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REVIEW

Advances in paclitaxel combinations for treating cervical cancer

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ABSTRACT

Introduction: Cervical cancer is the fourth common cancer in women worldwide. While, in the past, locally advanced stage disease was treated by pelvic radiotherapy, nowadays the National Cancer Institute strongly recommends chemoradiation protocols. Weekly cisplatin was previously the standard of care in this setting; however, the low response rate and the short median progression-free survival (PFS) of patients have led researchers to investigate combinatory regimens.

Area covered: This article is based on literature searches up until April 2019, with current trial registers also analyzed. All data available on this topic has been summarized in this narrative review.

Expert opinion: In recent years, it has been demonstrated that cisplatin-based doublets, and in particular, cisplatin plus paclitaxel, are superior to cisplatin as a monotherapy in terms of response rate and progression-free survival of patients with advanced cervical cancer. This double regime combined with bevacizumab is also considered the first-line option for metastatic or recurrent disease. Dose-dense paclitaxel in neo-adjuvant chemotherapy combinations is a promising option in patients with locally advanced cervical cancer. Exploration of novel biological therapies and *in vitro* combinations based on the use of paclitaxel is warranted.

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Cervical Cancer; investigational drugs; paclitaxel; chemotherapy; cytotoxic regimens; quality of life

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide. This tumor has a global incidence of 570.000 new cases and 311.000 deaths in 2018; the majority of death related to cervical cancer occur in Central and South America, the Caribbean, sub-Saharan Africa and South Asia [1]. Overall, the incidence of this disease has decreased in the world during the last two decades as screening tests are increasingly employed and pre-invasive lesions are early detected with subsequent optimal management [2].

The majority of cervical cancers are caused by specific types of human papillomavirus (HPV). Prophylactic vaccination for HPV offers the most effective method of primary prevention against HPV-related diseases. The use of the Pap test and HPV test, according to published guidelines, provides the most effective means of screening for cervical cancer [3].

The treatment of cervical cancer is based on disease stage: early-stage disease (stage Ia1-Ib1 according to International Federation of Gynecology and Obstetrics [FIGO] classification [4]) can be successfully treated by primary surgery, obtaining a 5-year survival rates of 85-95%. Chemoradiotherapy is usually used for locally advanced disease (FIGO stage Ib2-IVa). Before 1999–2000, locally advanced cervical cancer was treated by pelvic radiotherapy (50.4Gy) plus intracavitary low-dose-rate cesium-137 brachytherapy (30–35Gy) [5]; after five pivotal randomized phase III trials, demonstrating the improved survival outcomes by the addition of chemotherapy to the radiotherapy protocols [6–10], the National Cancer Institute (NCI) strongly recommends chemoradiation [11]. In fact, it is supposed that chemotherapy has a role of radiosensitizer, aiming also to eradicate occult metastatic tumor foci [5]. The specific regimens of radiation and chemotherapy in a neoadjuvant, adjuvant settings is defined according to the histological and cytological characteristics of tumor and patient's performance status [12].

Patients with early-stage disease treated by primary radical hysterectomy with either nodal metastasis, parametrial extension, or involved surgical margins have significant risk of local relapse: For this reason, adjuvant concurrent cisplatin-based chemotherapy and radiation therapy can positively impact progression-free survival (PFS) and overall survival (OS) [13]. Women without any high-risk factors but with significant local disease burden (in relation to tumor size, extent of myocervical invasion, and presence of vascular lymphatic invasion) have a significant risk for recurrence after radical surgery (these patients are considered an intermediate-risk group). In this population, a randomized trial demonstrated a progression-free benefit by using adjuvant radiation therapy [13]. Finally, cisplatin-based chemoradiation appears to be effective in increasing PFS and OS of patients with locally advanced stage disease, for which surgery is not suitable [13].

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Article highlights

- The National Cancer Institute (NCI) strongly recommends chemoradiation protocols instead of pelvic radiotherapy alone for locally advanced stage cervical cancer (FIGO Ib2–IVa).
- The platinum/paclitaxel combination tends to be the preferred regimen in terms of response rate (RR) and progression-free survival (PFS) in patients with locally advanced cervical cancer (FIGO Ib2–IVa).
- Dose-dense paclitaxel within neo-adjuvant chemotherapy combinations is feasible and effective for treating patients with locally advanced cervical cancer (FIGO Ib2–IVa).
- The doublet paclitaxel-cisplatin combined with bevacizumab is considered the preferred first-line regimen against metastatic, persistent and recurrent cervical cancer (FIGO IVb).
- Nab-paclitaxel (Albumin-Bound Paclitaxel) has proven activity and moderate toxicity in the treatment of drug-resistant, metastatic and recurrent cervical cancer.
- CDK (serine/threonine cyclin-dependent kinases) inhibitors are an innovative class of drugs; they could be an experimental approach enhancing the therapeutic efficacy of paclitaxel in advanced cervical cancer as well as to overcome the resistance to this cytotoxic drug.

This box summarizes key points contained in the article.

Several chemotherapeutic agents have been studied in combination with cisplatin to improve the regimen efficacy; among these, the combination of cisplatin and paclitaxel, a widely employed taxane, obtained better results than cisplatin alone in terms of response rate (RR) and PFS [14].

Currently, neoadjuvant chemotherapy followed by radical hysterectomy might be a suitable alternative for stage Ib2-IIb cervical cancer: platinum/paclitaxel combination tends to be the preferred regimen in neoadjuvant setting; in particular, preliminary data indicate that dose-dense regimens are feasible and effective [15]. Newer approaches in the management of locally advanced cervical cancer include the exploration of biological agents: Among them, bevacizumab, an anti-angiogenetic agent, seems to have marked the beginning of a new era in the context of the treatment of advanced cervical cancer, after its approval in 2014 for treating metastatic and recurrent disease [16].

The aim of this narrative review is to perform a complete overview of the current results and advances about use of paclitaxel for treating cervical cancer. A literature search was carried out to find all the published studies evaluating these topics until April 2019. Several electronic databases were used as data sources: Medline, PubMed, Embase, Science Citation Index via Web of Science. The following keywords were used: 'paclitaxel' and 'taxane' in combination with 'cervical cancer' or 'cervical carcinoma' or 'cervical neoplasia'. The papers selected for this review had been critically analyzed and all data available in the literature has been summarized in this narrative review. Current research registers (such as www.cliniclatrials.gov) were also analyzed.

2. Paclitaxel: chemical proprieties and mechanism of action

Paclitaxel is one of the most widely used chemotherapeutic agents together with doxorubicin and cisplatin, as first- or second-line treatment option for several cancers [17]. It is a diterpenoid organic compound derived from the bark and needles of the pacific yellow tree, isolated in 1971 and approved for medical use in 1993 [18] (Figure 1).

Paclitaxel mainly acts suppressing microtubule spindle dynamics [19]: In particular, it binds to the N-terminal 31 amino acids of the β-tubulin subunit in microtubule, stabilizing and increasing its polymerization (Figure 2) [20]. This process causes a blockage of metaphase-anaphase transitions, ultimately inhibiting cell mitosis as well as inducing apoptosis. At high therapeutic concentrations, paclitaxel suppresses microtubule detachment from centrosomes; however, it has been demonstrated that the suppression of microtubule dynamics occurs at lower concentrations than those needed for blocking cell mitosis [21].

Paclitaxel has a biphasic decline in plasma concentrations, with a mean terminal half-life ($t_{1/2}$) of up to 50 h following intravenous administration. This drug is 89–98% bound to plasma protein and it is mainly metabolized in the liver by cytochrome (CYP) 2C8 and CYP3A4. Its elimination route has not been entirely elucidated; about 12% of an administered dose is found in urine as unchanged molecule, indicating an extensive non-renal clearance; moreover, metabolites of paclitaxel have been found in the bile; among them, the primary one is 6a-hydroxy-paclitaxel [22].

The intravenous administration of paclitaxel is largely employed for treating ovarian, uterine and cervical cancers [23–27]. This drug has been also tested as an antiproliferative agent for preventing the restenosis after collocating coronary and peripheral stents, as it limits the growth of neointima (scar tissue) through a direct locally effect on the artery wall [28].

Concerning cervical cancer, according to the European Society for Medical Oncology (ESMO) clinical practice guideline published in 2017, paclitaxel has a significant role for the management of advanced/metastatic disease. Cisplatin-based doublets with topotecan or paclitaxel have demonstrated superiority in comparison to cisplatin monotherapy in terms of RR and PFS; moreover, paclitaxel and cisplatin combined with bevacizumab are considered the preferred first-line regimens for metastatic or recurrent cervical cancer in relation to the suitable balance between efficacy and safety-profiles. The combination of paclitaxel and carboplatin could be an alternative option for patients not candidate for receiving cisplatin, in particular, in relation to renal function [29].

Nevertheless, the administration of paclitaxel is severely limited due to very poor solubility, re-crystallization upon dilution and co-solvent-induced toxicity [30]. In fact, the most common side effects experienced with its use include hypersensitivity, alopecia, bone marrow suppression, hepatotoxicity, numbness, myopathy, neurotoxicity and diarrhea [30–32]. It has been suggested that the clinical toxicity of paclitaxel may be partly due to the presence of Chromophore EL, in which this drug is dissolved for delivery [31]. Nanoparticulate delivery systems based on cyclodextrins or drug encapsulation have been investigated in order to improve the solubility of paclitaxel; in this way, an amorphous form of paclitaxel, avoiding re-crystallization, tends to be protected from enzymatic degradation [32,33].

Other taxanes, such as docetaxel or cabazitaxel, have been proposed for the treatment of cervical cancer. Unlike paclitaxel, docetaxel exhibits linear pharmacokinetics and has

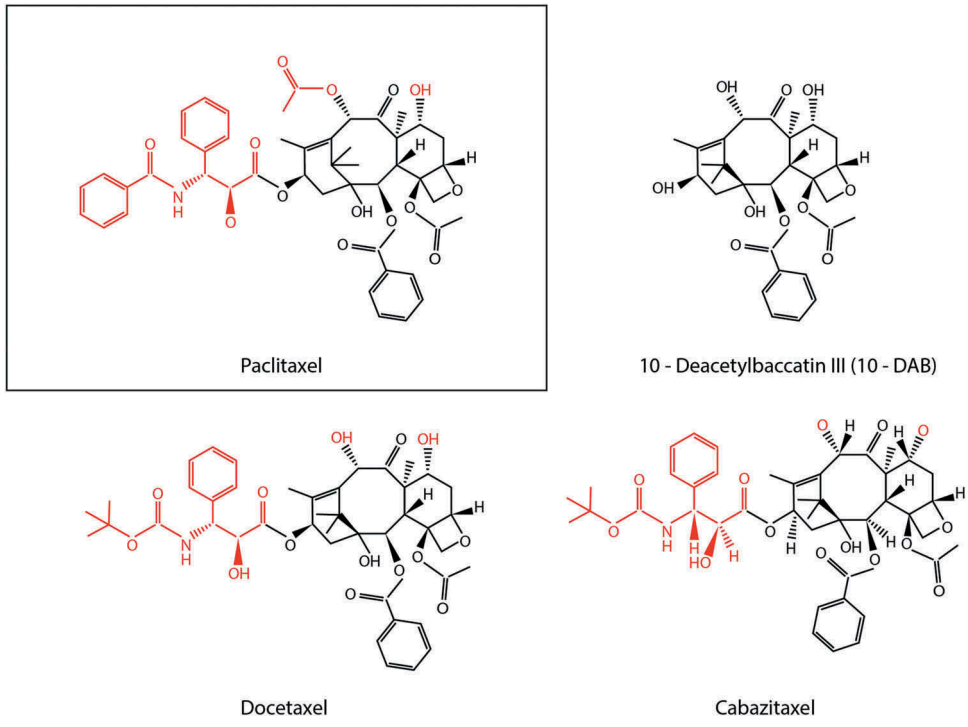

Figure 1. Paclitaxel and the other taxanes. The common molecular structure is colored in black; the specific molecular structure for each molecule is colored in red.

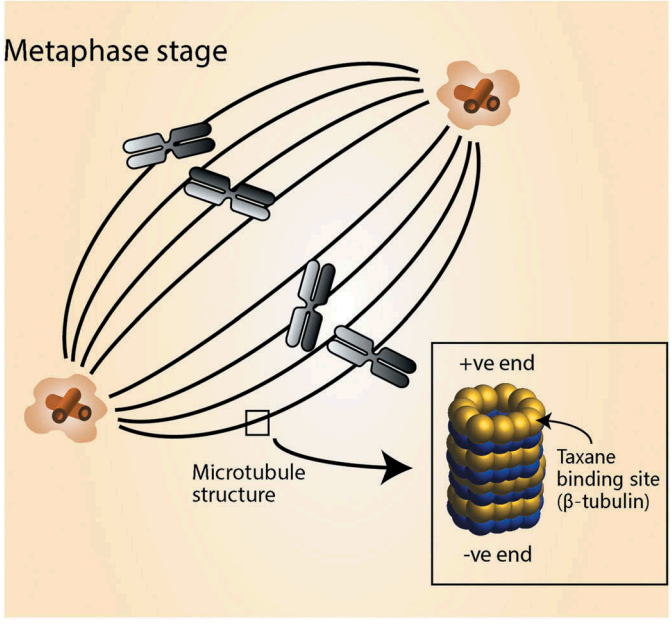

Figure 2. Intracellular mechanism of action of taxanes. They act suppressing microtubule spindle dynamics by binding to the N-terminal 31 amino acids of the ?-tubulin subunit. Stabilizing and increasing polymerization of ?-tubulin, these drugs cause the blockage of cell metaphase?anaphase transitions, inhibiting cell mitosis.

comparable pharmacodynamic activity [33,34]. However, the toxicity profiles of these agents tend to be different: whereas the administration of paclitaxel has been mainly associated with peripheral neuropathies and myalgias/arthralgias, docetaxel may be responsible for cumulative fluid retention. Similarly to paclitaxel, a relevant number of side effects have been associated with the solvents employed for diluting docetaxel (known as polysorbate 80). Although sensory neuropathies have been reported, their incidence with docetaxel administration is much lower, probably due to the different delivery vehicle [35]. Cabazitaxel, a recent member introduced in the taxane family, is a semisynthetic dimethyloxy derivative of docetaxel, designed to overcome the development of resistance related to docetaxel and the other taxanes [36]. This drug had an impressive antitumor activity in preclinical and clinical studies in docetaxel-refractory setting; until now, cabazitaxel has been only approved by the FDA for the treatment of hormone-refractory prostate cancer [37]. Unfortunately, all these agents have not been adequately tested in cervical cancer patients; therefore, more clinical trials are required to understand their therapeutic potential.

3. Paclitaxel in neo-adjuvant chemotherapy

Neo-adjuvant chemotherapy followed by radical surgery has been investigated for decades for treating patients with locally advanced cervical cancer [38]. The dose-dense is a chemotherapy treatment schedule in which drugs are given with less time between treatments compared with a standard chemotherapy treatment plan [39].

The main reason supporting this strategy is represented by the demonstrated activity of neo-adjuvant chemotherapy in terms of tumor volume reduction, increase of operability rate as well as control of micro-metastatic disease [40,41]. In addition, the theoretical concept according to which increased dose density would be more effective and less toxic that dose escalation [42,43] has fueled the efforts to evaluate this approach [44,45].

Table 1. Previous trials on paclitaxel and cytotoxic agents for the treatment of cervical cancer.

Regimen	Drugs	Phase Trial	Stage	Number of patients	Comparison	Year	Ref
Paclitaxel in neo-adjuvant chemotherapy							
	Paclitaxel + Cisplatin	II	IB2 to IIB	43	RR	2004	[30]
	Paclitaxel+ Ifosfamide + Cisplatin	II	Ib2-IVa	154	RR	2009	[41]
	Ifosfamide + Paclitaxel + Cisplatin	II	IVB or recurrent	57	RR	2002	[50]
	Paclitaxel + Ifosfamide + Cisplatin	I	Ib2-IVa	219	RR	2005	[51]
	Cisplatin + Paclitaxel	II	IB2, IIA2, or IIB	51	PFS, OS, AEs, RR, pCR	2017	[53]
	Paclitaxel + Carboplatin	II	Ib2-IVa	36	RR, PFS	2019	[54]
	Cisplatin + Adriamycin + Paclitaxel	II	IB2-IVa	30	RR, pCR, PFS; OS	2014	[76]
Paclitaxel in combination with cytotoxic agents							
	Paclitaxel + Cisplatin	II	IVB or recurrent	34	RR, PFS	1999	[71]
	Paclitaxel + Cisplatin vs Vinorelbine+ Cisplatin vs Gemcitabine + Cisplatin vs Topotecan + Cisplatin	III	Ib2-IVa and recurrent	513	OS, RR, PFS	2009	[74]
	Paclitaxel + Carboplatin vs Paclitaxel + Cisplatin	III	IVB or recurrent	253	OS	2012	[78]
	Paclitaxel+ Nedaplatin	II	Ib2-IVa or recurrent	50(5)	RR, OS, PFS	2012	[81]
Paclitaxel and biological therapy							
	Cediranib+ Carboplatin + Paclitaxel	II	IVB or recurrent	69	PFS	2015	[86]
	Cetuximab+Carboplatin+ Paclitaxel,	II	Ib2-IVa or recurrent	108	EFS, PFS, OS	2019	[49]
	Paclitaxel+ Cisplatin+ ABT-888	I	persistent or recurrent	36(2)	DLTs, RR	2015	[89]
Nab-Paclitaxel							
	Nab-paclitaxel	II	IV B and recurrent after progress or relapse the first-line cytotoxic drug treatment.	37(2)	RR, OS, PFS	2012	[96]

Adverse Events = AEs, Dose Limiting Toxicities = DLTs, Event-Free Survival = EFS, Overall Survival = OS, Pathological Complete Response = pCR, Progression-Free Survival = PFS, Response Rate = RR.

Several chemotherapeutic agents have been tested as neo-adjuvant chemotherapy in cervical cancer. Paclitaxel, cisplatin and ifosfamide (mainly in combined regimens) are considered the most active drugs in this setting [46,47] (Table 1).

3.1. Paclitaxel, cisplatin, and epirubicin

In 2004, Tambaro *et al*. evaluated three courses of paclitaxel (175 mg/m^2), cisplatin (100 mg/m^2) and epirubicin (CEP) (100 mg/m^2) as neo-adjuvant chemotherapy followed by surgery in 42 patients with FIGO stage Ib2–IVa cervical cancer. Thirty-two out of 42 (73.2%) patients underwent radical surgery. There were 8 complete or microscopic pathological responses (25%), 17 partial responses (53%) and 9 patients (28%) with stable disease. At the end of the chemotherapy cycle, a RR of 78.5% (95% CI, 63.8–93.2) was reported [48].

3.2. Paclitaxel, cisplatin and isofosfamide

Paclitaxel, cisplatin and isofosfamide (TIP) demonstrated objective RRs ranging from 46% to 67%. In particular, the Italian group MITO reported 33% of clinical complete responses and 15% of pathological complete responses [49] for this combination in locally advanced cervical cancer and recurrent-persistent disease. Treatment specifically consisted of paclitaxel (175 mg/m^2 given over 3 hours on day 1), cisplatin (50–75 mg/m^2 mg/m^2 on day 2), ifosfamide (5 g/m^2 on day 2) and mesna (5 g/m^2 given on day 2 and 3 g/m^2 given on day 3). In the neoadjuvant setting, the cycle was repeated every 3 weeks for a total of three courses. The most relevant side effect was myelotoxicity (91% of grade 3–4 adverse events) [50]. In the Studio Neo-AdjuvantePortio (SNAP) 01 trial, the administration of TIP obtained a higher RR than ifosfamide plus cisplatin, without a statistically significant difference in OS. In this trial, 219 patients were randomly assigned to ifosfamide (5 g/m^2 during 24 hours) plus cisplatin (75 mg/m^2), or paclitaxel (175 mg/m^2) plus ifosfamide (5 g/m^2 during 24 hours) and cisplatin (75 mg/m^2 every 3 weeks for three courses) [51]. The SNAP-02 trial demonstrated that TIP was more active than paclitaxel and cisplatin (25% versus 43% pathological RRs). Anyway, the triple regimen was responsible for a higher rate of adverse events (i.e. neutropenia in 76% and 26% of patients, respectively) [41].

3.3. Platinum plus paclitaxel-based dose-dense chemotherapy

Considering the substantial toxicity of TIP, Salihi *et al*. evaluated a dose-dense paclitaxel-based regimen in 36 patients affected by FIGO stage Ib1 to IIb cervical cancer. In particular, women received 9 weeks of paclitaxel (60 mg/m^2) plus carboplatin (AUC 2.7). Overall, nine patients had FIGO stage Ib1 (25%), 7 had stage Ib2 (19%), 3 had stage IIa (8%), and 17 had stage IIb cervical cancer (47%). At magnetic resonance imaging, 32 patients obtained a clinical response (89%; complete response in 11, partial response in 21 patients). Notably, thirty patients were suitable for surgery after chemotherapy; thirteen patients had pathologic lymph nodes on radiological evaluation before starting the chemotherapy. After chemotherapy, the lymph nodes were negative in 6 (47.0%) of these patients (pathologic complete remission). The estimated 5-year OS was 70.8%. Globally, this study demonstrated that neoadjuvant therapy based on paclitaxel-carboplatin dose-dense regimen had a RR comparable to TIP [52]. Tanioka *et al*. recently evaluated the effectiveness and safety of the combination of cisplatin plus dose-dense paclitaxel before and after radical hysterectomy for patients with stage Ib2, IIa2, or IIb cervical cancer [53]. Overall, 34

out of 51 patients (66.7%) had FIGO stage IIB disease. All the women received 3 cycles of dose-dense paclitaxel chemotherapy, based on cisplatin (75 mg/m^2, day 1) and paclitaxel (80 mg/m^2, days 1, 8, and 15); after surgery, another 2 cycles of the same chemotherapeutic regimen were administered. The RR and pathological complete responses were 94 and 28%, respectively. With a median follow-up of 58 months, the 2- and 5-year PFS were under 90%; the 2- and 5-year OS rates were 94.1 and 88.2%, respectively. The main grade 3 and 4 adverse events were neutropenia (34%), nausea (12%), appetite loss (10%), fatigue (6%), and anemia (6%). The authors demonstrated that dose-dense paclitaxel before and after surgery obtained a good long-term OS in patients with locally advanced cervical cancer.

In 2019, Ferrandina *et al*. reported the results of non-randomized phase II study assessing the efficacy of neo-adjuvant platinum/paclitaxel-based dose-dense chemotherapy followed by radical surgery in patients with locally advanced cervical cancer. The authors administered paclitaxel (80 mg/m^2) and carboplatin (AUC 2) for 6 weeks eventually followed by radical surgery (radical hysterectomy and pelvic/aortic lymphadenectomy). The overall RR after neo-adjuvant chemotherapy was 75% and radical surgery was finally performed in 29 (93.5%) patients; the reported 2-year PFS rate was 69%. However, as the optimal pathological response was only 16.1%, the authors decided to prematurely close the study. Grade 3 and 4 hematological toxicities occurred in 5 patients whereas surgical morbidity occurred in 14 patients. Although dose-dense neo-adjuvant paclitaxel/carboplatin was proven to be feasible and safe in patients affected by locally advanced cervical cancer, it failed to satisfactorily achieve the primary endpoint of this study. Moreover, acute and late toxicity associated with this chemotherapy regimen and a not negligible rate of surgery-related complications were noted [54].

Currently, novel neoadjuvant regimens for treating cervical cancer are being investigated in different trials. Among the others, a multi-center open-label phase II study had been organized for evaluating the combination of paclitaxel (7-day cycle schedule at 60 mg/m^2) and cisplatin (7-day cycle schedule at 40 mg/m^2) before radical hysterectomy and bilateral pelvic lymphadenectomy (2 weeks after last course) in women with squamous FIGO Ib2-IIa2 cervical cancer (NCT02432365). The results are not yet available.

4. Paclitaxel in chemotherapy for advanced, recurrent and metastatic cervical cancer

The main objective of medical therapy in advanced and recurrent cervical cancer (stages IVA and IVB) is palliation of symptoms, maintenance of quality of life and, whenever possible, prolongation of survival [55,56]. Although the benefit of chemotherapy in the advanced cervical cancer is still limited, cisplatin (23–30%), ifosfamide (16%), paclitaxel (17%) and topotecan (12.5%) demonstrated in previous trials modest RR [57–59].

A large proportion of women treated in the metastatic setting receive more than one line of systemic therapy. The standard of care in the first-line setting is combination chemotherapy with the addition of the anti-VEGF monoclonal antibody, bevacizumab, whilst there is currently no standard of care for second-line treatment [60]. So far, there is a need to understand what the best second-line treatment option could be. In patients receiving second-line platinum therapy, PFI ≥ 6 months (hazard ratio 0.22; P > 0.001) [61] and PFI ≥ 12 months [62] were prognostic of survival (hazard ratio 0.32; P = 0.021).

Overall, cisplatin and paclitaxel are considered the most active agents [63]. Single agent cisplatin has been the most employed option in this setting [64]; this cytotoxic drug also represents the key element for current combined regimens [65], including paclitaxel, topotecan, vinorelbine. These double regimens have shown encouraging results in phase II and phase III studies [48], with RR of 46%, 33% and 44%, respectively, in patients with metastatic and recurrent cervical cancer [66–68].

Currently, combined chemotherapy tends to be largely employed among women with advanced disease. The majority of trials investigated the use of bleomycin plus cisplatin, fluorouracil plus cisplatin, paclitaxel plus cisplatin, ifosfamide plus cisplatin, gemcitabine plus cisplatin and topotecan plus cisplatin [69].

4.1. Paclitaxel as monotherapy

The use of paclitaxel as monotherapy (170 mg/m^2 every three weeks) has been studied in a phase II trial published in 1996. This study enrolling previously untreated patients with advanced squamous cervical cancer showed a RR of 17%; for this drug; the main dose-limiting toxicity of the regimen was neutropenia [70].

4.2. Paclitaxel plus cisplatin

The combination of cisplatin and paclitaxel obtained better results than cisplatin in terms of RR and PFS; otherwise, the benefit on OS is controversial. In particular, this double regimen demonstrated 36% of RR in patients with stage IVb, recurrent, or persistent cervical cancer, nevertheless not improving the median OS, when compared with cisplatin alone [13] Rose *et al*. treated 47 patients affected by advanced cervical cancer with paclitaxel plus cisplatin, obtaining similar data; anyway, grade 3 and grade 4 neutropenia was detected in 15.9% and 61.4% of women, respectively [66].

It is well known that neurotoxicity is one of the main toxicities of the combination of cisplatin and paclitaxel. Papadimitriou *et al*. reported in a phase II study that 53% of patients developed some degree of neurotoxicity during this therapy; in particular, grade 3 neurotoxicity was experienced by 9% of them. In this study, thirty-four patients were treated in an outpatient basis with paclitaxel (175 mg/m^2 intravenously over a 3-hour period) followed by cisplatin (75 mg/m^2 intravenously) given with granulocyte colony-stimulating factor support. The chemotherapy was administered every 3 weeks for a maximum of six courses [71].

The phase III trial GOG protocol 169 was the first randomized controlled study investigating quality of life (QoL) in addition to clinical outcomes during and after the use of palliative chemotherapy in patients with advanced cervical cancer. It evaluated cisplatin (50 mg/m^2, every 3 weeks for six cycles) as monotherapy versus paclitaxel (135 mg/m^2) immediately

followed by cisplatin [69,72]. All the 264 patients included in the study had a performance status of 0–2, and more than 90% of the enrolled patients had received prior radiation. The addition of paclitaxel caused a significant improvement in RR (19% with cisplatin alone versus 36% with paclitaxel plus cisplatin, p = 0.002]; the median PFS was also increased from 2.8 months to 4.8 months (p < 0.001). However, the difference in median OS (8.8 vs 9.7 months) was not judged clinically relevant. Although grade 3 and 4 hematological toxicity was increased in the combination arm, it did not cause a reliable worsening of QoL. Notably, a not negligible number of patients (50 in the cisplatin group and 33 in the cisplatin plus paclitaxel group) dropped out because of disease progression, worsening of global health or early death [73].

In another GOG study, 513 patients were randomly assigned to paclitaxel (135 mg/m^2 over 24 hours) plus cisplatin (50 mg/m^2 day 2 every 3 weeks); vinorelbine (30 mg/m^2 days 1 and 8) plus cisplatin (50 mg/m^2 day 1 every 3 weeks); gemcitabine (1,000 mg/m^2 day 1 and 8) plus cisplatin (50 mg/m^2 day 1 every 3 weeks); or topotecan (0.75 mg/m^2 days 1, 2, and 3) plus cisplatin (50 mg/m^2 day 1 every 3 weeks). The authors reported a RR, PFS, and OS in favor of the paclitaxel and cisplatin arm compared with the other arms, although no significant statistical difference was detected. Vinorelbine or gemcitabine or topotecan plus cisplatin were not superior to paclitaxel plus cisplatin in terms of OS. Moreover, the trend in RR, PFS, and OS favored this latter combination, with an overall RR of 29.1% and an OS of 12.8 months. At the interim analysis, significant differences in the pattern of toxicity were demonstrated among different regimens: the combination of cisplatin and paclitaxel was most commonly associated with at least grade 3 neutropenia (78%), anemia (17%), nausea/vomiting (14/20%), and metabolic toxicity (18%). Patients receiving cisplatin and gemcitabine experienced the fewest grade 3 or greater toxicities. Two treatment-related deaths occurred in the cisplatin plus paclitaxel arm [74].

The substitution of carboplatin with cisplatin has been investigated in advanced or recurrent cervical cancer. According to the British Columbia (BC) Cancer Agency in Vancouver, since the early 2000s, carboplatin plus paclitaxel has been considered the standard treatment for advanced or recurrent cervical cancer. In 2005, Tinker *et al*. treated 25 patients with advanced or recurrent cervical cancer with carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m^2; 155 mg/m^2 if prior pelvic irradiation had been delivered, given as a 3-hour intravenous infusion) [55]; paclitaxel was administered prior to carboplatin; both drugs were delivered on day 1, and the cycles were repeated on a 28-day schedule for up to 6–9 cycles. The overall RR was 40% and the median OS was 21 months, despite the use of previous chemoradiation [13]. Carboplatin plus paclitaxel showed good tolerability; grade 1 or 2 anemia (68%) was the most frequently observed toxicity; at least, a higher RR and improvement of PFS was obtained over single agent cisplatin [50]. In 2008, Pectasides *et al*. demonstrated an overall RR of 53% [complete responses (16%), partial responses (37%)] by combining carboplatin to paclitaxel in 51 patients with an advanced or recurrent cervical cancer. The RR was higher in women with disease outside of a previously irradiated site in comparison to those with the disease in a previously irradiated field (68% versus 30%) (p = 0.011). Moreover, women previously treated with chemoradiation had a RR of 28%, while for those previously treated with radiotherapy alone the RR was 68% (p = 0.023) [65].

The Japanese Clinical Oncology Group (JCOG0505) organized a prospective, noninferiority, phase III trial comparing cisplatin plus paclitaxel to carboplatin plus paclitaxel in 246 patients with a performance status of 0–2. Median OS and PFS were nearly identical between study arms: specifically OS was 18.3 months for cisplatin plus paclitaxel and 17.5 months for carboplatin plus paclitaxel (HR 0.99; 90% CI 0.79–1.25); PFS was 6.9 months for cisplatin plus paclitaxel and 6.21 months for carboplatin plus paclitaxel (HR 1.04 95% CI 0.8–1.35). Grade 3/4 toxicities occurred within the expected ranges for each treatment arm when compared to the historical controls. However, the regimen containing cisplatin exhibited greater renal toxicity whereas the regimen containing carboplatin exhibited greater thrombocytopenia. In a secondary analysis on 117 patients not receiving prior platinum therapy, carboplatin plus paclitaxel was superior to the other association, with median OS of 23.2 versus 13.0 months, respectively (HR 1.57; 95% CI 1.06–2.32) [72]. These results highlighted the potential implications of acquired resistance in patients exposed to prior cisplatin-based chemoradiation.

A systematic review of the literature comparing cisplatin and paclitaxel to carboplatin and paclitaxel for treating recurrent or metastatic cervical cancer has been carried out in order to summarize clinical outcomes associated with both doublets [75,76]. Only randomized controlled trials were included, with a total of 17 eligible studies (7 for carboplatin plus paclitaxel, 9 for cisplatin plus paclitaxel and 1 for both) [56,66,67,71,74,77–80]. Objective RRs were reported in all 18 studies, globally ranging from 33% to 67.9% for studies on carboplatin plus paclitaxel and from 29.1% to 67% for studies on cisplatin plus paclitaxel. The combined objective RR estimated by the random-effects model was 48.5% (95% CI 37.9%–59.3%; P = <0.0001; I^2 = 75%) for carboplatin and 49.3% (95% CI 41.1%-57.5%; P = <0.0001; I^2 = 77.7%) for cisplatin-based chemotherapy. Notably, the results were slightly better for carboplatin combinations (50.3% vs 43%) but this was judged probably related to the greater number of patients exposed to chemotherapy in carboplatin-based arms (median: 55% vs 24%); moreover, among the randomized controlled trials identified in this systematic review, only Kitagawa *et al*. [78] directly compared carboplatin and paclitaxel with cisplatin plus paclitaxel. Overall, the authors concluded that the two treatments are equally efficacious in this setting; anyway, the combination of carboplatin and paclitaxel seems to have a more favorable toxicity profile; in fact, this association caused less frequent grade 4 neutropenia (45% vs 75%) and febrile neutropenia (7.1% vs 16%), grades 2–4 renal toxicity (4.8% vs 9.6%), and grades 2–4 nausea and/or vomiting (23% vs 36.8%). Currently, the use of paclitaxel and carboplatin is being assessed in several clinical trials (Table 2).

4.3. Paclitaxel plus nadeplatin

The use of paclitaxel in combination with nadeplatin has been investigated for treating patients with advanced cervical cancer. In 2012, Takekuma *et al*. evaluated the activity and toxicity of this combination in a population of 50 patients. The

Table 2. Ongoing clinical trials on paclitaxel and cytotoxic agents or radiotherapy for the treatment of cervical cancer.

Trial number	Phase	Drugs investigated	Indication	Main-end points	Trial significance
NCT01295502	I	Carboplatin (IV) Cisplatin (IV) Paclitaxel (IV) External beam radiation therapy Internal radiation therapy	Cervical cancer metastatic to the para-aortic lymph nodes	• MTD	Analyze the side effects and the best dose of paclitaxel and carboplatin after cisplatin monotherapy and radiotherapy for treating patients with stage IB-IVA disease.
NCT00309959	II	Albumin-bound paclitaxel (IV) Cisplatin (IV) Carboplatin (IV)	Persistent or recurrent cervical cancer	RR (at 5 years) OAE	Analyze efficacy and safety of nab-paclitaxel for treating patients with stage IVb disease.
NCT01667211	II	Albumin-bound paclitaxel (IV) Nedaplatin (IV)	Advanced, recurrent, or metastatic cervical cancer	RR	Investigate efficacy and tolerability of nab-paclitaxel plus nedaplatin in patients with advanced, recurrent metastatic disease.
NCT04017377	I	Radiation therapy + HDR intracavitary brachytherapy. Cisplatin + Nab-paclitaxel	Advanced cervical cancer	MTD/RD	A single arm, open-label Phase I clinical trial to evaluate the role of Nab-paclitaxel in combination with cisplatin and radiotherapy.

MTD = Maximum Tolerated Dose, OAE = observed adverse effects, RR = Objective Response Rate, OS = Overall Survival, RD = Recommended Dose, RR = Response Rate.

treatment consisted of paclitaxel (175 mg/m^2 over 3 hours) and nedaplatin (80 mg/m^2 intravenously over 1 hour on day 1 every 28 days) until progressive disease or adverse effects prohibiting further therapy. Overall, 31 patients out of 45 (62%) received prior radiotherapy and 23 patients (46%) received prior chemotherapy. The overall RR was 44.4% (11 complete responses and 8 partial responses); 22.2% of patients had stable disease. The median PFS was 7.5 months (95% C.I., 5.7, 9.4) and the median OS was 15.7 months (95% C.I., 9.4, 21.9). Grades 3 or 4 adverse events included neutropenia (n = 16, 32.7%), febrile neutropenia (n = 1, 2.0%), anemia (n = 9, 18.4%); non-hematologic toxicity was not judged severe [81]. Although an evaluation of this regimen in phase III trials is certainly needed, the combination of paclitaxel and nedaplatin demonstrates favorable antitumor activity and a better toxicity profile in comparison to cisplatin-based combinations [58,66,71,74,81].

4.4. Combinations of paclitaxel and biological therapy

The first targeted drug approved by the FDA in cervical cancer in 2014 was bevacizumab, a recombinant humanized monoclonal antibody directed against circulating vascular endothelial growth factor (VEGF). The approval of bevacizumab seems to have marked the beginning of a new era in cervical cancer treatment. Novel biological agents targeting several pathways and immunotherapy are being investigated in this setting currently, a vast number of agents targeting various molecular pathways including epidermal growth factor receptor (EGFR), mammalian target of rapamycin (mTOR), poly ADP-ribose polymerase (PARP), epigenetics and other biological mechanisms are under clinical investigation for treating cervical cancer. Some of this investigation drugs have been or are being tested in combination with paclitaxel [82] (Table 3).

4.4.1. Paclitaxel and antiagiogenic agents

After the conclusion of phase II studies reporting the interesting activity of bevacizumab in regimens not including the use of paclitaxel [83,84], the randomized multicenter GOG phase III 240 study was conducted to compare cisplatin (50 mg/m^2 IV day 1) plus paclitaxel (133–135 mg/m^2 IV day 1) or topotecan (0.75 mg/m^2 IV days 1–3) plus paclitaxel in combination or not with bevacizumab (15 mg/kg IV d1 every 21 days) in a 2:2 multifactorial design. Overall, 425 women with metastatic, recurrent and persistent cervical cancer were enrolled. From the results, an OS improvement of 3.7 months (17 versus 13.3 months, P = 0.004) and a RR improvement (48% versus 36%, P = 0.008) for women receiving bevacizumab regardless of their concomitant chemotherapy doublet back-bone was observed [85]. This trial led to the approval of bevacizumab for treating metastatic, recurrent and persistent cervical cancer in 2014. Several ongoing trials are evaluating the use of bevacizumab in combination with paclitaxel for advanced cervical cancer (Table 3). Among the others, a multicenter open-label single-arm phase II study is evaluating the safety and efficacy of bevacizumab (15 mg/kg intravenously once every 3 weeks) in combination with paclitaxel (175 mg/m^2 on day 1 every 3 weeks for at least 6 cycles) and carboplatin (5 mg/mL/min on day 1 every 3 weeks for at

Table 3. Ongoing clinical trials on paclitaxel and biological agents for the treatment of cervical.

Trial number	Phase	Treatment	Indication	Main Endpoints	Trial significance
NCT0391002	II	BCD-100 (IV) Bevacizumab (IV) Paclitaxel (IV) Cisplatin (or carboplatin) (IV)	Persistent, recurrent, or metastatic cervical cancer	RR (at 6 months)	A multicenter, open-label, single-arm study of efficacy, safety and pharmacokinetics of BCD-100, an anti-PD-L1 antibody, in combination with platinum-based chemotherapy and bevacizumab as first-line treatment in patients with stage IVb disease.
NCT03912415	III	Paclitaxel + cisplatin (or carboplatin) Bevacizumab BCD-100 (anti-PD-1)	Advanced cervical cancer	OS	A randomized, multicenter, double-blind, Phase 3 study of efficacy and safety of BCD-100 plus platinum-based chemotherapy with and without bevacizumab versus placebo plus platinum-based chemotherapy with and without bevacizumab.
NCT03635567	III	Pembrolizumab (IV) Paclitaxel (IV) Cisplatin (IV) Carboplatin (IV) Bevacizumab (IV)	Persistent, recurrent, or metastatic cervical cancer	PFS (at 2 years) OS (at 2 years)	A randomized, double-blind, placebo-controlled phase trial assessing efficacy and safety of pembrolizumab, an anti-PD-L1 antibody, plus one of four platinum-based chemotherapy regimens in women with stage IVb disease.
NCT03556839	III	Atezolizumab (IV) Bevacizumab (IV) Cisplatin (IV) Paclitaxel (IV)	Metastatic cervical cancer	OS (at 4 years)	A randomized phase trial assessing 1) the efficacy of combining atezolizumab, an anti-PD-L1 antibody, with cisplatin/paclitaxel/ bevacizumab. in stage IVb disease.; 2) the efficacy of this combination in relation to PD-L1 expression.
NCT03367871	II	Pembrolizumab (IV) Paclitaxel (IV) Cisplatin (IV) Carboplatin (IV) Bevacizumab (IV)	Recurrent, persistent, or metastatic cervical cancer	RR (up to 2 years)	A phase single-arm study evaluating the efficacy of the combination of standard chemotherapy plus bevacizumab with pembrolizumab, an anti-PD-L1 antibody, in women with stage IVb disease.
NCT02584478	I/II	Anlotinib (PO) Carboplatin (IV) Paclitaxel (IV)	Recurrent or metastatic cervical cancer	RP2D RR (at 1 year)	An open-label trial evaluating safety and efficacy of adding oral AL3818, a dual receptor tyrosine kinase inhibitor, to concurrently standard chemotherapy and as maintenance therapy for up to 12 months in patients with stage IVb disease.
NCT00997009	II	Paclitaxel (IV) Carboplatin (IV) Cetuximab	Advanced or recurrent cervical cancer	EFS	A randomized phase study assessing the activity of a combination of cetuximab, an anti-EGFR antibody, with carboplatin plus paclitaxel compared to chemotherapy alone in patients with stage IVb disease.
NCT02009579	II	Nintedanib (IV) Carboplatin (IV) Paclitaxel (IV)	Advanced, persistent, or recurrent cervical cancer	PFS (1.5 years)	A randomized double-blind phase study assessing efficacy of conventional carboplatin/paclitaxel plus nintedanib, a tyrosine kinase inhibitor, compared to conventional chemotherapy in patients with stage IVb disease.

EFS = event-free survival, EGFR = epidermal growth factor receptor, G-CSF = non-pegylated human granulocyte colony stimulating factor, GI = gastrointestinal, GU = genito urinary, OS = Overall Survival, PD-L1 = programmed death-ligand 1, PFS = Progression-free Survival, RP2D = Recommended Phase 2 Dose, RR = Objective Response Rate, TTP = Time to Progression, VEGF = vascular endothelial growth factor

least 6 cycles) in patients with metastatic, recurrent or persistent cervical cancer (NCT02467907). Considering the conclusion of the recruitment and the last update on clinicaltrials.gov on June 2019, the results of this trials are pending. Furthermore, the combination of newer anti VEGFR drugs, such as cediranib or anlotinib, with paclitaxel plus carboplatin is being investigated in current trials (NCT02584478).

The effect of cediranib combined with carboplatin and paclitaxel in patients with metastatic or recurrent cervical cancer has been evaluated in the CIRCCa trial, a randomized double-blind placebo-controlled phase II trial. Cediranib exerted a significant efficacy when added to carboplatin and paclitaxel. PFS was longer in the cediranib group (median 8.1 months [80% CI 7.4–8.8]) than in the placebo group (6.7 months [80% CI 6.2–7.2]), with a hazard ratio of 0.58 (80% CI 0.40–0.85; one-sided p = 0.032). However, an increase in toxic effects (mainly diarrhea, hypertension, and febrile neutropenia) was observed in patients receiving this triple regimen [86].

4.4.2. Paclitaxel and epidermal growth factor inhibitors

Cetuximab, an anti-EGFR antibody, has been evaluated in phase II clinical studies as monotherapy, in combination with conventional chemotherapy (not including paclitaxel) and/or radiotherapy. All the studies were conducted in patients with recurrent or refractory cervical cancer, globally demonstrating modest results [82]. Recently, 108 women with advanced and recurrent cervical cancer were randomized to carboplatin and paclitaxel for 6 cycles with or without cetuximab (400 mg/m^2 one week before starting the cytotoxic drugs, then 250 mg/m^2 weekly) until disease progression or unacceptable toxicity. Event-free survival was the primary endpoint. After a median follow-up of 23 months, 97 progressed and 61 died. Median event-free survival was 4.7 and 6.0 months (one-tail P = 0.43) by receiving carboplatin and paclitaxel and carboplatin and paclitaxel with the addition of cetuximab, respectively; median PFS was 5.2 and 7.6 months (one-tail P = 0.20), respectively; median OS was 17.7 and 17 months (one-tail P = 0.27), respectively. Moreover, there was no difference in the occurrence of severe adverse events with exception for skin toxicity [49].

4.4.3. Paclitaxel and PARP inhibitors

PARP enzymes catalyzes the poly ADP-ribosylation of proteins, which have a critical role in DNA repair for single strand breaks [87]. PARP inhibitors are able to block this complex of enzymes; for this reason, they have been investigated and are currently used in oncological therapy, in particular, for cancers with BRCA mutations [88]. As *in vitro* and *in vivo* studies have suggested that the activity of PARP inhibitors is not limited to tumors with these specific mutations, the effect of these drugs has been investigated also in cervical cancer, not usually associated with hereditary alterations. In a phase I trial, 44 patients received paclitaxel (175 mg/m^2 on day 1), cisplatin (50 mg/m^2 on day 2) and escalating doses of veliparib (from 50 to 400 mg orally two times daily on days 1–7). Cycles occurred every 21 days until progression. Objective RR for 29 women with measurable disease was 34% (95% CI, 20-53%); at 400 mg, the RR was 60% (n = 3/5; 95% CI, 23-88%). Median PFS and OS were 6.2 months (95% CI, 2.9–10.1) and 14.5 months (95% CI, 8.2–19.4), respectively. Dose limiting toxicities (n = 1) were a grade 4 dyspnea, a grade 3 neutropenia lasting ≥3 weeks and febrile neutropenia [89].

4.4.4. Paclitaxel and immunotherapy

Several ongoing trials are testing the addition of immune checkpoint inhibitors to chemotherapy and other targeted therapies (paclitaxel/carboplatin or cisplatin with bevacizumab) in unresectable or recurrent advanced cervical cancer (Table 3). The target of programmed cell death 1/programmed death ligand 1 (PD-1/PD-L1) pathway by using checkpoint inhibitors in order to break immunologic tolerance against tumor is promising [90]. In particular, BCD-100 [NCT03912415, NCT03912402], pembrolizumab [NCT03635567, NCT03367871] and atezolizumab [NCT03556839] are some of the experimental drugs investigated in this setting.

5. Nab-Paclitaxel

Nab-paclitaxel (Nanoparticle, Albumin-Bound Paclitaxel) is a 130-nanimeter, chromophore-free preparation of paclitaxel, which eliminates the need for pre-medication; it has a shorten infusion time and it may have an increased concentration in proximity to the tumor compared to standard preparation. Dose-limiting toxicities of nab-paclitaxel include myelosuppression and peripheral neuropathy [91,92].

Nab-paclitaxel is an FDA-approved drug for the treatment of metastatic breast cancer [93]. However, its activity has been reported in the management of metastatic non-small cell lung cancer, pancreatic and ovarian cancer and melanoma [94,95]. The improved therapeutic and cost-effective indexes of nab-paclitaxel have been demonstrated in comparison to docetaxel, despite its higher overall costs per patient [96].

Nab-paclitaxel has been evaluated for the treatment of recurrent cervical cancer in a phase II trial (as a part of the GOG-127). In this study, 35 taxane-naïve subjects were enrolled and treated with nab-paclitaxel (125 mg/m^2 over 30 minutes on days 1, 8 and 15 of a 28-day cycle). Results demonstrated moderate activity of this drug, with a median PFS and OS of 5.0 and 9.4 months, respectively. Ten subjects had a partial response and 15 subjects had stable disease [96]. In 2012, Alberts *et al*. carried out a study on nab-paclitaxel among 37 patients with persistent or recurrent squamous or non-squamous cervical cancer who have progressed after one prior cytotoxic regimen. Specifically, all the eligible patients had received one prior chemotherapy line and 27 of them (73.0%) had received prior radiation therapy with concomitant cisplatin. According to the favorable pharmacological characteristics of nab-paclitaxel, no premedication for preventing hypersensitivity reaction, nausea or vomiting was required. The median number of nab-paclitaxel cycles was 4 (range 1–15). Among 35 patients, 10 (28.6%, 95% CI: 14.6% – 46.3%) had a partial response and other 15 patients (42.9%) had stable disease. The median PFS and OS were 5.0 and 9.4 months, respectively. The only grade 4 event was neutropenia, which was experienced in 2 patients (5.7%) and resolved after dose reduction. Grade 3 neurotoxicity was reported in 1 (2.9%) patient, improving to grade 2 after dose discontinuation [96]. In 2016, Minion *et al*. evaluated the use of

nab-paclitaxel with or without bevacizumab in patients with recurrent cervical cancer failing prior chemotherapy (platinum plus paclitaxel or topotecan). The median number of nab-paclitaxel cycles was 6.5 (2–19). The median PFS and OS were 4.8 months and 8.9 months (n = 7), respectively. One woman discontinued nab-paclitaxel secondary to peripheral neuropathy, and one women had a vesicovaginal fistula while receiving the combination nab-paclitaxel and bevacizumab [97].

Currently, a single center, non-randomized, open phase II clinical study is evaluating the use of nab-paclitaxel plus nedaplatin for treating patients with advanced, recurrent metastatic cervical cancer (NCT01667211). The results of this trial are unknown despite being started in 2012. Moreover, another interventional open label phase II study is evaluating the activity and safety of nab-paclitaxel (125 mg/m^2 IV weekly on day 1, 8, and 15 every 28 days) for the treatment of patients with persistent or recurrent cervical cancer (NCT00309959). Considering that the last update for this trial on clinicaltrials.gov is on January 2019, the results of this study are still awaited.

It has been assumed that nab-paclitaxel in combination with cisplatin and radiotherapy may have anti-tumor activity in patients with cervical cancer. An ongoing trial on nab-paclitaxel has been started on July 2019. This is a single arm, open-label phase I trial, in which histologically proven stage IB2-IVA cervical cancer patients are being enrolling. These patients receive radiation therapy to pelvis (50.4 Gy in 28 fractions) followed by high-dose-rate intracavitary brachytherapy (30Gy in 5 fractions) with concurrent chemotherapy consisting in weekly cisplatin (40 mg/m^2) and an escalating dose of weekly nab-paclitaxel (from 10 mg/m^2 up to 70 mg/m^2) (NCT04017377) (Table 3).

6. In vitro investigational combinations of paclitaxel

The need for new strategies in the treatment of cervical cancer is demonstrated by the current willingness to test in *vitro* new molecules, eventually in association with conventional cytotoxic drugs, like paclitaxel.

Byun *et al*. investigated the antitumor effect of tetra arsenic oxide (As_4O_6; TAO) *in vitro* and *in vivo* in comparison with cisplatin and paclitaxel. The rational of this study was not only based on the previous satisfying results obtained *in vitro* (with the inhibition of the growth of human cervical cancer cell [Sinha cells] [98]) and *in vivo* (arsenic compounds have been used to treat chronic myeloid leukemia and Hodgkin's lymphoma for more than forty years [99],) but also, because TAO seems to have a synergistic effect in association with paclitaxel on several cancer cell lines (i.e. gastric, cervix, head and neck cancers). Its mechanism may be related to the induction of caspase-3 and PARP-dependent apoptosis [100].

Byun *et al*. observed that TAO inhibited growth and increased apoptosis of cervical cancer cell line (CaSki). More specifically, TAO, paclitaxel and cisplatin obtained, when used in monotherapy, similar rates of tumor apoptosis; anyway, after 48 hours from the administration, the combination of cisplatin and TAO demonstrated an increased apoptosis rate compared with the two other combined agents (cisplatin plus paclitaxel and paclitaxel plus TAO) [101]. The *in vivo* activity of TAO has been tested in a mouse xenograft model in which CaSki cells were implanted. In this prototype, TAO alone had a less antitumor effect than cisplatin or paclitaxel; otherwise, when TAO was employed in combination with the other chemotherapeutic agents, a stronger synergistic antitumor effect was obtained (in particular with cisplatin) [100]. In the future, TAO may be a good candidate for combined regimens with cisplatin or paclitaxel in patients with advanced cervical cancer [99].

Another strategy that seems to be challenging for the development of cervical anticancer therapies, is represented by acting on the cell cycle through the serine/threonine cyclin-dependent kinases (CDK) inhibitors [101,102]. CDK inhibitors act down-regulating survivin through the specific inhibition of its phosphorylation and the consequent disruption of the CDK1-mediated survival checkpoint, a major mechanism involved in cancer cell proliferation [101]. The aim of using these specific inhibitors in cervical cancer is based on the results of preclinical and clinical studies in which it was suggested a direct correlation between survivin expression and tumor cell susceptibility to paclitaxel as well as the ability of these inhibitors in increasing paclitaxel cytotoxicity [103].

In 2005, Pennati *et al*. investigated the cellular effects of a CDK inhibitor, NU6140, for inhibiting cell proliferation and cycle progression in HeLa cells. This study tested the ability of NU6140 to potentiate the apoptotic response to paclitaxel in comparison to purvalanol A, another CDK inhibitor [101]. NU6140 in combination with paclitaxel was capable of increasing more the cell apoptotic rate than paclitaxel plus purvalanol A.

Recently, Xi *et al*. provided preclinical evidence that AT7519, a multitargeted CDK inhibitor, may represent a suitable candidate to overcome chemoresistance in cervical cancer. The authors showed that AT7519 (IC50 range from 0.1 to 1 μM) is effective in treating a panel of chemoresistant cervical cancer cell lines, suppressing phosphorylation of CDK1, CDK2 and RNA polymerase II. More importantly, AT7519 at sublethal concentration remarkably augmented the inhibitory effects of fluorouracil (5-FU) and paclitaxel. The authors also confirmed *in vivo* the efficacy of this drug by using a paclitaxel-resistant cervical cancer xenograft mouse model. These promising findings could support future early clinical trials of combined regimen based on paclitaxel plus AT7519 for the treatment of cervical cancer [104].

7. Conclusion

The prognosis of metastatic, persistent and recurrent cervical cancer continues to be rather poor by using conventional chemotherapy. While the use of paclitaxel in neo-adjuvant chemotherapy combinations is growing employed, paclitaxel plus carboplatin currently represents the milestone of treatment of advanced cervical cancer. Nab-paclitaxel represents a recent investigational option, although prospective phase III trials are needed to validate the early promising findings of this drug. In the near future, novel biological drugs targeting several pathways, including angiogenesis, PARP or CDK, may represent innovative strategies to treat women affected by advanced cervical cancer. These agents may help to enhance the activity of conventional cytotoxic drugs. Nevertheless, there is an urgent need to correctly assess the efficacy of all

innovative strategies in further randomized controlled clinical trials. Moreover, the identification of specific mutations may provide the selection of a more personalized therapeutic program for treating these patients.

8. Expert Opinion

Despite advances in disease prevention by vaccine, screening and early detection/treatment, the global burden of cervical cancer represents a relevant issue. Treatment paradigms in the primary management of cervical cancer are well established. Early lesions are treated surgically and locally advanced lesions are managed by concurrent cisplatin chemotherapy and pelvic radiotherapy. At the moment, the use of neoadjuvant chemotherapy in locally advanced disease is considered yet investigational. For patients with advanced, persistent or recurrent cervical cancer, only systemic palliative chemotherapy can often be used. For this reason, the prognosis of these patients is poor and, thus, there is a need for effective novel chemotherapy regimens in this clinical setting.

Paclitaxel has been the first microtubule-stabilizing agent identified and considered as significant part of the standard chemotherapy regimens for treating cervical cancer. In particular, the combination of paclitaxel with platinum-derived drugs has represented and represents today the cornerstone of advanced cervical cancer therapy, in particular for women with recurrent and persistent disease.

Even if paclitaxel has a high activity against this neoplasia, the several disadvantages of this hydrophobic cytotoxic agent should be underscored. The need for prolonged infusion times and for premedication (steroids and/or histamine-release blocking agents) are limitations related to paclitaxel. Moreover, the pronounced neurotoxicity (peripheral sensory neuropathy) is a dose limiting and cumulative adverse event. Ultimately, the emergence of drug resistance related to this drug should be considered.

Currently, researchers are focalized on finding alternative taxanes derivatives. In 2005, the FDA approved the formulation of nab-paclitaxel. This drug not only has an improved solubility but also it has reduced systemic toxicity. Previous studies on nab-paclitaxel obtained preliminary promising results for treating cervical cancer; at the moment, some studies are ongoing (Table 2).

The remarkable clinical development of nab-paclitaxel has ensured investigators and various other nano-formulations and taxane conjugates have been researched. However, only a small part of the nano-formulations has reached the experimental clinical status. Poly(l-glutamic acid)-paclitaxel (PG-TXL) belongs to the few formulations reaching phase III clinical trials in oncology; unfortunately, the development of PG-TXL stopped in 2016 due to the inability to show significant improvement over current standard care; paclitaxel bound to DHA (a natural fatty acid) has advanced to phase III trials for metastatic melanoma; cabazitaxel, a semisynthetic derivative of docetaxel, obtained a notable antitumor activity in preclinical and clinical studies in docetaxel-refractory clinical settings. In contrast to the first-generation taxanes, this compound is a poor substrate for P-glycoprotein. Cabazitaxel was approved by the FDA in 2010 for the treatment of hormone-refractory prostate cancer. New studies on derivative of conventional taxanes for cervical cancer are demanding [105].

Regarding the issue related to drug resistance development during conventional therapies for cervical cancer, it could be interesting to identify clinical and tumor factors that may be predictive of non-response to cisplatin-based chemotherapy; this may allow identifying those patients who should participate to trials focalizing on other no platinum-containing regimens. In particular, it has been demonstrated that previous platinum-exposure, in combination or not to radiotherapy, tends to significantly reduce responses to subsequent platinum-based chemotherapy, regardless of the use of platinum type. It has been supposed that previous radiotherapy and/or chemotherapy may select radio and chemo-resistant clones. Moreover, severe radio-induced blood vessel disruption may lead to lower perfusion of the relapsed cancer and, therefore, reduced concentration of cytotoxic agents within the tumor. Hypoxia resulting from poor blood supply may lower the proliferating fraction of cancer and reduce the potential cytotoxic effects of chemotherapeutic agents.

The approval of bevacizumab for metastatic cervical and ovarian cancer paved the way to a new era in gynecological oncology [106]. The addition of innovative molecular targeted agents to cytotoxic drugs represents an exciting area, which should be fully investigated in the near future [107,108]. Several targeted drugs are being evaluated in ongoing clinical trials in combination with paclitaxel (Table 3): some of them reported preliminary encouraging results, although more data are needed for accurate conclusion on each combinatory regimen. As future trials are being designed, the addition of novel biologic agents will hopefully provide benefit to this population of patients. Moreover, potential enrollment on new phase II-III trials may allow for a rapid access to these investigational agents for women with advanced and recurrent cervical cancer.

At present, primary and acquired resistance to paclitaxel are common and significantly limit the clinical efficacy of this drug. Noninvasive tests are required to predict patients' response to paclitaxel. It may allow to avoid the often-devastating side effects of this drug in patients to who this compound would offer limited benefit. Ideally, in the near future optimal oncological therapy would be selected based on the presence of molecular markers individually predicting tumor susceptibility to chemotherapeutic agents. New evidence suggests that microtubule-binding proteins (MBPs) could regulate paclitaxel sensitivity in a wide range of cancer types; moreover, these proteins could also be handled to induce paclitaxel sensitivity. Improved understanding about how these proteins can be assayed and interpreted may allow to draw a conclusion on this topic. Thus, even if it has been 23 years since paclitaxel was approved by the FDA, there are still very active investigations in the clinical applications of this drug, especially through drug combinations or as next-generation toxoids. The development of the new formulation of paclitaxel as nano-formulations and taxane conjugates represent the new era for the

application of chemotherapy in patients with cervical cancer, especially those with advanced, persistent or recurrent stage.

Clinical trials on the use of novel molecules are required: the results could transform paclitaxel into the most suitable weapon for the treatment of cervical cancer.

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