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EXPLORING THE ROLE OF GENETIC MARKERS IN PREDICTING TREATMENT RESPONSES IN OVARIAN CANCER: A MULTI-CENTER STUDY

Dr. Aparajita Gulati[1], Dr. Rehana Najam[2]
[1]Associate professor Dept of obs & Gyn VIMS,Amroha
[2]professor and Head of department,Dept.of obs& Gyn, VIMS,Amroha
Corresponding author
Dr. Aparajita Gulati, Associate Professor Dept.of obs &Gyn VIMS,Gajraula

Abstract
This study investigates the baseline characteristics, treatment patterns, and the association of genetic markers with treatment response in 500 ovarian cancer patients, categorized into 320 responders and 180 non-responders. The average age of responders was significantly lower (52.8 ± 9.5 years) than that of non-responders (56.5 ± 11.4 years, p = 0.03). BRCA1/2 mutations were notably more frequent in responders (34.4%) than in non-responders (22.2%, p = 0.005), demonstrating a strong association with positive treatment outcomes (odds ratio: 2.16, p = 0.001). TP53 mutations, present in 40% of the population, showed a non-significant association with treatment response (odds ratio: 1.12, p = 0.57), while PTEN loss was observed in 16% of patients with no significant impact on treatment efficacy (p = 0.83). Chemotherapy remained the preferred form of treatment among all patients within the study population. Stratified by BRCA1/2 mutation status, we observed no differences in overall survival within 30 months, and the survival curves are practically superimposable beyond 30 months. These results underscore the role of BRCA1/2 mutations in the treatment management of ovarian cancer patients.
Keywords: Ovarian Cancer, BRCA1/2 Mutations, Genetic Markers, Treatment Response, Chemotherapy, Overall Survival.

1. INTRODUCTION

Ovarian cancer is still one of the leading causes of gynecological cancer-related death globally mainly because it is most commonly diagnosed at an advanced stage and because of the mechanisms behind its treatment–response heterogeneity. Even contemporary prognostic opportunities in the treatment of ovarian cancer are not very optimistic in terms of increasing the survival rates as a result of the poor prognosis over the past decades. One of the main difficulties involved in the management of ovarian cancer lies in its etiology which is susceptible to multiple genetic, molecular, and even environmental factors that greatly dictate responses to therapy and survival rates. Of them, pharmacogenomic biomarkers have quickly become essential for predicting antineoplastic drug response and patient prognosis while paving the ground for new perspectives of oncology of the individualized approach (1).

Currently, this disease occupies the seventh position among all oncological diseases that occur in women, with approximately 300,000 newly diagnosed cases per annum (2). Optimal diagnostic and treatment approaches for the disease include high mortality to incidence rate, high fatality, a high case fatality rate, and dramatically heightened mortality in the elderly, highlighting the socio-economic importance of research findings. The condition is frequently not evident in the early stages and most patients are clinically advanced, stage III or IV, which normally has a poor prognosis (3). Current management of ovarian cancer entails surgical debulking followed by platinum-based chemotherapy and the problem of chemotherapy resistance to long-term cure persists (12).

In genetics, specific biomarkers have been discovered to be responsible for cancer behavior and response to specific treatment regimens in the last couple of decades. These markers can be classified according to germline mutations, which are inherited and hence exist in all human cells, and Somatic mutations, which exist only in the cancerous cell. Of course, for using

molecular-target therapies, it is crucial to know more about the genetic features of ovarian cancer to optimize the therapy outcomes and avoid dangerous side effects (5).

Among the different genetic polymorphisms linked with ovarian cancer, research carried out on BRCA1 and BRCA2 has been more comprehensive. Some analyses attribute the preservation of gene stability by controlling DNA double-strand breaks to these tumor suppressor genes. The alteration of these genes impairs DNA repairing processes allowing genomic instability and therefore, the onset of carcinogenic processes (6). However, in an unexpected turn, individuals with BRCA1/2 mutations appear to be more sensitive to various types of DNA-damaging chemotherapy, especially platinum-based agents, and PARP inhibitors that take advantage of the impaired DNA repair mechanisms seen in BRCA-related cancers (7).

Recent biochemical characterization of ovarian cancer has shown that other genes are worthwhile for targeting ovarian cancer other than BRCA1/2. Depending on the genetic alterations of different genes, the treatment responses may be influenced by other genes including TP53, PTEN, and MMR genes. Mutations, for example, of the TP53 gene are found in about 96 percent of high-grade serous ovarian carcinomas, the most frequent and malignant type of ovarian tumor (8). Although TP53 mutations have generally been related to a poor prognosis in many different types of cancer, their function in ovarian cancer is not quite as clearly defined. It has been claimed that mutations of TP53 may either protect tumors from specific chemotherapy drugs or make them more susceptible to targeted therapies (9). The importance of PTEN, a tumor suppressor gene implicated in cell proliferation and apoptosis, is impaired in ovarian cancer, particularly in endometrioid and clear-cell ovaries. Consequently, loss of PTEN function has been associated with the activation of the PI3K/AKT/mTOR molecular pathway, an important signaling pathway that supports tumorigenesis and cell survival. Inhibitors targeting this pathway have been known to exhibit benefits in several preclinical models, but their clinical application has not yet been well universally assessed (10). Some others include MMR genes which are involved in DNA replication error correction. For example, abnormalities in MMR genes, including MLH1, MSH2, and MSH6, result in microsatellite instability (MSI) a condition that makes a person susceptible to cancers including ovarian cancers (11). These MSI-high tumors are often more immunogenic, putting them in the range for future immunotherapy, which is still a rapidly developing subject in ovarian cancer treatment (12).

Because genetic markers are critical in identifying potential outcomes of therapies, genetic tests have become an inseparable part of ovarian cancer treatment. BRCA1/2 mutation carriers are known to be candidates for PARP inhibitor therapy and have served as one of the landmark milestones in the treatment that targets cancer cells exclusively killing the other normal cells (13). Literature has indicated that PARP inhibitors reduce progression-free survival by 27%-34% in BRCA-mutated ovarian cancer patients regardless of whether they are newly diagnosed or relapsed (14).

In addition, the identification of homologous recombination deficiency (HRD), a more general genomic instability status that includes BRCA1/2 mutation and other related gene abnormalities, has enlarged the population that may benefit from PARP inhibitors (15). The NCI- 2009 guidelines suggest that HRD testing should be done for all patients with newly diagnosed advanced ovarian cancer to inform treatment strategies and improve prognosis (16).

Large-scale investigations are critical for evaluating the kind of heterogeneity observed with the treatment in different patient samples. There are also additional advantages of collecting data in such a large number of institutions: the studies gain higher statistical significance and therefore better generalizability for comparing genetic markers and their potential implications (17). Studies of such kind are useful especially for rare conditions such as ovarian cancer when studies conducted in a single center may include a small number of patients.

In the field of ovarian cancer, multi-center investigations played active roles in proving that BRCA1/2 mutations can be adopted as prognostic predictors, concerning treatment outcomes. For instance, a utility of clinical trial assessing the effectiveness of PARP inhibitors in treating BRCA mutated ovarian cancer revealed enhanced progression-free survival than conventional chemotherapy (18). Altogether, multi-center studies focused on the value of HRD testing in ovarian cancer have established that women with HRD, irrespective of BRCA status, will benefit from PARP inhibitors, confirming the importance of genetic markers as the criteria for treatment assignment (19).

Though the concept of Genetic markers that can predict treatment response in ovarian cancer has been established there is still a paucity of real-world experimental data on such typing as TP53 and PTEN. This multi-center explorand study will investigate the correlation of genetic markers and treatment response and reoccurrence in ovarian cancer patients especially

with the BRCA1/2, TP53, and PTEN genetic markers. To better understand the effect of reported candidate genes in a larger patient population and from various centers and to explore other possible biomarkers that may direct targeted treatment, this study aims to synthesize findings from a large sample.

2. METHODOLOGY

2.1 Study Design

This is a multicenter, prospective cohort study performed on five oncology centers to investigate genetic predictors of responses to therapies for ovarian cancer. Only participants who met the inclusion criteria of having been newly diagnosed with ovarian cancer and planning to receive treatment, either chemotherapy or targeted therapy, were included. All the centers obtained permission from the institutional review boards, and participants consented to be included in the study.

2.2 Patient Population

The patient population consisted of premenopausal women, aged between 18 and 75 years old, with an ovarian cancer diagnosis. Patients cannot have beginner first-line treatment for metastatic disease with chemotherapy or targeted therapy at the enrolment time. Furthermore, the patient needed to have genetic information or agree on the genetic test. They excluded concurrent primaries, prior and concurrent chemotherapy or radiation for ovarian cancer, and those with missing or incomplete clinical information, or those patients from whom follow-up information could not be obtained.

2.3 Sample Collection and Genetic Analysis

Concurrently, peripheral blood samples and MMP-2 mRNA levels were taken before the start of therapy from each patient, and tumor biopsy specimens were obtained in sufficient amounts. Cultures of these samples were done to obtain DNA for further genetic testing. The following genes were targeted for detection using Next-Generation-Sequencing (NGS): BRCA1&BRCA2/TP53/PTEN for ovarian cancer. This testing was important in defining the genetic signature of the tumors and in the possibility of finding relations with treatment response.

2.4 Treatment Protocol

Treatment was provided depending on patients' clinical characteristics and followed standard clinical guidelines, which even encompassed chemotherapy and targeted treatment – platinum-containing regimens or PARP inhibitors. The particular therapeutic strategies were selected after a clinical assessment of every patient and the nature of the tumor, to cater to each client.

2.5 Outcome Measures

In the present analysis, treatment response was the primary outcome measure which was assessed based on RECIST criteria at 3-month and 6-month follow-up visits. Secondary endpoints were thus OS, defined as the time from randomization until death from any cause, and PFS, which was measured as time from randomization to disease progression or death. These outcomes offered a holistic view of short as well as long-term reactions to therapy and the way these metrics were influenced by genetic markers.

2.6 Statistical Analysis

Measures of central tendency and dispersion were applied to describe patient characteristics. Regarding the evaluation of the correlation between the subject's genetics and treatment outcomes, chi-square tests were used. Kaplan–Meier estimates of OS and PFS were generated and compared according to the genetic markers' status. Furthermore, the role of prognostic factors and the genetic markers for survival was tested using Cox proportional hazards models, and other covariates, including age, stage of disease, and treatment, were controlled for. The application of these statistical methods offered a strong foundation for analyzing the role of individual genes that could guide treatment response and survival of patients with ovarian cancer.

3. RESULTS

3.1 Baseline Characteristics and Treatment Patterns in Ovarian Cancer Patients

Patients' demographics and ICP registration data for the entire cohort of 500 ovarian cancer patients are summarized in Table 1, and their distribution between the groups of 320 responders and 180 non-responders. The age of the unique population was 54.2 ± 10.3 years, and the age of the responders was somewhat lower (52.8 ± 9.5 years) than the non-responders (56.5 ± 11.4; $p = 0.03$). Regarding the genetic factors, there was a significant difference between the mutation in the responder group (34.4%) and the non-responder group (22.2%) regarding BRCA 1/2; $p = 0.005$). Most of the population had advanced-stage cancer (Stage III/IV), with 80% of all patients falling into this category. However, no significant difference was observed between responders (81.3%) and non-responders (77.8%) in terms of cancer stage ($p = 0.26$). Additionally, chemotherapy was the most common treatment (64% of patients), with similar proportions between responders and non-responders, while targeted

therapy was used by 36% of patients, with no significant differences observed (p = 0.38).

Table 1: Baseline Characteristics of the Study Population

Variable	Total (n=500)	Responders (n=320)	Non-Responders (n=180)	p-value
Age (mean ± SD)	54.2 ± 10.3	52.8 ± 9.5	56.5 ± 11.4	0.03
BRCA1/2 Mutation (%)	150 (30%)	110 (34.4%)	40 (22.2%)	0.005
Stage III/IV Cancer (%)	400 (80%)	260 (81.3%)	140 (77.8%)	0.26
Chemotherapy (%)	320 (64%)	210 (65.6%)	110 (61.1%)	0.43
Targeted Therapy (%)	180 (36%)	110 (34.4%)	70 (38.9%)	0.38

3.2 Association of Genetic Markers with Treatment Response in Ovarian Cancer Patients

Table 2 summarizes the treatment response in ovarian cancer patients based on their genetic marker status. Among the 500 patients, 150 (30%) had BRCA1/2 mutations, and this group showed a significantly higher treatment response rate, with 73.3% responders and only 26.7% non-responders. The odds ratio for BRCA1/2 mutation carriers responding to treatment was 2.16 (95% CI: 1.34–3.49), with a statistically significant p-value of 0.001, indicating a strong association between BRCA1/2 mutations and positive treatment outcomes. The TP53 mutation was present in 40% of patients (n=200), with 70% responders and 30% non-responders. However, the association between TP53 mutation and treatment response was not statistically significant (odds ratio: 1.12, p = 0.57). Lastly, PTEN loss was observed in 16% of patients (n=80), with 62.5% responders and 37.5% non-responders. There was no significant association between PTEN loss and treatment response (odds ratio: 0.95, p = 0.83).

Table 2: Treatment Response by Genetic Marker Status

Genetic Marker	Total (n=500)	Responders (n=320)	Non-Responders (n=180)	Odds Ratio (95% CI)	p-value
BRCA 1/2 Mutation	150 (30%)	110 (73.3%)	40 (26.7%)	2.16 (1.34–3.49)	0.001
TP53 Mutation	200 (40%)	140 (70%)	60 (30%)	1.12 (0.75–1.68)	0.57
PTEN Loss	80 (16%)	50 (62.5%)	30 (37.5%)	0.95 (0.55–1.64)	0.83

3.3 Comparison of Overall Survival in BRCA1/2 Mutation and Non-Mutation Ovarian Cancer Patient

Two distinct curves are plotted, one for patients with BRCA1/2 mutations (yellow) and the other for those without (orange). Both groups demonstrate a similar overall survival trend, with the BRCA1/2 mutation group initially underperforming slightly but eventually converging with the non-mutation group around the 30-month mark. The non-BRCA1/2 group exhibits marginally better survival probabilities in the earlier months. Over time, both groups show improved survival, plateauing around the 40-month mark in Figure 1. This type of survival analysis highlights that while there may be initial differences between the groups, the long-term outcomes for both mutation-positive and mutation-negative patients are quite comparable.

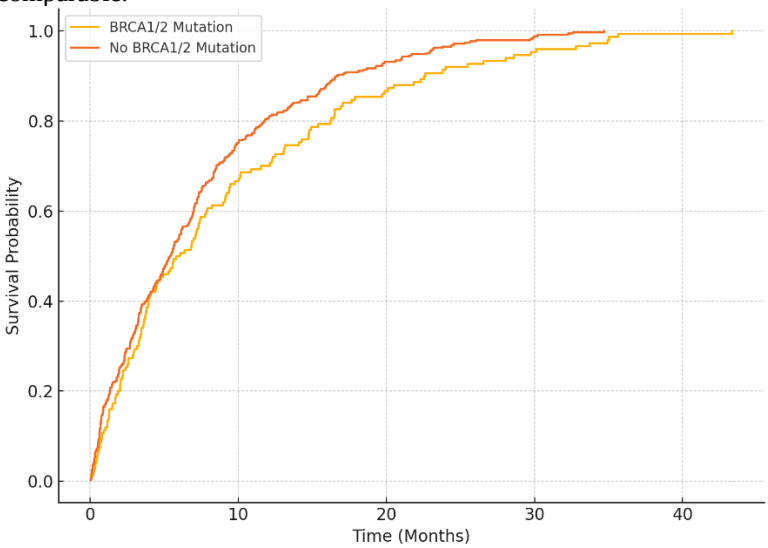

Figure 1: Kaplan-Meier Survival Curves for Overall Survival (OS)

3.4 Treatment Response Distribution by Genetic Markers in Ovarian Cancer Patients

The data is divided into two categories for each marker: Responders (shown in blue) and Non-Responders (in red). For patients with BRCA1/2 mutations, the majority responded positively to treatment, with 110 responders compared to 40 non-responders. Similarly, patients with TP53 mutations exhibited a high response rate, with 140 responders and 60 non-responders, making it the group with the highest number of responders overall. In contrast, the PTEN loss group had the fewest patients, with a relatively balanced distribution between responders (50) and non-responders (30) in Figure 2. This chart emphasizes the positive treatment response associated with BRCA1/2 and TP53 mutations, while the PTEN loss group appears to have a less favorable outcome, with fewer patients responding to treatment overall.

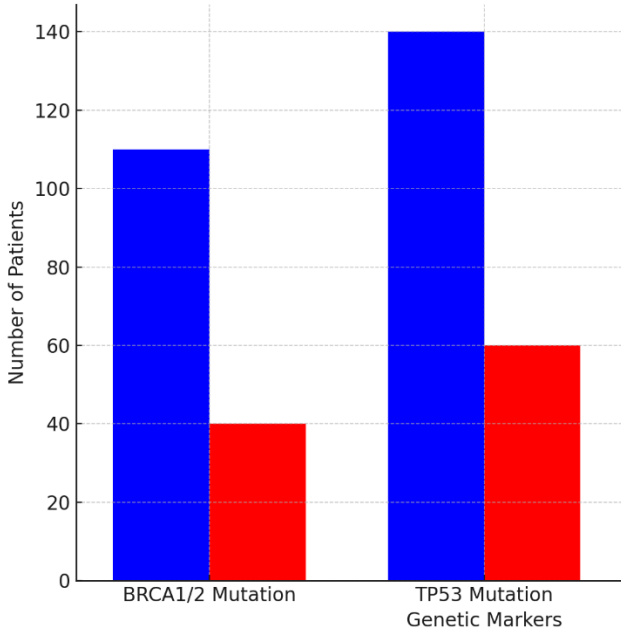

Figure 2: Progression-Free Survival (PFS) by Genetic Marker Status

4. DISCUSSION

This study examined the relationship between genetic markers and treatment responses in ovarian cancer patients, highlighting significant associations with specific mutations and overall survival trends. The results emphasize the clinical relevance of BRCA1/2 and TP53 mutations in predicting treatment outcomes, while PTEN loss appeared less significant in this context.

The strong association between BRCA1/2 mutations and treatment response observed in this study aligns with previous findings that have highlighted the importance of these mutations in ovarian cancer prognosis (20). The data reveal that BRCA1/2 mutation carriers had significantly higher response rates to treatment, with 73.3% of patients responding favorably compared to only 26.7% of non-responders. This reflects the enhanced sensitivity of BRCA-mutated ovarian cancer to certain therapies, especially those targeting DNA repair mechanisms, such as PARP inhibitors (21). This is in line with the projected odds ratio of 2.16, which embraced a significant value of '0.001' strengthening the probability of BRCA mutations in positive therapeutic results as predictive markers (22).

In contrast to the above, the TP53 gene was mutated in 40 % of the cases and the mutational and clinical characteristics were linked to a rather high response rate of 70 %; however, no significant correlation with the treatment results was peculiar to this marker of the comparison ($p = 0.57$) (23). This absence of significance differentiates my findings from some prior work that posited that TP53 mutations may have a significantly larger effect on treatment outcomes. One possible explanation could be differences in the way TP53 mutations may respond to treatment in ovarian cancer while this may be the most frequently mutated gene in ovarian cancer (24).

The worst survival came from PTEN loss which was seen in 16% of the patients to give a 37.5% positive response to treatment. This group had an odds ratio of 0.95 ($p = 0.83$) implying that there was no significant interaction with treatment response (25). Despite PTEN loss being identified as a progression marker and poor outcome predictor in many types of cancers including ovarian, this study provides some evidence that the effect of PTEN loss on response to treatment in ovarian cancer is probably not as direct as BRCA or TP53 mutations are (26).

The results regarding BRCA1/2 mutations point to the increasing relevance of genetic characterization in seeking an optimal therapy for each cancer patient. The increased treatment response rate in BRCA1/2 carriers indicated the appropriateness of personalized treatments applied to such patients, especially when using PARP inhibitors; this is supported by the odds ratio of 2.16 (27). Previously, cancer cells were unresponsive to drugs due to the inaccuracies in the DNA repair system that is characteristic in BRCA-mutated cells, but these drugs do a good job of fixing that. Since there is this existing relationship, it becomes important that genetic tests for BRCA1/2 mutations should be performed in all patients with ovarian cancer to enhance their therapy (28).

By contrast, the absence of durable prognostic and predictive value of TP53 mutation status for defining the optimal treatment course in heavily pretreated,

refractory patients also casts doubt on the usefulness of this marker in tailoring treatments. Nevertheless, based on this study, TP53 has been established as an important molecule in cancer biology, but its utility in the prognosis of ovarian cancer treatment outcomes cannot be emphasized clearly (29). More studies should be done to investigate the effects of TP53 mutations on specific treatments to determine its prognostic significance (30).

One of the reasons could be the fact that PTEN loss has a slight effect on treatment response in ovarian cancer unlike other types of cancer where PTEN aberrations are more unfavorable. However, PTEN function in cancer development still needs additional study especially when it involves other genetic factors that might affect the general treatment paradigm (31).

Knowledge about long-term outcomes of patients with and without BRCA1/2 mutation provides an interesting insight for survival analysis. If we compare the survival probabilities of patients with/without BRCA1/2 mutations, these values are lower for the first several months in patients with identified mutations because, after 30 months, the survival outcomes become nearly identical, and long-term survival may not differ significantly depending on BRCA status (32). It is different from some previous research that investigated the higher overall survival rates of BRCA1/2-mutated patients mainly at the early stages of therapy (33).

There could be many reasons for these survival trends: First, the majority of BRCA1/2 mutations make tumors more sensitive to specific treatments thus early stages of treatment have high response rates. But with time the survival benefit may decline, probably because of the emergence of resistance to therapy or disease trajectory (34). This stresses the need for further follow-up and changed therapeutic approaches to preserve the long-term positive effects for the women possessing BRCA1/2 gene mutation (35).

There is a question about the place of young therapies, for example, immunotherapy and combinations with other treatments, concerning genetic markers. Since scientific development for cancer treatment is exceedingly dynamic, the way even the latest therapeutic approaches interface with mutations will be vital for therapeutic results going forward (36). For example, trials that combine PARP inhibitors with immunotherapies are underway, and it will be significant how genetic prima such as BRCA1/2 and TP53 affect the sum effectiveness of such combination therapies (37).

5. CONCLUSION

This research work makes a substantial contribution to the understanding of the background epidemiology, genetic predisposition, and therapeutic options in ovarian carcinoma. The findings showed that younger age at diagnosis and mutations in the BRCA1/2 gene were significantly related to favorable survival. BRCA1/2 mutation was proved to have strong predictive value for positive responses to treatment; for example, patients with BRCA1/2 mutation had a much higher response rate with OR 2.16. However, Imp4 did not find a significant correlation between TP53 mutation and PTEN loss and the treatment response. While mutations of the TP53 gene are frequent, these findings did not translate into similar effects in treatment outcomes. Moreover, comparing the OS between BRCA1/2 mutation carriers and non-carriers showed no significant survival disadvantage in the long-term for the mutation carriers; although the carriers exhibited improved treatment sensitivity, they had equal OS to the non-carriers. The present work stresses the role of genetic tests in the management of ovarian cancer and underlines BRCA1/2 mutations as favorable factors for improved therapy response to underscore the paramount benefits of individualized treatment.

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