

Genomic profiling in gynaecological oncology: the future is now !

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Summary

Nowadays, thanks to next generation sequencing, it is simultaneously possible to search for driver mutations in hundreds of cancer-related genes with high sensibility and specificity, by exploiting formalin-fixed paraffin-embedded tumor material, from biopsy samples and surgical specimens, or circulating tumor DNA in the patient's blood. In addition to indicate the genomic alterations, this modern technology provides information about: the approved therapies in the patient's cancer type or in other tumor types for a personalized oncology; potential clinical trials; mutational burden and microsatellite instability (MSI). This last datum is particularly relevant because the U.S. Food & Drug Administration (FDA) has approved the use of pembrolizumab for all unresectable or metastatic, MSI-high or mismatch repair deficient, solid malignancies, among which there are 17-32% of sporadic endometrial carcinomas and 10-17% of sporadic ovarian cancers. Similarly, the FDA has approved olaparib for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer, characterized by deleterious or suspected deleterious germline or somatic mutations in 'breast cancer' (BRCA) genes, who are in complete or partial response to first-line platinum-based chemotherapy. Therefore, we are facing an era of innovation in gynaecological oncology, in which molecular profiling is joining immunomorphological typing for new health goals.

Key words: Next generation sequencing (NGS); Microsatellite instability (MSI); Mismatch repair (MMR); Breast cancer (BRCA) genes; Pembrolizumab; Olaparib.

The history of genomic profiling in cancer begins in 1986 when the Italian-American virologist Renato Dulbecco (February 22, 1914-February 19, 2012), Nobel Prize in Medicine for his researches on oncoviruses, wrote that a turning point in cancer research would have been the sequencing of human genome [1]. After four years, the ambitious Human Genome Project, whose logo was the Vitruvian man by Leonardo da Vinci (April 15, 1452-May 2, 1519), started, and it was successfully completed in 2003 [2]. Afterwards, the Cancer Genome Project, which operates within the International Cancer Genome Consortium, has been launched, with the aim to identify those mutations critical in the development of human cancers [3]. By the term 'oncogenomics', the scientific community refers to that branch of genomics which deals with cancer-related genes [4], focusing on genetic mutations, epigenetic alterations (promoter methylation, histone modification), and post-transcriptional silencing [5]. In turn, cancer-related genes can be distinguished into anti-oncogenes (e.g. BRCA1, BRCA2, CDKN2A, TP53), whose loss of expression leads to cancer, and into proto-oncogenes, which cause a tumor once overexpressed, such as growth factors (e.g. EGF), receptor tyrosine kinases (e.g. EGFR, HER2, NOTCH1, NTKR), cytoplasmic tyrosine kinases (e.g. ABL), cytoplasmic serine/threonine kinases (e.g. RAF), regulatory GTPases (e.g. RAS) and transcription factors (e.g. GATA3, MYC) [6,7]. Nowadays, thanks to next generation sequencing, based on hybrid

capture, it is simultaneously possible to search for driver mutations (gene rearrangements, copy number anomalies, base insertions, deletions or substitutions) in hundreds of cancer-related genes with high sensibility and specificity in a 10-days turnaround time, by exploiting formalin-fixed paraffin-embedded tumor material, from biopsy samples and surgical specimens, or circulating tumor DNA in the patient's blood [8,9]. In addition to indicate the genomic alterations, this modern technology provides information about: the approved therapies in the patient's cancer type or in other tumor types for a personalized oncology; potential clinical trials; mutational burden and microsatellite instability (MSI). This last datum is particularly relevant because the Food & Drug Administration (FDA) has approved the use of pembrolizumab, the well-known immune checkpoint inhibitor directed against the programmed cell death protein 1 (PD-1) receptor, for all unresectable or metastatic, MSI-high or mismatch repair (MMR) deficient, solid malignancies. Pembrolizumab has so become the first tissue-agnostic cancer drug [10]. MMR function is lost in 17-32% of patients affected by sporadic endometrial carcinoma [11,12] and in 10-17% of patients with sporadic ovarian cancer [13,14], not irrelevant percentages considering the therapies now available. Moreover, it can be lost in selected cases of hereditary breast-ovarian cancer syndrome, similar to what occurs for 'breast cancer' (BRCA) genes [15]. For this reason, the FDA has approved olaparib for the maintenance treatment of adult patients with



Figure 1. — The WCD logo has been developed by the Union for International Cancer Control (UICC) under a Creative Commons Attribution-ShareAlike 4.0 International License, in order to establish a global identity and to cement the day in calendars and activities around the world.

deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to first-line platinum-based chemotherapy [16]. Therefore, we are facing an era of innovation in gynaecological oncology, in which molecular profiling is joining immunomorphological typing [17]. On March 2019, the third national meeting about integrated oncology was held in Modena (Italy), during which this topic has been addressed for new health goals [18]. In the United States, it is estimated that there are 61,880 new cases per year of uterine corpus cancer and 22,530 new cases of ovarian tumors, of which 12,160 and 13,980 are respectively fatal [19]. Internationally, the World Cancer Day (WCD) is celebrated every year on February 4th: the 2019-2021 slogan is 'I Am and I Will', in order to raise awareness of cancer and to encourage its prevention, detection and treatment (Figure 1). Today, the awareness is growing to have also a novel real opportunity in the fight against gynaecological malignancies, the genomic profiling.

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Conflict of interest

The authors declare no conflict of interest.

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