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PD-1/PD-L1 immune checkpoint inhibitors in advanced cervical cancer

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Abstract

Programmed cell death-1 and programmed cell death ligand-1 (PD-1/PD-L1) blockage has become an important treatment modality after approval of pembrolizumab and nivolumab by Food and Drug Administration in advanced cancers. Patients with metastatic and recurrent cervical cancer have limited treatment options and usually receive palliative platinum-based chemotherapy without significant survival benefit. Recent studies provided support for usage of immune checkpoint inhibitors in advanced cervical cancer. Around 35% of cervical squamous cell carcinoma (C-SCC) and 17% of adenocarcinomas expressed PD-L1. Human Papilloma Virus status was also correlated with PD-L1 expression. PD-1/PD-L1 expression in tumor infiltrating inflammatory cells was higher in cervical cancer in comparison to endometrial and ovarian adenocarcinomas. In C-SCC diffuse PD-L1 expression as compared to marginal PD-L1 expression on the interface between tumor and stroma was a risk factor for poor disease-free and disease-specific survival rates. Higher numbers of infiltrating regulatory T cells in PD-L1 positive tumors was associated with better prognosis. The studies performed on other cancer types revealed PD-L1 tumor heterogeneity and transient marker expression. Drug-resistance to immune checkpoint inhibitors is also a potential problem. Currently Phase I/II clinical trials evaluating effects of PD-1 therapy are in progress for cervical carcinoma. Additional studies are required to develop novel biomarkers and for standard evaluation of PD-L1 testing in order to predict response to immune checkpoint inhibitors in all cancer types including cervical carcinoma.

Introduction

Cervical cancer is the third common gynecologic cancer and will affect 13,240 women in the United Stated with an estimated 4,170 deaths in 2018 [1]. Human Papilloma Virus (HPV) infection is an etiologic agent of precursor lesions, Cervical Intraepithelial Neoplasia (CIN), and invasive cervical carcinoma [2]. High-risk HPV subtypes, HPV 16 and 18 are the most carcinogenic types in progression of the disease [3]. In the last few decades, effective screening and preventive vaccines facilitated early detection of precursor lesions and improved survival outcomes [4]. For early staged cancer surgical removal through radical hysterectomy is the treatment of choice and concurrent chemoradiation (CCRT) is the standard treatment modality for locally advanced disease defined as stages IB2-IVA by International Federation of Gynecology and Obstetrics [5]. Recurrent and metastatic diseases develop in 15-61% of the women within the first two years after completion of primary treatment [6]. The management of recurrent cervical cancer depends on previous therapeutic modalities. In the presence of prior pelvic irradiation the prognosis is usually dismal and only curative therapy is pelvic exenteration procedure with high morbidity and mortality rates [7,8].

Majority of patients with recurrent and metastatic cervical carcinoma are treated with palliative chemotherapy [9]. Platinum-based combination therapies are the treatment of choice [10]. The addition of vascular endothelial growth factor inhibitors reduced hazard of disease progression and prolonged overall survival [11]. Epithelial growth factor inhibitors, targeting of PI3K/AKT/mTOR pathway and therapeutic vaccines are other new treatment modalities included in clinical trials of recurrent and metastatic diseases [12-14]. Currently immunotherapy was emphasized as maintenance therapy for high-risk patients with multiple positive pelvic lymph nodes, uterine corpus extension, and positive aortic nodes in patients treated with CCRT [15]. We will discuss below Programmed cell death-1 and programmed cell death ligand-1 (PD-1/PD-L1) immune checkpoint pathway and the potential role of PD-1/PD-L1 blockers in the treatment of cervical carcinoma.

PD-1/PD-L1 Immune checkpoint inhibitors

The immune checkpoints are critical to maintain tolerance against autoimmunity in physiologic conditions. PD-1 is a transmembrane protein and expressed in B and T immune cells. Its receptor PD-L1 is a member of B7 family and associated with antigen presenting cells such as dendritic and cancer cells [16]. PD-1 is expressed on memory cells in the peripheral blood of healthy individuals [17]. The PD-1/PD-L1 interactions leads to blockage of T cell activation by inhibiting TCR signal transduction and CD28-CD80 co-stimulation [18]. Several cancer types overexpress PD-L1, which serves as an immune resistance mechanism by inactivating T cells within tumor microenvironment [19,20]. Food and Drug Administration (FDA) recently approved PD-1/PD-L1 antibody-mediated blockage for metastatic melanoma, Non-small cell lung cancer (NSCLC), head and neck, kidney and urothelial carcinomas, Hodgkin lymphoma and microsatellite instability/mismatch repair (MMR) deficient cancers [21]. However, PD-1 signaling and the mechanism of action of PD-1/PD-L1 monoclonal antibodies are not completely understood.

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At the transcription level INF-ϒ is the major inducer of PD-L1 expression [22]. PD-L1 expression is also induced on activated immune cells including dendritic cells, macrophages, B cells, T cells and natural killer cells. The latter is mediated through cytokine/chemokine and STAT3 pathways [23]. The expression levels of PD-L1 on tumor cells did not always correlate with response to therapy in the literature [17]. The inconsistency is partly related to non-standard reading and different cutoff levels of PD-L1 antibody positivity. Based on clinical trials and response rates to therapy the predictive 50% cutoff of PD-L1 expression was included in the FDA indications of pembrolizumab in metastatic NSCLC (24). Another predictor of treatment response is high mutational load of tumors resulting in multiple neoantigens generated from an increased burden of nonsynonymous mutations [25]. The relation between PD-L1 expression levels and overall disease prognosis is also controversial. It has been associated with worse survival in some tumors such as esophageal, gastric, colorectal and pulmonary cancers [26,27]. PD-L1 expression on immune cells was a favorable prognostic factor in vulvar Squamous Cell Carcinoma (SCC) [28] and did not have any affect in prognosis in laryngeal and pharyngeal SCC [29].

PD-1/PD-L1 and cervical cancer

Persistent HPV infection is involved in the pathogenesis of both cervical squamous and adenocarcinomas. The expression levels of PD-1/PD-L1 were studied in relation to HPV status in cervical lesions. In one study there was no difference in mRNA expression of PD-L1 by qRT-PCR when comparing HPV DNA-positive and -negative women [30]. However PD-L1 expression was correlated with HPV-positivity and increased with CIN grade, and tumor metastasis in cervical cancer in a later study [31]. PD-L1 expression was reported in higher rates in squamous type (34%) compared to adenocarcinoma (17%) and adenosquamous carcinoma had a positive rate of 29% [32]. The difficulty in evaluating PD-L1 expression is partly due to heterogeneous nature of tumors. The expression of PD-L1 is not uniform and can be transient, thus PD-L1 immunohistochemistry staining varies with tumor locations [33,34]. These results may explain conflicting response rates to PD-L1 blockers with low PD-L1 expression levels. The genetic basis of increased PD-1/PD-L1 expression was explored in cervical and vulvar SCC samples. The genes encoding PD-L1 and PD-L2, *CD274* and *PDCD1LG2*, were co-amplified or gained extra chromosomes in 67% of cervical and 43% of vulvar SCC cases by Florescence in situ hybridization [35].

PD-1/PD-L1 expression levels were also studied in Tumor Infiltrating Inflammatory cells (TIL) in cervical carcinoma. PD-L1 positivity in TIL component of cervical squamous cell cancers was higher in comparison to endometrial and ovarian adenocarcinomas [36]. TIL can also play a role in predicting response to anti-PD-L1 therapies [37] and therefore evaluating amount of TIL and their functional status can be complimentary to PD-L1 expression levels in tumors. Karim et al showed more than half of TIL expressed PD-1 and only 19% of tumor cells had positivity with PD-L1 in cervical cancers. In addition the expression of PD-L1 did not show a direct impact on patient survival but patients with a relative excess of infiltrating regulatory T cells displayed a better survival when the tumor was PD-L1 positive [38]. The expression levels and pattern were also correlated with survival outcomes in other studies. In SCC of cervix, disease-free and disease-specific survival rates were significantly poorer in patients with diffuse PD-L1 expression as compared with patients with marginal PD-L1 expression on the interface between tumor and stroma [39]. The same study showed disease-specific survival was worse in cervical adenocarcinoma patients with PD-L1-positive tumor-associated macrophages compared with adenocarcinoma patients without PD-L1-positive tumor-associated macrophages. Contrary to these reports, neither expression of PD-L1 nor density of $CD8^+$ T cells in pretreatment specimen was associated with progression-free or overall survival in patients with advanced cervical cancer in a later study [40].

Immune checkpoint inhibitors and drug resistance

Another potential problem in immune checkpoint inhibitor treatment is primary and acquired drug resistance [41]. In cervical cancer there is not much data related to duration and mechanisms of drug resistance. A recent clinical trial showed 17% response rate to anti-PD-L1 treatment in 24 patients with PD-L1 positive tumors [42]. The presence of inactivating mutations in *JAK1*, *JAK2* and beta2-microglobin genes in cancer cells correlated with lack of primary response in melanoma and colon cancer [43]. It has also been shown that tumors acquire resistance through PD-L1 up-regulation [44] and can escape immune surveillance by decreased expression of MHC, increased PD-L2 expression on PD-L1 negative tumor cells, stromal remodeling, epithelial mesenchymal transition and compensatory PD-L1 expression on host cells including T cells [45,46]. The tumor cells can activate PD-L1 expression independently of inflammatory signals via multiple oncogenic signaling pathways including PI3K/AKT, ALK/STAT3 and MEK/ERK/STAT1 [47-49]. On the other hand, Transforming Growth Factor-beta (TGF-β) signaling pathway suppresses Th1 and cytotoxic T-cells while promoting the generation and activity of Treg cells [50]. TGF-β impairs the adaptive anti-tumor immunity by directly inhibiting clonal expansion and cytotoxicity of $CD8^+$ cytotoxic T cells and inducing expression of Foxp3 to suppress $CD4^+$ T cells [51-53]. TGF-β1 enhances PD-1 expression through SMAD3 dependent way on antigen-specific T cells in cancer [54]. In support of latter findings tumor-derived TGF-β decreases Special AT-rich sequence protein *(Satb1)* expression through binding SMAD proteins to its promotor. *Satb1* regulates epigenetic regression of PD-1 on activated T cells [55]. Finally lack of response to PD-L1 therapy in metastatic urothelial carcinoma was associated with a signature TGF-β signaling in fibroblasts [56].

Conclusion

Clinical use of immune checkpoint inhibitors is new and promising treatment modality in advanced and recurrent cancers. Currently there are multiple phase I/II clinical trials evaluating effect of anti-PD-1/PD-L1 therapy in cervical cancer [57]. Some of these include anti-cytotoxic T-lymphocyte associated antigen (CTLA4) as a combination therapy. Ipilimumab, an anti-CTLA4 antibody, was tolerable in patients with advanced cervical cancer but it did not show significant single-agent activity [58]. Targeting multiple immunologic pathways especially potential antagonists of PD-1/PD-L1 pathway may overcome innate and acquired resistance to anti-PD-L1 therapy.

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