Critical Reviews in Oncology / Hematology 137 (2019) 9–17

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Systemic therapy in cervical cancer: 30 years in review

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ARTICLE INFO

Keywords:
Cervical cancer
Chemotherapy
Targeted therapy
Immunotherapy

ABSTRACT

Advanced-inoperable cervical cancer is a challenging entity due to increased percentage of locoregional and distant recurrences. Furthermore, recurrent cervical cancer not amenable to radical treatment as well as de novo metastatic disease are considered incurable with dismal prognosis. Well-designed clinical trials conducted during the last 30 years have revealed the active chemotherapeutic agents as well as their optimal combinations. The rational approach that has led to the current treatment algorithms as well as the introduction of targeted therapies based on the knowledge of the molecular pathogenesis of the disease are discussed in this review.

1. Introduction

"Prevention is better than cure" wrote Hippocrates and this is particularly true for cervical cancer. Currently, the third most common cause of cancer worldwide and one of the most important causes of cancer-related death (Jacques et al., 2010), cervical cancer incidence and mortality are anticipated to decline in the forthcoming years with the approval of Human Papilloma Virus (HPV) vaccines. In addition, early detected cervical cancer remains a curable disease, treated by surgical resection and concurrent chemoradiation (Monk et al., 2007). However, cervical cancer still represents a major public health problem even in developed countries: 54 517 new cases of invasive cervical cancer are diagnosed in Europe every year and 24 874 women die of this disease. The burden is even greater in developing countries that account for the 90% of the women that die from cervical cancer worldwide (Jacques et al., 2010), underlying the need for improved therapeutic options.

Currently, chemotherapy is used in patients with cervical cancer as an addition to definitive locoregional treatments (surgery or radiotherapy) to improve their outcome, as well as palliative therapy for patients with recurrent or *de novo* metastatic disease. These treatment modalities are applied independent of the histology of the disease that may impact prognosis as well as response to treatment. Squamous cervical carcinomas are the predominant histology accounting for 75% of cases. Adenocarcinomas represent 20% but its incidence is constantly rising possibly due to the implementation of screening programs (Williams et al., 2015). In addition, TCGA analysis has revealed specific clusters of cases defined by different molecular features that could serve as potential therapeutic targets (The Cancer Genome Atlas Research N et al., 2017). Furthermore, targeted therapies have emerged as a new asset that could improve along with cytotoxic therapies the survival of patients with advanced disease. These three aspects of systemic therapy usage in advanced or metastatic cervical cancer will be analyzed in this review.

2. Chemotherapy as a part of multimodality approach for the cure of advanced cervical cancer

Historically, locally advanced cervical cancer was treated with external beam radiation. In 1999 though, a new approach was adopted for the treatment of advanced cervical cancer (Rose, 2002, 2000). This year the National Cancer Institute (NCI) released a Clinical Announcement stating that cisplatin-based chemotherapy, concurrent with radiotherapy was the new standard of care for locally advanced cervical carcinoma (The National Cancer Institute Clinical Announcement on Cervical Cancer, 1999). This decision was based on five phase III randomized clinical trials that were then announced (Eifel et al., 2004; Peters et al., 2000; Keys et al., 1999; Morris et al., 1999; Rose et al., 1999; Whitney et al., 1999). Criticism regarding the differences in the treatment of control arms and inconsistency on the definition of outcomes between trials led to a meta-analysis based on individual patient data from previous randomized trials. This meta-analysis confirmed the established notion that concurrent chemoradiation (CCRT) outweighs radiotherapy alone offering an absolute survival benefit of 6% in 5 years (from 60 to 66%) (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008). An analogous improvement was also

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https://doi.org/10.1016/j.critrevonc.2019.02.009
Received 21 July 2018; Received in revised form 9 December 2018; Accepted 24 February 2019

seen in disease free survival and locoregional or distant recurrence rate, despite the benefit of chemoradiotherapy on overall survival was decreasing with increasing disease stage (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008). To address this issue, a large randomized trial comparing chemoradiotherapy with weekly cisplatin versus radiotherapy alone was conducted in patients with clinical stage IIIB squamous carcinoma of the cervix (Shrivastava et al., 2018). The study confirmed the superiority of combined radiotherapy in both OS and DFS and the magnitude of benefit was analogous to previously presented studies (Shrivastava et al., 2018).

Despite these advances in cervical cancer treatment 5-year OS for stage II patients reaches 65% and this percentage drops to 40% for patients with more advanced disease (stage III-IVA) (Monk et al., 2007). Therefore, the disease will recur in a substantial percentage of patients and unfortunately, then the prognosis is rather dismal. The role of chemotherapy in improving survival is therefore further exploited in three directions:

a Is weekly cisplatin regimen the best option for CCRT?
b Could adjuvant chemotherapy after established chemoradiation improve the outcome for all or a subset of patients?
c Could neoadjuvant chemotherapy in conjunction with surgery set an alternative to chemoradiation?

2.1. Chemotherapy regimens used in concurrent chemoradiation

Three of the initial randomized clinical trials that were referenced in the NCI announcement in 1999 did not use weekly cisplatin at 40 mg/m^2 as the preferred regimen for concurrent CCRT. In the RTOG90-01 protocol (Eifel et al., 2004), the SWOG/RTOG/GOG intergroup study (Peters et al., 2000) and the GOG85 trial (Whitney et al., 1999) cisplatin at doses ranging from 50 to 75 mg/m^2 and continuous 5-FU infusion for 4 days were administered each 3 weeks concurrent with radiotherapy. In the GOG120 protocol that used the same eligibility criteria with the GOG85 trial, both the initial publication (Rose et al., 1999) as well as the long term follow-up (Rose et al., 2007) showed that the weekly cisplatin regimen was equally effective with a cisplatin/5FU/hydroxyurea combination in terms of disease free survival and overall survival. Treatment with cisplatin alone was though less toxic than the three drug combination (Rose et al., 1999). In addition, the progression free survival at 6 years for the cisplatin/5FU combination in the GOG85 protocol (Whitney et al., 1999) was equivalent with the progression free survival at 4 years with cisplatin alone in the GOG120 protocol (Rose et al., 1999). Since the combination regimen adds to toxicity, once per week cisplatin administration concurrent with radiotherapy was established as the standard of care for advanced cervical cancer (Monk et al., 2007). Randomized trials that examined the benefit of cisplatin-based CCRT are summarized in Table 1.

Up to now there are no phase III randomized trials directly comparing the weekly cisplatin regimen either with cisplatin-based combinations or with other regimens, apart from the GOG165 protocol (Lanciano et al., 2005). This study compared the standard cisplatin regimen with continuous 5FU administration during the radiation period in patients with IIb to IVa cervical cancer, but it was prematurely closed due to futility (Lanciano et al., 2005). Despite these evidence support weekly cisplatin as the optimal radiosensitizing regimen for CCRT in advanced cervical cancer, this idea was later set in doubt. Randomized trials examining CCRT with non-platinum containing regimens indicated superiority of CCRT versus radiotherapy alone (Lorvidhaya et al., 2003; Roberts et al., 2000; Thomas et al., 1998). The Cochrane individual patient data metanalysis examining all randomized trials showed that the benefit associated with chemoradiotherapy may not be associated with platinum (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008). Despite this conclusion is not based on direct comparisons, it is suggested that non-platinum based chemoradiotherapy also provides benefit versus radiotherapy

Table 1
Randomized trials comparing Radiotherapy with Cisplatin-based concurrent Chemoradiation as definitive treatment for cervical cancer.

Author	Stage	Number of patients	Comparison	Chemotherapy	HR for OS
Eifel et al., 2004	IB-IIA with T > 5 cm, IIB-IVA	389	RT vs CCRT	Cisplatin 75 mg/m^2 D1 and 5-FU 4000 mg/m^2 D1-5 q3w	0.49 (95%CI 0.36-0.66) in favor of CCRT
Peters et al., 2000	IA_2 -IIA	243	RT vs CCRT	Cisplatin 70 mg/m^2 D1 and 5-FU 4000 mg/m^2 D1-4 q3w	1.96 against RT
Whitney et al., 1999	IIB-IVA	368	RT + HU vs CCRT	Cisplatin 50 mg/m^2 D1 and 5-FU 4000 mg/m^2 D2-5 q4w or Hydroxyurea 80 mg/m^2 twice a week	0.74 (95%CI 0.58-0.95) in favor of CCRT with Cisplatin-5FU
Rose et al., 1999, 2007	IIB-IVA	575	RT + HU vs CCRT	**Arm A**: Cisplatin 40 mg/m^2 weekly, **Arm B:** Cisplatin 50 mg/m^2 D1 and 5-FU 4000 mg/m^2 D2-5 q4w and Hydroxyurea 2 g/m^2 twice a week, **Arm C:** Hydroxyurea 3 g/m^2 twice a week	Arm A vs C: 0.57 (95%CI 0.43-0.75) and Arm B vs C: 0.51 (95%CI 0.38-0.67)
Keys et al., 1999	IB	374	RT vs CCRT	Cisplatin 40 mg/m^2 weekly	0.54 (95%CI 0.34-0.86) in favor of CCRT
Morris et al., 1999	IIB-IVA	403	RT vs CCRT	Cisplatin 75 mg/m^2 D1 and 5-FU 4000 mg/m^2 D1-5 q3w	0.48 (95%CI 0.35-0.67) in favor of CCRT
Shrivastava et al., 2018	IIIB	850	RT vs CCRT	Cisplatin 40 mg/m^2 weekly	0.82 (95%CI 0.68-0.98) in favor of CCRT

HR = Hazard Ratio, OS = Overall Survival, RT = Radiotherapy, CCRT = Concurent Chemoradiation, HU = Hydroxyurea, 5FU = 5 – Flurouracil.

Table 2
Randomized studies examining the role of Neoadjuvant Chemotherapy prior to definitive Radiotherapy in cervical cancer.

Author	Stage	Number of patients	Comparison	Chemotherapy	OS
Chiara et al., 1994	IIB-III	64	RT vs CT + RT	Cisplatin 60 mg/m^2 q2weeks for 2 Cycles prior RT and for 4 Cycles after RT completion	3-year OS 83% for RT vs 72% for CT + RT
Leborgne et al., 1997	IB-IVA	96	RT vs CT + RT	Cisplatin 50 mg/m^2 and Vincristine 1 mg/m^2 D1,11 and 21, Bleomycin 25 mg/m^2 D1-3,11-13 and 21-23 prior to RT	mOS 53 months RT vs 32months (CT + RT)
Souhami et al., 1991	IIIB	107	RT vs CT + RT	Cisplatin 50 mg/m^2 D1,22, Vincristine 1 mg/m^2 D1,8,22,29, Mitomycin 10 mg/m^2 D1, Bleomycin 10U weekly for 3 cycles prior to RT	5-year OS 39% for RT vs 23% for CT + RT
Sundf et al., 1996	IIIB-IVA	96	RT vs CT + RT	Cisplatin 100 mg/m^2 D1 and 5-FU 1000 mg/m^2 D1-5 q3w for 3 cycles prior to RT	mOS 22 months RT vs 26 months (CT + RT)
Symonds et al., 2000	IIB-IVA	204	RT vs CT + RT	Methotrexate 100 mg/m^2 and Cisplatin 50 mg/m^2 q2weeks for 3 cycles prior to RT	3-year OS 40% for RT vs 47% for CT + RT
Tattersall et al., 1995	IIB-IVA	260	RT vs CT + RT	Cisplatin 60 mg/m^2 and Epirubicin 110 mg/m^2 q3w for 3 cycles prior to RT	mOS 37 months RT vs 22 months (CT + RT), P = NS
Herod et al., 2000	IB-IVA	177	RT vs CT + RT	Bleomycin 30UI, Ifosfamide 5 g/m^2 Cisplatin 50 mg/m^2 q3w for 2-3 cycles prior to RT	mOS 24 months RT vs 36 months (CT + RT), P = NS

OS = Overall Survival, RT = Radiotherapy, CT = Chemotherapy, NS = Non-significant, UI = International Units.

alone and could be used as an alternative in women that cannot tolerate cisplatin (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008).

Several smaller studies have also investigated the optimal CCRT regimen in various settings. Triweekly cisplatin was not superior to the weekly regimen in adjuvant chemoradiation in patients with IB to IIB disease that had already undergone radical hysterectomy and pelvic lymph node dissection (Lee et al., 2011). The 5-day triweekly scheme was superior to weekly administration in regards to local relapse rate (Nagy et al., 2012). In patients with more advanced disease though (stages IIB-IVA) triweekly cisplatin at 75 mg/m^2 was more efficacious than the weekly regimen in a small open-label randomized trial (Ryu et al., 2011). Platinum analogs have also been tested either alone or in combination in small studies: Carboplatin and the platinum analogue nedaplatin that is under investigation in Japan have shown activity and the results in some studies are very promising that may warrant further investigation in phase III trials (Lee et al., 2007; Kim et al., 2006; Niibe et al., 2008).

2.2. The role of adjuvant chemotherapy in the treatment of advanced cervical cancer

The role of adjuvant chemotherapy after CCRT in advanced cervical cancer has not been fully elucidated. Despite CCRT, disease will recur in approximately 40% of patients and perhaps adjuvant chemotherapy could offer improved control of subclinical micrometastasis. This was initially indicated in the Cochrane metanalysis showing that adjuvant chemotherapy reduced substantially the risk of death when added to CCRT (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008). Analogously, a phase III trial comparing the established CCRT regimen with chemoradiation with a gemcitabine/cisplatin weekly scheme followed by 2 additional cycles of chemotherapy with the same combination (Dueñas-González et al., 2011) proved superiority of the gemcitabine cisplatin combination in terms of PFS, OS and relapse rate (Dueñas-González et al., 2011). However, these studies were never planned to address the role of adjuvant chemotherapy (Peters et al., 2000; Dueñas-González et al., 2011; Kantaradzic et al., 2004). It should also be noted that the improved efficacy of the gemcitabine/cisplatin regimen was associated with increased Grade 3/4 hematological and gastrointestinal toxicities and 4 deaths in the experimental arm (Dueñas-González et al., 2011). Also, due to the study design, the exact role of adjuvant chemotherapy cannot be easily interpreted. The ongoing OUTBACK study (GOG274, NCT01414608) will answer the role of adjuvant chemotherapy, as patients in the experimental arm will receive in addition to the established CCRT, four cycles of paclitaxel and carboplatin. It should be noted though that a recent phase III trial examining the role of paclitaxel/carboplatin chemotherapy prior to established CCRT in patients that had undergone surgery for IB to IIB cervical cancer, did not show improvement in PFS (Sehouli et al., 2012).

2.3. The role of neoadjuvant chemotherapy in the treatment of locoregional cervical cancer

Neoadjuvant chemotherapy (NACT), used prior to radical locoregional treatments surgery or radiotherapy, is an attractive option for primary cervical cancer. Since cervical cancer is considered chemosensitive (Friedlander et al., 1983), the rationale of NACT is based on possible tumor shrinkage that would constitute operable a previously inoperable disease and the killing of the hypoxic fraction of cancer cells that would provide radiosensitivity to the remaining mass. Under this perspective, several studies were conducted during 80 s and 90 s examining the effect on NACT prior to radiotherapy that was considered that period the standard of care for locally advanced disease. In these studies cisplatin (Chiara et al., 1994), platinum based regimens (Leborgne et al., 1997; Souhami et al., 1991; Sundf et al., 1996;

Symonds et al., 2000; Tattersall et al., 1995; Herod et al., 2000) or vinorelbine (Lacava et al., 1997) were used for NACT, but no survival benefit was demonstrated versus radiotherapy alone. Randomized studies, examining the role of NACT prior to definitive RT in cervical cancer are presented in Table 2. A phase II trial, prospective, non-randomized in a reference center in Brazil testing neoadjuvant Gemcitabin-Cisplatin for 2 cycles followed by Chemoradiation in locally advanced disease did not manage to improve overall response rate (de Azevedo et al. (2017)). According to a meta-analysis including 18 trials incorporating NACT prior to radiotherapy, there was a survival advantage for NACT but only when higher doses of cisplatin were used ($> 25\,mg/m^2$) for short courses (Anon, 2003). That was attributed to the development of resistant tumor clones dependent on the schedule and the intensity of the chemotherapy regimen used (Anon, 2003) and NACT prior to radiotherapy was never incorporated into common clinical practice.

NACT could though be of interest prior to radical surgical treatment of cervical cancer. This is a common practice in developing countries where access to radiotherapy is rather limited (Basile et al., 2006) and is based on the rationale of tumor shrinkage allowing for complete excision with negative surgical margins (Sardi et al., 1990). This modality has already been tested in several trials showing benefit over surgery alone. A retrospective study of an Italian group, which included 245 patients who received NACT with a platinum regimen followed by radical surgery, revealed that grading, tumor size at diagnosis and parametrial involvement influence 5-year OS and 2-year PFS with the exception of tumor grade (Marchetti et al., 2018). The most compelling data though against the neoadjuvant approach in cervical cancer were recently presented (Gupta et al., 2018). In a randomized phase III study comparing in locally advanced (stages IB2 to IIB) squamous cervical cancer NACT – comprising of three cycles of paclitaxel and carboplatin – followed by radical surgery with CCRT, the later resulted in superior Disease Free Survival (Gupta et al., 2018). This further enhanced the notion that CCRT remains the standard of care for these patients. With a slight different chemotherapy backbone these approaches are now being compared also in the EORTC 55994 (NCT00039338) study. The accrual has been completed and 626 patients mainly with squamous histology (84.2%) have been enrolled. The pathologic Complete Response rate in the NACT followed by radical hysterectomy arm was 22.3% (del Carmen and Rice, 2017). However, the primary endpoint in this study is overall survival, and the results are eagerly anticipated within 2019.

3. Chemotherapy for recurrent or metastatic cervical cancer

Despite the existence of population screening programs for early detection and the regulatory approval of Human Papilloma Virus vaccines, approximately 6% of the women with cervical cancer are presented with metastatic disease (Friedlander and Grogan, 2002). Furthermore, the disease will recur in one third of the patients receiving primary treatment for locally advanced disease. Historically, cisplatin monotherapy at $50\,mg/m^2$ every three weeks was considered as the standard of care since the publication of the GOG26 clinical trial (Thigpen et al., 1979, 1981). That was a phase II study conducted by the GOG to recognize active agents against recurrent gynecological malignancies. In that era, radiotherapy was the established treatment for patients with locally advanced disease. Therefore, most of the patients included in the GOG26 study were chemonaive resulting in 50% response rate to cisplatin treatment (Thigpen et al., 1981). The overall response rate in the study – including patients previously treated with chemotherapy – reached 38% with acceptable toxicity (Thigpen et al., 1981). Subsequent clinical trials evaluated the efficacy of different schedules and doses of cisplatin administration (Bonomi et al., 1985; Lele and Piver, 1989; Reichman et al., 1991). These studies achieved response rates between 17%–38% and failed to increase median time to progression or overall survival in comparison to the standard regimen. Platinum analogs carboplatin and iproplatin were also evaluated in an effort to reduce toxicity (Weiss et al., 1990; Arseneau et al., 1986; Lira-Puerto et al., 1991; McGuire et al., 1989), but the results were inferior to that of the established cisplatin regimen.

The early phase II trials showing significant response to cisplatin included predominantly chemotherapy naïve patients. The introduction of chemoradiation with cisplatin as the primary treatment of patients with locally advanced cervical cancer as well as the modest survival of the patients with recurrent or metastatic disease despite palliative chemotherapy prompted the investigation of non-platinum compounds activity in cervical cancer. Among several drugs tested in phase II trials paclitaxel (McGuire et al., 1996; Kudelka et al., 1996) – especially in cervical non-squamous carcinomas (Curtin et al., 2001) – camptothecin derivatives irinotecan (Verschraegen et al., 1997; Lhommé et al., 1999; Look et al., 1998a) and topotecan (in 5-days dosage schedules) (Muderspach et al., 2001; Bookman et al., 2000), vinorelbine (Morris et al., 1998) and ifosfamide (Carvellino et al., 1990) showed modest activity in this group of patients treated with cisplatin.

The above results also prompted to combine these agents with cisplatin attempting to combinations of paclitaxel and cisplatin (Moore et al., 2004), ifosfamide with mesna and cisplatin (Omura et al., 1997) and topotecan – used in a 3-day regimen at $0{,}75\,mg/m^2$ to reduce myelotoxicity – with cisplatin (Long et al., 2005) were compared with the established cisplatin monotherapy. All three combinations increased Progression Free Survival but only the combination of topotecan with cisplatin increased median overall survival statistically significant (Long et al., 2005). In the later protocol (GOG 179) there was also a third comparison arm using the Methotrexate Vinblastine Adriamycin Cisplatin (MVAC) regimen that had shown substantial activity in previous phase II studies (Papadimitriou et al., 1997; Long et al., 1995), but that arm was suspended early due to treatment related deaths (Long et al., 2005). It should also be noted that the GOG179 was conducted in parallel with the approval of cisplatin as radiosensitizing agent in locally advanced disease. Therefore, while balanced in both investigational groups, 40% of patients had not received prior radiosensitizing cisplatin and Cox regression analysis showed that the effect of combination regimen was less beneficial in the population that had received chemoradiation despite remained statistical significant (Long et al., 2005).

GOG179 demonstrated the superiority of the topotecan cisplatin combination over cisplatin monotherapy in the metastatic/recurrent setting in terms of overall survival. In the GOG 169 protocol the paclitaxel – cisplatin combination did not met its primary endpoint to increase OS in comparison to cisplatin. However, this combination was also active and the result was possible confounded by the inclusion of patients with PS = 2, since poor performance status is a well established adverse prognostic factor in cervical carcinomas (Moore et al., 2010). The same period two other platinum-based combination also increased PFS demonstrating activity in recurrent cervical cancer, namely cisplatin in combination with either vinorelbine (Morris et al., 2004) or gemcitabine (Brewer et al., 2006). In the light of these studies, GOG conducted the 204 protocol aiming to compare initially paclitaxel – cisplatin and topotecan – cisplatin combinations. After the publication of phase II studies two more arms with gemcitabine – cisplatin and vinorelbine-cisplatin combinations were added in the protocol. This study (Monk et al., 2009a) was though terminated early after interim analysis for futility. No superiority between arms was demonstrated in terms of OS, PFS and Response, despite there was a trend in all these endpoints favouring paclitaxel – cisplatin as the preferred combination. Regarding toxicities, myelotoxicity was less for the gemcitabine-cisplatin regimen, in combination. Therefore, despite the early termination of this study due to futility, it provided valuable information that may help tailoring the appropriate therapy for each patient.

Despite the improvements in management of metastatic or recurrent cervical cancer through the above presented studies, only about a third of the patients will respond to the treatment and median overall

survival does not exceeds 12 months. In addition, recurrence of locally advanced disease after chemoradiation may be an indication of resistance to platinum containing regimens. To address these issues investigators evaluated platinum based triplets and quartlets containing active regimens as well as non-platinum combinations. While many of these multi-drug combinations showed substantially activity in small phase II studies (Papadimitriou et al., 1997; Long et al., 1995; Buxton et al., 1989; Ramm et al., 1992; Murad et al., 1994; Zanetta et al., 1999; Stornes et al., 1994; Fanning et al., 1995; Alberts et al., 1981; Weiner et al., 1988; Rustin et al., 1988), these results were not reproduced in phase III trials (Long et al., 2005; Bloss et al., 2002). Finally, the GOG240 protocol has recently investigated the activity of the paclitaxel-topotecan combination based on data showing synergistic activity of the camptothecin derivatives with microtubule inhibitors (Bahadori et al., 2001). In the interim analysis though, this non-platinum combination was not superior to the paclitaxel-cisplatin regimen as presented in the 2013 ASCO conference (Tewari et al., 2013).

Non-inferiority of Paclitaxel-Carboplatin combination compared to Paclitaxel-Cisplatin combination was concluded once again in the JCOG0505 trial which compared these two regiments in patients who had received maximum one cisplatin-containing line of chemotherapy including chemoradiation and no prior taxane therapy (Kitagawa et al., 2015). Paclitaxel-Carboplatin combination proved itself non-inferior regarding progression-free survival 6.2 vs 6.9 months, HR, 1.041; 95% CI, 0.803–1.351) and overall survival (17.5 vs 18.3 months, HR 0.994; 90% CI 0.789–1.253). Cisplatin combination proved superior mainly in the subgroup of patients who had not been previously exposed to it. Administration of paclitaxel in a 3-hour infusion rather than in 24-hour infusion, along with the results shown before suggests that Paclitaxel-Carboplatin is a viable combination especially in patients who had undergone prior platinum chemotherapy.

4. The role of targeted and biological therapies in the recurrent or metastatic cervical cancer

About one third of patients with recurrent or metastatic cervical cancer will respond to platinum-based chemotherapy. However, these responses are usually partial and of short duration. Therefore, the benefit associated with cytotoxic chemotherapy in these patients has reached a plateau offering a median survival of approximately a year. This underlines the need to improve our understanding over the pathogenesis of the disease and to recognize molecular targets with therapeutic potential.

Cervical cancer is a HPV-related disease. The proteins of the viral oncoproteins E6 and E7 degrade p53 and pRb proteins respectively, abrogating these two major cellular oncosuppressive pathways, allowing uncontrolled cellular proliferation (Ibeanu, 2011). In addition to that key molecular event, E6 and E7 oncoproteins also deregulate the apoptotic machinery, the expression of the cellular adherence proteins and the terminal differentiation of the cervical epithelial cells, the expression of the telomerase (hTERT) gene (Jiang et al., 2012) and finally angiogenesis (Ibeanu, 2011). Regarding the later, it is known that E7 enhances the transcriptional activity of Hypoxia Inducible Factor 1 (HIF1a) – a potent inducer of VEGF – and also that both E6 and E7 augment the expression of VEGF splice variants (Toussaint-Smith et al., 2004) (Fig. 1). Furthermore, increased expression of VEGF adversely affects survival in cervical cancer patients treated with radiotherapy (Gaffney et al., 2003).

To investigate the clinical efficacy of anti-VEGF therapies in cervical cancer GOG conducted a phase II study (GOG-227C) in patients with metastatic or recurrent cervical cancer that had previously received radiotherapy and up to two lines of chemotherapy (Monk et al., 2009b). In this population monotherapy with the anti-VEGF antibody bevacizumab resulted in objective responses in 11% of the patients, while PFS and OS were 3,4 and 7,29 that was comparable with the historical data of phase II trials examining several chemotherapy regimens in cisplatin pretreated patients (Bookman et al., 2000; Look et al., 1998b; Mannel et al., 2000; Rose et al., 1996, 1998; Schilder et al., 2000). In another phase II trial, bevacizumab was added to the cisplatin-topotecan combination showing significant activity. Median OS in this study reached 13,2 months but with substantial toxicity since about 75% of the patients required hospitalization for toxicities management (Zighelboim et al., 2013). These findings prompted to a phase III trial examining the role of bevacizumab incorporation in the standard chemotherapeutic regimens for recurrent or metastatic cervical cancer (GOG-240). Final analysis showed that bevacizumab addition improved both PFS and OS (17.0 months vs. 13.3 months; hazard ratio for death, 0.71; 98% confidence interval, 0.54 to 0.95; P = 0.004 in a one-sided test) in comparison to chemotherapy alone – independent of the chemotherapeutic regimen used (platinum-based or non-platinum) (Tewari et al., 2013). Bevacizumb increased median OS by approximately 4 months and this is the first time that a biological agent improved overall survival in gynecological cancers. Increased rate of known adverse events (bleeding, thromboembolic events, gastrointestinal fistulas, hypertension) was noted in patients receiving bevacizumab, without though affecting patients' quality of life in a significant manner (Tewari et al., 2013).

Currently, no predictive biomarkers have been identified for bevacizumab administration, not only for cervical cancer but for the remaining indications of the drug as well. Several studies have revealed possible prognostic role of VEGF expression in cervical carcinomas (Gadducci et al., 2013). However, these results should be further validated prospectively. GOG-240 study prospectively validated the prognostic significance of Moore's criteria (African-American ancestry, ECOG-PS 1, pelvic disease, prior platinum based treatment and PFS of less than 1 year) (Moore et al., 2010). Despite, the subgroup analysis in this study revealed that the survival benefit from the addition of bevacizumab to chemotherapy was consistent across all groups (Tewari et al., 2014), the magnitude of benefit was greatest in the moderate and high risk subgroups according to Moore criteria (5.8 months increase in median OS) (Tewari et al., 2015). In the low-risk subgroup though the benefit from bevacizumab addition was small [HR for OS 0.96 (95% CI 0.51–1.83, $P = 0.9087$].

Tyrosine Kinase Inhibitors (TKIs) with anti-angiogenic activity have been also tested in recurrent cervical cancer. No objective responses were noted in a phase II study with sunitinib in patients that had received up to one prior chemotherapy regimen (Mackay et al., 2010). Instead, a higher rate of fistula formation was observed in this population (Mackay et al., 2010). Responses were also poor with another multikinase inhibitor, pazopanib that was tested in a phase II trial in chemotherapy naïve patients (study VEG105281) (Monk et al., 2010). Overall response rate reached 9%, but median OS was approximately 50 weeks (Monk and Pandite, 2011) that is comparable with historical data from other active agents in cervical cancer (Tewari and Monk, 2005). Finally, the dual VEGF-R2 and bFGF-R inhibitor brivanib is under examination in the GOG-227 G protocol in patients that have received at least one prior chemotherapy regimen for their cervical cancer.

Apart from angiogenesis, EGFR activated pathways are also implicated in the pathogenesis of cervical carcinomas. EGFR is overexpressed in the majority of newly diagnosed cervical carcinomas, is an adverse prognostic factor for the survival of these patients and is also predicts poor response to cytotoxic agents and radiotherapy (Noordhuis et al., 2009; Kersemaekers et al., 1999). Although EGFR inhibition seemed a promising therapeutic target phase II studies investigating either EGFR tyrosine kinase inhibitors (erlotinib and gefitinib) monotherapy in pre-treated patients for recurrent or metastatic disease (Goncalves et al., 2008; Schilder et al., 2009), or cetuximab (an anti-EGFR monoclonal antibody) as monotherapy (Santin et al., 2011) or in combination with cisplatin (Farley et al., 2011) showed only limited activity. Finally, the VEG105281 study apart from pazopanib also examined the efficacy of the dual EGFR and Her-2/new tyrosine kinase

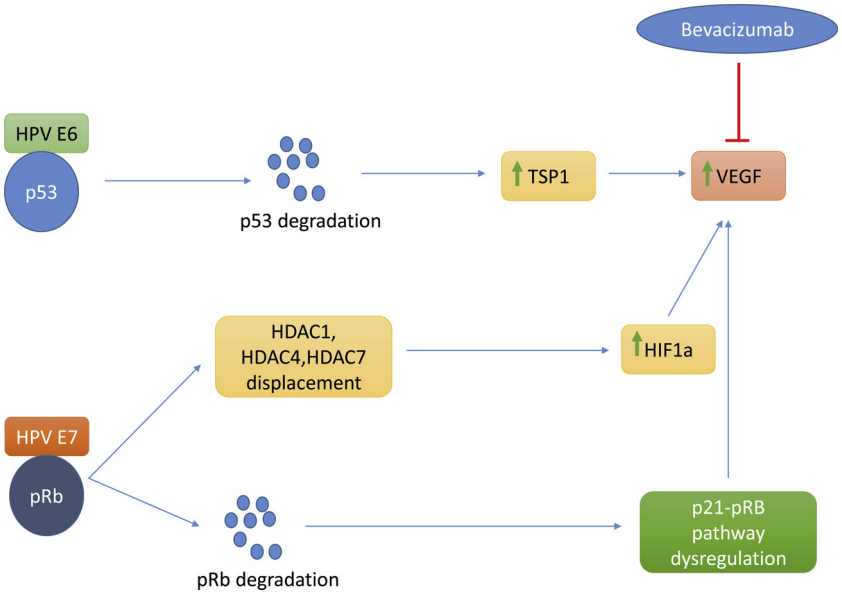

Fig. 1. Molecular pathways of HPV infection and targets for therapy.

inhibitor lapatinib as well as their combination investigating the activity of the dual inhibition of angiogenesis and EGFR driven pathways. The combination arm was terminated in the interim analysis due to futility and increased toxicity, while lapatinib monotherapy produced poor responses (5%) and had a shorter PFS in relation to pazopanib (Monk et al., 2010).

5. Recent advances in the use of immunotherapy in cervical cancer

There is a strong rationale supporting the use of immunotherapy in cervical cancer due to the implication of HPV in its oncogenesis leading to antigens production. Under this perspective, several immunotherapeutic approaches have been tested in cervical cancer treatment.

ADXS11-001 is a live attenuated *Listeria monocytogenes* bioengineered molecule secreting an HPV-16-E7 fusion protein which targets HPV transformed cells, by promoting the differentiation of cytotoxic T-Lymphocytes, which infiltrate the tumor and destroy cancer cells. A Phase II clinical trial, included 110 Indian patients with recurrent or persistent cervical carcinoma treated with ADXS11-001 at 1×10^9 CFU (Colony Forming Units) with or without cisplatin (Basu et al., 2018). This study demonstrated an overall disease control rate of 43% and a 36% rate of 12-month survival. A phase III trial, testing ADXS11-001 plus chemo-radiation in high-risk locally advanced cervical cancer, is currently ongoing (Clinical trials.gov NCT02853604).

Recently, anti-PD1 antibody pembrolizumab granted FDA approval for use in patients with metastatic cervical cancer that have received at least one prior line of chemotherapy. The approval was based on the results of the KEYNOTE-158 and KEYNOTE-028 studies. KEYNOTE-028 was a phase Ib study of Pembrolizumab in 24 patients with squamous cervical cancer that expressed PD-L1 (Frenel et al., 2017). The study reported durable responses in 17% of patients with a safety profile consistent with that seen in other tumor types (Frenel et al., 2017). KEYNOTE-158 was a phase II basket study that tested the efficacy of pembrolizumab as monotherapy in patients with 11 cancer types. The cervical cancer cohort included 98 patients with advanced disease that had failed at least one prior line of treatment (Chung et al., 2018). In this study, patients were enrolled independent of PD-L1 status. Overall Response Rate was 13.3% with 3 patients achieving complete response. Most of the responses were durable and mOS reached 9.4 months. It should be noted though that no responses were noted in this study among patients whose tumors did not express PD-L1 (Combined Positive Score-CPS < 1) (Chung et al., 2018) and FDA approval of this agent in cervical cancer is restricted to PD-L1 positive patients (CPS ≥ 1).

Analogously, the anti-PD1 antibody nivolumab has also shown significant activity in advanced pretreated cervical cancer (Hollebecque et al., 2017). In a phase I/II study conducted in an unselected population of recurrent/metastatic pretreated cervical cancer patients, nivolumab monotherapy resulted in 26% overall response rate and a mPFS of 5.5 months (Hollebecque et al., 2017). Based on these encouraging results, several ongoing trials test the efficacy of combinatorial approaches among anti-PD1/PD-L1 agents and either other immunostimulatory drugs or bevacizumab. In addition, the safety and efficacy of both nivolumab and pembrolizumab as well as the anti-CTLA4 agent ipilimumab are currently tested along with chemoradiation for patients with locally advanced cervical cancer.

Finally, adoptive T-cell transfer therapy has also shown promising results in patients with metastatic cervical cancer. Treatment with a single infusion of tumor-infiltrating T-cells selected for HPV E6 and E7 reactivity has resulted in response of the disease in three out of the nine enrolled patients (Stevanović et al., 2015). In two patients, complete regression of the disease was noted. These results support the therapeutic potential of this approach and an E7 T-cell receptor gene therapy clinical trial is underway (NCT 02858310) (Jin et al., 2018).

6. Conclusion

Recurrent or metastatic cervical carcinoma, not amenable to locoregional treatment is an incurable disease with poor prognosis. Advances in the management of advanced disease as well as the improvement of chemotherapeutic regimens and the incorporation of targeted agents in the metastatic setting have increased median overall survival over 12 months. Furthermore, immunotherapy emerges as a novel therapeutic pillar that could provide durable responses in a percentage of patients with recurrent disease. However, recent failure of anti-EGFR agents underlines the need for improved understanding of the biology of the disease, in order to develop more efficient therapies in the future.

Conflict of interest

ML: MSD, Honoraria, AK: None, ID: MSD Greece employee, MAD: Bristol-Myers Squibb: Honoraria, AB: Roche: Advisory, Research

support.

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