Genetic Mutation Assay in Ovarian Cancer Patient

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ABSTRACT

Ovarian cancer is the third most common cases of cancer among Indonesian women. It has a poor prognosis with a moderate to low 5-year survival rate with conventional therapy. Targeted therapies, immunotherapies, and novel treatment approaches are being explored in clinical trials, offering potential improvements in survival rates and outcomes, unfortunately, not every patient responds to these therapeutic modalities. It takes a molecular assay to predict which patient has a response to this therapy. Genome instability is one of the unique characteristics found in most cancers in humans. Ovarian cancer patients with mutations of BRCA1 or BRCA2, have been found to exhibit high sensitivity to PARP inhibitor therapy. Targeting the Homologous Recombinant Deficiency (HRD) that was caused by BRCA mutations and inhibiting PARP-mediated DNA repair, would result in the death of cancer cells. Conclusion: molecular assay from ovarian cancer tissue would have the benefit to predict response to PARP inhibitor targeted therapy.

Keywords: cancer; ovarian cancer; BRCA mutation; homologous recombinant deficiency

INTRODUCTION

Ovarian cancer is a significant health problem for women. It is the one of the most cases of cancer in women worldwide and the second most case in gynecological cancer. The exact frequency of ovarian cancer case varies across different regions and populations. Ovarian cancer remains a significant cause of cancer-related deaths of women. Ovarian cancer is also a serious health problem in Indonesia. It was one of the top five cancers affecting women in Indonesia. According to the Global Burden of Cancer Study, ovarian cancer is the among top 3 highest case of cancer among Indonesian women (1). In 2023, it is estimated that 19,710 cases record, with the death case up to 13.270 case. Based on the data from 2016-2020 the rate of new cases of ovarian cancer was 10.3 per 100,000 women per year. The death rate was 6.3 per 100,000 women per year. Approximately 1.1 percent of women will be diagnosed with ovarian cancer at some point during their lifetime, based on 2017–2019 data (2).

The risk of developing ovarian cancer increases with age. Most occur in women of age more than 50 years. Also, women with certain risk factors, such as a parent or elder history of ovarian and breast cancer, certain mutations of genes (such as BRCA1 and BRCA2), a history of endometriosis case, or others. Woman who has never been pregnant, can be at high risk. Early-stage ovarian cancer often presents with minimal or nonspecific clinical symptoms. This can make it difficult to diagnose early-stage cancer. As a result, ovarian cancer is often too late to be diagnosed at an advanced stage when it has already gotten worse beyond the ovaries. This is the main reason why it contributes to the high death rate (3).

Ovarian cancer has a relatively poor prognosis compared to other types of cancer. Early-stage ovarian cancer, which is confined to the ovary, is associated with a better prognosis.

The prognosis for ovarian cancer also depends on a variety of factors, including the stage of the cancer at diagnosis, tumor grade (how abnormal the cancer cells look under a microscope), type of cancer, age and overall health of patient, and the effectiveness of the therapy received before (4).

SURVIVAL RATE OF OVARIAN CANCER

Unfortunately, ovarian cancer is often asymptomatic or presents with nonspecific symptoms at an early stage, which can lead to a delay in diagnosis. In addition, ovarian cancer can spread within the abdominal cavity, making it difficult to treat and leading to a higher chance of recurrence. Ovarian cancer is often associated with a relatively low survival rate, particularly when diagnosed at advanced stages. Ovarian cancer is often associated with relatively low survival rates, especially when diagnosed at an advanced stage. Conventional therapies, such as surgery and chemotherapy, are the main treatment options for ovarian cancer and can increase survival rates. However, the prognosis of ovarian cancer remains challenging. Survival rate of ovarian cancer varies based on the stage at diagnosis. The 5-year survival rate for ovarian cancer is higher when the cancer is already diagnosed at an early stage and has not spread and getting worse. However, the majority of ovarian cancer cases are diagnosed at late stages where the cancer has already spread to distant areas within the abdomen or beyond. In advanced-stage ovarian cancer, the five-year survival rate is lower compared to early-stage cases. The effectiveness of conventional treatments can be limited in these situations due to the aggressive nature of the disease, making it difficult to completely eradicate all cancerous tissue (5).

The best prognosis found in patients with stage I. Recurrence and mortality only found in 1 from 17 patients examined.

Patients with unstaged disease have a higher risk of recurrence 10 times and higher risk of mortality 20 times. These results are consistent with the clinical perspective that in higher disease stages is difficult to perform optimal debulking surgery. It is also consistent with studies stating that the advanced stage is a significant independent prognostic factor for. In early stage with no residual tumor, and adequate chemotherapy associated with higher DFS and 3-year survival rate and were significant prognostic factors affecting recurrence and mortality in patients of nonepithelial ovarian cancer (6).

MECHANISM OF CANCER
Genome instability one of the unique characteristics found on most cancers in human. Genetic changing accumulation can be happened in single nucleotide mutations or bigger chromosome arrangement. It can predispose cells towards malignity then result in death of cell. Moreover, instability on genome caused cancer cells to sustain and survive under repairing mechanism and adapt to their internal environment by evolving mechanisms to resist different therapies. The estimation data is that a single nucleic in human cell is subjected to average 70,000 lesions of DNA every day, which is around 10 to 50 lesions are DNA double strand breaks (DSBs). DNA double strand breaks can cause some mutations, translocation of chromosomes, or re-arrangements of chromosome associated with cancer, diabetes, and other Disease (7).

Genomic instability and homologous recombination deficiency (HRD) are interconnected concepts related to the maintenance and stability of genetic material within cells. Genomic instability refers to the tendency of a cell or organism's genome to undergo alterations, such as mutations, deletions, insertions, or rearrangements. It can be caused by both internal and external factors, including errors in DNA replication (BRCA1, BRCA2), exposure to mutagens, environmental toxins, radiation, or deficiencies in DNA repair mechanisms (8).

Homologous recombination is mechanism that repairs the DNA double-strand breaks (DSBs). Homologous recombination deficiency is the impaired or reduced ability of a cell to repair DSBs effectively using the HR mechanism. HR is deficient or impaired (HRD), the cell's ability to repair DSBs is compromised, leading to an increased frequency of unrepaired or mis repaired DNA lesions.   Homologous recombination repair is a mechanism that accurately repairs DSBs) by using a non-damaged homologous template from DNA sequence. HRR is a highly effective pathway to ensures the faithful restoration of the original DNA sequence at the site of the break (9).

Cells with HRD have a reduced ability to repair DNA double-strand breaks accurately. As a consequence, they may resort to alternative DNA repair mechanisms that are less accurate, such as non-homologous end joining (NHEJ). NHEJ can cause alteration of genetic material at the repair site, increasing the risk of genomic instability, mutations, and chromosomal rearrangements. HRD is often associated with an increased susceptibility to certain cancers, particularly breast, ovarian, and prostate cancers, as well as other genetic diseases (9).

Other genetic and epigenetic alterations can also lead to HRD in ovarian cancer include: 1) Mutations in HRR Genes such as PALB2, RAD51, RAD51C, RAD51D, and others, 2) Epigenetic Modifications: Epigenetic changes, such as DNA methylation or histone modifications, can affect the expression and function of genes involved in HRR and, 3)Genomic Alterations: Ovarian cancer cells may exhibit large-scale genomic alterations, such as deletions,

rearrangements, or copy number alterations, that disrupt the HRR pathway. BRCA1 and BRCA2 are gene that have significant roles in homologous recombination repair (HRR) pathway. BRCA1 and BRCA2 mutation are commonly associated with hereditary ovary cancer (10). PARP inhibitors are a type of targeted cancer drugs that exploit the synthetic lethality concept of cancer cells with HRD. When PARP is inhibited in cells with HRR or BRCA mutations, it leads to damaged DNA accumulation and moreover caused death of cell. Ovarian cancer patients with mutations of BRCA1 or BRCA2, have been found to exhibit high sensitivity to PARP inhibitor therapy through synthetic lethality. Targeting the HRD caused by BRCA mutations and inhibiting PARP-mediated DNA repair, resulting in death of cell (11).

MOLECULAR ASSAY FOR OVARIAN CANCER
CT Scan in one of the methods to evaluate ovarian tumor. Patients with suspected ovarian tumors needs to be proven according to the pathologic results. RMI examination combined with abdominal pelvic CT scan gives better results in diagnosing ovarian cancer compared to only using an RMI examination or abdominal pelvic CT scan alone. Another method to examine ovarian cancer is molecular assay (12).

It is essential to acknowledge that significant progress has been made in the therapy of ovarian cancer in recent times. Clinical trials are currently investigating targeted therapies, immunotherapies, and another type of treatment approaches, which hold promise for enhancing survival rates and the outcomes. Moreover, individual factors including a patient's general health, response to treatment, and genetic characteristics can also impact the prognosis. Some molecular assay is used to predict patient's has response for the therapy include, 1) BRCA mutation in blood (germline), 2) BRCA mutation in tissue (germline & somatic), 3) Assessing genomic instability: Homologous Recombinant Deficiency (HRD): more than half of all high-grade serous ovarian cancers have an HRD phenotype, and 4) BRCA and HRD status: predict response therapy to PARP inhibitor (13).

Assessing the BRCA status is important for evaluating the potential advantages of PARP inhibitor therapy in ovarian cancer. PARP inhibitors have demonstrated significant effectiveness in treating ovarian cancers that undergo mutations in the BRCA1 or BRCA2 genes. BRCA1 and BRCA2 are genes responsible for suppressing tumor formation and participating in DNA repair mechanisms. Mutations in these genes, particularly when inherited from parents as germline mutations, can result in impaired DNA repair processes and a heightened susceptibility to certain cancers, including ovarian cancer (13).

PARP inhibitors exploit a concept called synthetic lethality. They target an enzyme named poly (ADP-ribose) polymerase (PARP), which is involved in repairing DN. In cancers with BRCA mutations, the PARP pathway is already compromised. By inhibiting PARP, the DNA repair capacity of cancer cells is further disrupted, leading to their death (11).

Therefore, the assessment of BRCA status is crucial for recognize patients who are more likely to respond positively to PARP inhibitor therapy. Patients with either germline or somatic BRCA1/2 mutations have shown enhanced response rates and better progress of survival when treated with PARP inhibitors. Moreover, regulatory agencies such as Olaparib, niraparib, and rucaparib have approved PARP inhibitors for the treatment of advanced ovarian cancer in patients with BRCA mutations.

It is important to mention that BRCA testing not only has relevance for PARP inhibitor therapy but also holds implications for assessing the risk and managing family members who may have a raised risk of developing cancer due to the presence of these genetic mutations. Therefore, the assessment of BRCA status plays a significant role in guiding treatment decisions and identifying patients who could potentially benefit from PARP inhibitor therapy in ovarian cancer (14).

BRCA mutation testing for ovarian cancer can be conducted using either blood or tissue samples, depending on various factors. The choice of sample type is depended by factors such as sample availability, the type of mutation being tested (germline or somatic), and the specific laboratory conducting the test. For germline BRCA testing, blood samples are commonly used. Germline mutations are inherited genetic changes that can be present in all cells of the body, including blood cells. Blood samples are obtained through a simple blood draw and contain DNA from both normal and cancerous cells if present. Tissue samples obtained from the tumor itself are used for somatic mutation testing. Somatic mutations are genetic changes specific to cancer cells and are not inherited. These tissue samples are obtained through biopsies or surgical procedures. It is important to note that the choice of sample may be influenced by the type of BRCA mutation being tested (germline or somatic). Germline testing is typically performed to identify inherited genetic mutations that may have an influence not only on the patient but also on their family members. On the other hand, somatic testing is conducted to identify genetic alterations specific to the tumor cells, which may have implications for treatment decisions (15).

HOMOLOGOUS RECOMBINATION DEFICIENCY IN OVARIAN CANCER CELLS

The mechanism of PARP inhibitor therapy is closely related to homologous recombination deficiency (HRD) through synthetic lethality. Cells with HRD, become highly reliant on pathway to repair DNA, such as base excision repair (BER) or non-homologous end joining (NHEJ) to maintain DNA. PARP inhibitors work by selectively inhibiting the PARP enzyme's activity, preventing the repair of ssDNA breaks through the BER pathway. In cancer cells with HRD, the loss of PARP activity in combination with the pre-existing HRD leads to a failure in repairing DNA (16).

The use of poly (ADP-ribose) polymerase (PARP) inhibitors in patients with HRD can use different pathways of DNA repairing mechanisms, through synthetic lethality. The efficacy of PARP inhibitors therapies is rised not only in ovarian cancers displaying germline or somatic BRCA mutations but also in cancers in which HRD is caused by other another etiology (13).

If HRR pathway function is neglected, HRD cancer cells rely on error prone mechanisms of DNA repair, such as non-homologous end joining (NHEJ), to repair DSBs. However, NHEJ often results in errors, leading to genomic instability, chromosomal rearrangements, and cell death. Inhibition of HRD and PARP leads to damaged DNA accumulation of the cancer cells that cannot be adequately repair. It triggers cell death through the induction of apoptosis or other pathways (17).

The damaged DNA accumulations, induces cell death in HRD cancer cells while sparing normal cells with intact HRR. PARP inhibitors have shown significant clinical benefit in treating HRD-associated cancers, such as ovarian and breast cancers from BRCA mutations. The mechanism of PARP inhibitor therapy involves exploiting the synthetic lethality concept in cancer cells with HRD.

By inhibiting PARP, it prevents the process of repairing ssDNA breaks in cells with compromised HRR pathways. The accumulation of DNA damage, particularly double-strand DNA breaks, inducing death of cell in HRD cancer cells while sparing non-cancer cells with intact HRR. PARP inhibitors have shown significant clinical benefit in treating HRD-associated cancers, such as ovarian and breast cancers with BRCA mutations, and are under investigation for their potential in other HRD-related malignancies (18).

CONCLUSION

Genetic mutation assay of ovarian cancer offers prognostic significance and predicts response to PARP inhibitor monoclonal antibody therapy.

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