STUDY REPORT SYNOPSIS

Japan CHARLOTTE: CHARacterizing the cross-sectionaL approach to Ovarian cancer: geneTic TEsting of *BRCA*

Milestones:

Overall plan	Study period
Scheduled date for registration of the 1st case	December, 2016
Scheduled date for registration of the last case	February, 2018
Scheduled date of the final visit to hospital by the last case	July, 2018
Scheduled date of the data base locking	July, 2018

Phase of development: Observational Study

Sponsor: AstraZeneca

Author:

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Background/rationale: *BRCA* gene mutations are associated with hereditary ovarian cancer. *BRCA* plays a key role in genome integrity, and mutations result in an increased risk for ovarian cancer. Furthermore, *BRCA* is associated with drug susceptibility, including platinum agents. Various guidelines recommend *BRCA* testing in ovarian cancer patients. However, data on germline *BRCA* (g*BRCA*) mutation frequency in ovarian cancer in Japan are scarce. The aim of this study was to determine g*BRCA1/2* mutations in Japanese ovarian cancer patients, stratified by clinicopathological characteristics. Patients' satisfaction with pre-test genetic counseling was also evaluated.

Objectives:

Primary objectives

Assessment of the ownership ratio of g*BRCA*m in the newly diagnosed patients with epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer in Japan.

Secondary objectives

1. Ownership ratio of g*BRCA*m when stratified according to the patients' demographics
2. Evaluation of patient satisfaction with the explanation of germline BRCA testing

Study design: This multi-centered, cooperative and epidemiological observation study is so designed to investigate the ownership ratio of g*BRCA*m in the newly diagnosed patients with epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer because such a ratio has not yet been adequately clarified in Japan.

The newly diagnosed eligible patients with epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer shall be asked to participate in this study in order of diagnosis. After obtaining their consents by the written informed consent following appropriate explanation, investigations about the demographic information including the cancer family history shall be performed. Subsequently, blood is collected for investigation about germline BRCA testing. In addition, histological classification shall be conducted based on the resected tumor tissues.

Data source: Patients' medical charts were reviewed for demographic data, medical history, and information regarding ovarian cancer. Family history of cancer was obtained during pre-test genetic counseling at the first visit. Data collected included patient demographic and clinical characteristics (date of birth, age), medical history, medications, menopausal status, obstetric history, and blood biochemical testing (cancer antigen 125). Data were also collected regarding ovarian cancer, including date of diagnosis, pathological and histological type, and grade upon diagnosis and International Federation of Gynecology and Obstetrics (FIGO) classification. Blood samples from all eligible patients were collected in 10-mL ethylenediaminetetraacetic acid tubes and centrally tested for the presence or absence of known g*BRCA* mutations (g*BRCA1* and g*BRCA2*) by Myriad Genetics, Inc. (Salt Lake City, Utah, USA).

Study population: Eligible patients were registered in serial order (to avoid selection bias) by the respective attending physicians throughout the study period. The inclusion criteria were as follows: Japanese females aged ≥20 years, newly diagnosed with ovarian cancer, with histologically confirmed diagnosis, based on surgically resected specimens, and with histological specimens evaluated by central pathological review. Patients were excluded if they had an acute or chronic disease, a mental illness that could affect the study results as determined by their physician, or if their participation in the study was judged to be inappropriate by their physician. Patients were also excluded based on the centrally assessed histological classification of the surgically resected specimen.

Inclusion criteria:

1. The subject can attach the signature to the Informed Consent Form (ICF), besides having his/her intention to put the signature.

2. Female Japanese at more than 20 years of age

3. The newly diagnosed patients whose epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer is histologically confirmed as FIGO from the subject to obtain their utmost understandings. Limited to histopathological diagnosis based on resected tumor specimens (except the cytodiagnosis by ascites paracentesis)

4. The histopathological specimens can be submitted to the central pathological judgment.

5. Within 60 days after diagnosis of epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer, the patient's written consent has been obtained.

Exclusion criteria:

1. In case of the subjects who are diagnosed to have acute or chronic physical or severe mental diseases except cancer, and about whom the attending responsible physician makes judgement to say that participation of these subjects would possibly increase the risks or would probably disturb the interpretation of the study results.
2. In case of the subjects whose registration for the study is judged by the attending responsible physician as inappropriate.

Statistical methods: Descriptive statistics were used for baseline demographic and clinical characteristics, with n (%) for categorical variables and mean ± standard deviation for continuous variables. The full analysis set consisted of all patients who underwent g*BRCA* mutation testing and had histological specimens available for central pathology confirmation.

The prevalence of g*BRCA1/2* mutations was calculated, along with 95% CIs, for all patients, and was stratified by patient background factors, diagnosis, histological classification, staging presence or absence of family history of cancer in close relatives, and by type of cancer in

family history. All statistical analyses were performed using Statistical Analysis Software (SAS) 9.4 (SAS Institute, Cary, NC, USA).

Results:A total of 634 patients were included. The mean age was 56.9 years, 84.2% had epithelial ovarian cancer, 48.4% had International Federation of Gynecology and Obstetrics (FIGO) stage I–II cancers, and 51.1% had stage FIGO III–IV cancer. Nearly all patients (99.5%) received pre-test genetic counseling for *BRCA* testing by either an obstetrician-gynecologist (42.0%) or a clinical genetic specialist (42.0%). The overall prevalence of g*BRCA1/2* mutations was 14.7% (93/634), with g*BRCA1* mutations (9.9%) more frequent than g*BRCA2* mutations (4.7%). High-grade serous carcinoma showed a prevalence of g*BRCA* mutations at 28.5%. Most patients were satisfied with pre-test counseling, irrespective of the professional position of the service provider.

Conclusion: The overall prevalence of gBRCA1/2 mutations in ovarian cancer patients in this study was 14.7%, with a higher prevalence of gBRCA1 over gBRCA2. While high-grade serous carcinoma and family history, particularly of ovarian cancer, showed a somewhat higher prevalence of gBRCA mutations, there were no subgroups with considerably high gBRCA mutation prevalence overall. Current findings indicate that gBRCA testing should be performed in all patients with ovarian cancer. Additionally, most patients were satisfied with the pre-test counseling provided, irrespective of the professional position of the service provider.

Publications: Published in International Journal of Gynecological Cancer