Chapter

Implications of BRCA1 and BRCA2 Mutations in Mexico

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Abstract

BRCA 1 or BRCA 2 mutations have played a role in understanding its risk for several different cancer like breast, ovarian, prostate, and pancreatic cancer Knowing that biology is king, and its determination plays a role in prognosis for patients with cancer. Several recommendations have been made focusing on which population should have BRCA mutational status determined. This determination could help seek targeted therapy that could have a beneficial impact on cancer patients. Having this said, efforts have been made to determine if our Mexican population has the same prognosis when BRCA mutation is present when compared to global reports. As well as researching founder mutations that could help understand our Mexican population. This chapter seeks to describe and analysis this current scenario in Mexican population with BRCA mutation.

Keywords: BRCA1, BRCA2, BRCA 1/2, breast cancer, ovarian cancer, prostate cancer, Latin cancer patients, Mexican cancer patients, Mexico, founder mutations

1. Introduction

BRCA 1 or BRCA 2 mutations, implicate a different prognosis depending on the type of neoplasm its associated with. Having this said, in ovarian cancer, those with BRCA mutational status have been associated with a better prognosis compared to those without BRCA mutational status [1]. This also seems to be the case in breast cancer, although different reports have concluded mixed results in the scene that BRCA mutational is not always associated with a better cancer prognosis [2, 3]. These mixed results could probably be explained by different factors, taking in account race, country of origin which could represent different founder BRCA mutations. We would like to describe the prevalence of BRCA 1/2 in Mexico, as well as founder mutations of BRCA in our population, and the impact it translates in our daily practice.

2. BRCA 1/2 mutations and breast cancer in Mexico

Breast cancer is the most common neoplasm worldwide, this also seems to be the case in Mexico; with 195,499 new cases of cancer reported in 2020 of which 15.3%

(29,929) where associated with breast cancer [4]. Breast cancer has incremented in its incidence and mortality in Mexico during the last three decades, according to the last report made by the Epidemiology Department in the Secretary of Health, with an initial incidence of 10.76 cases per 100,000 habitants to 26.1 cases per 100,000 habitants in women of 25 years of age or older [5]. This clearly depicts how breast cancer is considered a public health problem that requires a focused diagnosis with an accurate treatment, considering the different epidemiology set in our country.

Although breast cancer is the most common cancer, as is mostly reported in the rest of the world there a few differences to consider. In Mexico, the mean age of diagnosis is 52.5 years, considered 10 years younger when compared to the rest of the world. Of these patients, approximately 13.3% are 40 years of age or younger at time of diagnosis [6, 7].

The associations between risk factors and breast cancer in the Latin American population have been considered complex due to the extensive diversity of cultures and ancestral origins that may be contributing for the risk of breast cancer [8].

Mexico has had a demographic, epidemiological and economic transition that has favored the increase of risk factors for breast cancer (increased age, obesity and diabetes) [9]. This younger population should be considered relevant since screening for BRCA 1 or BRCA 2 mutation is recommended for patients younger than 45 years of age with a family history of breast cancer [10].

Some international recommendations for searching for BRCA mutations vary according to associations and regions. For example The National Comprehesive Cancer Network (NCCN) recommends testing in: diagnosis of breast cancer in a patient under 45 years of age, patient between 45 and 50 years of age with synchronous or metachronous breast cancer or associated with a first-degree relative with ovarian, breast, prostate, pancreas, and breast cancer older than 51 years with ovarian cancer, pancreas and finally patient of any age with: triple negative breast cancer, male breast cancer and in which the result can define the use of a PARP inhibitor. The European Society for Medical Oncology (ESMO) recommends BRCA determination in patients with breast cancer if the age upon diagnosis is 40 years or less, as well as those with bilateral breast cancer at the age of 50 or less, and in those with triple negative breast cancer at the age of 60 or less. Two first degree relatives with breast cancer, ovarian cancer, prostate cancer, pancreatic cancer is also motive for BRCA mutational status determination [11].

These screening recommendations are also following in our clinical practice, because there aren't current guidelines in Mexico for the determination of mutation in BRCA 1 and/or BRCA2 extrapolating international guideline recommendations in our daily practice.

Although much of our daily practice is extrapolated from international guidelines. BRCA 1/2 mutations have been a source of investigation for the past decade. In Mexico a prevalence of varying from 17.4 to 30% of BRCA 1 or 2 mutations has been described, [12, 13] which is higher than what has been reported in our countries with 3% in all patients diagnosed with breast cancer, and 20% in those with high-risk families [14]. We previously mentioned that breast cancer is diagnosed at a younger age in Mexico, this could partially explain why prevalence in BRCA mutations is different from what has been described in other countries. Not only is our prevalence different, but also the subtype of breast cancer associated with BRCA mutations. In general, Basal-like subtype breast cancer is associated with BRCA 1 mutation and BRCA 2 with Luminal B-like subtype [15]. In Latin America, 37.1% with BRCA mutations have positive Estrogen and Progesterone receptors, with only 17.8% considered

Triple negative with BRCA mutation, although this was not analyzed according to the type of BRCA mutation [13]. This proves that breast cancer is an heterogenous disease that also differs between countries. This led to an effort in investigating the presence of founder BRCA mutations in Mexico. The Hispanic mutation panel (HISPANEL) was designed due to the need of an inexpensive accessible screening tool to properly diagnosis patients with high for BRCA mutations.

HISPANEL incorporates 115 BRCA mutations observed in Hispanic women. It is estimated that among Mexican women with breast or ovarian cancer it has a sensitivity of 68% [14]. This panel led to the discovery of the first Mexican BRCA founder mutation, BRCA1 ex9–12del large rearrangement, which is present in 12% of all BRCA1 mutations in patients with family history of breast cancer [16].

This was further studied in patients without family history of breast cancer, where 67% patients with locally advanced breast cancer and only 2% with metastatic disease were analyzed [17]. This should be considered an important subjective of discussion due to adjuvant treatment in locally advanced breast cancer as well as second line treatment for metastasis breast cancer with Olaparib [18]. This will further be described in the treatment section. Surprisingly, out of 96 patients with breast cancer analyzed, 29% patients had BRCA1 ex9–12del founder mutation [17].

Some recurrent mutations found in the Mexican population are shown in **Table 1** [19].

This leads us to think that BRCA mutation should be determined in patients with 50 years of age or younger and breast cancer diagnosis, independent of family history for breast cancer. BRCA1 ex9–12del mutation is not routinely analyzed when searching for BRCA mutations in breast cancer patients. An important aspect to consider when determining BRCA mutations is the presence of copy-number variants (CNV), which are hypothesized to have a better prognosis since they are less susceptible to reversal mutations leading to less resistance to DNA-damaging therapies [20]. This was shown in a cohort study from the HISPANEL population, where those patients with BRCA CNV had better overall survival (OS) when compared to those with BRCA pathologic variants at 10 years; respectively 100% vs. 78.6% [13]. The growing access to diagnostic tests for BRCA mutational status could help analyze this information at a larger scale. What is true is due to recent approbation by the Federal Commission for the Protection Against Sanitary Risks (COFEPRIS) for the use of a PARP inhibitor name Olaparib, there has been collaborations with different laboratories in performing a BRCA mutational status test across the country. This has allowed to further indicate PARP inhibitors as a 2nd line treatment option in triple negative metastatic breast cancer, as well as an in hormonal receptor positive HER2 negative metastatic breast cancer, according to NCCN guidelines [18].

Olaparib, a PARP inhibitor, is also used for triple negative early disease breast cancer with residual disease after neoadjuvant chemotherapy, and those with tumor size of 2 cm or axillary node-positive disease who received standard adjuvant

BRCA1 Variant	**BRCA2**
Ex9–12del	3492insT
185delAG	E49X
R71G	G2793R
R1443X	

Table 1.
BRCA mutations found in Mexican patients.

chemotherapy. In the case of hormone receptor positive HER2 negative early breast cancer, those who received standard adjuvant chemotherapy, who had 4 pathologically confirmed positive lymph nodes or those who received neoadjuvant chemotherapy with a CPS + EG score of 3 or more, should receive Olaparib; considering these scenarios only in those the germline BRCA mutations [21].

For patients with somatic BRCA mutations, there is only information in metastatic breast cancer, which was analyzed in a Phase II clinical trial, observing an objective response of 50%, for those with BRCA somatic mutations [22]. This is an important aspect to consider when determining BRCA mutational status in our patients, considering that most of the information, and approval for certain drugs are in BRCA germline mutations. The difference of at least objective response between germline mutations and somatic BRCA mutations when using PARP inhibitors, like Olaparib, has not been studied in Mexican population with breast cancer. This could be an area of clinical investigation in our field, considering higher access to BRCA mutational determination tests in certain parts of the country.

Another aspect to consider is the sequence of treatment in when to initiate PARP inhibitors in metastatic breast cancer. Most guidelines (ESMO, NCCN) recommend initiating after progressive disease to first line palliative therapy [18, 23]. This could seem straightforward, due to the fact the Olaparib and Talazoparib are not associated with overall survival benefit [24, 25] considering that other first line palliative options are associated with this oncologic outcome (overall survival). This should be considered with caution, considering BRCA germline patients have a different biologic behavior. To set an example, although there is no doubt the CDK4/6 inhibitors combined with hormonal therapy revolutionized different oncologic outcomes in hormone receptor positive HER2 negative metastatic breast cancer, this does not seem to be the case in patients with germline BRCA mutational status. Overall survival is lower in patients with gBRCA mutational status patients who were treated with CDK4/6 inhibitors when compared to those with wild type BRCA mutational status [26], considering this information. It could also be a field of opportunity in investigation frontline CDK 4/6 inhibitors with hormonal therapy versus PARP inhibitors, not only in our Mexican population, but also in other countries. The same question could be asked for HER2 positive patients, where PARP inhibition with antiHER2 therapy has been shown to enhance the effect of antiHER2 therapy like trastuzumab [27].

3. BRCA 1/2 mutations and ovarian cancer in Mexico

Ovarian cancer represents the 14th most common cancer in Mexico, according to GLOBOCAN 2020, ranking itself in 12th place for mortality [4]. This risk could be increased for those with BRCA mutations, from 1.2% to 39–44% in those with BRCA1 mutations and 11–17% in BRCA mutations [28, 29]. This also seems to persist in Mexican patients, with a risk of 40% for ovarian cancer in those BRCA mutations [30]. Not only BRCA mutational status is considered a risk for Ovarian cancer, but it also implicates a prognosis factor, as well as a therapeutic opportunity due to the use of poly (ADP-ribose) (PARP) inhibitors [31]. When analyzing it's prognosis value, those with BRCA1 mutational status have a worse recurrence free survival when compared with those with BRCA2 in Mexican patients with ovarian cancer [30]. This is also true when analyzing the same founder mutation, previously mentioned in the breast cancer section. Those with BRCA1 ex9–12del, which was present in (28.2%) of 179 patients analyzed compared to other BRCA1 mutations had a better recurrence free survival [30]. Knowing that BRCA

mutational status has a prognosis value, this clearly reflects the necessity to have more access to BRCA tests in our population. Not only, does mutational prognosis value, but also a therapeutic opportunity. PARP inhibitors, such as Olaparib have different clinical indications, such as maintenance therapy after 1st line therapy, as well after maintenance therapy after 2 or more lines of chemotherapy [32]. In Mexico, those patients treated with Olaparib had a median progression-free survival of 12 months after 2 lines or more of chemotherapy vs. 8.3 months after 4 or more lines of chemotherapy [33]. These results are similar to what was reported in the SOLO-2 trial reporting a median progression-free survival with olaparib (19·1 months [95% CI 16·3–25·7]) than with placebo (5·5 months [5·2–5·8]; hazard ratio [HR] 0·30 [95% CI 0·22–0·41], p < 0·0001); there was also benefit in in overall survival of 51·7 months (95% CI 41·5–59·1) with olaparib and 38·8 months (31·4–48·6) with placebo (hazard ratio 0·74 [95% CI 0·54–1·00]; p = 0·054, [34, 35]. Considering the previous outcomes, it's clear why all patients which ovarian cancer, should be tested for BRCA mutational status. If a founder mutation determination is available, it should be performed. In an observational study 107 out of 377 patients were with BRCA mutation, of which 77 patients (72.9%) had BRCA1 mutation where 27.3%of these patients had the founder mutation BRCA1-Del ex9–12. When analyzing progression-free survival, patients treated with Olaparib with BRCA1-Del ex9–12 had a longer progressive free survival when compared to the rest of Mexican patients with BRCA 1 or BRCA 2 mutation treated with Olaparib [36].

4. BRCA 1/2 mutations and prostate cancer in Mexico

Although Prostate cancer is the most common cancer in Men in Mexico, [4], where those with BRCA mutational status have a higher risk of developing prostate cancer, only 1.2% to 3.2% are associated to BRCA2 mutations, even less cases to BRCA1 [37]. Although the prevalence of BRCA2 mutational status es low, it's presence is considered of poor prognosis. When compared with the general population with prostate cancer, those with BRCA2 mutation had a 12-year cancer-specific survival of 61.8% compared to 94.3% to those without BRCA2 mutation [38]. Due to its low prevalence, as well as low access to BRCA diagnosis tests, information on its impact in Mexico is scarce. In an observational study performed in a tertiary hospital in Mexico City, out of 22 patients with Castration naïve and Castration resistant prostate cancer, only 3 patients had BRCA mutational status. Contrary to global incidence, in this study BRCA1 mutational status more common than BRCA2, where all 3 patients had castration resistant prostate cancer [38]. Due to the recent approval of Olaparib in the metastatic setting in Mexico, there is not any prospective data showing its use and impact in Mexico. Even though we lack information from our population, we believe that BRCA mutational status should be determined primarily based on family history of other BRCA-related cancers.

5. Concluding remarks

As it most Latin American countries, in Mexico access to diagnosis tests is primarily an obstacle that has been resolving in the last year having more access to BRCA determination with the help of distant programs sponsored by private companies which the intention to detect which patients could benefit from PARP inhibitors. This access could help us determinate the prognosis in our population to those with BRCA

mutations, as well as its impact when treated with PARP inhibitors, most of them are approved in our country. This specific population requires a directed investigation as was the case with breast and ovarian cancer where those with founder mutations had a different prognosis and response to treatment. Access not only to BRCA mutation diagnosis test, but also to founder mutations determinations is an objective that should be available in the next years to come.

Conflict of interest

The authors declare no conflict of interest.

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