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Scientific letters

Surgical implications of multigenic testing during neoadjuvant chemotherapy treatment in high-risk women with breast cancer

Implicaciones quirúrgicas de paneles multigénicos durante el tratamiento quimioterápico neoadyuvante en mujeres de alto riesgo con cáncer de mama

Breast cancer (BC) is the most common cancer in women, and the leading cause of death in women.[1] Ovarian cancer (OC) is the gynaecological cancer with the highest mortality rate.[2] Hereditary cancer accounts for 8%–10% of all tumours diagnosed. Approximately 5%–10% of BCs and 10%–15% of OCs are hereditary, and 25% have been linked to germline mutations in BRCA1/2.[1]

The aim of our study was to analyse the usefulness of multigene panels (MP) in patients with BC undergoing treatment with neoadjuvant chemotherapy (NCT) with clinical criteria for genetic study of hereditary cancer (Table 1).

We conducted a prospective, observational study at the Hospital Juan Ramón Jiménez, Huelva, during the years 2019−2020. Of a total of 98 women with locally advanced BC who were candidates for treatment with NCT, 19 patients (19.4%) were included (Table 2).

Multigene panels by DNA extraction from peripheral blood were performed by next-generation sequencing (NGS). Pathogenic variants (PV) or probably pathogenic variants (PPV) found were confirmed by multiplex ligation-dependent probe amplification or multiplex ligation-dependent probe amplification (MLPA). BRCA1, BRCA2, CDH1, PTEN, STK11, TP53, ATM, BRIP1, CHEK2, PALB2, MSH6, RAD51C, RAD51D, MSH2, MLH1, MUTYH and PMS2 genes were analysed. Participants signed an informed consent form, the centres' protocols on the publication of patient data were followed, and the privacy of the subjects was respected. Data analysis was carried out using SPSS® version 22 statistical software.

The median age was 45 years (IQR: 40–50). In 31.6% of the cases a PV was identified: four in BRCA1 (21.05%), one in MUTYH (5.26%) and one in CHEK2 (5.26%). Thirteen patients had non-informative (negative) BRCA. All patients with BRCA1 PV opted for surgery for their breast cancer and risk-reducing mastectomy (RRM) of the contralateral breast, and 75% also had risk-reducing salpingo-oophorectomy (RRSO) in the same surgical procedure. Risk-reducing surgery (RRS) was not performed in patients with PV in the CHEK2 and MUTYH genes because it was not indicated after reviewing the family history.

The development of NGS has improved the ability to study numerous genes at the same time while reducing costs. Hereditary breast and ovarian cancer syndrome (HBC and OCS) is linked to PV/PPV in genes with high (BRCA1/2, TP53, PALB2, PTEN) and moderate penetrance (CHEK2, CDH1, among others).[4,5]

In our case, the result was obtained prior to surgery, so the genetic study was useful in those carriers of PV in high-risk

Table 1 – Clinical selection criteria of genetic study.

A single case. Irrespective of the family:
Woman affected by BC and OC (goal/synchronic)
BC ≤ 40 years
Bilateral BC (the first tumour ≤40) or triple negative BC ≤60 years
Non mucinous high grade epithelial OC or primary tubal or peritoneal tumour
BC in a male
Two or more cases First degree relative (parents, children and siblings) and second grade (grandparents, grandchildren, uncles and aunts, nephews and nieces):
Bilateral BC at any age +BC< 50 years
BC and OC
2 BC < 50 years
Three or more cases. Direct relatives with BC and/or OC:
≥ 3 BC ± OC

BC, breast cancer; OC, Ovarian cancer.
Llort Pursals and Ramón y Cajal[3].

Table 2 – Patient characteristics.

Individual	Age	Immunohistochemical	Criteria	Type of mutation	RRM	RRSO
1	38	Her 2	>1 case	BRCA1	Yes	Yes
2	42	Triple negative	>1 case	BRCA non-informative	No	No
3	41	Triple negative	Single case	BRCA non-informative	No	No
4	48	Triple negative	>1 case	BRCA1	Yes	Yes
5	53	Luminal B1	>1 case	BRCA1	Yes	Yes
6	46	Luminal B1	>1 case	BRCA1	Yes	No
7	50	Triple negative	>1 case	BRCA non-informative	No	No
8	48	Luminal B2	>1 case	BRCA non-informative	No	No
9	28	Triple negative	Single case	MUTHY	No	No
10	45	Luminal B2	Single case	CHEK2	No	No
11	42	Triple negative	>1 case	BRCA non-informative	No	No
12	45	Luminal B2	Single case	BRCA non-informative	No	No
13	51	Luminal A	>1 case	BRCA non-informative	No	No
14	37	Luminal B1	>1 case	BRCA non-informative	No	No
15	50	Triple negative	>1 case	BRCA non-informative	No	No
16	32	Triple negative	Single case	BRCA non-informative	No	No
17	40	Luminal A	>1 case	BRCA non-informative	No	No
18	48	Triple negative	Single case	BRCA non-informative	No	No
19	50	Luminal A	>1 case	BRCA non-informative	No	No

RRM, reduced risk mastectomy; RRSO, bilateral risk-reducing salpingo-oophorectomy.

genes for HBC and OCS. Tumour intervention and RRS of the contralateral breast and RRSO was planned for those who wanted it. All interventions were performed in patients carrying BRCA1, as no PV were found in other high-risk genes (BRCA2, PALB2, TP53, among others). This is due to the low prevalence of these genes in the population, which is around 6% of families with hereditary cancer syndrome.[5] In cases with negative (non-informative) results, RRM was not indicated. The benefit of RRS in moderate risk genes (ATM, CHEK2, etc.) is controversial and will be agreed on the basis of family history and patient preferences after a detailed explanation of the risks and benefits. It has not been demonstrated that in these cases the overall survival of the intervened patients is increased. In patients carrying PV in the CHEK2 gene, it could be offered in those cases with high familial burden or assessed in carriers of a deletion variant (del1100C) despite low familial burden. The del1100C appears to contribute to an increased risk of BC compared to other PV in this gene. A case-control study reported an OR of 2.55 (95% CI 2.10–3.10, $p < .001$).[6] On the other hand, MUTYH is a gene associated with attenuated familial adenomatous polyposis when PV are detected in homozygosis, characterised by a high risk of colorectal cancer (CRC). [7] The increased risk of BC and CRC in the heterozygous form has not been demonstrated in several studies. In these cases, colonoscopy follow-up is recommended based on a family history of first/second-degree CRC.[8]

BRCA1/2 genes with VP/VPP account for approximately 20%–25% of all HBC and OCS,[9] which is consistent with our findings. For this reason, in places where it is difficult to access a genetic study by NGS where the study time is expected to be prolonged, we could initially request the study of only the BRCA1/2 genes by MLPA and, in the event of obtaining a non-informative study, consider extending the rest of the genes depending on the family history. This would shorten the time of the result, reduce costs and improve the performance of the study.

To conclude, the use of Mp by NGS is a useful tool in the diagnosis of HBC and OCS, given that we found a high prevalence of PV that justifies the need to study these patients, benefiting from the intervention of the tumour and RRS in the same surgical act.

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International cooperation for general surgeons: Results of the national survey about the implication and importance of the Spanish surgery in international cooperation

Cooperación internacional para especialistas en cirugía general: resultados de la encuesta nacional sobre la importancia y la implicación de la cirugía española en cooperación internacional

According to the Declaration of Human Rights and the World Health Organisation (WHO) the attainment of the highest standard of health is a fundamental human right.[1,2] In a world of increasing inequalities it seems that we are far from achieving this.

In terms of global health, surgery has been neglected due to the high cost of its activities and on consideration that its ability to reduce the global burden of disease is relatively low. The global burden of disease is a comparative magnitude of health loss due to diseases, injuries and risk factors according to age, sex and geographical location in specific moments in time.[3,4] However, surgical treatment is necessary to reduce this burden up to 30%. Countries with higher disease burden are less able to manage this.[5,6] Difficulty of access, the high costs of treatment or inequalities between high income and lower-middle income countries are the main restricting factors.[3,7,8] Lack of qualified healthcare personnel and the use of obsolete or damaged instruments reduce quality and increase complications.[3] On the other hand, high quality surgery is cost-effective, increasing patients' quality of life and reducing the economic impact of disease in low and middle-income countries.[9,10]

Surgical associations participate in the implementation of training campaigns, in the development of surgical campaigns or by creating bilateral agreements and relationships with fellow international associations. From its Humanitarian Collaboration Group (GCH for its initials in Spanish), the Spanish Association of Surgeons (AEC for its initials in Spanish) promotes training initiatives, alliances and project sustainability, solidifying the role of the surgeon within Global Surgery. The relationship of its members with humanitarian collaboration needs to be known in order to report actions and establish priorities. To this end, a 20-question survey was designed to ask about participation in projects, as well as the perceived importance and training in international cooperation and humanitarian collaboration ((ICHC).

The survey received 570 responses. Respondents were mostly practicing specialists (80,4%), the majority of whom were women (51%), and performed general surgery 62%) or coloproctology (12,5%). Mean age was 46 years. By age groups there was an increase in the presence of women of new generations. Seventy-three per cent of those who had participated in a humanitarian collaboration campaign had done so in surgical projects. There was a difference between the age groups in terms of participation and a strong interest in taking part in a project amongst those who had not already done so (Table 1).

Fifty-eight per cent of those who had participated in a surgical project were male. Only 28% of female surgeons had participated in surgical projects, compared with 40% of males. Fifty per cent of female surgeons had not participated in any surgical project but would like to do so. There was an upward trend in female participation in ICHC projects among the new generations (Fig. 1).

Ninety per cent stated their desire to be part of a project in the future. It was considered essential (52%) or at least important (37%) to be trained and/or have participated in ICHC projects at some time.