Advancements in Cervical Cancer Prevention and Management of Persistent, Recurrent, and Metastatic Disease: 2016 Update

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Abstract

Cervical cancer is the third most common cancer in women worldwide and can be mostly prevented with vaccination; however, the prognosis of advanced, recurrent, or metastatic cervical cancer remains poor. Several chemotherapy regimens have some activity in advanced cervical cancer; nevertheless, cisplatin and paclitaxel are still considered the most effective treatments and the standard of care. The addition of bevacizumab in combination with chemotherapy has shown improved overall survival. Other targeted agents have shown limited activity so far. Immunotherapy is emerging as a promising treatment for cervical cancer. We review treatment options for advanced cervical cancer, recent developments for the management of locally advanced tumors, potential preventive strategies, and promising targeted therapies in advanced and recurrent cervical cancer and their implications in clinical practice.

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Introduction

Cervical cancer is the third most common cancer in women worldwide and is diagnosed in nearly 13,000 women in the United States and in nearly 530,000 women globally each year.[1,2] The human papilloma virus (HPV) is the primary cause of cervical cancer worldwide. HPV is implicated in over 99% of cases and its sexual transmission is preventable with vaccination.[3]

Current treatment for cervical cancer can yield cures in 60% to 90% of women with early-stage (localized and regional) cervical cancer.[4] However, the prognosis for women with advanced or recurrent cervical cancer remains poor. About 13% of women have metastatic disease at diagnosis, with a 5-year survival rate of 16.5%.[4]

Progress in the management of cervical cancer has been slow. Over the last 60 years, a few major advances have been accomplished. First, the introduction of the Pap smear as a screening method in the 1950s, which led to a 60% or higher decrease in death from cervical cancer.[5] Second, though 50 years later, five randomized trials demonstrated a 30% to 60% reduction in the risk of death with the addition of cisplatin to radiation therapy, which led the National Cancer Institute to issue a clinical alert recommending its use in 1999, the benefits of which have since been confirmed in retrospective studies.[6] Since then, further agents with any benefit in overall survival were lacking, until most recently in 2014 when the addition of bevacizumab to combination chemotherapy showed a 3.7-month advantage in OS.[7]

The development of therapies that selectively target specific molecular pathways involved in tumorigenesis is ongoing, and may lead to other major advances in the management of cervical cancer. We briefly discuss the literature behind HPV vaccination, and then focus on reviewing current and emerging therapies in locally advanced, recurrent, and metastatic cervical cancer and their role in clinical practice.

Prophylactic HPV Vaccines

An important step forward to potentially decrease the burden of cervical cancer was the development of the quadrivalent HPV vaccine with prophylaxis against HPV types 6, 11, 16, and 18, which was approved by the FDA in 2006 and with high documented rates of protective efficacy (88% to 100%).[8] A nine-valent vaccine with non-inferior protective efficacy against HPV types 6, 11, 16, 18, in addition to 96.7% protective efficacy against five more oncogenic types (31, 33, 45, 52, and 58)[9] was approved by the FDA in December 2014. However, despite their high efficacy, suboptimal vaccination rates persist in the United States.[10] Three arguments are frequently raised regarding HPV vaccination—the endpoints of the clinical trials were high grade cervical lesions and not cancer, safety concerns, and that screening with cervical cytology is enough to prevent cervical cancer. To address each of these arguments:

1) It is true that the clinical trials evaluating the efficacy of these vaccines were not designed to demonstrate a decrease in the incidence of cancer. However, the development of high grade cervical lesions is a necessary step in the biological progression to invasive cancer.[11] Therefore, it is expected that a reduction in HPV infection will necessarily lead to a lower incidence of cancer. In addition, HPV infection and high grade cervical lesions represent an important health problem, as it is estimated that in the

United States the incidence of high grade cervical lesions is 360 per 100,000 women aged 20 to 29 years.[12] Although decreased incidence of cervical cancer after HPV vaccination has not been reported, a 64% decrease in HPV prevalence has been observed in the US after introduction of the vaccination program.[13]

2) The safety of the vaccines has been well demonstrated. Large studies, with over one million vaccine doses did not identify any adverse outcomes or statistically significant increased risks that met criteria for causal relationship.[14,15] Concern about potential serious side effects such as multiple sclerosis and other demyelinating diseases, including optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, and neuromyelitis optica have been reported.[16,17] However, more recent, thorough evaluations have failed to show any causal relationship between HPV vaccination and these demyelinating diseases.[18]

3) The fact that 13,000 women are diagnosed annually with cervical cancer in the US demonstates that screening alone is not enough to eradicate this disease.

Standard Chemotherapy

As mentioned above, the introduction of concurrent chemotherapy with radiation therapy led to significant improvements in survival. Until recently, the use of chemotherapy was otherwise limited to patients with metastatic or recurrent cancer.

In 2010, Dueñas-González et al reported the results of a phase 3 randomized trial that evaluated outcomes with the addition of gemcitabine to concurrent cisplatin chemo-radiotherapy followed by adjuvant chemotherapy with gemcitabine/cisplatin.[19] In this study, statistically significant improvements in 3-year progression-free survival (PFS), overall PFS, and overall survival (OS) were observed. These findings led to the development of the OUTBACK trial, an ongoing study conducted by the International Gynecologic Cancer Intergroup to evaluate if 3 additional courses of systemic adjuvant carboplatin and paclitaxel lead to improved outcomes when compared to standard chemo-radiation alone (NCT01414608). The results of this study are eagerly anticipated.

For the vast majority of patients with recurrent or metastatic disease, chemotherapy has represented the only treatment option. However, it is important to remember that in patients with limited metastatic disease in the para-aortic nodes, central pelvic recurrences, or solitary lung metastasis, long-term survival can be achieved with surgical resection and/or radiation therapy.[20-25]

Several chemotherapy agents, including alkylating agents, antimetabolites, anthracyclines, and microtubular inhibitors, were reported to have activity as single agents in previously untreated patients.[26] Traditionally, cisplatin has been considered the most active drug,[27] and current evidence suggests that platinum-based combination regimens may be more effective. The combination of cisplatin and paclitaxel yields a higher response rate (RR) and improved PFS compared with single-agent cisplatin, but does not improve OS.[28] However, there are potential benefits to quality of life. The combination of cisplatin and topotecan compared with single-agent cisplatin showed an improvement in overall response rate (ORR), PFS, and OS (**Table 1**).[29] However, the toxicities were significant, with 70% of patients in the cisplatin/topotecan arm having grade 3 or 4 neutropenia (compared with 1.4% in cisplatin arm).

The efficacy of four platinum-based doublets was evaluated in a large randomized trial.[30] Patients were randomly assigned to cisplatin in combination with either paclitaxel, vinorelbine, gemcitabine, or topotecan. This study reported that vinorelbine, gemcitabine, and topotecan were not superior to paclitaxel in terms of OS, although a trend in response rate (RR), PFS, and OS favored paclitaxel (**Table 1**).

To help identify patients who would least benefit from cisplatin-based chemotherapy, Moore et al, identified 5 prognostic factors that independently conferred a poor response to cisplatin-based combinations (African American, performance status > 0, pelvic disease, prior radiosensitizing cisplatin, and PFS < 1 year), with patients having 4 to 5 risk factors being high risk with response rates of only 13%, and thus poor candidates for cisplatin-based chemotherapy (to be considered for non–cisplatin-based chemotherapy or investigational trials).[31]

Due to its more favorable toxicity profile, the combination of carboplatin plus paclitaxel could be a reasonable alternative to paclitaxel/cisplatin. In a recent phase 3 randomized trial, 253 women with recurrent or metastatic cervical cancer were treated with paclitaxel/cisplatin (TP) or paclitaxel/carboplatin (TC).[32] Overall no significant differences were observed in PFS or OS (**Table 1**). TP was associated with more grade 4 neutropenia (75% vs 45.2%), febrile neutropenia (16% vs 7.1%), grade > 3 nausea and vomiting (6.4% vs 3.2%), and increased creatinine (9.6% vs 4.8%). TC was associated with higher incidences of anemia (44.4% vs 31.2%), thrombocytopenia (24.6% vs 3.2%), and sensory neuropathy (4.8% vs 0%). Additionally, the proportion of non-hospitalization periods, which was used as a surrogate for better quality of life, was higher in the TC arm. The fact that TC is non-inferior and with a better toxicity profile suggests that it should be the preferred treatment. It should be noted though, that in women not previously treated with cisplatin, TC resulted in a much lower median OS compared with the standard doublet of TP (13 vs 23.2 months). Therefore, in platinum-naïve patients, a cisplatin-based regimen is still the treatment of choice.

Additional treatment options outside of platinum-based therapy are limited. Ifosfamide, paclitaxel, topotecan, irinotecan, capecitabine, pemetrexed, vinorelbine, and nab-paclitaxel are among the most active single agents, while docetaxel, gemcitabine, and ixabepilone were found to have minimal activity.[33-48] **Table 2** summarizes the activity of some of these agents when used as second-line treatment.

Encouraging activity was reported in a phase 2 study with S-1.[49]

TABLE 1. Phase 3 Randomized Trials of Frontline Therapy for Advanced Cervical Cancer

Author	Treatment	N	ORR (%)	PFS (months)	*P*	OS (months)	*P*
Miller[35]	Cisplatin TP	134 130	19 36	2.8 4.8	<.001	8.8 9.7	NS
Long[22]	Cisplatin ToP	146 147	13 27	2.9 4.6	.014	6.5 9.4	.021
Monk[23]	TP VP GP ToP	103 108 112 111	29.1 25.9 22.3 23.4	5.82 3.98 4.70 4.57	 .06 .04 .19	12.87 9.99 10.28 10.25	 .71 .90 .89
Tewari[7]	Chemotherapy Chemotherapy/ Bevacizumab	225 227	5.9 8.2	5.9 8.2	.002	13.3 17.0	.004
Kitagawa[25]	TP TC	123 121	6.9 6.2	6.9 6.2	.053	18.3 17.5	.032

GP indicates gemcitabine/cisplatin; NS, not stated; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; TC, paclitaxel/carboplatin; TP paclitaxel/cisplatin; ToP, topotecan/cisplatin; VP, vinorelbine/cisplatin.

S-1 is an oral fluoropyrimidine consisting of tegafur (a prodrug of 5-fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil). In this study, 36 patients received a median of 4 cycles with an ORR of 30.6%. The median time to progression and the median survival time were 5.2 and 15.4 months, respectively. These promising results led to a randomized phase 3 study evaluating the efficacy and safety of S-1 with cisplatin versus single-agent cisplatin in patients with stage IVB, recurrent, or persistent carcinoma of the cervix, which completed accrual in April 2016 but results have not yet been published (NCT00770874). S-1 was also recently combined with irinotecan in a phase 1 trial, which thus far demonstrated an acceptable toxicity profile.[50]

Targeted Agents

Angiogenesis Inhibitors and Bevacizumab

Targeting angiogenesis to block the growth of nutrient-supplying blood vessels in cancerous tumors has been the latest most efficacious adjunct to the treatment of advanced cervical cancer. Since 2006, small studies suggested that the combination of bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, and chemotherapy was highly active in advanced cervical cancer.[51,52] A phase 2 multicenter trial then evaluated single-agent bevacizumab among women with persistent or recurrent squamous cell carcinoma of the cervix.[53] In this single-arm study, all patients had been exposed to at least one prior chemotherapy regimen (both cisplatin- and non–cisplatin-based) and most had received prior radiation (82.6%) or hysterectomy (56%). Bevacizumab was shown to have acceptable toxicity with few grade 3 or 4 adverse events, including hypertension (n = 7), thromboembolism (n = 5), gastrointestinal (n = 4), anemia (n = 2), other cardiovascular (n = 2), vaginal bleeding (n = 1), neutropenia (n = 1), and grade 4 urinary fistula (n = 1). One death occurred due to infection. It also showed clinical activity, with a median PFS of 3.40 months (95% CI, 2.53-4.53 months) and OS of 7.29 months (95% CI, 6.11-10.41 months). The study suggested that bevacizumab merited further investigation in phase 3 trials.

The most significant and practice-changing study for the management of advanced cervical cancer was GOG 240, a phase 3 randomized study in which women diagnosed with recurrent, persistent, or metastatic cervical cancer who had only received chemotherapy used concurrently with radiation for locally advanced non-metastatic disease were enrolled.[7] A total of 452 women were randomized into a factorial 2 × 2 design study, where approximately half the patients received topotecan with paclitaxel and the other half received cisplatin and paclitaxel. Additionally, about half of the patients in each of these treatment groups received bevacizumab with their chemotherapy. The addition of bevacizumab to combination chemotherapy was associated with an improvement of 3.7 months in median OS (**Table 1**). The difference in OS translated into an HR for death of 0.71 in favor of the addition of bevacizumab (*P* = .004). Response rates were 48% with bevacizumab and 36% with chemotherapy alone (*P* = .008). As a secondary outcome in the study, topotecan-paclitaxel did not outperform cisplatin-paclitaxel, even among patients with prior exposure to cisplatin. There was significantly more toxicity in patients who received bevacizumab compared to those who received chemotherapy alone, and was representative of the known

bevacizumab toxicities with grade ≥2+ hypertension (29% vs 2%), grade ≥3+ thromboembolic events (8% vs 1%), and grade ≥3+ gastrointestinal/genitourinary fistulas (6% vs < 1%). The study did not distinguish the differences in toxicity profile between the combination chemotherapy regimens. However based on previous trials, it is expected that the use of topotecan-paclitaxel causes more fatigue, leukopenia, and neutropenia, and significantly more thrombocytopenia and anemia compared with cisplatin-paclitaxel.[32]

Despite the toxicities, the addition of bevacizumab showed acceptable safety, and patients did not report a statistically significant decrease in quality of life. In fact, a follow-up study used functional assessment scores (including physical, social, functional, and emotional well-being, as well as neurotoxicity and pain scores) to evaluate the health-related quality of life of the patients in GOG 240 up to 9 months after treatment.[54] This follow-up study showed no significant deterioration in health-related quality of life for the patients who received bevacizumab in addition to chemotherapy. Patients in GOG 240 were also analyzed in a prospective manner per the Moore prognostic criteria previously mentioned (African American, performance status > 0, pelvic disease, prior cisplatin, PFS < 365 days), and it was determined that patients with high risk scores (4 to 5) were the ones who truly benefited from the addition of bevacizumab (HR for death 0.53, 95% CI, $P = .0196$).[55] On the other hand, patients with low risk scores (0 to 1) were found to derive little benefit from bevacizumab (HR, 0.96; 95% CI, $P = .9$), and should thus be considered for alternate therapies or clinical trials, rather than subjecting them to the side effects of bevacizumab that could in turn disqualify them from other trials.

Multiple other antiangiogenics, primarily in the form of VEGF or VEGF-R tyrosine kinase inhibitors, have been studied with variable results (**Table 2**). Sunitinib, pazopanib, and brivanib have had minimal activity.[56-58] Most recently, cediranib demonstrated significantly prolonged PFS when added to chemotherapy, in addition to the highest proportion of patients with a disease response compared to any regimen in advanced cervical cancer,[59] leading to proposals of future trials studying cediranib as maintenance therapy in bevacizumab-responders.[60]

Other Targets

Cervical cancer has underlying complex genomics with a multitude of possible underlying mutations.[61] Multiple ongoing studies aim at evaluating the efficacy of targeted agents. However, other targeted agents, such as EGFR inhibitors (erlotinib, lapatinib, cetuximab) or mTOR inhibitor (temsirolimus) were found to have minimal activity.[57,62-64] The results of these studies are summarized in **Table 2**.

Early studies suggest that combination of targeted agents with chemotherapy may be an effective approach. Nimotuzumab, a humanized IgG1 monoclonal antibody-targeting *EGFR*, showed tolerable toxicity and efficacy when combined with single-agent chemotherapy (gemcitabine or cisplatin) in a pilot study of advanced cervical cancer.[65] Although no partial or complete responses were observed in this study, the stable disease rate was 35%, PFS was 5.43 months, and OS was 9.97 months.

In a phase 1 study, veliparib, a poly-ADP-ribose polymerase (PARP) inhibitor, in combination with cisplatin/paclitaxel for advanced cervical carcinoma achieved a response rate of 34% at all dose levels and 60% at the maximum dose level, with dose-limiting toxicities being dyspnea and febrile neutropenia.[66] Veliparib was also evaluated in combination with topotecan in a phase 1 to 2 trial, however it showed minimal activity with only 2 out of 27 patients achieving a partial response.[67]

Other potential targets include HER2, WEE1, Notch signaling, heat shock protein 90, and other PARP inhibitors.[68] However, most of these studies are at their infancy, either in the preclinical phase or unpublished pilot clinical studies.

Immunotherapy

Targeted therapies can be limited in malignancies with a high degree of genomic complexity, given that new pathways can lead to resistance and result in short-lived responses.[69] Immunotherapy for cancer, which bypasses this complication, has had enormous advances in the most recent years, beginning a new era of research in oncology. Immunosuppression is one of the greatest risk factors for cervical cancer, as increased rates of this malignancy have been noted in women with AIDS, organ transplantation, end-stage renal disease, autoimmune disease on immune-suppressants, or a smoking history.[70]

Adoptive T-Cell Therapy

Adoptive T-cell therapy (ATC) identifies autologous T cells that aim for a specific target, expands them through culture media *ex vivo*, and then infuses them back into the patient as tumor-infiltrating lymphocytes (TIL). TILs can then recognize and eliminate widespread target tumor cells in the treatment of advanced malignancies.[64] ATC has been shown to mediate complete responses in B-cell hematologic malignancies and melanoma,[71] but until recently has had limited data in epithelial malignancies.

A novel study investigated use of HPV-targeted ATC therapy in metastatic cervical cancer.[72] In this study, T cells were harvested from patients and the ones targeting HPV viral protein E6 and E7 were preferentially selected and expanded. Billions of these expanded T cells were then infused as TILs into each patient. Nine patients received lymphocyte-depleting conditioning chemotherapy (cyclophosphamide and fludarabine), followed by a single infusion of these HPV-TILs and aldesleukin (recombinant IL-2). One patient achieved partial response and 2 patients achieved a complete response. These two complete responses were still ongoing at 22 months and 15 months after treatment. Most common toxicities were from the conditioning regimen and included grade

TABLE 2. Second-Line and Emerging Therapy for Advanced Cervical Cancer

Author	Treatment	N	ORR (%)	PFS (months)	OS (months)
Cytotoxic chemotherapy					
Bookman[28]	Topotecan	45	12.5	2.1	6.6
Muggia[37]	Vinorelbine	44	13.7	NS	NS
Miller[23]	Pemetrexed	29	15	3.1	7.4
Lorusso[36]	Pemetrexed	43	13.9	10 weeks	35 weeks
Alberts[38]	Nab-paclitaxel	37	28.6	5.0	9.4
Garcia[39]	Docetaxel	27	8.7	3.8	7.0
Schilder[40]	Gemcitabine	22	4.5	2.1	6.5
Garcia[31]	Capecitabine	26	15.4	2.9	5.9
Katsumata[42]	S-1 (Tegafur)	36	30.6	5.2	15.4
Burotto[41]	Ixabepilone	41	9.7	2.3	5.84
Targeted Therapy					
Monk[46]	Bevacizumab	46	10.9	3.4	7.29
Mackay[49]	Sunitinib	19	0	3.5	NS
Monk[50]	Lapatinib Pazopanib	78 74	5 9	17.1 weeks 18.1 weeks	39.1 weeks 50.7 weeks
Schilder[55]	Erlotinib	28	37	37	37
Santin[56]	Cetuximab	38	37	37	37
Chan[51]	Brivanib	28	37	37	37
Tinker[57]	Temsirolimus	38	3.0	3.52	37
Symonds[52]	Cediranib/Chemotherapy	34	64	8.1	NS
Cetina[58]	Nimotuzumab/Chemotherapy	17	0	5.43	9.97
Thacker[59]	Veliparib/Chemotherapy	34	34	--	--
Immunotherapy					
Stevanovic[65]	HPV-targeted ATC Therapy	9	33.3	NS	NS
Petit[66]	ADXS11-01 Listeria Vaccine	110	11	10.5	NS
Satoshi[68]	Peptide Cocktail Vaccine	21	9.5	NS	15.4

NS indicates not stated; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

3 and 4 myelosuppression, neutropenia, fever, and diarrhea. This study provided encouraging results, and further investigation is warranted.

Therapeutic Vaccines

Another promising agent in development is ADXs11-01 (axalimogene filolisbac), a vaccine consisting of live attenuated *Listeria monocytogenes* bioengineered to secrete an HPV16-E7 fusion protein, which, when recognized by antigen-presenting cells, activates T helper cell immunity and generates cytotoxic T cells that target HPV-E7-transformed cells in the tumor, while simultaneously suppressing the immunologic tolerance within the lesions. In a phase 2 study of ADXS11-001 in the treatment of persistent or recurrent cervical cancer in Indian women, patients previously treated with up to two prior lines of therapy were randomized to ADXS11-001 with or without cisplatin.[73] In this study of 110 patients, 12-month OS was 36%, RR was 11%, and disease control rate was 43%. Prior therapy, baseline performance status, and the addition of cisplatin had no effect on survival or response.

Another ongoing phase 1/2 study of ADXS11-001 in 26 patients recently published preliminary data showing a 12-month OS of 38.5%; subgroup analysis of 18 patients who received at least 3

doses of the vaccine showed a median OS of greater than 1 year and 12-month OS rate of 55.6%.[74] These results are remarkable considering that in over 20 phase 2 studies by the Gynecologic Oncology Group in advanced cervical cancer from 1998 to 2015, the 12-month OS rate has never significantly exceeded 30%.[74] The FDA has already approved the initiation of a phase 3 trial (NCT02853604).

Peptide vaccines similarly elicit immunity through the injection of a peptide epitope (usually a target within the tumor) into the patient, leading to the same aforementioned mechanism of T-cell mediated immunity against the tumor. Recently, a phase 2 study of a peptide cocktail vaccine (which includes the VEGF receptor peptide) in advanced cervical and ovarian cancer was presented, showing that out of the 21 cervical cancer patients, 2 complete responses were observed, with a median OS of 15.4 months.[75] There were no major adverse events, showing that peptide vaccines can be safe and effective in cervical cancer.

Though many other studies have assessed the effect of different therapeutic vaccines in both early and advanced cervical cancer, many have yielded uninterpretable results or minimal activity, while others are new and in pre-clinical stages.[76]

Monoclonal Antibodies: Inhibiting Inhibitors

Based on the marked clinical efficacy of immune checkpoint inhibitors in other malignancies and the fact that immunosuppression is known to play an important role in cervical cancer, inhibitors of the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and inhibitors of the programmed cell death protein 1 (PD-1) are currently being studied. This inhibition boosts the immune system's ability to fight the tumor by compromising T-cell activation, and also impacts the tumor's defense against the immune system by suppressing effector functions such as proliferation and cytokine secretion.

Preliminary data from a phase 1b study of pembrolizumab (PD-1 inhibitor) in 24 patients with advanced cervical cancer showed promising results with an ORR of 12.5% (all partial responses) and 6-month PFS and OS rates of 13% and 66.7%, respectively.[77] It was well tolerated, with most common toxicities being pyrexia and rash (>10%), 20.8% of patients having grade 3 toxicities, and no grade 4 or 5 toxicities. A phase 2 trial is currently underway (NCT02628067).

Multiple monoclonal antibodies are currently in clinical trials with highly anticipated results, including nivolumab (NCT02257528, NCT02488759), ipilumumab (NCT01711515, NCT01693783), and durvalumab/tremelimumab (NCT01975831).

Discussion

The treatment of persistent, recurrent, or metastatic cervical cancer has historically had a slow progress, with evidence presented in this review showing how platinum agents became the backbone of combination therapy. Cisplatin is preferred for patients who are cisplatin-naïve as it yields better responses, however, as shown by Kitagawa et al, carboplatin is non-inferior and with a better toxicity profile, and otherwise preferred in patients who have already been exposed to cisplatin.[32]

With the advances in anti-angiogenesis therapy, targeted agents, and immunotherapy, treatment of advanced cervical cancer is continuing to move forward. The addition of bevacizumab to combination chemotherapy in 2014 was a remarkable advancement, being the first study to find an improved OS (by 3.7 months) since cisplatin was recognized as a key agent in 1999.[7] Nonetheless, despite the strong evidence suggesting improved OS in patients who receive bevacizumab in addition to combination chemotherapy, there is a significant financial cost of bevacizumab that must be taken into account when providing treatment. The cost of chemotherapy plus bevacizumab is approximately 13.2 times more expensive than chemotherapy alone, adding nearly $74,000 for every 3.5 months.[78] Moderately discounting the cost of bevacizumab (perhaps through the availability of biosimilars) significantly affects its affordability. Management of the toxicities that bevacizumab adds over standard chemotherapy (eg, hypertension, thromboembolism, fistulization) also adds to the overall healthcare cost. A valid concern is the effect that additional side effects of adding bevacizumab may have on the patient's quality of life. However, as previously mentioned no significant deterioration in health-related quality of life for the patients who received bevacizumab in addition to chemotherapy has been reported.[54] Nonetheless, it must be considered that bevacizumab is best indicated for patients with high-risk prognostic factors, while patients with low-risk prognostic factors should be spared of potential bevacizumab toxicities in light of reduced benefit, and be considered for other clinical trials.[55] In cervical cancer, bevacizumab is currently only approved for use in persistent, recurrent, or metastatic disease when combined with chemotherapy. It has otherwise been studied in less-advanced cervical cancer in a phase 2 trial, which yielded encouraging efficacy results and was well tolerated when combined with chemo-radiation[79]; however, a large, phase 3 trial is still warranted.

Although the addition of bevacizumab was an exciting advancement, it is important to remember that this survival advantage is still short-lived, and that given the complex genomics of cervical cancer, targeted therapies overall can eventually find resistance when the tumor learns to thrive through an alternate pathway. It is, therefore, still imperative to investigate further therapies. Given that cervical cancer is associated with an immunosuppressed state, the role of immunotherapies (including adoptive cell therapy, therapeutic vaccines, and monoclonal antibodies against checkpoint inhibitors) is an evolving and exciting new area of research that can potentially lead to further advancements.

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