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PD-1 as a predictor of antitumor immune resistance Its detection perspectives and correction possibilites in cervical cancer

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ABSTRACT

Cervical cancer is one of the most common gynecological tumors, and the majority of early-stage cervical cancer patients achieve good recovery through surgical treatment and concurrent chemo radiotherapy (CCRT). However, for patients with recurrent, persistent, metastatic cervical cancer, effective treatment is rare, except for bevacizumab combined with chemotherapy. Programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors might be a novel choice to improve the clinical outcomes of these patients. Thus far, some pivotal trials, including Keynote 028, Keynote 158 and Checkmate 358, have indicated established clinical benefit of PD-1/PD-L1 inhibitors in cervical cancer. In light of these data, the FDA has approved pembrolizumab for patients with recurrent or metastatic cervical cancer with disease progression during or after chemotherapy. There are also some ongoing studies that may provide more evidence for the PD-1/PD-L1 pathway as a therapeutic target in cervical cancer. In this review, we have summarized the status and application of PD1/PD-L1 inhibitors in clinical trials for the treatment of cervical cancer and suggested some future directions in this field.

1. Introduction

Cervical cancer is one of the most common gynecological tumors. More than 569,847 women are diagnosed with cervical cancer annually worldwide, resulting in over 311,365 deaths [1]. Although the incidence of cervical cancer has been greatly reduced by the use of HPV vaccines and cervical cancer screening [2], cervical cancer is second in terms of morbidity among gynecological tumors in developing countries [3]. Over 70% of cervical cancer cases diagnosed in developing countries are locally invasive or metastatic, contributing to the high mortality rate of cervical cancer. The 5-year OS rate of local cervical cancer can achieve approximately 75–85% through effective treatments such as surgery CCRT, etc. [4]. Nevertheless, the 5-year OS of recurrent, persistent, metastatic cervical cancer is only approximately 15%. The poor prognosis is mainly due to limited therapeutic options [5]. The majority of these patients can only be treated with palliative chemotherapy [6], in which platinum-based chemotherapies were the prior choice [14]. In 2014, the GOG 240 trial indicated that when bevacizumab was added to the chemotherapy, the ORR was

improved from 36 to 48% [7], and the OS could be prolonged from 13 to 17 months for recurrent, persistent, metastatic cervical cancer, thus laying the foundation for the first-line choice of combining bevacizumab with chemotherapy for this population [8]. However, for those who progress during the first-line treatment, the lack of effective second-line treatment remains to be the main reason for the high mortality rate [9]. Currently, immune checkpoint inhibitors [10], especially PD1/PD-L1 inhibitors [11], have achieved favorable efficacy in treating multiple solid tumors [12], including cervical cancer [13]. Accumulating evidence has demonstrated that PD-1/PD-L1 inhibitors may be a promising approach for cervical cancer treatment.

2. Conclusions

Although there are a few studies suggesting the potential feasibility of PD-1/PD-L1 inhibitors for the treatment of cervical cancer, a consideration should be made for the clinical application of PD-1/PD-L1 inhibitors. The inadequate number of cases included and the insufficient follow-up time are the main defects of all the studies, leading to the unavailability of data regarding OS, PFS, AEs, drug resistance and the treatment mechanism as well. These data are very pivotal not only for obtaining a more convincing result, but also for guiding physicians to select the appropriate patients for PD-1/PD-L1 inhibitors.

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