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Ovarian Cancer Drug Response Assays for Precision Medicine

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INTRODUCTION

A significant global health issue is cancer. Cancer causes one out of every six fatalities, according to the World Health Organization (WHO), making it the second leading cause of death after cardiovascular disease. The American Cancer Society predicts that there will be 606,520 cancer-related deaths and 1,806,590 new diagnoses in the United States in just 2020.

For the clinical management of the majority of cancers, traditional cancer therapy modalities like surgery, radiation therapy, and chemotherapy still hold sway. Despite the fact that these treatments have improved the overall survival of many cancer patients, their effects may only be felt by a small number of tumours that are particularly responsive to treatment. Additionally, these treatments may cause long-term side effects. Targeted therapies and immunotherapy have emerged as novel cancer treatments as a result of the evolution of cancer treatment paradigms over the past few decades from organ-centric approaches to genotype-driven precision medicine approaches.

DESCRIPTION

Clinical trials and drug development processes are increasingly integrating companion diagnostics, which can pinpoint patients who will most likely benefit from a specific anti-cancer therapy. In 1998, the United States Food and Drug Administration (FDA) approved the use of trastuzumab (HERCEPTIN) in a subset of patients with breast cancer based on assays that detected HER2 overexpression. Another FDA-approved companion diagnostic that determines whether non-small cell lung cancer (NSCLC) patients should receive nivolumab (OPDIVO) is the PD-L1 immunohistochemistry (IHC) 28-8 PharmDx assay [1].

The FDA most recently authorised the VENTANA PD-L1 (SP142) assay in 2016 as a companion diagnostic for deciding which NSCLC and bladder cancer patients would receive atezolizumab treatment (TECENTRIQ). In 2018, the FDA approved Olaparib (Lynparza) for the maintenance treatment of women with advanced epithelial ovarian, fallopian tube, or peritoneal cancer that has a BRCA mutation and a favourable response to platinum-based first-line chemotherapy. For patients with advanced ovarian cancer who have BRCA mutations, there are currently two companion diagnostics approved by the FDA: BRACAnalysis companion diagnostic (CDx) (Myriad Genetic Laboratories, Salt Lake City, UT, USA) and Foundation One CDx (Foundation Medicine, Cambridge, MA, USA). Despite the fact that biomarker-directed patient stratification has significantly improved cancer patients' clinical outcomes. Only a small number of targeted treatments fall within its scope. Furthermore, most frontline anti-cancer therapies lack response-predictive biomarkers. Alternative methods are therefore needed to enable the clinician to examine how the patient's tumour cells react to various anti-cancer therapeutics.

Live patient tumour cells are exposed to different chemotherapeutic and other agents in drug-response assays, which are in vitro platforms used to test the sensitivity of the patient's tumour cells to the drugs. In the case of ovarian cancer, the development of such assays is crucial because the majority of patients who receive the standard platinum-based chemotherapy eventually develop recurrent disease that is resistant to the medication. The median overall survival of ovarian cancer patients with platinum resistant disease is approximately one year due to the lack of efficient second-line chemotherapies. As a result, the treatment of patients with ovarian cancer urgently requires novel therapeutic approaches. Recent years have seen a lot of promise in the

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personalised treatment of ovarian cancer patients by molecular targeted therapies. Anti-angiogenic inhibitors and poly (ADP-ribose) polymerase (PARP) inhibitors are two FDA-approved targeted drugs for ovarian cancer that have demonstrated an encouraging benefit for progression-free survival. However, only a small percentage of patients benefit from these targeted medications. Consequently, validated in vitro assays that can assess specific tumour responses to chemotherapy or targeted therapies could be used as an important clinical tool for the customization of cancer patient care [2].

In the vast majority of drug-response assays, primary patient tumour cells are cultured in a 2D or 3D cell culture setting and then exposed to cytotoxic drugs. The type of cell culture technique employed may have an impact on how well these assays perform [3]. In this review, we looked at the potential of various 2D and 3D cell culture models as ovarian cancer drug sensitivity testing tools. Wherever possible, we have taken steps to address the drawbacks and limitations of these assays. A deeper comprehension of these preclinical models, in our opinion, may aid in advancing research projects aimed at creating assays for efficient drug screening and clinical management of ovarian cancer.

Drug tested on consumers

Chemo-response assays (CRAs) are ex vivo drug-response assays created to assess a patient's tumour cells' receptivity to or resistance to clinically useful chemotherapy agents. The majority of CRAs created so far have similar principles and practises, which include gathering primary patient tumour samples, isolating tumour samples into single cells, establishing in vitro cell cultures, administering chemotherapeutic agents, determining whether cells survived or died, statistical analysis, and drug sensitivity prediction. Microculture-Kinetic (MiCK) assay (DiaTech Oncology, Nashville, TN, USA) and ChemoFx assay (Helomics, Pittsburgh, PA, USA) are two CRAs that have undergone commercial testing in the US. Both tests make use of 2D cell culture platforms. Neoplastic cells are isolated from patient tumour samples, seeded in a 2D cell culture environment, and exposed to serially diluted chemotherapeutic drugs that cause apoptosis in tumour cells as part of the MiCK assay. A density-by-time curve is produced by measuring the optical density (OD), a substitute for apoptosis, of cells over time.

The degree of drug-induced apoptosis serves as a gauge of the tumour cells' receptivity to the drug under investigation. The chemo-response of tumour cells from various cancer types, including hematologic, breast, lung, and gynecologic malignancies, has been studied using this assay. Patients with ovarian cancer have also undergone clinical trials with the MiCK assay [4].

It does this in two ways. First, it employs a cell-culture technique that promotes the growth of epithelial cells while reducing the confounding effects of other cell types. To confirm that the majority of the cells are epithelial, immunocytochemistry steps are added to the workflow of this process as a complement. Second, it can test core needle biopsy samples because of the low cellular volume needed for this assay (as little as 35 mm3 of tissue). Finally, the high level of automation in this assay enables the use of a variety of drug concentrations. This test has been used to forecast the chemo-response of a variety of solid tumors, such as breast and ovarian cancer. Chemotherapy sensitivity and resistance assays should not be used outside of clinical trial settings, according to American Society of Clinical Oncology (ASCO) guidelines from 2011 [5]. The majority of the CRAs that are currently on the market test drug sensitivity using 2D cell culture models. There is mounting evidence that cancer cells in 2D culture behave very differently from actual tumour cells in the body. Many researchers have shifted their attention to the use of 3D cell culture models, which may be more representative of tumour architecture than 2D models, due to the limitations with current 2D cell culture-based assays.

Mina Bissell and her team proposed that a reciprocal and dynamic interaction between cells and their surrounding extracellular matrix (ECM) can modulate gene expression in the early 1980s, setting the stage for the significance of this interaction [6]. As 3D cell culture techniques developed over time as a result of research into this model, 3D organoids started to be used as a preferred model for analysing complex malignant tumours. Cells can interact with the ECM and one another to form organoids using the 3D culturing technique. Numerous pieces of evidence point to a striking difference between how tumour cells react to cytotoxic agents in 2D and 3D cell culture models. As a result, these 3D culture models are widely used.

CONCLUSION

In conclusion, this article looks at current chemo-response assays and how they might help patients with ovarian cancer have a better clinical outcome by foretelling ex vivo therapeutic responses. These assays must incorporate supporting tumour microenvironment cells for better disease modelling in vitro, be compatible with automation and high throughput analysis in a cost-effective manner, and use cell culture models that replicate the actual tumour architecture. Validation of these assays through well-planned prospective, blinded, multi-center clinical trials is also crucial for clinical translation. We believe that reliable bioassay-directed treatment selection could not only enhance patients' quality of life but also lessen the financial burden brought on by the expenses involved in administering less effective treatment regimens.

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