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Mini Review

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Novel Biomarkers are Emerging in Cervical Adenocarcinoma: A Short Review

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Abstract

In recent years, the search for traditional Chinese medicines (TCM) for treating patients with critical and/or life-threatening diseases has attracted much attention in the pharmaceutical industry. However, the evaluation of safety and efficacy of a TCM under investigation has been criticized due to its subjectivity (i.e., experience based rather than scientific based). Thus, statistical validation of study endpoints (usually based on a quality of-life-like instrument) is essential to have an accurate and reliable clinical assessment of the performance of the TCM under study. Hsiao et al. [1] proposed some statistical methods for calibration/validation of Chinese study endpoints against Western clinical endpoints in terms of the performance characteristics of validity, reliability, and ruggedness under a valid study design. In this article, we proposed some innovative study designs for calibration/validation of Chinese study endpoints against Western clinical endpoints. under certain considerations of study design.

Keywords: Validity, Reliability, Calibration, Validation

Introduction

Cervical adenocarcinoma (ADC) represents a heterogeneous group of tumors, associated with different biological behaviors and variable outcomes [1]. Although their prevalence has increased over the past decades, reaching the 20-25% of all cervical malignancies in developed countries [2-4], there are still less frequent than the squamous cervical carcinoma (SCC). For this reason, there are no large series' studies in literature and consequently the oncogenetic pathways of ADC have not been fully elucidated yet.

The Question Is: Which Biomarkers Might Have a Predictive Role?

The role of infection with human papillomaviruses (HPV) is well-known, however it is not sufficient to induce carcinogenesis: further genetic and epigenetic alterations, as well as the peculiar interaction between infected cells, host immune response and tumor microenvironment (TME) are necessary to promote malignant transformation and progression. Some examples.

a) Genomic alterations in phospoinositide 3-kinase (PI3K) are detected also in cervical cancer [5,6], associated to mutations of PTEN, MAPK and AKT1 [7-11].

b) A hypoxic TME and an altered neo-angiogenesis is a common feature in solid tumors. In cervical cancer, a high expression level of hypoxia-inducible factor 1α(HIF-1α) is associated with a worse prognosis [12-14].

c) In general, we could assume that immunosuppressive and immunogenic tumor- infiltrating immune cells influence the prognostic landscape also in cervical cancer, which is highly related to and modulated by HPV [15].

Several studies demonstrated the overexpression of programmed death ligand 1(PD-L1) in cervical SCC and its potential utility [16-19]. Moreover, different clinical trials have been conducted regarding immune checkpoint inhibitors (ICIs) and tumor-infiltrating lymphocytes (TILs), including programmed death 1(PD-1), PD-L1, programmed death ligand 2(PD-L2), and cytotoxic T-lymphocyte-associated protein 4(CTLA-4) [20-22].

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As mentioned above, all these studies are regarding mostly SCC; on the other hand, few and contrasting data are available specifically on ADC, due to the small number of patients included in these cohorts. Similarly, the mismatch repair proteins (MMR) are still under investigation, although defects in this repair system can increase mutation rates and promote cancer initiation and progression, such as in patients with Lynch Syndrome [23,24].

Very recently has been published an investigation evaluating the expression of PD-L1 and the MMR status, trying to highlight the potential correlation with clinicopathological features [25], in a mono-series of 39 patients. Although it was a small sample size, it seems to be a correct approach for studying this particular subgroup of cervical cancer. Previous studies, such as Bonneville, et al. [26] did not analyze separately SCC from ADC [26], consequently a potential different biological status couldn't emerge. Evaluating a cohort formed only by ADCs, highlighted a significantly higher number of MMRd cases, suggesting a pivotal role of this dysregulation in adenocarcinoma's oncogenesis. Moreover, due to the correlation between tumor-infiltrating lymphocytes (CD8+), PD-L1 expression and MMRd tumors observed by others author among gynecologic malignancies, it focused the attention also on PD-L1 protein expression.

Comparing to the contradictory results of previous studies [27-32], the novel research [25] showed no PD-L1 expression (<1%) in ADCs, independently of the MMR status or other clinic-pathological variables, with the only exception of invasive stratified mucin cancer (iSMC), which has been recently described as a peculiar morphologic histotype with evident HPV infection-related features, and frequently associated with a brisk tumor inflammatory infiltrate [33].

Thus, the emerging data underlined the potential role of MMRd.as an early event in ADC tumorigenesis, considering that either invasive or in situ lesions can host this molecular alteration, supporting this assumption. Of course, distinguishing the germline or somatic nature of MMRd mutations remains crucial, particularly because of the increased lifetime risk of several solid malignancies in patients harbouring a germline mutation. This underpins the importance of the screening for Lynch syndrome also in ADC, confirming the importance of genetic counselling. On the other hand, PD-L1 seems to not play a pivotal role in ADC, except for iSMC. Of course, this interesting exception need to be further investigated, anyway it reveals the heterogeneity of ADCs one more time.

Conclusion

In conclusion, a broad spectrum of protein biomarkers is still being investigated, considering not only the neoplastic cell population, but also the complex interactions with TME and cervical microbiota [34] to predict prognosis and treatment response. May be, finding a predictive unique marker is utopian, while evaluating multiple expression levels of proteins in a combined analyse could be the right way to run across.

Conflicts of Interest

The authors declare no conflict of interest.

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