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Pharmacologic Management of Advanced Cervical Cancer: Antiangiogenesis Therapy and Immunotherapeutic Considerations

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Abstract

As a consequence of disparities in access to and utilization of preventative healthcare, the incidence and death rates from cervical cancer remain substantial in the face of indisputable evidence that screening saves lives. While disparities persist, there will be an urgent need for research into the treatment of advanced forms of this disease. In this review, we explore the evolution of the treatment of metastatic, recurrent, and persistent cervical cancer from cytotoxic agents to targeted therapy. We discuss why targeted therapies are unlikely to produce sustained responses alone but may be more successful in combination with immunotherapies. We also provide a rationale for the potential next phase in treatment of this challenging disease—combined therapy with antiangiogenic agents and immune checkpoint inhibitors. In doing so, we highlight recent paradigm shifts within cancer therapeutics, including the shift in focus from the tumor cell itself to the tumor microenvironment, and from stimulating the immune system to inhibiting the inhibitors of an adequate immune response.

1 Introduction

The incidence and death rates from cervical cancer remain substantial in the face of indisputable evidence that screening saves lives. The most recent data available from the International Agency for Research on Cancer (IARC) indicate that cervical cancer was diagnosed in 528,000 women and was responsible for 266,000 deaths worldwide in 2012 [1]. In the US, which has funded a national screening program for low income, uninsured women since 1991, approximately 1 in 10 women aged 21–65 years have not been screened for cervical cancer in the past 5 years [2]. This ratio increases to 1 in 4 women aged 21–65 years without health insurance or a regular healthcare provider. The persistent disparities in preventative care are also reflected in human papillomavirus (HPV) vaccine uptake rates. Only half of adolescent girls in the US receive the HPV vaccine by the recommended age of 13 years, as put forth by the Advisory Committee on Immunization Practices (ACIP) [3]. As

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one may predict, a recent systematic review found that higher vaccine uptake was associated with factors related to access to care (e.g. having health insurance, having a healthcare provider as a source of information), a history of successful negotiation of healthcare resources (e.g. receipt of childhood vaccines, more frequent healthcare utilization), and higher medical literacy (e.g. higher vaccine-related knowledge, positive vaccine attitudes) [4].

Reducing disparities in access to and utilization of preventative healthcare is a slow and arduous process. As long as disparities remain in existence, there will be an urgent need for research into the treatment of advanced cervix cancer. Women with widely metastatic, recurrent, or persistent disease comprise a challenging population. Largely from racial/ethnic minorities and lower socioeconomic backgrounds [5], they comprise a group of women in very poor health. Many have been pre-irradiated and have experienced radiation toxicity [6]. A long-standing history of tobacco use also appears to be present in a large proportion of patients, leading to problems related to nicotine dependence and tobacco-induced effects on the cardiovascular system. These factors contribute to the challenge of caring for this patient population.

In this review, we will explore the evolution of the treatment of metastatic, recurrent, and persistent cervical cancer from cytotoxic agents to targeted therapy. We will also provide a rationale for the potential next phase in treatment of this challenging disease—combined therapy with antiangiogenic agents and immunotherapy, specifically the immune checkpoint inhibitors.

2 Limitations of Cytotoxic Agents

Cisplatin has been recognized as the chemotherapeutic backbone for the treatment of advanced stage or recurrent cervical cancer since 1981, when the Gynecologic Oncology Group (GOG) published the results of a phase II trial that investigated cisplatin at a dose of 50 mg/m^2 at an infusion rate of 1 mg/min every 3 weeks in patients with stage IVB or recurrent cervical cancer [7]. With an overall response rate (RR) of 38 % in this trial, cisplatin was deemed highly active as a single agent in patients with both pelvic and extra-pelvic disease. In addition to setting the benchmark for future clinical trials designed to assess the efficacy and tolerability of other single-agent regimens, none of which were subsequently found to outperform cisplatin, this trial foreshadowed the dilemma of acquired platinum resistance. While three complete and eight partial responses (RR 50 %) were observed among 22 patients who had not received any prior chemotherapy, there were only two partial responses (RR 17 %) among 12 patients who had received prior chemotherapy.

The debate surrounding acquired platinum resistance was brought to the forefront during the development of cisplatin combination regimens by the GOG. GOG protocol 169, which compared single-agent cisplatin (C) with cisplatin plus paclitaxel (CP), found that the addition of paclitaxel resulted in a significant improvement in RR [19 (C) vs. 36 % (CP); $p = 0.002$] and progression-free survival (PFS) [2.8 (C) vs. 4.8 months (CP); $p < 0.001$], but no statistically significant difference in median overall survival (OS) [8.8 (C) vs. 9.7 months (CP)] [8]. The subsequent platinum-containing doublet to be compared with single-agent

cisplatin was cisplatin plus topotecan (CT) in GOG protocol 179 [9]. Not only did GOG 179 confirm a significant difference in RR [13 (C) vs. 27 % (CT); $p = 0.004$] and PFS [2.9 (C) vs. 4.6 months (CT); $p = 0.014$] between the two arms but it also became the first prospective clinical trial to demonstrate an OS advantage [6.5 (C) vs. 9.4 months (CT); $p = 0.017$] of any combination regimen over cisplatin alone. However, critical review of the trial results called into question the statistical significance of the OS benefit. Specifically, there was found to be a 6 % point difference in RR between the single-agent cisplatin backbone in GOG 169 and GOG 179.

The underperformance of single-agent cisplatin in GOG 179 compared with historical cohorts has been attributed to the increasing rate of acquired cisplatin resistance [10]. In 1999, the results of five landmark trials in locally advanced cervical cancer [11–15] stimulated a rare National Cancer Institute (NCI) Clinical Alert urging providers to consider the concurrent administration of cisplatin-based chemotherapy to all patients receiving radiation for cervical cancer [16]. This paradigm shift in the upfront treatment of locally advanced disease was clearly reflected in differences in patient characteristics between women enrolled in GOG 169 compared with women enrolled in GOG 179. Among the 264 eligible patients enrolled in GOG 169 between August 1997 and March 1999, 30 % of patients in the cisplatin arm and 24 % of patients in the cisplatin–paclitaxel arm had previously received concurrent cisplatin chemosensitizing radiation. In contrast, among the 356 eligible patients enrolled in GOG 179 between June 1999 and December 2002, 56 % of patients in the cisplatin arm and 58 % of patients in the cisplatin– topotecan arm had previously received concurrent cisplatin chemosensitizing radiation.

In a head-to-head comparison of cisplatin–paclitaxel and cisplatin–topotecan in GOG 204, which compared four cisplatin-containing doublets, cisplatin–paclitaxel outperformed cisplatin–topotecan in RR, PFS, and OS, although the differences were not statistically significant [17]. The same was found of cisplatin–paclitaxel in comparison with cisplatin plus gemcitabine and cisplatin plus vinorelbine. GOG 204 remains the largest randomized trial in recurrent cervical cancer and is regarded as the definitive trial through which cisplatin–paclitaxel emerged in 2009 as the chemotherapy standard for advanced cervical cancer. Furthermore, it is the first trial in patients with stage IVB, recurrent, or persistent cervical cancer with a median survival of greater than 1 year.

3 Incorporating Targeted Therapy in Treatment Protocols

Given the limited gains in median survival in a progressively restricted population of patients, perhaps the greatest contribution of these preceding GOG trials in advanced cervical cancer was to establish an urgent need for innovative approaches to therapy. The top priorities became (1) the investigation of non-platinum combinations; and (2) the incorporation of targeted agents into traditional cytotoxic regimens. Both priorities were subsequently addressed in GOG protocol 240, a prospective, phase III, randomized trial performed in the US, Canada, and Spain [18]. GOG 240 utilized a two-by-two factorial design to create a fourarm trial exploring platinum and non-platinum doublets with and without the antiangiogenic agent bevacizumab, a recombinant humanized monoclonal antibody that blocks angiogenesis by binding vascular endothelial growth factor (VEGF) and

preventing its binding to the VEGF receptor. Topotecan was selected as the substitute for cisplatin in the non-platinum doublet on the basis of laboratory data showing synergy between topotecan and microtubule-interfering agents [19] and a phase II trial by Tiersten and colleagues [20] in which the regimen was active in patients who had previously received radiation therapy. Bevacizumab was selected as the targeted agent given its single-agent activity in heavily pretreated recurrent cervical carcinoma [21] following extensive preclinical studies revealing the strong positive correlation between increased expression of VEGF and the invasive phenotype [22–25].

By the time of the scheduled interim analysis at 173 patient deaths (the first data freeze) in 12.5 months, it was clear that topotecan was not a superior substitute for cisplatin. Not only did the topotecan–paclitaxel regimen have no significant effect on OS [hazard ratio (HR) for death 1.20; 99 % confidence interval (CI) 0.82–1.76] but it was also associated with a significantly higher risk of progression compared with cisplatin–paclitaxel (HR 1.39; 95 % CI 1.09–1.77). Even after stratification by previous exposure to platinum, no significant difference in mortality was observed.

By the time of a subsequent data freeze at 271 patient deaths in 20.8 months, it was found that the addition of bevacizumab to either doublet improved the median OS compared with chemotherapy alone by 3.7 months (17.0 vs. 13.3 months; HR for death 0.71; 98 % CI 0.54–0.95), as shown in Fig. 1. A significant improvement was also seen in PFS (17.0 vs. 13.3 months; HR for death 0.71; 98 % CI 0.54–0.95) and RR (48 vs. 36 %; relative probability of response 1.35; 95 % CI 1.08–1.68; $p = 0.008$). Additionally, the number of patients who experienced a complete response to chemotherapy plus bevacizumab was double that of patients who experienced a complete response to chemotherapy alone (28 vs. 14; $p = 0.03$). The treatment benefit of bevacizumab remained present in subgroup analysis of age, performance status, race, squamous histologic type, status with respect to prior platinum exposure, recurrent or persistent disease, and pelvic location of the target lesion.

The PFS and OS benefit provided by bevacizumab does not appear to come at the cost of severe toxicity and quality of life (QOL). While bevacizumab-containing regimens were significantly more likely to lead to hypertension of grade 2 or higher (25 vs. 2 %; $p < 0.001$), no patient was forced to discontinue bevacizumab because of hypertension. Gastrointestinal or genitourinary fistulas of grade 3 or higher (6 vs. 0 %; $p = 0.002$) and thromboembolic events of grade 3 or higher (8 vs. 1 %; $p = 0.001$) also occurred more frequently among patients who received bevacizumab, but were rare, on the whole, and did not result in a difference in fatality (1.8 vs. 1.8 %; $p = 1.0$). Perhaps, most importantly, the addition of bevacizumab to cytotoxic chemotherapy did not result in any significant deterioration in health-related QOL, as measured by the Functional Assessment of Chronic Illness Therapy–Cervix Cancer trial outcome index (FACT–Cx TOI) score [26].

Following 346 deaths, the planned protocol-specified final analysis of OS was recently reported on 28 September 2014 at the European Society of Medical Oncology Annual Meeting [27]. Regimens containing bevacizumab continued to demonstrate a significant improvement in OS over chemotherapy alone (16.8 vs. 13.3 months; HR for death 0.765;

95 % CI 0.62–0.95; $p = 0.0068$). This OS benefit was sustained beyond 50 months, as evidenced by the survival curves remaining separated.

4 Beyond Targeted Therapy

Moore et al. established five important prognostic factors in recurrent cervical cancer that predict a poor response to conventional cytotoxic therapy: recurrence in the irradiated field (pelvis), prior radiosensitizer (cisplatin), time interval from diagnosis to first recurrence less than 1 year, performance status greater than zero, and African American ancestry [28]. In a pooled analysis of GOG 110, 169, and 179, patients in the high-risk category (four or five risk factors) were estimated to have an RR to platinum-based chemotherapy of only 13 %, and median PFS and OS of 2.8 and 5.5 months, respectively. GOG 240 not only prospectively validated the 'Moore criteria' but also revealed that the benefit of incorporating antiangiogenesis therapy was prolonged and possibly more robust in the high-risk group [29, 30]. Thus, antiangiogenesis therapy opens a window of opportunity in even the least responsive subset of patients. While this is encouraging, targeted therapies are unlikely to produce sustained responses.

Targeted therapies act by blocking essential biochemical pathways or mutant proteins that are required for tumor cell growth and survival. The ideal use of targeted therapies is in cancers with a single dominant driver mutation and a small mutational load [31]. When used in this scenario, monotherapy directed against the overused or aberrant pathway can induce a striking regression without overwhelming toxicity for the patient. The quintessential example is the successful use of imatinib, a tyrosine kinase inhibitor, to treat chronic myeloid leukemia (CML) bearing the Philadelphia chromosome (bcr-abl gene translation). However, most cancers are extremely heterogeneous. To treat a cancer with multiple driver mutations and a large mutational load, multi-targeted therapy is essential. Complicating matters further is our lack of a validated method to identify the best targets for therapy. Tumor profiling created from a single tumor sample is likely to miss other driver mutations present at other sites within the primary tumor or within metastases.

Cervical cancer must certainly be categorized among malignancies with complex genomes. Ojesina and colleagues recently reported a comprehensive genetic landscape analysis for cervical cancer by performing whole exome sequencing analysis of 115 cervical carcinomanormal paired samples, transcriptome sequencing of 79 cases, and whole genome sequencing of 14 tumor-normal pairs [32]. Among previously known somatic mutations, mutations at *PIK3CA*, *PTEN*, and *STK11* were present in 14, 6, and 4 % of squamous cell cervical carcinomas, respectively. Novel somatic mutations in squamous cell cervical carcinomas included recurrent E322K substitutions in the *MAPK1* gene (8 %), inactivating mutations in the *HLA-B* gene (9 %), and mutations in *EP300* (16 %), *FBXW7* (15 %), *NFE2L2* (4 %) *TP53* (5 %), and *ERBB2* (6 %). They also observed somatic *ELF3* (13 %) and *CBFB* (8 %) mutations in 24 adenocarcinomas. Gene expression levels were significantly related to HPV integration sites.

The degree of genomic complexity not only determines the strength of response but also the duration of response to targeted therapy [31]. The more complex the genome, the more

quickly a patient is likely to recur. Targeted therapies exert a pressure of selection on cancer cells. Emergence of drug-resistant variants can occur in two ways: the target itself changes through mutation so that it no longer interacts well with the targeted therapy and/or the tumor finds a new pathway to achieve tumor growth that does not depend on the target.

Numerous molecular pathways have been targeted in the treatment of cervical cancer [33]. With the exception of the success of bevacizumab, results from phase II trials have not been encouraging and have not led to prospective phase III trials. The challenges of applying targeted therapy to a heterogeneous cancer can be appreciated in the attempts to inhibit epidermal growth factor receptor (EGFR). EGFR, one of the most extensively targeted proteins in cervical cancer research, is a transmembrane receptor involved in signaling pathways critical for cell survival. Overexpression of this protein has been shown to correlate with resistance to cytotoxic chemotherapy and radiation in squamous cell cancers [34–37] and, specifically, to prognosis and tumor aggressiveness in cervical cancer [38]. Despite EGFR expression in 54–71 % of cervical cancer patients, single agent cetuximab, an anti-EGFR antibody, failed to result in a clinical response in patients with recurrent or persistent disease [39]. The same was found for monotherapy with two different anti-EGFR tyrosinekinase inhibitors in several phase II trials [40, 41]. Acquired resistance to therapy has been attributed to dysregulation of EGFR internalization or degradation, EGFR-dependent activation of human epidermal growth factor receptor 2 (HER2; ErbB2) and ErbB3, and increased signaling of alternative receptor tyrosine kinases, such as cMET [42].

5 Focusing on the Tumor Microenvironment

Unknowingly, a clinical rationale for incorporating bevacizumab in the management of advanced cervical cancer is predicated upon a simple observation at the time of colposcopy: vascular markings in women with abnormal Papanicolaou tests are hallmarks for invasive disease [18]. Keeping this in mind, it is reasonable to hypothesize that the success of bevacizumab in the treatment of advanced, recurrent, and persistent cervical cancer, compared with other targeted therapies, is likely a reflection of the drug's ability to modify the tumor microenvironment (TME), rather than act on tumor cells directly. Another well-known fact argues in favor of complementing the antiangiogenic effect of bevacizumab with immunotherapy to best tackle the TME (Fig. 2). Immunosuppression is one of the greatest risk factors for cervical cancer. It is not only women with AIDS or a history of organ transplant who are at increased risk for cervical cancer but also women with a significant smoking history, end-stage renal disease, and some autoimmune disorders [43].

The combination of targeted therapies and cancer immunotherapies offer a number of possible synergies that have not been well-studied to date. Vanneman and Dranoff [44] hypothesized that immunotherapies may convert short-lived tumor responses to targeted therapies into long-lasting remissions in which sustained host immune responses against multiple cancer-associated antigens delay the development of potentially lethal drug-resistant tumor cell clones. They propose several ways in which targeted therapies may create a favorable window for immunotherapy to achieve potent cytotoxicity. Highly effective therapies may significantly reduce tumor burden, resulting in a concomitant reduction in tumor-associated inflammation and immunosuppression. Even less effective

therapies may suspend tumor cell proliferation and trigger tumor cell senescence, providing an opportunity for tumor clearance by T cells. Additionally, the release of large amounts of antigenic debris upon tumor cell death may allow dendritic cells (DCs) to prime anti-tumor immune responses. Last but not least, many targeted therapies have secondary roles of modulating immune responses, which is particularly important considering that immunotherapies are optimized by a multimodal approach.

VEGF inhibition, specifically, has been shown to shift DC differentiation toward mature DCs capable of priming T cells and away from myeloid-derived suppressor cells (MDSC), a highly immunosuppressive cell type. In 1996, Gabrilovich and colleagues were the first to demonstrate that VEGF, more than any other soluble factor in tumor cell supernatants, dramatically affects the functional maturation of DCs [45]. After culture in breast and colon cancer cell supernatants, immature CD34+ DCs from human cord blood were found to be morphologically distinct from mature DCs and were significantly restricted in their ability to induce T-lymphocyte proliferation, as assessed by the mixed lymphocyte reaction (MLR). Abnormalities in the exposed DCs included low levels of major histocompatibility complex (MHC) class II expression and a reduced ability to take up soluble antigen. This effect was found to be dependent on the concentration of the supernatant, reproducible after exposure to recombinant human VEGF alone, and inhibited by neutralizing antibodies against VEGF. The observed DC dysfunction could be reproduced in mouse models following an in vivo infusion of recombinant VEGF [46]. Additionally, the immune cell profile shifted to favor immature myeloid cells and B cells. The proposed mechanism of action was inhibition of the activity of the transcription factor NF-κB in bone marrow progenitor cells.

These same authors were among the first investigators to demonstrate the benefit of combining anti-VEGF antibody and immunotherapy [47]. In two mouse tumor models (D459 and MethA sarcoma), anti-VEGF antibody alone significantly improved the number and function of DCs in lymph nodes and spleens, but did not affect the rate of tumor growth. Therapy with peptide-pulsed DCs alone slowed tumor growth but only during the period of treatment. Combined treatment with anti-VEGF antibody and peptide-pulsed DCs resulted in a much more prolonged and pronounced antitumor effect that was associated with the induction of a significant cytotoxic lymphocytic response.

Additional attempts have been made at combining anti-VEGF antibody with other forms of immunotherapy in both the preclinical and clinical arenas. Using the B16 melanoma model, an anti-VEGF antibody combined with adoptive T cell transfer intensified tumor infiltration, deceased tumor growth, and prolonged survival compared with either monotherapy [48]. The success of the combined therapy was attributed to increased infiltration of transferred T cells into tumor. In a multicenter, randomized, double-blind, phase III trial, 649 patients with previously untreated metastatic renal cell carcinoma (mRCC) were randomized to receive interferon α-2a (9 MIU sub-cutaneously three times weekly) and bevacizumab (10 mg/kg every 2 weeks), or interferon α-2a and placebo [49]. Median PFS was significantly longer in the bevacizumab plus interferon-α group than in the control group (10.2 vs. 5.4 months; HR 0.63; 95 % CI 0.52–0.75; $p = 0.0001$). At the time of publication, OS data had not yet matured. Clearly, exploration of the best combinations with bevacizumab has only just begun.

6 Inhibiting the Inhibitors

A recent paradigm shift away from a focus on stimulating the immune system to a focus on inhibiting the inhibitors of an adequate immune response has occurred within immunotherapeutics. Evidence has mounted that immunosuppression is a particularly important component of the TME in both pre-invasive and invasive cervical neoplasia. In one study in patients with cervical intraepithelial neoplasia (CIN), cervical lymphocytes were collected using cytobrushes and analyzed using flow cytometry [50]. Investigators found that the proportions of cervical CD4+ T cells that were T-regulatory cells (Tregs) were significantly higher in CIN non-regressors than in CIN regressors. The proportion of Tregs has also been shown to be significantly higher in cervical cancer specimens compared with CIN specimens ($p < 0.001$) [51], as well as in cervical cancer specimens taken from patients with lymph node metastases compared with those without ($p < 0.05$). These differences have been found to be clinically significant. Immunohistochemistry (IHC) of 40 biopsy samples collected from cervical cancer patients in China revealed that the 5-year survival rate was significantly lower in patients who had a high percentage of Tregs among all CD4+ and CD8+ tumor-infiltrating lymphocytes (TILs) compared with those patients who had a lower percentage (35.3 vs. 88.9 %; $p = 0.001$) [52].

It is not only subsets of lymphoid cells but also subsets of myeloid cells that promote immune tolerance in cervical cancer [53, 54]. Several studies have shown that the number of macrophages in cervical specimens progressively increases with disease severity [55–57]. In locally advanced cervical cancer, specifically, polarization of tumor-associated macrophages (TAMs) toward an immunosuppressive phenotype has been associated with poor response to chemoradiation and shorter survival [58]. A factor that is likely to be contributing to these poor outcomes is the ability of TAMs to promote lymphangiogenesis [59, 60].

Among the emerging strategies of tackling immune tolerance, immune checkpoint inhibitors offer great promise to gynecologic oncologists who seek to modulate the TME. Immune checkpoints refer to a variety of inhibitory pathways employed by the immune system to maintain self-tolerance and minimize collateral damage during physiologic responses to pathogens. Many of these pathways are initiated by ligand-receptor interactions on the surface of immune cells and are thus logical targets for monoclonal antibodies. T cells are particularly susceptible to manipulation as they rely on co-stimulatory and co-inhibitor molecules to appropriately respond to antigen recognition by the T-cell receptor (TCR).

Cytotoxic T-lymphocyte-associated antigen (CTLA)-4, also known as cluster of differentiation 152 (CD 152), was the first immune checkpoint receptor to be clinically targeted [61]. Found exclusively on T cells, it predominantly regulates the amplitude of the early stages of T-cell activation, allowing for a return to homeostasis following a T-cell-mediated immune response. T-cell activation and proliferation requires paired interactions at the surface of an antigen-presenting cell (APC) and T cell. The first signal is antigen-specific and is generated when peptide loaded on an MHC class I or II molecule interacts with the TCR. The second signal is antigen non-specific and is produced when B7-1/B7-2 ligand on the APC interacts with the CD28 receptor on the T cell. Following activation, T cells upregulate and translocate CTLA-4 receptors to the cell surface, which bind to B7 with a

greater avidity than CD28. CTLA-4 successfully outcompetes CD28 to generate an inhibitory signal that suspends T-cell proliferation and cytokine secretion (Fig. 3). Ipilimumab, a fully human monoclonal antibody against CTLA-4, has been approved by the US FDA for the treatment of unresectable or metastatic melanoma since 25 March 2011 [62].

Programmed cell death protein 1 (PD-1), also known as CD 279, was the subsequent immune checkpoint receptor to be clinically targeted. Although PD-1 and CTLA-4 belong to the same CD28 family of TCRs, they assume very different roles in the downregulation of an inflammatory response. While CTLA-4 predominately regulates T-cell activation within secondary lymphoid organs, PD-1 predominately regulates T-cell effector function within peripheral tissues [61]. PD-1 can be expressed transiently or chronically on T cells, depending on the duration of antigen exposure. In the setting of an acute infectious insult, PD-1 expression is induced when T cells become activated. The interaction of PD-1 with its ligand, PD-L1 or PD-L2, found on a diverse array of immune cells as well as inflamed tissues, results in downstream signaling that inhibits T-cell cytotoxicity and cytokine release (Fig. 4). Chronic stimulation prevents the remethylation of the PD-1 gene, leading to continued expression of the PD-1 receptor. Using mice chronically infected with the lymphocytic choriomeningitis virus (LCMV), Barber et al. [63] were the first to show that PD-1 heralds T-cell exhaustion, a state characterized by loss of function and proliferative capacity. PD-1 expression was subsequently shown to have a strong correlation to an exhausted phenotype in CD8+ TILs [64], as well as immunosuppressive myeloid cells. Within the last year, two PD-1 pathway inhibitors, pembrolizumab and nivolumab, have been approved by the US FDA for the treatment of unresectable or metastatic melanoma [65, 66].

Both inhibitory pathways appear to play a role in the progression of cervical cancer. In an assessment of the pattern of CD28 and CTLA-4 expression in T cells from peripheral blood of patients with advanced disease, investigators found lower proportions of freshly isolated and ex vivo stimulated CD4+CD28+ and CD8+CD28+ T cells and markedly higher proportions of CTLA-4+ T cells in cervical cancer patients than in controls [67]. Cervical cancer patients also exhibited abnormal kinetics of surface CTLA-4 expression, with the peak at 24 h of stimulation, in contrast to corresponding normal T cells, which demonstrated maximum CTLA-4 expression at 72 h of stimulation. Examination of 115 cervical cancer specimens with three-color fluorescent IHC to study the number and phenotype of tumor-infiltrating T cells revealed that over half of both the infiltrating CD8+ T cells and CD4+FOXP3+ T cells expressed PD-1, irrespective of PD-L1 or PD-L2 expression by tumors [68]. Conversely, the presence of PD-L1 on tumor cells was associated with a significantly higher intraepithelial infiltration by FOXP3+ T cells, but not CD8+ T cells. In a third study, flow cytometry of immune-cell subsets in tumor-positive versus tumor-negative lymph nodes (LN+, LN–) demonstrated increased surface levels of both CTLA-4 and PD-1 in LN+ patients compared with LN– patients [69]. Positive lymph nodes were also found to have increased rates of Tregs and MDSCs, confirming previous findings.

7 The Next Phase in Clinical Trials

Assessment of the clinical benefit of immune checkpoint inhibition has emerged as a priority of the NCI. In November 2013, the NCI's Cancer Therapy Evaluation Program (CTEP) released a mass solicitation for phase II trials of nivolumab in underrepresented solid tumor types, including cervical cancer.

The precedence for a trial combining bevacizumab with an immune checkpoint inhibitor has been established by a phase Ib study in patients with various solid tumors, including colorectal cancer, cutaneous lesions, and mRCC) [70]. In this study, bevacizumab was administered for one 21-day cycle, and the humanized monoclonal anti-PD-L1 antibody MPDL3280A was added for the second cycle and continued. Data from the patient subset with mRCC were recently reported at the Genitourinary Cancers Symposium. Of ten patients with mRCC, four experienced partial responses and four had prolonged stable disease (≥24 weeks). In comparison, the objective RR for bevacizumab alone in this setting is 10 %, and that for MPDL3280A alone is 15 %. The combination also enhanced CD8+ T-cell infiltration and chemokine expression. MPDL3280A appeared to be well-tolerated without exacerbating bevacizumab-associated adverse events (AEs). Figure 5 presents a proposed clinical trial of combination antiangiogenesis therapy and immunotherapy in metastatic, recurrent, or persistent cervical cancer.

In looking forward to new trials in patients with advanced, recurrent, and persistent cervical cancer, the incorporation of immune checkpoint inhibitors into the current standard of care will require the adoption of several new protocols in the design of clinical trials. First, patients will need to be closely monitored for immune-related AEs (irAEs), which are the most common treatment-related toxicities [61]. In response to the AE profile of ipilimumab in patients with metastatic melanoma, guidelines have been created for early diagnosis and treatment of irAEs, with the FDA detailing management algorithms for irAEs on their Risk Elimination and Management System (REMS) website [71]. These guidelines will likely prove helpful while testing begins in a new patient population.

Second, patients will need to be assessed for a treatment response in a non-traditional manner. In total, four distinct patterns of response to immune checkpoint inhibition have emerged: (1) timely regression of index lesions; (2) a slow but steady decline in tumor burden after stabilization of disease; (3) an initial increase in existing tumor burden followed by a delayed response; and (4) the appearance of new lesions followed by a delayed response [72]. The latter three patterns of response are not seen with traditional cytotoxic therapies and may be associated with improved immuno-oncologic outcomes, reflecting the time required to establish antitumor immunity [73]. These unusual response patterns have catalyzed the creation of the immune-related response criteria, which differ in significant ways from the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [74] and modified World Health Organization (WHO) criteria [73]. Specifically, the formation of new lesions does not preclude categorization into ‘partial response’ or ‘stable disease.’ Given the above, the FDA have developed clinical considerations for immunotherapies, describing a series of clinical situations in which sponsors may elect to continue therapy despite evidence of disease progression.

8 Conclusion

Improving OS has been extremely difficult in patients with metastatic, recurrent, and persistent cervical cancer. During the era of chemotherapeutics, the OS benefit demonstrated in several GOG trials was questioned by differences in the characteristics of enrolled patients, specifically an increase in the percentage of patients with prior exposure to cis-platin and the restriction of patients to GOG performance status 0–1. Alongside the increasing popularity of targeted therapies, GOG 240 revealed a clear benefit of adding bevacizumab to platinum and non-platinum chemotherapy doublets. This promptly led to regulatory approval of bevacizumab for the treatment of advanced cervical cancer in the US, England, Switzerland, the EU, Australia, Hong Kong, Israel and at least five other countries in the Middle East, and Brazil and ten other Latin American countries. The South American countries have demonstrated that even poorer nations may be willing to cover the cost of the drug for underserved women following the lobbying of regulatory agencies and governmental programs. Given that biosimilars have been available on the European market since 2006, Europe is likely to be the testing ground for significant cost reductions in antiangiogenesis therapy with the use of biosimilars, 15 of which are in development. In a recent cost-effectiveness study of bevacizumab using updated survival and toxicology data, biosimilars led to a hypothetical 75 % reduction in cost [75].

Despite this progress, there remains an urgent need to improve on the results of GOG 240, given the limited gain in OS and the absence of any cures. The question we have proposed is: how do we best use the 4 months provided by the addition of bevacizumab? We believe that the answer may lie in the sequential administration of immune checkpoint inhibitors to patients deriving benefit from antiangiogenesis therapy prior to progression.

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Key Points

Because cervical cancers are derived from high-risk human papillomavirus infection, virally driven tumor angiogenesis results in a vulnerability to antiangiogenesis therapies.

The combination of antiangiogenic agents and cancer immunotherapies may provide a therapeutic option through which the tumor microenvironment can be altered.

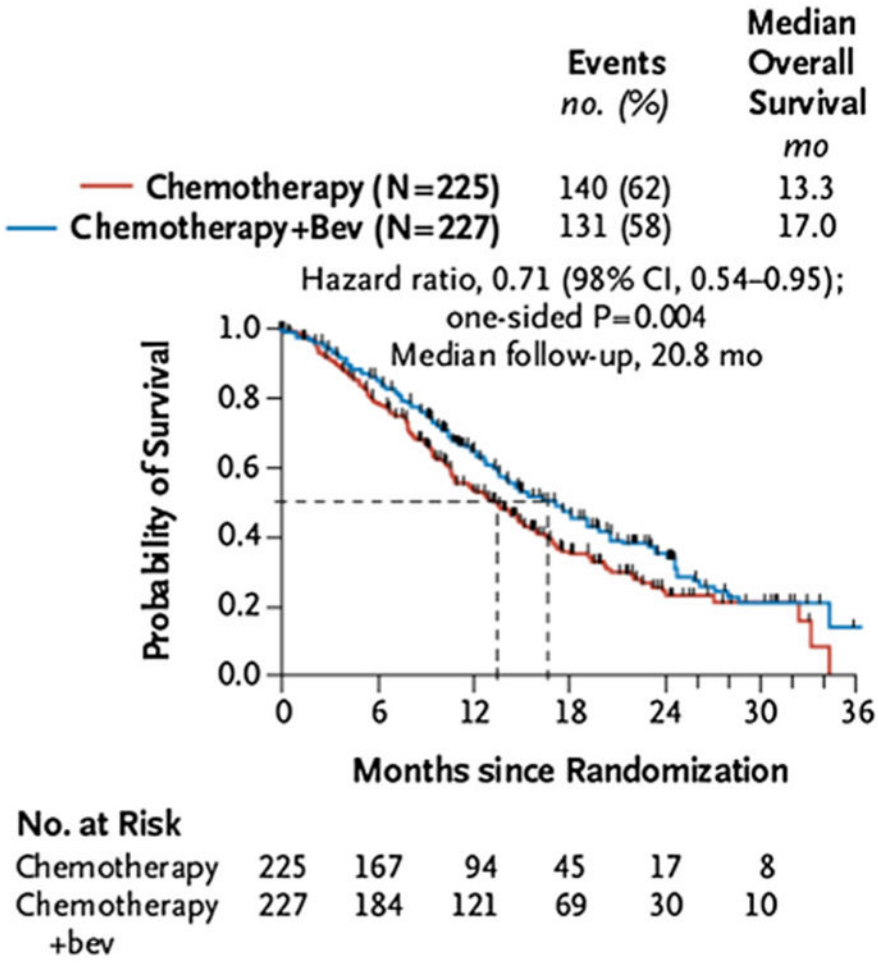

Fig. 1.

Median overall survival of patients with advanced cervical cancer treated with chemotherapy with and without bevacizumab in Gynecologic Oncology Group protocol 240. Reproduced from Tewari et al. [18], with permission. Copyright owned by the Massachusetts Medical Society. *BEV* bevacizumab, *CI* confidence interval

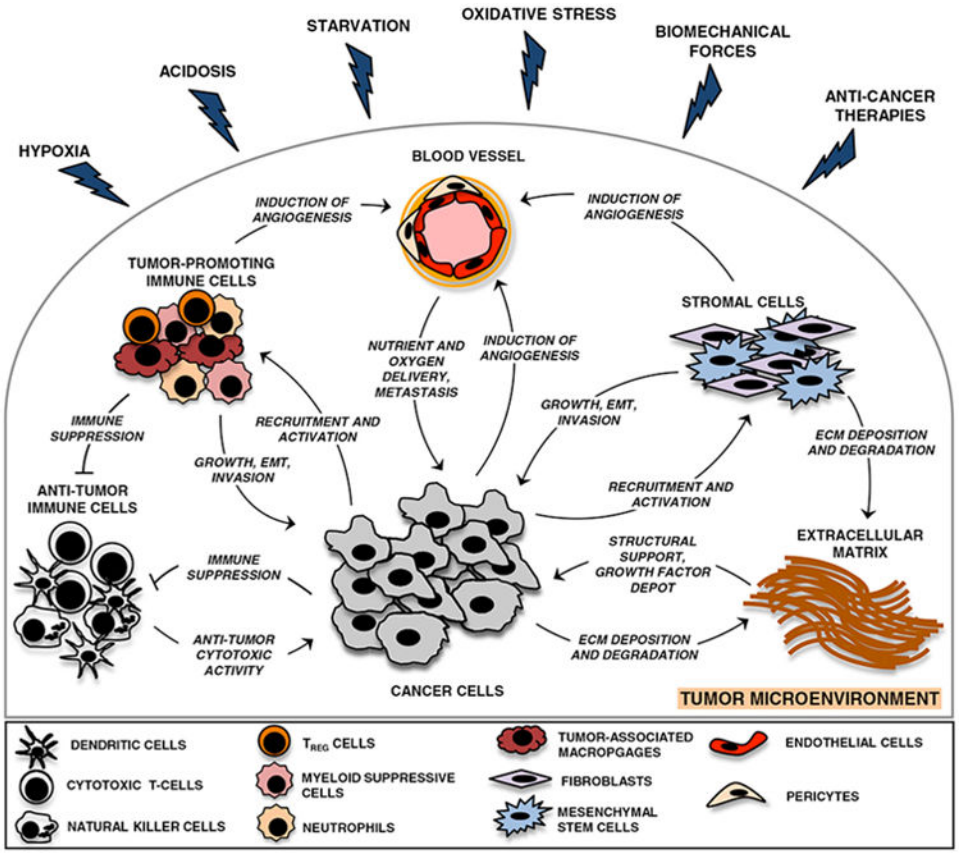

Fig. 2.

Complex cellular interactions influenced by various stressors in the tumor microenvironment. Among their most skillful tactics, cancer cells promote angiogenesis and suppress immune responses to create favorable conditions for tumor growth and dissemination. This figure first appeared in the *Journal of Extracellular Vesicles* [76], which is published Open Access under a Creative Commons license, and was developed from the authors' work on hypoxia-dependent intercellular signaling via secreted vesicles with exosome characteristics [77]. Reprinted from Kucharzewska and Belting [76], with permission. *ECM* extracellular matrix, *EMT* epithelial–mesenchymal transition, *Treg cells* regulatory T cells

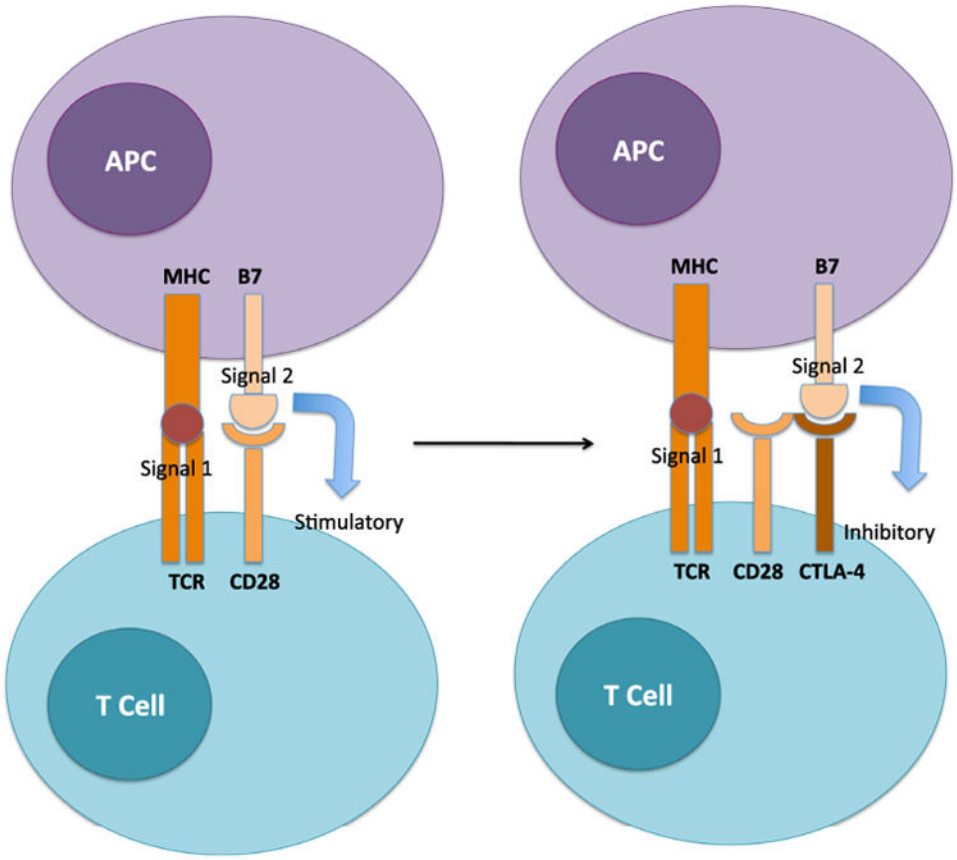

Fig. 3.

The physiologic role of CTLA-4 is to regulate the amplitude of the early stages of T-cell activation. Paired interactions at the surface of an APC and T cell are essential for T-cell activation and proliferation. The first signal occurs when peptide loaded on an MHC class I or II molecule interacts with the TCR. The second signal occurs when B7-1 or B7-2 ligand on the APC interacts with the CD28 receptor on the T cell. Following activation, T cells upregulate and translocate CTLA-4 receptor molecules to the surface, which bind to B7 with a higher avidity than CD28. CTLA-4 inhibits the T-cell response not only by disrupting the essential relationship between B7 and CD28 but also by actively delivering inhibitory signals to the cell, which involve the activation of PTPs. PTPs are known to regulate various cell signaling events, such as mitogenic activation, metabolic control, transcription regulation, and cell migration. Reprinted from Longoria et al. [78], with permission *CTLA-4* cytotoxic T-lymphocyte-associated antigen 4, *APC* antigen-presenting cell, *MHC* major histocompatibility complex, *TCR* T-cell receptor, *PTPs* protein tyrosine phosphatases

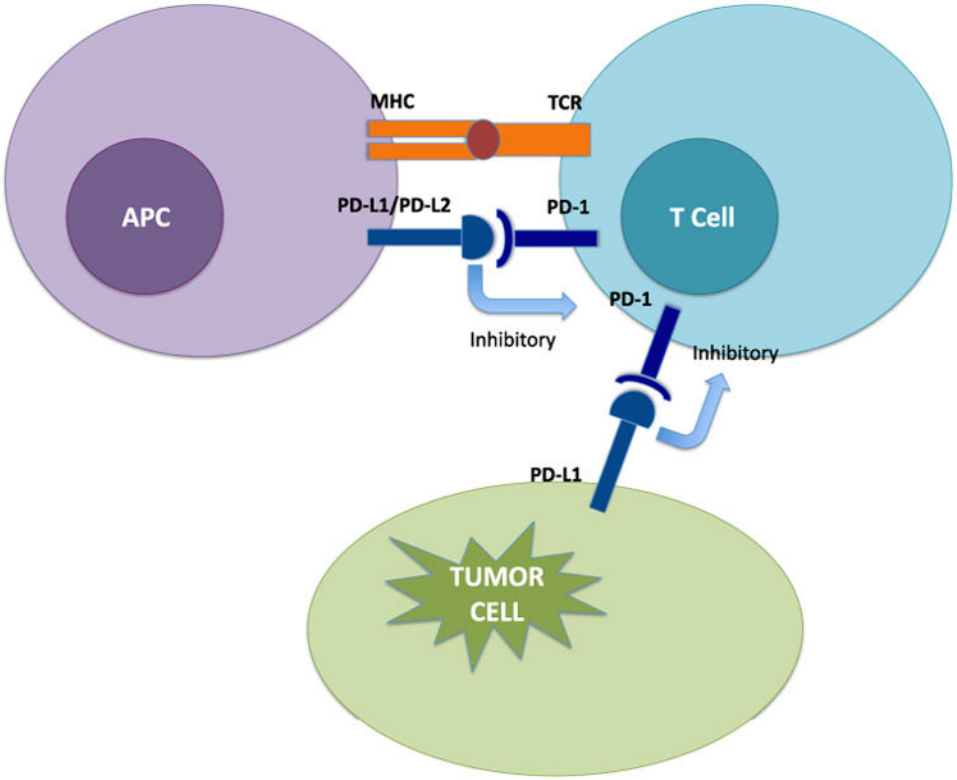

Fig. 4.

The physiologic role of PD-1 is to regulate T-cell effector function within peripheral tissues. Activated T cells upregulate the PD-1 receptor, while inflammatory signals, such as IFN-γ, induce the expression of its ligands, PD-L1 or PD-L2, in the periphery. This receptor-ligand interaction results in downstream signaling that inhibits T-cell cytotoxicity and cytokine release. Chronic antigen exposure leads to high levels of persistent PD-1 expression, which induces a state of T-cell exhaustion or anergy. Reprinted from Longoria et al. [78], with permission *PD-1* programmed cell death protein 1, *IFN* interferon, *APC* antigen-presenting cell, *MHC* major histocompatibility complex, *TCR* T-cell receptor

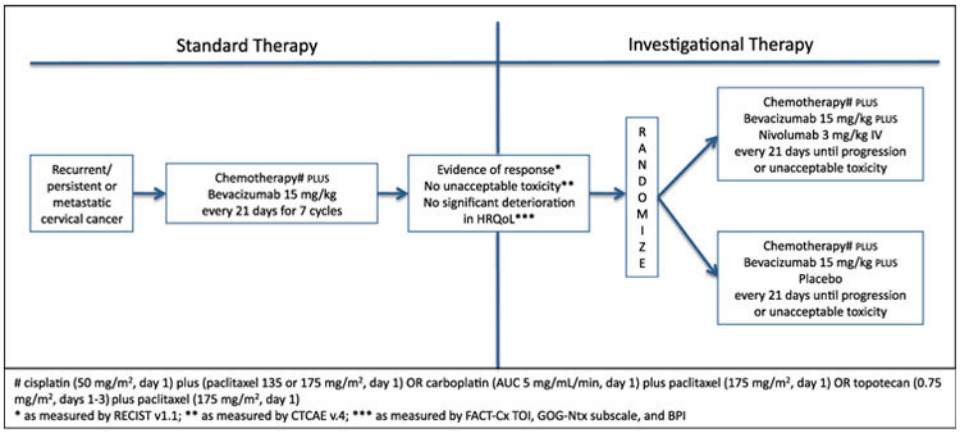

Fig. 5.

Proposed schema to study the combination of bevacizumab and nivolumab as a complement to standard chemotherapy in advanced cervical cancer in a randomized, phase II, placebocontrolled trial. *AUC* area under the curve, *BPI* Brief Pain Inventory, *CTCAE* Common Terminology Criteria for Adverse Events, *FACT–Cx TOI* Functional Assessment of Chronic Illness Therapy–Cervix Cancer trial outcome index, *GOG–NTx* Gynecologic Oncology Group–Neurotoxicity, *HRQoL* health-related quality of life, *RECIST* Response Evaluation Criteria In Solid Tumors, *IV* intravenously