Ovarian Cancer: Difference between BRCA1 5382insC Carrier and Non-carrier FOC Patients

Ovarian cancer (OC) is one of the important causes of death within gynecological tumors in the western world, with a 5-year survival rate of approximately 30% in advanced-stage disease(152). About 10-15% of all OC patients report a positive family history of the disease and can be included as “familial ovarian cancer (FOC).(11,12) FOC patients were defined as those with a history of ovarian cancer in two or more family members or in combination with common cancer diagnosed at a young age.(11,12)

Most hereditary and familial OCs are associated with germline mutations in BRCA1 or BRCA2. (153-155) Basically, there are three founder mutations in BRCA genes, two in BRCA1 (BRCA185delAG, BRCA15382insC) and one in BRCA2 (BRCA2 6174delT).(156) BRCA1 5382insC mutation are present in different ethnic groups, including Ashkenazi Jews, Icelanders, and Russians. (156) Sequencing is the gold standard technique to detect the previous mutations.(157) One of the sequencing by synthesis techniques is pyrosequencing which has the advantages of being sensitive, specific and cost-effective.(157)

To date, in Egypt, there has not been yet any published study detecting BRCA1 185delAG and BRCA15382 insC mutations among FOC patients.

Therefore, fifty Egyptian FOC patients were included in the present study to investigate the previous mutations using the pyrosequencing technique.

In the current study, BRCA1 5382insC mutation was not identified among controls. However, four out of fifty patients showed heterozygous BRCA1 5382insC mutation; a carrier frequency of 8%, CI(2.2-19.2). That is comparable to the international frequency values;5-15%. (158) Similarly, Agnieszka synoweic et al, who conducted a study on 125 FOC polish patients, found that 12 patients had BRCAI 5382insC mutation (a carrier frequency of 9.6%).(159)Also, Moslehi et al, reported 14 out of 208 FOC patients had BRCA15382insC mutation (carrier frequency of 6.7%).(160)

Moreover, in the present study, there were two main significant differences between BRCAI5382insC carrier and non-carrier FOC patients. The first significant difference was the response to standard chemotherapy during the studying period; platinum taxane combination (Fisher Exact test, p=0.046). Twenty non-carrier patients (43.5%) showed a good response to chemotherapy (platinum-sensitive), while the remaining 26 non-carrier patients (56.5 %) were platinum-resistant. For carriers, all four patients (100%) showed a good response to chemotherapy.

Many studies showed favorable outcomes in BRCA1 mutation carriers than noncarriers. Tamar Safra et al, who analyzed retrospectively 256 FOC patients, reported that 84% of BRCA1 mutation carriers (including 5382insC) were platinum-sensitive while 16% of BRCA1 mutation carriers were platinum-resistant.(161) Also, for non-carriers, most of them (60%) were platinum-sensitive, while 40% of them were platinum-resistant (chi-square test, P=0.001)(160) Additionally, Vencken et al, found that 87% of BRCA1 mutation carriers (including 5382insC)

are platinum-sensitive after the first-line of chemotherapy that in comparison to non- mutation carrier patients (Chi-square test, P = 0.002). (162) Similarly, Tan et al, demonstrated that most of BRCA-associated FOC patients showed good response to platinum-based agents than nonmutation carrier patients. It has been postulated that this favorable outcome may be due to increased platinum sensitivity in BRCA mutation carriers. (163) Since BRCA genes are important for repairing DNA break via homologous recombination.(164) Therefore, BRCA mutation carriers are unable to repair damaged DNA which make them hypersensitive to DNA-damaging treatments such as platinum chemotherapy; cisplatin or carboplatin (intravenous). (164,165)

On contrary, few studies such as Tingya shi et al did not find any significant difference between carriers and non-carriers regarding the chemotherapeutic response. (166)

Oral PARP inhibitor e.g. olaparib has been recently received food and drug administration (FDA) approval and European medicine agency (EMEA) for treatment of recurrent OC with mutated BRCA1/2 or maintenance therapy for platinum-sensitive ovarian cancer respectively.(167,168) There are several hypotheses that explain the enhanced responsiveness of BRCA-mutation carriers to PARP inhibitors. (167) The most convincing of these is that PARP inhibitors lead to accumulation of ssDNA damage, which is converted to double-strand breaks (DSBs) during subsequent cellular replication .(169) Accumulation of unrepaired DSBs results in cytotoxicity and cell death, this is known as synthetic lethality.(170)

The second significant difference found between BRCA15382insC carriers and noncarriers was concerning the number of affected family members (Monte carlo test, p=0.009). For nonmutation carriers, 38 patients (82.6%) reported one family member who was affected, while 8 patients (17.4%) reported two family members affected. For carriers, one patient (25%) reported one family member affected with colon cancer, two patients (50%) reported two family members affected with colon, ovarian, and breast cancer and one patient (25%) reported three family members affected with ovarian and breast cancer.

Similarly, Shi T et al, reported that patients with BRCA1 (including BRCA1 5382insC) mutations exhibited significantly higher rates of family history of breast or OC (45.7%) and other cancers (39.1%), compared to those without BRCA1 mutations (PAlso, Moslehi al, demonstrated that BRCA1 mutation carriers were present in 78% of women with two or more affected relatives (breast or ovarian cancers.(160)

On the other hand, for BRCA1185delAG, we did not find either heterozygous or homozygous mutations either among FOC patients or among controls. The frequency of the previous mutation among the different population are variable. For example, Revital B et al, from Murraco found a low carrier frequency of 1.1%.(171) However, Sirisha P et al, from India reported a relatively higher carrier frequency of 16.4%.(172)

Collectively, screening of BRCA1 5382 insC using such an affordable technique; pyrosequencing among FOC patients who have two or more affected family members would assist in predicting the patient outcome. Those carriers may be sensitive to platinum, and even patients who are platinum-resistant would benefit from alternative oral target therapy (PARP-inhibitor.)