Personalized Medicine in Ovarian Cancer: A Perspective From Mexico

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Abstract

Ovarian cancer (OC) represents a serious health problem worldwide. In Mexico, most OC patients are detected at late stages, consequently making OC one of the leading causes of death in women after reaching puberty. Personalized medicine (PM) provides an individualized therapeutic opportunity for treating each patient relying on "omic" tools to match the correct drug with the specific pathogenic genomic signature. PM can help predict the best therapeutic option for each affected woman suffering from OC. In recent years, Mexico has made contributions to the PM of OC; however, it still has a long way to go for its full implementation in the country's health system.

Keywords: Personalized medicine; Ovarian cancer; Targeted therapies; Mexico

Introduction

Ovarian cancer (OC) is the eighth leading cause of cancer death among women worldwide and the sixth in Mexico. The incidence of OC increases over the women's lives and about half of them are 63 years or older [1]. Estimations of incidence, mortality and prevalence for OC can be visualized in Table 1 [2].

Ovarian carcinomas are a heterogeneous group of neoplasms that are generally classified based on type and degree of differentiation (tumor grade). Early diagnosis is a challenge due to the lack of pathognomonic signs and symptoms for this condition. Most of the time these malignancies are detected after the disease has already spread beyond the pelvis (stage III-IV) with a survival rate or 20% or less [3].

About 85-90% of malignant OC cases correspond to epithelial ovarian carcinomas that can be classified into four different types: serous carcinomas (52%), clear cell carcinoma (6%), mucinous carcinoma (6%) and endometrioid carcinoma (10%) [4].

The standard initial management of epithelial OC consists of surgical staging, operative tumor debulking and administration of chemotherapy. Conventional chemotherapy is a platinum/taxane regime, although, depending on the type of OC and its molecular profile, different types of chemotherapy drugs can be used. Adverse side effects, resistance, and recurrence of the disease after chemotherapy are major reasons to use targeted therapies; personalized medicine (PM) has a higher chance to effectively combat the tumor [5].

Current clinical and classification therapeutic hallmarks of OC are summarized in Figure 1.

The Role of Genetics in OC

The comprehensive genomic analyses of tumors using next generation sequencing (NGS) technology by the collaborative network of The Cancer Genome Atlas (TCGA) have drawn genetic landscapes and molecular profiles for different types of cancers, with a central goal of identifying new potential therapeutic targets.

In 2011, TCGA deciphered the genome of the OC by analyzing 489 tumoral samples of high-grade serous OC and revealed a particular signature of genes found significantly mutated: *TP53* (96%), *BRCA1* (9%) and *BRCA2* (8%). Other six significantly associated genes were: *CSMD3*, *NF1*, *CDK12*, *FAT3*, *GABRA6* and *RB1* [6].

The comprehensive molecular profiling of patient tumors has accelerated the adoption of PM in oncology. When analyzing gene activity patterns, one expression signature of 108 genes was found to be associated with a poor patient survival period. Specific molecular profiles such as particular gene mutations, distinctive transcriptional patterns and altered cellular signaling pathways play a pivotal role in the design of targeted therapies [6].

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Table 1. OC in Numbers in Mexico and the World According to Globocan 2018

	Worldwide	Mexico
Incidence	295,414	4,759
Mortality	184,799	2,765
Prevalence	762,663	12,942

OC: ovarian cancer.

PM

The US National Human Genome Research Institute (NHGRI), an institute from the US National Institutes of Health (NIH), defines the PM as an emerging practice of medicine that uses an individual's genetic profile to guide medical decisions for the prevention, diagnosis and treatment of a disease [7]. PM is also called precision medicine, individualized medicine, stratified medicine, targeted medicine and genomic medicine.

Even before the Human Genome Project was launched (three decades ago), a decade and a half earlier a pioneering genomic sequencing project in which one of the authors participated (HAB-S) explored the potential value of genomic knowledge into clinical diagnostic tests to predict response to treatments utilizing a particular genomic feature. This first translational research in genomics was possibly thanks to the achievement of the world record for sequencing the largest piece of the human genome that corresponds to the growth hormone locus [8]. It consisted in the invention of a polymerase chain reaction (PCR)-based predictive test for the response to the treatment with recombinant growth hormone.

In recent years, PM has made considerable progress in the diagnosis and treatment of gynecological cancers. Table 2 [9-26] shows some relevant advances of PM in OC.

It is well known that genetic background plays an important role in the genesis of OC. The Data Portal of the National Cancer Institute "Genomic Data Commons" harbors a collection of 3,401 characterized cases of OC, of which only 64 (1.8%) correspond to Hispanic or Latino ethnicity [27], which indicates the need for such studies as a prerequisite to bringing the promise of PM to this ethnicity.

PM by allowing to match each patient's genome with the right treatment (at the right dose) [27], has made a case in breast and ovarian tumors. Women affected by these tumors frequently carry mutations in the *BRCA1* and *BRCA2* genes. These genes produce tumor suppressor proteins that help repair damaged deoxyribonucleic acid (DNA) and thus ensure the genetic stability of the cell. But when cancer cells carry mutated versions of these genes, they become more sensitive to anticancer agents that act by damaging DNA, such as cisplatin. In this sense, drugs directed to inhibit the only other DNA repairing mechanism left, the poly (ADP ribose) polymerase (PARP), have been found to arrest the growth of said
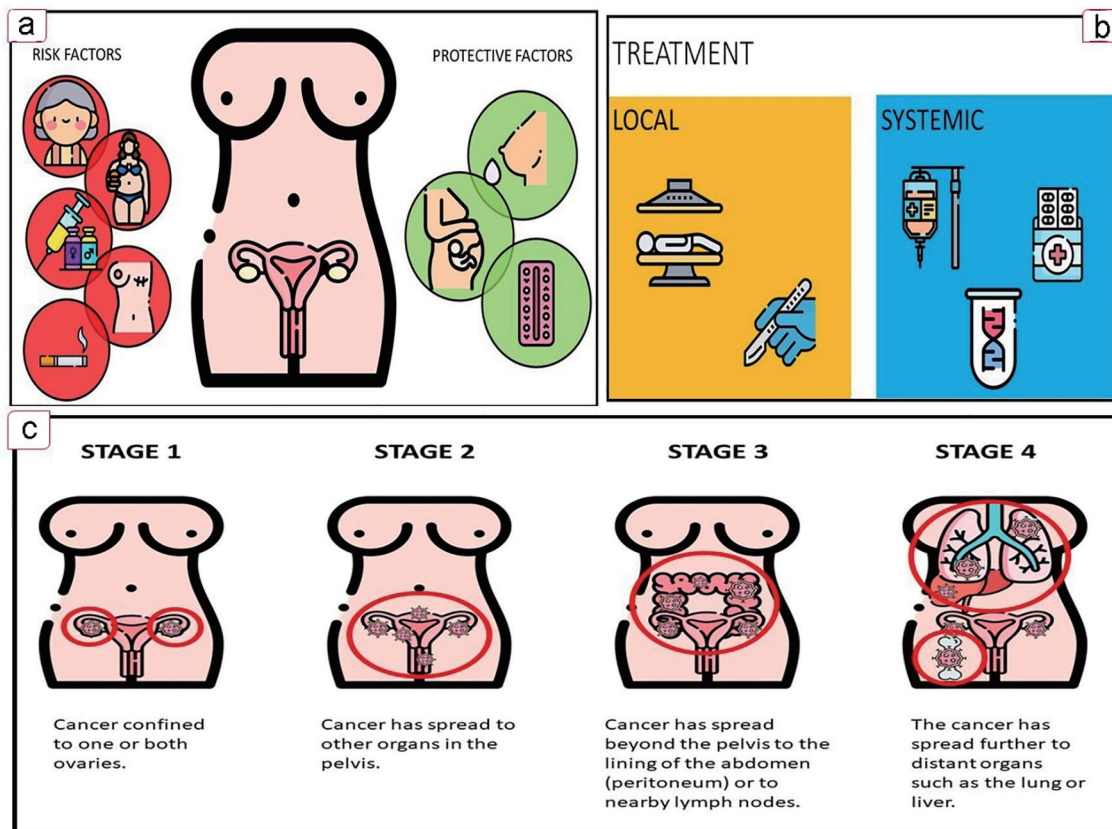

Figure 1. Key features of OC. (a) Associated factors. (b) Treatment options. (c) OC FIGO staging. OC: ovarian cancer.

Table 2. Milestones in PM of OC

Year	Landmark	Reference
2007	VEGF-targeted therapy showed to be effective in the treatment of OC.	[9]
2007	OC screening calculated the OC risk of an individual by analyzing serial CA-125 values via ROCA and made it possible to choose the right dose of medication.	[10]
2007	The OCSI was created, anticipating being useful for early diagnosis and in this way improving personalized treatments.	[11]
2008	Biomarkers for OC, like HE4, were shown to be over-expressed in epithelial OC. Examining values of 11 markers showed that the combination of HE4 and CA-125 had the highest predictive value of this study.	[12]
2008	Screening OC patients for *BRCA* mutations allowed a new personalized treatment with a PARP inhibitor (AZD2281 blocks the pathway used by *BRCA* mutated cells to repair DNA damage).	[13]
2010	Use of bevacizumab as the leading molecular targeted agent for OC. Identification of biomarkers to select patients for bevacizumab treatment became an advance because it was well tolerated.	[14]
2011	*DICER1* mutations were found in non-epithelial ovarian tumors. Aberrant miRNA processing resulted from *DICER1* could be a specific feature in the development of certain types of non-epithelial OC.	[15]
2010	*PIK3CA* mutations could predict response to PI3K/AKT/mTOR inhibitors. *PIK3CA* mutations are known to be common in 12% of OC.	[16]
2010	Introduction of neoadjuvant chemotherapy in OC: right therapy to the right person.	[17]
2015	The first genetic map of how HGSC evolves in response to chemotherapy was created. At least four molecular events were associated with acquired resistance.	[18]
2015	*ADAMTS* mutations were found as a possible predictor of chemosensitivity in OC without *BRCA1* or *BRCA2* mutations.	[19]
2015	A GWAS for MOC identified three risk associations at 2q13, 2q31.1 and 19q13.2.	[20]
2015	The relation between EZH2 and ARID1A is a potentially effective treatment target for ovarian clear cell carcinoma, where < 50% of ARID1A is mutated and shows a low response to platinum-based chemotherapy.	[21]
2015	*BRCAs* mutations were detected in 28% of samples of OC cases.	[22]
2016	AHT after surgery becomes a personalized medicine approach for helping extend the OS of the patients with OC.	[23]
2016	Development of a cancer therapy program using integrative genomic data. Therapeutic recommendations were made after considering the genetic and genomic alterations profiles.	[24]
2016	Four commercial tools were compared to identify therapeutic recommendations for a given genetic mutation in cancers.	[25]
2018	A total of 180 *BRCAs* genetic variants in sporadic OC tumors were found from Mexican patients.	[26]

ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs; AHT: adjuvant hormone therapy; AKT: protein kinase B; ARID1A: AT-rich interaction domain 1A; CA-125: cancer antigen-125; DNA: deoxyribonucleic acid; EZH2: enhancer of Zeste homolog 2; GWAS: genome-wide association study; HE4: human epididymis protein 4; HGSC: high-grade serous ovarian cancer; miRNA: microribonucleic acid; MOC: mucinous ovarian carcinoma; mTOR: mammalian target of rapamycin; OC: ovarian cancer; OCSI: Ovarian Cancer Symptom Index; OS: overall survival; PARP: poly (ADP-ribose) polymerase; PIK3CA: p110α subunit of phosphatidylinositol 3-kinase; PM: personalized medicine; ROCA: risk of ovarian cancer algorithm; VEGF: vascular endothelial growth factor.

BRCA-mutated cancer cells [28]. The benefit of *BRCA* testing is to determine the feasibility to draw upon this approach to effectively combat these cancers. AncestryDNA, Helix and 23andMe are international biotech companies offering *BRCA* testing, while in Mexico, companies like ours (Vitagenesis) offer *BRCA* testing as a companion diagnostics. Other predictive molecular testing biomarkers for OC include genes like *ATM*, *BRiP1*, *CHEK2*, *PALB2*, *RAD51C* and *RAD51D*.

Mexico in the Fight Against OC

In Mexico, cancer mortality has had a rising trend, and the same applies to OC. A study lead by Gomez-Dantes et al stated that the population growth contributed to a 36% increase in OC deaths between 1990 and 2013 [29].

Since 2016, the Mexican government has provided support for the fight against OC by the promotion of campaigns for its detection alluding to the International OC Day (May 8). Moreover, in 2018, 15 Mexican medical institutions were certified by the Ministry of Health to serve OC patients with full coverage by the Seguro Popular (just recently replaced by the National Institute of Health for Wellness), with at least one of each located in the following Mexican states: Campeche, Chiapas, Chihuahua, Colima, Durango, Estado de Mexico, Guanajuato, Jalisco, Queretaro, San Luis Potosi, Tamaulipas and Yucatan.

Clinical trials within research institutions are essential in the development of PM. However, currently, there are only four active clinical studies involving Mexican institutions, patients diagnosed with OC and registered in the NIH. Two of them focused on treatment, one more on diagnosis techniques and finally one on the treatment of thrombocytopenia as an

Table 3. Current Clinical Studies for OC in Mexico [30]

Title of the study	Recruitment countries	Research sites in Mexico	Dura-tion	Subjects (world-wide/national)
Phase III, open-label, randomized, controlled, multi-center study to assess the efficacy and safety of Olaparib monotherapy versus physician's choice single-agent chemotherapy in the treatment of platinum-sensitive relapsed ovarian cancer in patients carrying germline *BRCA* 1/2 mutations.	Argentina, Belgium, Brazil, Canada, Czechia, Hungary, Israel, Italy, Republic of Korea, Mexico, Poland, Spain, and the United States of America	Oaxaca Site Management Organization, S.C., Oaxaca, Oaxaca	6 years	411/64
Hyperthermic intraperitoneal chemotherapy in ovarian carcinoma clinical-stage IIIC and IV during interval laparotomy. Phase II study.	Mexico	National Institute of Cancerology of Mexico	3 years	100/100
Validation of HISPANEL in Mexican patients with a high risk of hereditary breast and ovarian cancer syndrome.	Mexico	National Institute of Cancerology and Tec-Salud-Tecnologico de Monterrey	4 years	1,290/700
Phase 3 randomized placebo-controlled double-blind study of Romiplostim for the treatment of Chemotherapy-induced Thrombocytopenia in patients receiving chemotherapy for treatment of non-small cell lung cancer (NSCLC), ovarian cancer, or breast cancer.	United States of America, Argentina, Austria, Brazil, Bulgaria, Chile, Colombia, Greece, Hungary, Mexico, Peru, Poland, Portugal, Romania, Russian Federation, Spain, Turkey, and Ukraine	Oaxaca Site Management Organization, S.C., Oaxaca, Oaxaca and not specified research sites in San Luis Potosi, San Luis Potosi and La Paz, Baja California Sur	1 year	162/10

OC: ovarian cancer.

adverse effect of chemotherapy. Table 3 [30] enlists the OC clinical studies in which Mexico is participating.

Achievements of the PM in Mexico

Several milestones have contributed to the emergence of PM in Mexico. After creating the first center in Latin-America dedicated to genomics, the Center for Genomic Biotechnology of the National Polytechnic Institute in 1999, our preceding academic laboratory joined the planning committee that proposed the creation of the National Institute of Genomic Medicine (Instituto Nacional de Medicina Genomica) that was inaugurated in 2004. Its mission calls for contributing to the Mexican health system by developing scientific research leading to the medical application of genomic knowledge through cutting-edge technology in this new scientific discipline.

Later in 2014, the Latin American Association of Personalized Medicine (ALAMP, for its acronym in Spanish) was founded in Mexico City to promote personalized treatments based on the molecular profile.

And more recently, in an effort to promote the development and technological modernization of Mexico, the National Council on Science and Technology (Consejo Nacional de Ciencia y Tecnologia, CONACyT) established the National Laboratories that promote PM such as the National Laboratory of Personalized Medicine (LAMPER) and ours National Laboratory for Specialized Research, Development and Innovation Services (LANSEIDI), whose main objectives are to offer: 1) Highly specialized services; 2) High-level training of human resources (masters and doctors in biotechnological innovation, human ge-

netics, and PM); 3) Collaborations with government, industry, academia and society; and 4) State-of-the-art R&D in PM.

Regarding efforts to bring the promise of PM to OC Mexican patients, key milestones are: 1) The description of the first Mexican founder *BRCA1* mutation, ex9-12del, germline deletion of exons 9-12 [31]; 2) The formulation of an anti-angiopoietin therapy with trebananib for recurrent OC [32]; 3) The detection of *BRCAs* mutations in 28% (26/92) of a cohort of OC cases in 2015 [22]; 4) The development of a simple and low-cost screening method for the Mexican founder mutation (*BRCA1* ex9-12del) based on quantitative polymerase chain reaction (qPCR) [33]; 5) The role of microRNAs in its angiogenesis [34]; 6) The characterization of let-7d-3p in the apoptosis and sensitization to chemotherapy in OC cells [35]; 7) The identification of the proteomic profile of ascites in epithelial OC [36]; 8) The identification of 76 polymorphic variants in northeast Mexican patients with sporadic OC (50 of those variants were not previously reported) [26]; 8) The discovery of molecular components involved in OC pathogenesis, such as the hypoxia-regulated miRNAs (HypoxamiRs) Profiling Identify, that identified the miR-765 as a regulator of the early stages of tumor vasculogenesis [37] to mention one.

Challenges of the PM in Mexico

Table 4 describes the US Food and Drug Administration (FDA) approved drugs for the treatment of OC, highlighting the current three approved anti-PARP therapies: Olaparib (Lynparza), Rucaparib (Rubraca) and Niraparib (Zejula) [38]. So far, only Olaparib has been introduced to our country.

Table 4. FDA-Approved Drugs for the Treatment of OC [38]

Drug	Manufactures	Administration	Dose	Approval	Mexico
Tepadina (thiotepa)	Adienne SA	Injection	15 mg/vial	1959	No
Platinol (cisplatin)	Hq Spclt Pharma	Injection	75 mg/m^2	1978	Yes
Doxil (doxorubicin hydrochloride liposome)	Baxter healthcare Corp.	Injection	2 mg/mL	1995	Yes
Genzar (gemcitabine hydrochloride)	Lilly	Injection	200 mg base/vial	1996	Yes
Taxol (paclitaxel)	Bristol-Myers Squibb	Injection	175 mg/m^2	1998	Yes
Hycamtin (topotecan hydrochloride)	SmithKline Beecham Pharmaceuticals	Injection	1.5 mg/m^2	1998	Yes
Alkeran (melphalan)	Glaxo Wellcome, Inc.	Tablets	0.2 mg/kg	2001	Yes
Paraplatin (carboplatin aqueous solution)	Bristol-Myers Squibb	Injection	Determined by doctor	2003	Yes
Doxorubicin hydrochloride	Sun Pharm	Injection	50 mg/m^2	2013	Yes
Lynparza (Olaparib)	AstraZeneca	Capsules, tablets	300 mg	2014, 2017	Yes
Rubraca (Rucaparib)	Clovis Oncology, Inc.	Tablets	600 mg	2016	No
Zejula (Niraparib)	Tesaro, Inc.	Capsules	300 mg	2017	No
Avastin (bevacizumab)	Genetech, Inc.	Injection	25 mg/mL	2018	Yes

FDA: Food and Drug Administration; OC: ovarian cancer.

The conventional treatments are usually tested on broad populations and are prescribed based on statistical averages. Sometimes this works effectively in some patients but not for some others due to the differences at the genome level. Recently, it has been growing the development of advancements of these differences thanks to the omics technologies (genomics, epigenomics, transcriptomics, proteomics and metabolomics). Those advances have shown a wide variability of cancer molecular profiles, including the OC. In addition to the correct choice of treatment according to the molecular profile of cancer, it is mandatory to take into account pharmacoeconomic considerations in order to cope with such expensive treatments and diagnostic techniques in health systems [39].

Mexican patients affected by OC can profit from PM by gaining access to individualized diagnosis to stratify them according to treatment options, while care providers will be able to better predict effective treatment for their diseases, leading to optimization of time, costs, safety and efficacy of health care. For all those reasons, it is a priority for our National Health System to increase genetic assessment in the near future.

Genetic Counseling: The Big Next Step for a PM in Mexico

The US National Society of Genetic Counselors defines genetic counselors as professionals who have specialized education in genetics and counseling to provide personalized guidance to patients for making decisions about their genetic condition. Their role is to analyze personal and family medical records, execute a risk assessment, advice about the advantages and limitations of genetic testing, help in decision making and support psychosocially these patients [40].

Genetic counseling is a well-known medical specialty in first-world countries, such as Canada, the USA and the European Union. However, Mexico has not adopted genetic counseling as a separate profession, and across 32 Mexican states, only Mexico City has at least one medical geneticist per 100,000 inhabitants [41]. Mexico has not yet adopted genetic counselor as a separate profession, with the medical geneticists providing these services [41]. Although there have been advances in recognizing the importance of genetic counseling in Mexico, the country is lacking infrastructure for genetic services. The lack of genetic services and the deficient knowledge about the field is a public health concern related to geographic diversity and the high concentration of geneticists and infrastructure in only the capital of the country. The correct use of counseling has the power to help address the issues related to the limited access of genetic services in the country providing an additional type of healthcare; in this way, genetic counselors could be able to prevent cancer deaths that occur due to some types of cancers with a major hereditable risk (estimated in about 14%) [42].

Mexico has the potential to access genetic counseling services such as other countries with similar income; for example, in other upper-middle-income countries (Malaysia, Cuba and South Africa) and even in low-income countries (India and

Indonesia), genetic counselors play an important role, either independently or alongside physicians, as part of a multidisciplinary team [41].

Conclusions

Nowadays, cutting-edge molecular tools are part of routine health care and the forthcoming of cancer diagnostic by providing insights towards personalized therapy.

Gynecological cancers can also benefit from these insights, especially OC, which represents a serious worldwide health problem in women because of its heterogeneous molecular composition and unavailable effective diagnosis. PM can improve diagnosis, prognosis and prediction in OC by stratifying patients according to their molecular profile. Recently, Mexico has made progress towards the implementation of PM in its health system. However, it still has a long way to go.

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Conflict of Interest

The authors declare no conflict of interest in carrying out this research.

Author Contributions

LEFG: conceptualization, writing, review, editing and design of figures and tables; IGDV: conceptualization, writing, review, editing and design of tables; JGM: writing, editing and design of tables; EAVA: writing, editing and design of tables; SABB: review, editing and design of figures; HABS: conceptualization, writing, review, editing, funding and responsible for the overall content.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

OC: ovarian cancer; PM: personalized medicine; NGS: Next Generation Sequencing; TCGA: The Cancer Genome Atlas; NHGRI: National Human Genome Research Institute; NIH: National Institutes of Health; DNA: deoxyribonucleic acid; PARP: poly (ADP ribose) polymerase; LAMP: Latin American Association of Personalized Medicine; CONACyT: National Council on Science and Technology; LAMPER: National Laboratory of Personalized Medicine; LANSEIDI: National Laboratory for Specialized Research, Development and Innovation Services; qPCR: quantitative polymerase chain reaction; HypoxamiRs: hypoxia-regulated miRNAs; FDA: Food and Drug Administration

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