 mg/m ² d1, 8, 15 q28	S, NS	10	0%
Topotecan	Bookman [71] *	1.5 mg/m ² d1–5 q21	S	40	12.5%
	Muderspach [72] **	1.5 mg/m ² d1–5 q28	S	43	19%
Irinotecan	Verschraegen [73] *	125 mg/m ² × 4 wks q42	S	42	21%
	Lhommè [74] **	350 mg/m ² q21	S	51	16%
Pemetrexed	Goedhals [75] **	500–600 mg/m ² q21	S	34	18%
	Miller [76] *	900 mg/m ² q21	S, NS	27	15%
Altretamine	Rose [77] *	260 mg/m ² q21	S	26	0%
Oral VP-16	Rose [78] *	40–50 mg/m ² /d × 21d q28	S	17	12%
Nab-PTX	Alberts [79] *	125 mg/m ² d1, 8, 15 q28	S, NS	35	29%

* prior chemotherapy; ** no prior chemotherapy (except as a radiation sensitizer). Legend: CBDCA, carboplatin; S, squamous cell carcinoma; IFO, ifosfamide; NS, non squamous cell carcinoma; VNR, vinorelbine; GEM, gemcitabine; PTX, paclitaxel; DCX, docetaxel; VP-16, etoposide; Nab-PTX, Nab-paclitaxel.

3. Combination Chemotherapy

In the phase II trials reported in Table 2, the combination of CDDP with other drugs, with additive or synergistic activity and non-overlapping toxicity, obtained response rates of 21–50%, with a median PFS of 4.8–10.5 months and a median OS of 6.4–25+ months [44,81–93]. These regimens usually

achieved higher response rates and longer PFS compared with single-agent CDDP, but at the cost of greater toxicity and with no improvement in OS. Still again, response rates were sharply higher in non-irradiated (57–70%) than in irradiated areas (15–36%).

Table 2. Phase II trials of cisplatin-based doublets in metastatic, persistent, or recurrent carcinoma of the uterine cervix.

Agent	Author	Dose	Histology	Patients	Response Rate
CDDP + 5-FU	Bonomi [81] *	CDDP 50 mg/m ² d1 + 5FU 1000 mg/m ² q21	S	5	22%
	Kaern [82] *	CDDP 100 mg/m ² d1 + 5FU 1000 mg/m ² d 1–5 q21	S	32	47%
CDDP + CAPE	Benjamin [83] *	CDDP 50 mg/m ² d1 + CAPE 1000 mg/m ² bid d1–4 q21	S, NS	16	50%
CDDP + BLEO	Daghestani [84] ^	CDDP 120 mg/m ² d1 + BLEO 10 mg/m ² bolus d1 + BLEO 10 mg/m ² d1–5 or 1–7 q21–28	S, NS	24	54%
CDDP + IFO	Coleman [85] *	CDDP 50 mg/m ² d1 + IFO 1.5 g/m ² d 1–5 q21	S	42	38%
	Cervellino [86] *	CDDP 20 mg/m ² d1–5 + IFO 2.5 g/m ² d 1–5 q28	S	30	50%
	Omura [87] *	CDDP 50 mg/m ² d1 + IFO 5 g/m ² 24 h q21	S	151	31%
CDDP + GEM	Burnett [88] *	CDDP 50 mg/m ² d1 + GEM 1250 mg/m ² d1, 8 q21	S	17	42%
CDDP + PTX	Rose [89] *	CDDP 75 mg/m ² d2 + PTX 135 mg/m ² 24 h d 1 q21	S	41	46%
	Papadimitriou [90]*	CDDP 75 mg/m ² d1 + PTX 175 mg/m ² d1 q21 + G-CSF	S, NS	34	47%
		CDDP 75 mg/m ² d2 + PTX 135 mg/m ² 24 h d1 q28	S, NS	20	45%
	Moore [44] *	CDDP 50 mg/m ² d2 + PTX 135 mg/m ² 24 h d1 q21	S	130	38%
CDDP + VNR	Gebbia [92] *	CDDP 80 mg/m ² d1 + VNR 25 mg/m ² d1, 8 q21	S, NS	42	48%
CDDP + tirapazamine	Smith [93] *	CDDP 75 mg/m ² d1 + tirapazamine 260 mg/m ² q21	S, NS	53	32%

* no prior chemotherapy; ^ prior chemotherapy in 2 patients. Legend: CDDP, cisplatin; 5-FU, 5-fluorouracil; S, squamous cell carcinoma; CAPE, capecitabine; NS, non-squamous cell carcinoma; BLEO, bleomycin; IFO, ifosfamide; GEM, gemcitabine; PTX, paclitaxel; G-CSF, granulocyte-colony-stimulating factor; VNR, vinorelbine.

The GOG179 trial randomized 356 patients with stage IVb or recurrent or persistent squamous and nonsquamous cell cervical carcinoma unsuitable for surgery and/or radiotherapy with curative intent to receive either single-agent CDDP (50 mg/m²) q21 or topotecan (0.75 mg/m² d1–3) + CDDP (50 mg/m² d1) q21 or methotrexate + vinblastine + doxorubicin + CDDP (MVAC regimen) every 28 days (q28) [94]. The MVAC arm was early discontinued because of four toxic deaths, principally due to neutropenic sepsis, among 63 patients. CDDP + topotecan achieved a higher response rate ($p = 0.004$), a longer median PFS (adjusted Relative Risk (RR) = 0.738 (95% Confidence Interval (CI) = 0.578–0.942) and a longer OS (adjusted RR = 0.77, 95%CI = 0.600–0.992) compared with single-agent CDDP, associated with an increased incidence of severe adverse events, and especially of grade 3–4 neutropenia (70% versus 1.4%) and thrombocytopenia (31.3% versus 3.4%) (Table 3). The addition of topotecan to CDDP improved PFS and OS both in patients who had received prior CDDP as radiation sensitizer and in those who had not. GOG179 is the first randomized trial able to demonstrate an OS benefit for CDDP-combination chemotherapy versus single-agent CDDP in this clinical setting.

Table 3. Phase III trials of cisplatin-based chemotherapy in metastatic, persistent, or recurrent carcinoma of the uterine cervix.

Author	Agent	Patients	RR	Median PFS	Median OS
Long [94]	CDDP 50 mg/m ² d1 q21	146	13%	2.9 months	6.5 months
	CDDP 50 mg/m ² d1 +TOP 0.75 mg/m ² d 1–3 q21	147	27% <i>p</i> = 0.004	4.6 months <i>p</i> = 0.0075	9.4 months <i>p</i> = 0.021
Monk [95]	PTX 135 mg/m ² (24 h) d1+ CDDP 50 mg/m ² d2 q21	103	29.1%	5.82 months	12.87 months
	VNR 30 mg/m ² d1, 8 + CDDP50 mg/m ² d1 q21	108	25.9% *	3.98 months **	9.99 months ***
	GEM 1000 mg/m ² d1,8 + CDDP 50 mg/m ² d1 q21	112	22.3% *	4.70 months **	10.28% months ***
	TOP 0.75 mg/m ² d1–3+ CDDP 50 mg/m ² d1 q21	111	23.4% *	4.57 months **	10.25 months ***
Kitagawa [96]	PTX 135 mg/m ² (24 h) d1 + CDDP 50 mg/m ² d2 q21	127	58.8%	6.9 months	18.3 months
	PTX 175 mg/m ² (3 h) d1 + CBDCA AUC5 d1 q21	126	62.6% <i>p</i> = 0.665	6.2 months ^	17.5 months ^^
Tewari [97]	CDDP 50 mg/m ² d1+ PTX 135–175 mg/m ² d1 ± BEV 15 mg/kg d1 q21		48%	8.2 months	17 months
	TOP 0.75 mg/m ² d1–3 + PTX 175 mg/m ² d1 ± BEV 15 mg/kg q 21				
	BEV + CT (the two regimen combined)		36%	5.9 months	13.3 months
	CT alone (the two regimen combined)		<i>p</i> = 0.008	<i>p</i> = 0.002	<i>p</i> = 0.004

* OR (95%CI) for reference arm (PTX + CDDP) to other doublets: VNR + CDDP, 1.17 (0.54–2.58); GEM + CDDP, 1.43 (0.65–3.19); TOP + CDDP, 1.34 (0.61–2.98); ** HR (95%CI) for reference arm (PTX + CDDP) to other doublets: VNR + CDDP, 1.36 (0.97–1.90); GEM + CDDP, 1.39 (0.99–1.96); TOP + CDDP, 1.27 (0.90–1.78); *** HR (95%CI) for reference arm (PTX + CDDP) to other doublets: VNR + CDDP, 1.15 (0.79–1.67); GEM + CDDP, 1.323 (0.91–1.92); TOP + CDDP, 1.26 (0.86–1.82); ^ HR: 1.041 (95%CI = 0.803–1.351); ^^ HR: 0.994 (90%CI = 0.789–1.253); Legend: RR, response rate; PFS, progression free survival; OS, overall survival; CDDP, cisplatin; TOP, topotecan; PTX, paclitaxel; VNR, vinorelbine; GEM, gemcitabine; CBDCA, carboplatin; AUC, area under curve; BEV, bevacizumab; CT, chemotherapy; OR, Odds Ratio; CI, confidence interval; HR, Hazard Ratio.

Monk et al. [95] randomly allocated 513 patients with stage IVB, recurrent, or persistent squamous and nonsquamous cell cervical cancer to undergo either PTX + CDDP or vinorelbine + CDDP or gemcitabine + CDDP or topotecan + CDDP 50 (Table 3). Although the trial was stopped early at a planned interim analysis for futility, there was a trend in response rate, PFS, and OS in favor of CDDP + PTX. The rate of severe neutropenia was approximately 50% with all regimens except gemcitabine + CDDP where it was approximately 15%. There were 11 toxic deaths, but no correlation was found with the chemotherapy regimen.

A randomized phase III trial, including 253 patients with recurrent or metastatic squamous and nonsquamous cell cervical cancer who had undergone one or less one platinum-based-treatment and no prior taxane, demonstrated a noninferiority in terms of OS of the combination of PTX + carboplatin (CBDCA) compared with PTX + CDDP [96] (Table 3). However, among the patients who had not received prior CDDP, median OS was worse for PTX + CBDCA arm (13.0 versus 23.2 months; Hazard Ratio (HR) = 1.571; 95%CI = 1.062–2.324).

CDDP-based three- or four-drug regimens obtained no clear improvement in the clinical outcome compared with CDDP-based doublets [98–102]. In a randomized trial enrolling 287 patients with advanced, recurrent, or persistent squamous cell cervical carcinoma, the addition of bleomycin (30 U over 24 h) to CDDP (50 mg/m²) + IFO (5 g/m² over 24 h) q21 did not change response rate, PFS, and OS [98]. Whereas TIP appears to be the most active regimen as NACT followed by radical surgery, this combination chemotherapy achieved response rates of 46–67% and a median OS of 6–19 months in patients with recurrent, persistent, or metastatic disease, similar to those obtained with CDDP-based doublets [99–101]. Response rates ranged from 36% to 52% in irradiated sites and from 60% to 75% in areas outside the previous radiotherapy fields. The excision repair cross-complement 1 (ERCC1) status appears to be a predictive and prognostic factor in this clinical setting. This nucleotide excision repair gene is involved in resistance to platinum compounds in different malignancies [103–107]. A study performed on 45 tissue samples from patients with recurrent or metastatic cervical cancer treated with CDDP + IFO with or without PTX, reported that high ERCC1 expression was an independent poor predictor of both PFS (HR = 2.473, 95% CI = 1.146–5.339) and OS (HR = 3.187, 95% CI = 1.346–7.546) [106]. In another study on 32 women with recurrent or metastatic disease undergoing platinum-based chemotherapy, the patients with high ERCC1 expression experienced a lower response rate (15% versus 74%, $p = 0.001$), a shorter PFS (HR = 2.428; 95%CI = 1.145–5.148), and a shorter OS (HR = 2.322; 95% CI = 1.051–5.29) compared to those with low ERCC1 expression [106].

The analysis of 428 advanced cervical cancer patients treated with a CDDP-based regimen in the GOG trials 110 [87], 169 [44] and 179 [94] detected that five factors, i.e., Black women (Odds Ratio(OR) = 0.49, 95%CI = 0.28–0.83), performance status >0 (OR = 0.60, 95%CI = 0.38–0.94), pelvic disease (OR = 0.58, 95%CI = 0.38–0.90), prior radiosensitizing chemotherapy (OR = 0.52, 95%CI = 0.32–0.85), and time interval from diagnosis to first recurrence <1 year (OR = 0.61, 95%CI = 0.39–0.95) were independent predictors of poor response to treatment [108]. The patients were classified to be at low-risk, mild-risk, or high-risk, according to whether they had ≤1 factor, 2–3 factors, or 4–5 factors, and the corresponding median PFS and OS were 6.34 months and 11.10 months, 4.60 months and 9.17 months, and 2.79 months and 5.49 months, respectively. This predictive model was externally validated using GOG trial 149 [98] data that had comparable patient characteristics.

4. Bevacizumab

In a phase II GOG trial, single-agent bevacizumab (BEV) (15 mg/kg q21) was administered to 46 patients with persistent or recurrent squamous cell carcinoma of the cervix [109]. Eleven patients (24%) survived progression free for at least 6 months, and 5 patients (11%); experienced partial responses. The median response duration was 6.21 months, and median PFS and OS for all patients were 3.40 months and 7.29 months, respectively.

Four-hundred and fifty-two patients with recurrent, persistent, or metastatic squamous and nonsquamous cell cervical cancer enrolled in the GOG 240 bi-factorial trial were randomized to receive

chemotherapy (CDDP+ PTX or topotecan + PTX) with or without BEV (Table 3) [97]. The combination of topotecan + PTX was chosen on the basis of both laboratory data, detecting a synergistic anticancer activity when the two drugs were administered sequentially [110], and clinical data from a phase II study showing that this regimen was generally well tolerated and active [111]. In the GOG 240 trial, topotecan + PTX (either with or without BEV) had a higher risk of progression (HR = 1.39; 95%CI = 1.09–1.77) and a trend to higher risk of death (HR = 1.20; 99%CI = 0.82–1.76) compared to CDDP + PTX (either with or without BEV) [97]. The addition of BEV to chemotherapy (with two regimens combined) significantly improved response rates ($p = 0.008$), PFS (HR = 0.67, 95%CI = 0.54–0.82), and OS (HR = 0.71; 98%CI = 0.54–0.95). CDDP + PTX + BEV had a HR for death of 0.68 (95%CI = 0.48–0.97) compared with CDDP + PTX, and topotecan + PTX + BEV had a HR for death of 0.74 (95%CI = 0.53–1.05) compared with topotecan + PTX. The incorporation of BEV significantly increased the rates of grade ≥ 2 hypertension (25% versus 2%), grade ≥ 3 gastrointestinal or genitourinary fistulas (6% versus 0%), and grade ≥ 3 thrombo-embolic events (8% versus 1%).

An update of the study with a longer follow-up confirmed that chemotherapy + BEV was associated with a longer OS compared with chemotherapy alone (HR = 0.77, 95%CI = 0.62–0.95) [47]. There was no negative rebound after progression while receiving BEV, since post-progression survival was not significantly different between the patients treated with chemotherapy + BEV and those treated with chemotherapy alone. These results represent the proof-of-concept of the efficacy of anti-angiogenesis therapy in cervical cancer.

Other studies have confirmed the efficacy of BEV combined with CDDP + PTX in patients with persistent, recurrent, or metastatic carcinoma of the uterine cervix [112,113]. According to a systematic review of 23 studies, CDDP + PTX + BEV and topotecan + PTX + BEV were likely to prolong OS compared with non-BEV-containing therapies, and CDDP + PTX + BEV had the highest probability of being the most efficacious regimen [112]. Response rates and fistula rates with CBDCA + PTX + BEV are similar to those reported with CDDP + PTX + BEV [114,115]. The risks and benefits of the addition of BEV to chemotherapy should be exhaustively discussed with the patient herself, taking into account the increased probability of fistula formation, especially in the case of locally persistent or recurrent disease after radiotherapy or CCRT [116–118]. Hypoalbuminemia is an additional risk factor for fistula formation [119].

Tewari et al. [120] retrospectively classified the patients enrolled in the GOG 240 trial in three subgroups based on the predictive factors of poor response to chemotherapy suggested by Moore et al. [108]. The application of the Moore's criteria classified most patients in the mid-risk subset (67%), whereas low-risk and high-risk patients accounted for 19% and 14%, respectively, of the entire population. The HRs of death for treating with BEV in low-risk, mid-risk, and high-risk subgroups were 0.96 (95% CI = 0.51–1.83; $p = 0.9087$), 0.673 (95%CI = 0.5–0.91; $p = 0.0094$), and 0.536 (95%CI = 0.32–0.905; $p = 0.0196$), respectively. Therefore, BEV could be avoided in previously irradiated low-risk patients, since the OS advantage given by the addition of this antiangiogenic agent is not significant.

5. Immune Checkpoint Inhibitors

Recent data seem to suggest a promising role for immune checkpoint inhibitors in the treatment of patients with advanced carcinoma of the uterine cervix [121–124].

The anti-programmed death [PD]-1 antibody nivolumab (240 mg every 14 days) obtained an objective response in 26% of 19 patients with recurrent or metastatic cervical cancer and in 20% of 5 patients with recurrent or metastatic vaginal/vulvar cancer [122]. As for the former, the median duration of response was not yet reached after a median follow-up of 19.2 months.

The phase II KEYNOTE-158 study, investigating the anti-PD-1 antibody pembrolizumab (200 mg q21) in several cancer types, included 98 patients with pretreated advanced squamous and nonsquamous cell cervical cancer [123]. Of these 82 had PD-ligand 1 (PD-L1)-positive tumors, according to the PD-L1 IHC 22C3 pharmDx assay, and 77 had undergone more than one chemotherapy line for recurrent or metastatic disease. The measure of PD-L1 expression was the combined positive

score (CPS), defined as the ratio of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) to the total number of tumor cells $\times 100$. A tumor was considered to be PD-L1 positive if CPS was >1 . There were 3 complete responses and 9 partial responses, with an overall response rate of 12%, and all 12 responses were detected in patients with PD-L1-positive tumors. Nine of the 12 responses were still ongoing after >9 months of follow-up. The safety profile was the same previously reported for pembrolizumab in patients with advanced cancer, and no novel adverse event occurred. Based on these results, the Food and Drug Administration (FDA) has approved pembrolizumab for patients with recurrent or metastatic cervical cancer in progression on or after chemotherapy whose tumors were PD-L1 positive.

Several trials of immune checkpoint inhibitors are currently ongoing in metastatic, recurrent, or persistent cervical cancer (Table 4). One of the most interesting is the phase III, randomized BEATcc (NCT03556839) trial which will enroll a total of 404 women with squamous and nonsquamous cell carcinoma of the uterine cervix [125]. Patients will be randomly allocated to receive either CCDP (50 mg/m²) + PTX (175 mg/m²) + BEV (15 mg/kg) q21 or the same regimen plus atezolizumab (1200 mg q21). Complete responders after ≥ 6 cycles will be allowed to continue only on biologic therapy, i.e., BEV or BEV + atezolizumab. OS is the primary endpoint of the study which is estimated to close in 2022.

Table 4. Ongoing trials with immune checkpoint inhibitors in metastatic, recurrent, or persistent carcinoma of the uterine cervix.

NCT Number	Trial
NCT02257528	A phase II evaluation of Nivolumab, a fully human antibody against PD-1, in the treatment of persistent or recurrent cervical cancer
NCT03972722	An open, multi-center, single-arm phase II clinical study to evaluate the efficacy and safety of recombinant fully human anti-PD-1 monoclonal antibody (GLS-010 injection) in patients with recurrent or metastatic cervical cancer
NCT03104699	A phase 1/2, open-label, multiple ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological, and clinical activity of AGEN2034 (Balstilimab, anti-PD-1 antibody) in subjects with metastatic or locally advanced solid tumors, with expansion to second line cervical cancer
NCT03808857	Phase II clinical study to evaluate the efficacy and safety of GB226 (Genolimzumab, anti-PD-1 antibody) in treatment of recurrent or metastatic cervical cancer patients with PD-L1 positive who failed in platinum-based chemotherapy
NCT03676959	A clinical study of PD-L1 antibody ZKAB001 (Drug Code) in recurrent or metastatic cervical cancer. An open-label, dose-escalation, bi-weekly phase I clinical trial in treating patients with recurrent or metastatic cervical cancer
NCT01693783	A phase 2 study of Ipilimumab (anti-CTLA antibody) in women with metastatic or recurrent HPV-related cervical carcinoma of either squamous cell or adenocarcinoma histologies
NCT03894215	A two-arm, randomized, non-comparative, phase 2 trial of AGEN2034 (Balstilimab, anti-PD-1 antibody) as a monotherapy or combination therapy with AGEN1884 (Zalifrelimab, anti-CTLA antibody) or with placebo in women with recurrent cervical cancer (Second Line) RaPiDS
NCT03495882	A phase 1/2, open-label, multi-arm trial to investigate the safety, tolerability, pharmacokinetics, biological, and clinical activity of AGEN1884 (Zalifrelimab, anti-CTLA4 antibody) in combination with AGEN2034 (Balstilimab, Anti-PD-1 antibody) in subjects with metastatic or locally advanced solid tumors and expansion into select solid tumors (cervical)
NCT03816553	SHR-1210 (Camrelizumab), a novel anti-PD-1 antibody, in combination with apatinib ¹ in patients with metastatic, persistent or recurrent cervical cancer: a single-arm, open label, multi-center, phase II study
NCT03826589	Avelumab (anti-PD-L1 antibody) with Axitinib ² in persistent or recurrent cervical cancer after platinum-based chemotherapy a proof-of-concept study (ALARICE Study)

Table 4. Cont.

NCT Number	Trial
NCT03912415	An international randomized double-blind clinical trial of BCD-100 (Prolgolimab anti-PD-1 antibody) plus platinum-based chemotherapy with and without Bevacizumab versus placebo plus platinum-based chemotherapy with and without Bevacizumab as first-line treatment of subjects with advanced cervical cancer
NCT03635567	A phase 3 randomized, double-blind, placebo-controlled trial of Pembrolizumab (anti-PD1- antibody) (MK-3475) plus chemotherapy versus chemotherapy plus placebo for the first-line treatment of persistent, recurrent, or metastatic cervical cancer (KEYNOTE-826)
NCT03257267	An open-label, randomized, phase 3 clinical trial of REGN2810 (Cemiplimab, anti-PD-1antibody) versus investigator’s choice of chemotherapy (pemetrexed, gemcitabine, topotecan, irinotecan, or vinorelbine) in recurrent or metastatic cervical carcinoma
NCT03228667	QUILT-3.055: a phase IIb, single-arm, multicohort, open-label study of ALT-803 ³ in combination with PD-1/PD-L1 checkpoint inhibitor in patients who have disease progression following an initial response to treatment with PD-1/PD-L1 checkpoint inhibitor therapy (several types of tumor including cervical cancer)
NCT02921269	A phase 2 study of Atezolizumab (MPDL3280A, anti- PD-L1 antibody) in combination with Bevacizumab in patients with recurrent, persistent or metastatic cervical cancer
NCT03556839	A randomized phase III trial of platinum chemotherapy plus paclitaxel with Bevacizumab and Atezolizumab (anti-PD-L1 antibody) versus platinum chemotherapy plus paclitaxel and Bevacizumab in metastatic (stage IVB), persistent or recurrent carcinoma of the cervix (BEATcc)

Legend ¹ tyrosine kinase inhibitor that selectively inhibits the vascular endothelial growth factor receptor (VEGFR)-2, ² tyrosine kinase inhibitor that selectively inhibits VEGFR-1, -2 and -3. ³ interleukin (IL)-15 superagonist.

6. Other Agents

6.1. Phosphatidylinositol 3-Kinase (PI3K)/AKT/Mammalian Target of Rapamycin (mTOR)Inhibitors

6.1.1. Basic Research

Activation of phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway sometimes occurs in cervical cancer [126–129]. PIK3catalytic subunit α (PI3KCA) mutations have been found in 14–25% of adenocarcinomas and in 37.5–48% of squamous cell carcinomas of the uterine cervix [126,128].

PI3K pathway was strongly activated in PTX-resistant HeLa and ME180 cell lines established from metastatic sites of cervical cancer compared to parental cells, and the combination of PTX and a PI3K inhibitor revealed a synergistic antiproliferative activity by enhancing PTX-induced S and G2/M arrest in PTX-resistant cell lines [130]. Therefore, therapeutic strategies targeting PI3K pathway could revert the chemoresistance of cervical cancer cells to PTX and could provide an promising research perspective for the management of patients with this malignancy.

6.1.2. In Human Studies

A retrospective study conducted on 82 squamous and nonsquamous cell cervical cancer patients treated with CCRT showed that PIK3CA mutational status correlated with a worse OS (HR = 6.0; 95%CI = 2.1–17.5) in FIGO stage Ib/II disease, but not in stage II–IVa disease (HR = 1.0, 95%CI = 0.32–3.1) [127]. Very few and conflicting clinical data are currently available in the literature as for the use of PI3K/AKT/mTOR pathway targeted agents [128,131,132]. A phase II trial of temsirolimus (25 mg iv q28) reported a partial response in one (3%) and a stable disease in 19 (58%) of 33 patients with recurrent, unresectable locally advanced, or metastatic squamous and nonsquamous cell carcinoma of the uterine cervix [131]. The single patient with a partial response experienced no evidence of progression for 13.9 months, whereas the median duration of stable disease was 6.5 months with no correlation with PTEN and PIK3CA status. A phase I clinical study on 55 patients with metastatic

or recurrent squamous and nonsquamous cell cervical cancer, of which 22 had PIK3CA mutations and/or PTEN loss, found that those patients treated with PI3K/AKT/mTOR targeted agents (such as temsirolimus) matching the aberrations in this pathway achieved a longer median PFS (6.0 months versus 1.5 months, $p = 0.026$) than those who did not receive such matched therapy [128]. Conversely, in a phase II trial, the combination of the pan-AKT inhibitor GSK2141795 and the MEK inhibitor trametinib obtained no confirmed response in 14 patients with squamous and nonsquamous cell persistent or recurrent carcinoma of the uterine cervix [133].

6.2. Poly (Adenosine diphosphate (ADP)-Ribose) Polymerase (PARP) Inhibitors (PARPi)

6.2.1. Basic Research

Poly (adenosine diphosphate (ADP)-ribose) polymerase (PARP) inhibitors (PARPi) exert anti-proliferative effects on human cervical cancer cell lines [132,134,135]. PARPi are still at the basic research phase, but promising. Bianchi et al. [134] reported that none of 9 primary cervical cancer cell lines had homologous recombination (HR) deficiency, but 3 of these showed strong PARP protein activity, i.e., PAR expression, and were very high sensitive to olaparib in vitro. This PARPi caused cell cycle arrest in the G2/M phase and induced apoptosis. In vivo antitumor activity of olaparib was tested in severe combined immunodeficiency (SCID) mice who were given a subcutaneous injection of human cervical cancer cells. Animals treated with olaparib experienced a slower tumor growth and a prolonged survival compared to controls. PAR expression might be a novel biomarker able to identify a subset of cervical cancer patients who could benefit from PARPi. Additional studies with PARPi alone or combined with other agents are strongly warranted, especially in patients with radiotherapy and/or chemotherapy-resistant disease.

The α -specific PI3K inhibitor alpelisib and the PARPi talazoparib synergized to inhibit cervical cancer cell proliferation, migration, and invasion in vitro and in vivo [135]. Cancer cells with aberrant PI3K activation were more responsive to these combined agents. Besides catalytic activity, talazoparib trapped PARP on damaged DNA and induced cytotoxic effects. Alpelisib could co-operate with talazoparib to increase PARP trapping on chromatin and to induce severe DNA damage.

6.2.2. In Human Studies

Roszik et al. [136] found a significantly higher expression of DNA repair genes, especially those involved in HR and mismatch repair pathways, in tumor tissues compared with adjacent normal tissues from 28 patients with recurrent cervical cancer who underwent pelvic exenteration. High-risk HPV E6 and E7 reduced the ability of the HR pathway to complete double-strand break repair by approximately 50%, thus leading to HR deficiency [137]. The combination of immune checkpoint inhibitors and PARPi should be investigated in patients with recurrent cervical cancer. NCT04068753 is an ongoing phase II trial of niraparib in combination with the anti-PD-1 antibody dostarlimab in this clinical setting.

7. Conclusions

Cervical cancer patients with distant or loco-regional recurrences not amenable by surgery or radiotherapy have a very poor prognosis, and pharmacological treatment options have only a palliative intent. CDDP-based doublets have obtained response rates of 21–50%, with a median PFS of 4.8–10.5 months and a median OS of 6.4–25+ months in this clinical setting. A phase III randomized trial has shown a trend in response rate, PFS and OS in favor of CDDP + PTX compared with CDDP + vinorelbine, CDDP + gemcitabine or CDDP + topotecan. The addition of BEV to CDDP + PTX significantly improved PFS and OS, but increased the risk of adverse events and especially of grade >3 gastrointestinal or genitourinary fistulas. BEV could be avoided in previously irradiated low-risk women according to Moore's criteria, where the OS benefit is small. Pembrolizumab has been approved by the FDA for patients with recurrent or metastatic cervical cancer in progression on or after chemotherapy

whose tumors were PD-L1 positive, and several interesting trials with immune checkpoint inhibitors are currently ongoing. PARP inhibitors and PI3K inhibitors are still at the basic research phase, but promising.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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